



Results

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Journal of Computational Chemistry, 34 (1), January, 2013.
 Journal of Computational Chemistry, 34 (2), January, 2013.
 Journal of Molecular Modeling, 18 (12), December, 2012.
 Molecular Simulation, 39(1), 2013.

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1. APPLICATIONS

1.1. Small Molecules

Medicinal Chemistry and Drug Design

Recognition of Imipenem and Meropenem by the RND-Transporter MexB Studied by Computer Simulations

Nadine Schwierz, Dominik Horinek, Susanne Liese, Tobias Pirzer, Bizan N. Balzer, Thorsten Hugel, and Roland R. Netz [Freie Universität Berlin]

J. Am. Chem. Soc., **134**, 19146–19158, 2012.

Basic understanding of the means by which multidrug efflux systems can efficiently recognize and transport drugs constitutes a fundamental step toward development of compounds able to tackle the continuous outbreak of new bacterial strains resistant to traditional antibiotics. We applied a series of computational techniques, from molecular docking to molecular dynamics simulations and free energy estimate methods, to determine the differences in the binding properties of imipenem and meropenem, two potent antibiotics of the carbapenem family, to MexB, the RND transporter of the major efflux system of *Pseudomonas aeruginosa*.

Computational screening for new inhibitors of M. tuberculosis mycolyltransferases antigen 85 group of proteins as potential drug targets

Shachi Gahoi, Rahul Shubhra Mandal, Nikita Ivanisenko, Priyanka Shrivastava, Sriyans Jain, Ashish Kumar Singh, Muthukurrusi Varieth Raghunandanan, Swarna Kanchan, Bhupesh Taneja, Chhabinath Mandal, Vladimir A. Ivanisenko, Anil Kumar, Rita Kumar, Open Source Drug Discovery Consortium & Srinivasan Ramachandran [G.N. Ramachandran Knowledge Centre for Genome Informatics]

J. Biomol. Stru. and Dyn., **31**, 30-43, 2013.

The group of antigen 85 proteins of *Mycobacterium tuberculosis* is responsible for converting trehalose monomycolate to trehalose dimycolate, which contributes to cell wall stability. Here, we have used a serial enrichment approach to identify new potential inhibitors by searching the libraries of compounds using both 2D atom pair descriptors and binary fingerprints followed by molecular docking. Three different docking softwares AutoDock, GOLD, and LigandFit were used for docking calculations. In addition, we applied the criteria of selecting compounds with binding efficiency close to the starting known inhibitor and showing potential to form hydrogen bonds with the active site amino acid residues.

 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: Naresh Aerra Rational Labs, Hyderabad., India Sambasivareddy M RR Labs Inc., San Diego, CA.

Medicinal Chemistry and Drug Design (Cont'd)

Identification of old drugs as potential inhibitors of HIV-1 integrase – human LEDGF/p75 interaction via molecular docking

Guoping Hu, Xi Li, Xianqiang Sun, Weiqiang Lu, Guixia Liu, Jin Huang, Xu Shen, Yun Tang [East China University of Science and Technology]

J. Mol.Mod., **18**, 4995-5003, 2012.

Integration of viral-DNA into host chromosome mediated by the viral protein HIV-1 integrase (IN) is an essential step in the HIV-1 life cycle. In this process, human protein Lens epithelium-derived growth factor (LEDGF/p75) is discovered to function as a cellular co-factor for integration. LEDGF/p75-HIV-1 IN interaction represents an attractive target for anti-HIV therapy. In this study, approved drugs were investigated for the finding of potential inhibitors on this target. Via molecular docking against the LEDGF/p75-binding pocket of HIV-1 IN, 26 old drugs were selected from the DrugBank and purchased for bioassays.

Selectivity and activation of dopamine D3R from molecular dynamics

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

J. Mol.Mod., **18**, 5051-5063, 2012.

D₃ receptor, a member of dopamine (DA) D₂-like receptor family, which belongs to class A of G-protein coupled receptors (GPCRs), has been reported to play a critical role in neuropsychiatric disorders. Recently, the crystal structure of human dopamine D₃ receptor was reported, which facilitates structure-based drug discovery of D₃R significantly. We dock D₃R-selective compounds into the crystal structure of D₃R and homology structure of D₂R. Then we perform 20 ns molecular dynamics (MD) of the receptor with selective compounds bound in explicit lipid and water. Our docking and MD results indicate the important residues related to the selectivity of D₃R.

Leishmania donovani pteridine reductase 1: comparative protein modeling and protein–ligand interaction studies of the leishmanicidal constituents isolated from the fruits of Piper longum

Shakti Sahi, Parul Tewatia, Sabari Ghosal [Amity University]

J. Mol.Mod., **18**, 5065-5073, 2012.

Visceral leishmaniasis or kala-azar is caused by the dimorphic parasite *Leishmania donovani* in the Indian subcontinent. Treatment options for kala-azar are currently inadequate due to various limitations. Currently, drug discovery for leishmaniasis is oriented towards rational drug design; the aim is to identify specific inhibitors that target particular metabolic activities as a possible means of controlling the parasites without affecting the host. Based on a homology model derived for recombinant pteridine reductase isolated from a clinical isolate of *L. donovani*, we carried out molecular modeling and docking studies with these compounds to evaluate their binding affinity.

Development of 3D-pharmacophore model followed by successive virtual screening, molecular docking and ADME studies for the design of potent CCR2 antagonists for inflammation-driven diseases

Rajesh Singh [National Institute of Pharmaceutical Education and Research], Anand Balupuri & M. Elizabeth Sobhia

Molecular Simulation, **39**, 49-58, 2013.

In order to elucidate the essential structural features for CC chemokine receptor 2 (CCR2) antagonism, 3D-pharmacophore hypotheses were built based on a set of known compounds. The hypotheses were developed with the aid of HypoGen module within Discovery Studio 2.5 program. Multiple validation approaches provided the confidence in utilising the predictive pharmacophore models developed in this study. The most predictive pharmacophore model (Hypo1) was found to be statistically significant along with its ability to predict activities of the known CCR2 antagonists.

1.2. Biopolymers

Bioinformatics and Cheminformatics

DAFS: simultaneous aligning and folding of RNA sequences via dual decomposition

Kengo Sato [Keio University], Yuki Kato, Tatsuya Akutsu, Kiyoshi Asai, and Yasubumi Sakakibara

Bioinformatics. **28**, 3218–3224, 2012.

It is well known that the accuracy of RNA secondary structure prediction from a single sequence is limited, and thus a comparative approach that predicts a common secondary structure from aligned sequences is a better choice if homologous sequences with reliable alignments are available. However, correct secondary structure information is needed to produce reliable alignments of RNA sequences. We develop DAFS, a novel algorithm that simultaneously aligns and folds RNA sequences based on maximizing expected accuracy of a predicted common secondary structure and its alignment.

Swfoldrate: Predicting protein folding rates from amino acid sequence with sliding window method

Xiang Cheng, Xuan Xiao [Jing-De-Zhen Ceramic Institute], Zhi-cheng Wu, Pu Wang and Wei-zhong Lin

Proteins: Stru. Fun. & Bioinf., **81**, 140–148, 2013.

Protein folding is the process by which a protein processes from its denatured state to its specific biologically active conformation. Understanding the relationship between sequences and the folding rates of proteins remains an important challenge. . In this study, the long-range and short-range contact in protein were used to derive extended version of the pseudo amino acid composition based on sliding window method. This method is capable of predicting the protein folding rates just from the amino acid sequence without the aid of any structural class information.

Protein Secondary Structure

Mechanical Transition from α -Helical Coiled Coils to β -Sheets in Fibrin(ogen)

Artem Zhmurov, Olga Kononova, Rustem I. Litvinov, Ruxandra I. Dima, Valeri Barsegov [University of Massachusetts, Lowell], and John W. Weisel

J. Am. Chem. Soc., **134**, 20396–20402, 2012.

We characterized the α -to- β transition in α -helical coiled-coil connectors of the human fibrin(ogen) molecule using biomolecular simulations of their forced elongation and theoretical modeling. The force (F)–extension (X) profiles show three distinct regimes: (1) the elastic regime, in which the coiled coils act as entropic springs ($F < 100$ – 125 pN; $X < 7$ – 8 nm); (2) the constant-force plastic regime, characterized by a force-plateau ($F \approx 150$ pN; $X \approx 10$ – 35 nm); and (3) the nonlinear regime ($F > 175$ – 200 pN; $X > 40$ – 50 nm).

Protein Structure Prediction

3Drefine: Consistent protein structure refinement by optimizing hydrogen bonding network and atomic-level energy minimization

Debswapna Bhattacharya and Jianlin Cheng [University of Missouri]

Proteins: Stru. Fun. & Bioinf., **81**, 119–131, 2013.

One of the major limitations of computational protein structure prediction is the deviation of predicted models from their experimentally derived true, native structures. The limitations often hinder the possibility of applying computational protein structure prediction methods in biochemical assignment and drug design that are very sensitive to structural details. Here, we propose a two-step refinement protocol, called 3Drefine, to consistently bring the initial model closer to the native structure. The first step is based on optimization of hydrogen bonding (HB) network and the second step applies atomic-level energy minimization on the optimized model using a composite physics and knowledge-based force fields.

Comparative or Homology Modeling

Modeling the Closed and Open State Conformations of the GABA_A Ion Channel - Plausible Structural Insights for Channel Gating

R. S. K. Vijayan, Neha Trivedi, Sudipendra Nath Roy, Indrani Bera, Prabu Manoharan, Pavan V. Payghan, Dhananjay Bhattacharyya, and Nanda Ghoshal [CSIR - Indian Institute of Chemical Biology]

J.Chem. Infor. and Mod. **52**, 2958–2969, 2012.

Recent disclosure of high resolution crystal structures of *Gloeobacter violaceus* (GLIC) in open state and *Erwinia chrysanthemii* (ELIC) in closed state provides newer avenues to advance our knowledge and understanding of the physiologically and pharmacologically important ionotropic GABA_A ion channel. The present modeling study envisions understanding the complex molecular transitions involved in ionic conductance, which were not evident in earlier disclosed homology models. In particular, emphasis was put on understanding the structural basis of gating, gating transition from the closed to the open state on an atomic scale. Homology modeling of two different physiological states of GABA_A was carried out using their respective templates.

Protein Confirmational Analysis

Relationship between helix stability and binding affinities: molecular dynamics simulations of Bfl-1/A1-binding pro-apoptotic BH3 peptide helices in explicit solvent

Vivek Modi, Dilraj Lama & Ramasubbu Sankararamakrishnan [Indian Institute of Technology Kanpur]

J. Biomol. Stru. and Dyn., **31**, 65-77, 2013.

The anti-apoptotic protein Bfl-1, also known as A1, belongs to the Bcl-2 family of proteins and interacts with pro-apoptotic Bcl-2 counterparts to regulate programmed cell death. As demonstrated for other anti-apoptotic Bcl-2 proteins, Bfl-1/A1 has also been shown to be overexpressed in various human cancers and hence they are attractive targets for anticancer drugs. Apart from the length and amino acid composition, a BH3 peptide's ability to form a stable helical structure has been suggested to be important for its high binding affinity. Molecular dynamics simulations of three BH3 peptides derived from the pro-apoptotic proteins Bak, Bid, and Bmf were carried out each for a period of at least 100 ns after 2 ns equilibration run.

Protein Conformational Analysis (Cont'd)

Dead-end elimination with perturbations (DEEPer): A provable protein design algorithm with continuous sidechain and backbone flexibility

Mark A. Hallen, Daniel A. Keedy and Bruce R. Donald[Duke University Medical Center]

Proteins: Stru. Fun. & Bioinf., **81**, 18–39, 2013.

Computational protein and drug design generally require accurate modeling of protein conformations. This modeling typically starts with an experimentally determined protein structure and considers possible conformational changes due to mutations or new ligands. The DEE/A* algorithm provably finds the global minimum-energy conformation (GMEC) of a protein assuming that the backbone does not move and the sidechains take on conformations from a set of discrete, experimentally observed conformations called rotamers.

Protein Dynamics

The Molecular Mechanism Underlying Mechanical Anisotropy of the Protein GB1

Yongnan Devin Li, Guillaume Lamour, Jörg Gsponer, Peng Zheng, Hongbin Li [University of British Columbia]

Biophysical Journal. **103**, 2361–2368, 2012.

Mechanical responses of elastic proteins are crucial for their biological function and nanotechnological use. Loading direction has been identified as one key determinant for the mechanical responses of proteins. However, it is not clear how a change in pulling direction changes the mechanical unfolding mechanism of the protein. Here, we combine protein engineering, single-molecule force spectroscopy, and steered molecular dynamics simulations to systematically investigate the mechanical response of a small globular protein GB1.

On the Relationship between Peptide Adsorption Resistance and Surface Contact Angle: A Combined Experimental and Simulation Single-Molecule Study

Nadine Schwierz, Dominik Horinek, Susanne Liese, Tobias Pirzer, Bizan N. Balzer, Thorsten Hugel, and Roland R. Netz [Freie Universität Berlin]

J. Am. Chem. Soc., **134**, 19628–19638, 2012.

The force-induced desorption of single peptide chains from mixed OH/CH₃-terminated self-assembled monolayers is studied in closely matched molecular dynamics simulations and atomic force microscopy experiments with the goal to gain microscopic understanding of the transition between peptide adsorption and adsorption resistance as the surface contact angle is varied. In both simulations and experiments, the surfaces become adsorption resistant against hydrophilic as well as hydrophobic peptides when their contact angle decreases below $\theta \approx 50^\circ$ – 60° , thus confirming the so-called Berg limit established in the context of protein and cell adsorption.

Detailed Structure of the H₂PO₄[−]–Guanosine Diphosphate Intermediate in Ras-GAP Decoded from FTIR Experiments by Biomolecular Simulations

Fei Xia, Till Rudack, Qiang Cui, Carsten Kötting, and Klaus Gerwert [Shanghai Institutes for Biological Sciences]

J. Am. Chem. Soc., **134**, 20041–20044, 2012.

Essential biochemical processes such as signal transduction, energy conversion, or substrate conversion depend on transient ligand binding. Thus, identifying the detailed structure and transient positioning of small ligands, and their stabilization by the surrounding protein, is of great importance. In this study, by decoding information from Fourier transform infrared (FTIR) spectra with biomolecular simulation methods, we identify the precise position and hydrogen network of a small compound, the guanosine diphosphate (GDP)–H₂PO₄[−] intermediate, in the surrounding protein–protein complex of Ras and its GTPase-activating protein.

Protein Dynamics (Cont'd)

Unraveling the Mechanisms of Nonradiative Deactivation in Model Peptides Following Photoexcitation of a Phenylalanine Residue

Momir Mališ, Yohan Loquais, Eric Gloaguen, Himansu S. Biswal, François Piuze, Benjamin Tardivel, Valérie Brenner, Michel Broquier, Christophe Juvet, Michel Mons[Lab. Francis Perrin, URA 2453], Nađa Došlić, and Ivan Ljubić

J. Am. Chem. Soc., **134**, 20340–20351, 2012.

The mechanisms of nonradiative deactivation of a phenylalanine residue after near-UV photoexcitation have been investigated in an isolated peptide chain model (N-acetylphenylalaninylamide, NAPA) both experimentally and theoretically. Lifetime measurements at the origin of the first $\pi\pi^*$ state of jet-cooled NAPA molecules have shown that (i) among the three most stable conformers of the molecule, the folded conformer NAPA B is ~ 50 -times shorter lived than the extended major conformer NAPA A and (ii) this lifetime is virtually insensitive to deuteration at the NH_2 and NH sites. Concurrent time-dependent density functional theory (TDDFT) based nonadiabatic dynamics simulations in the full dimensionality, carried out for the NAPA B conformer, provided direct insights on novel classes of ultrafast deactivation mechanisms, proceeding through several conical intersections and leading in fine to the ground state.

Dissociation of Membrane-Anchored Heterotrimeric G-Protein Induced by G_α Subunit Binding to GTP

Maxime Louet, Landry Charlier, Jean Martinez, and Nicolas Floquet [Université Montpellier 2]

J. Chem. Infor. and Mod. **52**, 3022–3027, 2012.

Heterotrimeric G-proteins' activation on the intracellular side of the cell membrane is initiated by stimulation of the G-Protein Coupled Receptors (GPCRs) extra-cellular part. This two-step activation mechanism includes (1) an exchange between GDP and GTP molecules in the G_α subunit and (2) a dissociation of the whole $G_{\alpha\beta\gamma}$ complex into two membrane-anchored blocks, namely the isolated G_α and $G_{\beta\gamma}$ subunits. In this study, we first built a membrane-anchored intermediate $G_{\alpha\beta\gamma}$:GTP complex. This model was then equilibrated by molecular dynamics simulations before the Targeted Molecular Dynamics (TMD) technique was used to force the G_α subunit to evolve from its inactive (GDP-bound) to its active (GTP-bound) conformations, as described by available X-ray data.

Side-Chain Dynamics Reveals Transient Association of $\text{A}\beta_{1-40}$ Monomers with Amyloid Fibers

Janarthanan Krishnamoorthy, Jeffrey R. Brender, Subramanian Vivekanandan, Nicole Jahr, and Ayyalusamy Ramamoorthy [University of Michigan, Ann Arbor]

J. Phys. Chem. B., **116**, 13618–13623, 2012.

Low-lying excited states that correspond to rare conformations or transiently bound species have been hypothesized to play an important role for amyloid nucleation. Despite their hypothesized importance in amyloid formation, transiently occupied states have proved difficult to detect directly. To experimentally characterize these invisible states, we performed a series of Carr–Purcell–Meiboom–Gill (CPMG)-based relaxation dispersion NMR experiments for the amyloidogenic $\text{A}\beta_{1-40}$ peptide implicated in Alzheimer's disease.

Protein Dynamics (Cont'd)

Molecular Dynamics Simulation Study on the Molecular Structures of the Amylin Fibril Models

Weixin Xu [Nanyang Technological University], Haibin Su, John Z. H. Zhang, and Yuguang Mu

J. Phys. Chem. B., **116**, 13991–13999, 2012.

The structural characterization of amyloid fibers is one of the most investigated areas in structural biology. Recently, protofibril models for amylin, i.e., the 37-residue human islet amyloid polypeptide or hIAPP were suggested by two groups based on NMR (Biochemistry 2007, 46, 13505–13522) and X-ray (Protein Sci. 2008, 17, 1467–1474) techniques. However, there are significant differences in the two models which maybe originate from the polymorphic nature of amylin fibrils. To obtain further insights into the packing and stability features of the different models, we performed a series of molecular dynamics simulations on them.

Shape evolution with temperature of a thermotolerant protein (PeaT1) in solution detected by small angle X-ray scattering

Xueqing Xing, Quan Liu, Wei Wang, Kunhao Zhang, Tang Li, Quan Cai, Guang Mo, Weidong Cheng, Dehong Wang, Yu Gong, Zhongjun Chen, Dewen Qiu and Zhonghua Wu [Chinese Academy of Agricultural Sciences]

Proteins: Stru. Fun. & Bioinf., **81**, 53–62, 2013.

The protein elicitor from *Alternaria tenuissima* (PeaT1) presented excellent thermotolerance and potential application in agriculture as a pesticide. Previous synchrotron radiation circular dichroism study demonstrated that the secondary structures in PeaT1 protein are reversible with temperature change. To further clarify the mechanism of its thermotolerance, synchrotron radiation small angle x-ray scattering (SAXS) technique was used to study the shape change of PeaT1 protein with temperature in this article. Ab initio structure restorations based on the SAXS data revealed that PeaT1 protein has a prolate shape with a P_2 symmetry axis along the prolate anisometric direction.

Free Energy Calculations

Rationalization of stereospecific binding of propranolol to cytochrome P450 2D6 by free energy calculations

Gabor Nagy, Chris Oostenbrink [University of Natural Resources and Life Sciences]

Europ. Biophys. Jou., **41**, 1065-1076, 2012.

Cytochrome P450 2D6 is a major drug-metabolising enzyme with a wide substrate range. A single-point mutation introduced in this enzyme induces stereoselective binding of R and S-propranolol whereas the wild type has no preference. The system has previously been studied both experimentally and computationally (de Graaf et al. in *Eur Biophys J* 36:589–599, 2007a). The in silico study reported hysteresis and significant deviations from closure of thermodynamic cycles, probably because of lack of sampling. Here, we focus on the effect of prolonged simulation time and enhanced sampling methods, such as Hamiltonian replica exchange, to reduce these problems and to improve the precision of free energy calculations.

Free energy calculations (Cont'd)

A convective replica-exchange method for sampling new energy basins

Yannick G. Spill, Guillaume Bouvier and Michael Nilges [Unité de Bioinformatique Structurale]

J. Comp. Chem. **33**, 132–140, 2013.

Replica-exchange is a powerful simulation method for sampling the basins of a rugged energy landscape. The replica-exchange method's sampling is efficient because it allows replicas to perform round trips in temperature space, thereby visiting both low and high temperatures in the same simulation. However, replicas have a diffusive walk in temperature space, and the round trip rate decreases significantly with the system size. These drawbacks make convergence of the simulation even more difficult than it already is when bigger systems are tackled. Here, we present a simple modification of the exchange method. In this method, one of the replicas steadily raises or lowers its temperature.

Ligand Binding/Docking

Molecular Interactions of Alzheimer's Biomarker FDDNP with A β Peptide

Christopher Lockhart, Dmitri K. Klimov [George Mason University]

Biophysical Journal. **103**, 2341-2351, 2012.

All-atom explicit solvent model and replica exchange molecular dynamics were used to investigate binding of Alzheimer's biomarker FDDNP to the A β_{10-40} monomer. At low and high concentrations, FDDNP binds with high affinity to two sites in the A β_{10-40} monomer located near the central hydrophobic cluster and in the C-terminal. Analysis of ligand- A β_{10-40} interactions at both concentrations identifies hydrophobic effect as a main binding factor. However, with the increase in ligand concentration the interactions between FDDNP molecules also become important due to strong FDDNP self-aggregation propensity and few specific binding locations.

Unbinding Pathways of GW4064 from Human Farnesoid X Receptor As Revealed by Molecular Dynamics Simulations

Weihua Li, Jing Fu, Feixiong Cheng, Mingyue Zheng, Jian Zhang, Guixia Liu, and Yun Tang [East China University of Science and Technology]

J.Chem. Infor. and Mod. **52**, 3043–3052, 2012.

Farnesoid X receptor (FXR, NR1H4) is a member of a nuclear receptor superfamily, which plays important roles in bile acid homeostasis, lipoprotein and glucose metabolism, and hepatic regeneration. GW4064 is a potent and selective FXR agonist and has become a tool compound to probe the physiological functions of FXR. Until now, the mechanism of GW4064 entering and leaving the FXR pocket is still poorly understood. Here, we report a computational study of GW4064 unbinding pathways from FXR by using several molecular dynamics (MD) simulation techniques.

Ligand Binding / Docking (Cont'd)

Multiple Interaction Regions in the Orthosteric Ligand Binding Domain of the $\alpha 7$ Neuronal Nicotinic Acetylcholine Receptor

Yunde Xiao [Targacept, Inc.], Philip S. Hammond, Anatoly A. Mazurov, and Daniel Yohannes

J.Chem. Infor. and Mod. **52**, 3064–3073, 2012.

Neuronal nicotinic receptors (nAChRs) belong to the Cys-loop family of ligand-gated ion channels and are formed from five subunits either as homologous or heterologous, oligomeric receptors, and are of interest as targets for treatment of a variety of central and peripheral nervous system disorders. Using a model of the homopentameric $\alpha 7$ nAChR extracellular region derived from the homologous acetylcholine binding protein (AChBP) from *Aplysia California*, binding modes of structurally diverse, high affinity $\alpha 7$ ligands were examined by docking to the orthosteric ligand binding domain.

Comparing aminoglycoside binding sites in bacterial ribosomal RNA and aminoglycoside modifying enzymes

Julia Romanowska [University of Warsaw], Nathalie Reuter and Joanna Trylska

Proteins: Stru. Fun. & Bioinf., **81**, 63–80, 2013.

Aminoglycoside antibiotics are used against severe bacterial infections. They bind to the bacterial ribosomal RNA and interfere with the translation process. However, bacteria produce aminoglycoside modifying enzymes (AME) to resist aminoglycoside actions. AMEs form a variable group and yet they specifically recognize and efficiently bind aminoglycosides, which are also diverse in terms of total net charge and the number of pseudo-sugar rings. Here, we present the results of 25 molecular dynamics simulations of three AME representatives and aminoglycoside ribosomal RNA binding site, unliganded and complexed with an aminoglycoside, kanamycin A.

Enzyme Catalysis

Computational Design of an α -Gliadin Peptidase

Sydney R. Gordon, Elizabeth J. Stanley, Sarah Wolf, Angus Toland, Sean J. Wu, Daniel Hadidi, Jeremy H. Mills, David Baker, Ingrid Swanson Pultz, and Justin B. Siegel [University of Washington, Seattle]

J. Am. Chem. Soc., **134**, 20513–20520, 2012.

The ability to rationally modify enzymes to perform novel chemical transformations is essential for the rapid production of next-generation protein therapeutics. Here we describe the use of chemical principles to identify a naturally occurring acid-active peptidase, and the subsequent use of computational protein design tools to reengineer its specificity toward immunogenic elements found in gluten that are the proposed cause of celiac disease. The engineered enzyme exhibits a k_{cat}/K_M of $568 \text{ M}^{-1} \text{ s}^{-1}$, representing a 116-fold greater proteolytic activity for a model gluten tetrapeptide than the native template enzyme, as well as an over 800-fold switch in substrate specificity toward immunogenic portions of gluten peptides.

Enzyme Catalysis (Cont'd)

Prediction of inter domain interactions in modular polyketide synthases by docking and correlated mutation analysis

Gitanjali Yadav, Swadha Anand & Debasisa Mohanty
[National Institute of Immunology, Aruna Asaf Ali Marg]

J. Biomol. Stru. and Dyn., **31**, 17-29, 2013.

Polyketide synthases (PKSs) are huge multi-enzymatic protein complexes involved in the biosynthesis of one of the largest families of bioactive natural products, namely polyketides. The specificity of interactions between various catalytic domains of these megasynthases is one of the pivotal factors which control the precise order in which the extender units are joined during the biosynthetic process. We have developed a computational method for exploring the binding interface between two proteins, and used it to identify the interacting residue pairs, which govern the specificity of recognition between acyl carrier protein (ACP) domain and two core catalytic domains, namely the ketosynthase (KS) and acyl transferase (AT).

Catalytic Mechanism and Product Specificity of Oxidosqualene-Lanosterol Cyclase: A QM/MM Study

Bo-Xue Tian and Leif A. Eriksson [University of Gothenburg]

J. Phys. Chem. B., **116**, 13857–13862, 2012.

Oxidosqualene-lanosterol cyclase (OSC) is a key enzyme in the biosynthesis of cholesterol. The catalytic mechanism and the product specificity of OSC have herein been studied using QM/MM calculations. According to our calculations, the protonation of the epoxide ring of oxidosqualene is rate-limiting. Wild-type OSC (which generates lanosterol), and the mutants H232S (which generates parkeol) and H232T (which generates protosta-12,24-dien-3- β -ol) were modeled, in order to explain the product specificity thereof.

Protein-Protein Interactions

A method for integrative structure determination of protein-protein complexes

Javier Velázquez-Muriel, Pavel Strop, Hong Liang, Kristin A. Krukenberg, Maofu Liao, Ho Min Kim, Solmaz Sobhanifar, Volker Dötsch, Arvind Rajpal, Jaume Pons, David A. Agard, Yifan Cheng, and Andrej Sali [University of California, San Francisco]

Bioinformatics. **28**, 3282-3289, 2012.

Structural characterization of protein interactions is necessary for understanding and modulating biological processes. On one hand, X-ray crystallography or NMR spectroscopy provide atomic resolution structures but the data collection process is typically long and the success rate is low. On the other hand, computational methods for modeling assembly structures from individual components frequently suffer from high false-positive rate, rarely resulting in a unique solution. Here, we present a combined approach that computationally integrates data from a variety of fast and accessible experimental techniques for rapid and accurate structure determination of protein-protein complexes.

Protein Protein Interactions (Cont'd)

How Good Are State-of-the-Art Docking Tools in Predicting Ligand Binding Modes in Protein-Protein Interfaces?

Dennis M. Krüger, Gisela Jessen, and Holger Gohlke
[Heinrich-Heine-University]

J.Chem. Infor. and Mod. **52**, 2807–2811, 2012.

Protein-protein interfaces (PPIs) are an important class of drug targets. We report on the first large-scale validation study on docking into PPIs. DrugScore-adapted AutoDock3 and Glide showed good success rates with a moderate drop-off compared to docking to “classical targets”. An analysis of the binding energetics in a PPI allows identifying those interfaces that are amenable for docking. The results are important for deciding if structure-based design approaches can be applied to a particular PPI.

Combining coarse-grained nonbonded and atomistic bonded interactions for protein modeling

Martin Zacharias [Technische Universität München]

Proteins: Stru. Fun. & Bioinf., **81**, 81–92, 2013.

A hybrid coarse-grained (CG) and atomistic (AT) model for protein simulations and rapid searching and refinement of peptide-protein complexes has been developed. In contrast to other hybrid models that typically represent spatially separate parts of a protein by either a CG or an AT force field model, the present approach simultaneously represents the protein by an AT (united atom) and a CG model. The interactions of the protein main chain are described based on the united atom force field allowing a realistic representation of protein secondary structures.

Membrane Proteins and Lipid Peptide Interactions

Phase Transitions in Coarse-Grained Lipid Bilayers Containing Cholesterol by Molecular Dynamics Simulations

Kaiser Waheed, Richard Tjörnhammar, Olle Edholm
[AlbaNova University Center]

Biophysical Journal. **103**, 2125–2133, 2012.

Coarse-grained simulations of model membranes containing mixtures of phospholipid and cholesterol molecules at different concentrations and temperatures have been performed. A random mixing without tendencies for segregation or formation of domains was observed on spatial scales corresponding to a few thousand lipids and timescales up to several microseconds. The gel-to-liquid crystalline phase transition is successively weakened with increasing amounts of cholesterol without disappearing completely even at a concentration of cholesterol as high as 60%.

How cholesterol is distributed between monolayers in asymmetric lipid membranes

Semen O. Yesylevskyy[National Academy of Sciences of Ukraine], Alexander P. Demchenko

Europ. Biophys. Jou., **41**, 1043–1054, 2012.

The distribution of cholesterol in asymmetric lipid bilayers was studied by extensive coarse-grained molecular dynamics simulations. The effects of the lipid head group charge, acyl chain saturation, spontaneous membrane curvature and surface tension of the membrane were investigated. Four asymmetric bilayers containing DOPC, DOPS, DSPC or DSPS lipids were simulated on a time scale extended to tens of microseconds.

Membrane Proteins and Lipid Peptide Interactions (Cont'd)

Carbohydrate Recognition by the Antiviral Lectin Cyanovirin-N

Yukiji K. Fujimoto and David F. Green [Stony Brook University]

J. Am. Chem. Soc., **134**, 19639–19651, 2012.

Cyanovirin-N (CVN) is a cyanobacterial lectin with potent antiviral activity and has been the focus of extensive preclinical investigation as a potential prophylactic for the prevention of the sexual transmission of the human immunodeficiency virus (HIV). Here we present a detailed analysis of carbohydrate recognition by this important protein, using a combination of computational methods, including extensive molecular dynamics simulations and molecular mechanics/Poisson–Boltzmann surface area (MM/PBSA) energetic analysis.

Dynamic clustering of lipids in hydrated two-component membranes: results of computer modeling and putative biological impact

Darya V. Pyrkova, Natalya K. Tarasova, Nikolay A. Krylov, Dmitry E. Nolde, Vladimir M. Pentkovsky & Roman G. Efremov [Russian Academy of Sciences]

J. Biomol. Stru. and Dyn., **31**, 87-95, 2013.

Delineation and analysis of lateral clustering of lipids in model bilayers is an important step toward understanding of the physical processes underlying formation of lipid domains and rafts in cell membranes. Computer modeling methods represent a powerful tool to address the problem since they can detect clusters of only few lipid molecules – this issue still resists easy characterization with modern experimental techniques. In this work, we propose a computational method to detect and analyze parts of membrane with different packing densities and hydrogen bonding patterns.

FIPSDock: A new molecular docking technique driven by fully informed swarm optimization algorithm

Yu Liu, Lei Zhao, Wentao Li, Dongyu Zhao, Miao Song and Yongliang Yang [Dalian University of Technology]

J. Comp. Chem. **33**, 67–75, 2013.

The accurate prediction of protein–ligand binding is of great importance for rational drug design. We present herein a novel docking algorithm called as FIPSDock, which implements a variant of the Fully Informed Particle Swarm (FIPS) optimization method and adopts the newly developed energy function of AutoDock 4.20 suite for solving flexible protein–ligand docking problems. The search ability and docking accuracy of FIPSDock were first evaluated by multiple cognate docking experiments. In a benchmarking test for 77 protein/ligand complex structures derived from GOLD benchmark set, FIPSDock has obtained a successful predicting rate of 93.5%.

Multi-Scale Simulation of the Simian Immunodeficiency Virus Fusion Peptide

Jean-Marc Crowet [University of Oxford, South Parks Road], Daniel L. Parton, Benjamin A. Hall, Sven Steinhauer, Robert Brasseur, Laurence Lins, and Mark S. P. Sansom

J. Phys. Chem. B., **116**, 13713–13721, 2012.

Fusion peptides of type I fusion glycoproteins are structural elements of several enveloped viruses which enable the fusion between host and virus membranes. It is generally suggested that these peptides can promote the early fusion steps by inducing membrane curvature and that they adopt a tilted helical conformation in membranes. Although this property has been the subject of several experimental and in silico studies, an extensive sampling of the membrane peptide interaction has not yet been done. In this study, we performed coarse-grained MD simulations in which the lipid bilayer self-assembles around the peptide.

Membrane Proteins and Lipid Peptide Interactions (Cont'd)

Understanding the Interaction of Block Copolymers with DMPC Lipid Bilayer Using Coarse-Grained Molecular Dynamics Simulations

Samira Hezaveh, Susruta Samanta, Antonio De Nicola, Giuseppe Milano, and Danilo Roccatano [Jacobs University Bremen]

J. Phys. Chem. B., **116**, 14333–14345, 2012.

In this paper, we present a computational model of the adsorption and percolation mechanism of poloxamers (poly(ethylene oxide) (PEO) and poly(propylene oxide) (PPO) triblock copolymers) across a 1,2-dimyristoyl-sn-glycero-3-phosphocholine (DMPC) lipid bilayer. A coarse-grained model was used to cope with the long time scale of the percolation process. The simulations have provided details of the interaction mechanism of Pluronics with lipid bilayer. In particular, the results have shown that polymer chains containing a PPO block with a length comparable to the DMPC bilayer thickness, such as P85, tends to percolate across the lipid bilayer.

Nucleic Acids

Groove Binding Mechanism of Ionic Liquids: A Key Factor in Long-Term Stability of DNA in Hydrated Ionic Liquids?

Aneesh Chandran, Debostuti Ghoshdastidar, and Sanjib Senapati [Indian Institute of Technology Madras]

J. Am. Chem. Soc., **134**, 20330–20339, 2012.

Nucleic acid sample storage is of paramount importance in biotechnology and forensic sciences. Very recently, hydrated ionic liquids (ILs) have been identified as ideal media for long-term DNA storage. Hence, understanding the binding characteristics and molecular mechanism of interactions of ILs with DNA is of both practical and fundamental interest. Here, we employ molecular dynamics simulations and spectroscopic experiments to unravel the key factors that stabilize DNA in hydrated ILs. Both simulation and experimental results show that DNA maintains the native B-conformation in ILs.

Very efficient search for nucleotide alignments

Milan Randić [Drake University, Des Moines]

J. Comp. Chem. **33**, 77–82, 2013.

We describe a very efficient search for nucleotide alignments, which is analogous to the novel very efficient search for protein alignment. Just as it has been the case with the alignment of proteins, based on 20×20 adjacency matrices for amino acids, obtained from a superposition of labeled amino acids adjacency matrices for the proteins considered, one can construct labeled matrices of size 4×4 , listing adjacencies of nucleotides in DNA sequence. The matrix elements correspond to 16 pairs of adjacent nucleotides. To obtain DNA alignments, one combines information in the corresponding matrices for a pair of DNA nucleotides.

2. METHODOLOGY

Molecular Dynamics

Theoretical Study of the Mechanism of the Hydride Transfer between Ferredoxin–NADP⁺ Reductase and NADP⁺: The Role of Tyr303

Isaias Lans, Milagros Medina[Universidad de Zaragoza], Edina Rosta, Gerhard Hummer, Mireia Garcia-Viloca, José M. Lluch, and Àngels González-Lafont

J. Am. Chem. Soc., **134**, 20544–20553, 2012.

During photosynthesis, ferredoxin–NADP⁺ reductase (FNR) catalyzes the electron transfer from ferredoxin to NADP⁺ via its FAD cofactor. The final hydride transfer event between FNR and the nucleotide is a reversible process. Two different transient charge-transfer complexes form prior to and upon hydride transfer, FNR_{rd}–NADP⁺ and FNR_{ox}–NADPH, regardless of the hydride transfer direction. Recently, a molecular dynamics (MD) theoretical approach was used to provide a putative organization of the active site that might represent a structure close to the transient catalytically competent interaction of Anabaena FNR with its coenzyme, NADP⁺.

The substitutions G245C and G245D in the Zn²⁺-binding pocket of the p53 protein result in differences of conformational flexibility of the DNA-binding domain

S.S. Pintus[Institute of Cytology and Genetics SB RAS], N.V. Ivanisenko, P.S. Demenkov, T.V. Ivanisenko, S. Ramachandran, N.A. Kolchanov & V.A. Ivanisenko

J. Biomol. Stru. and Dyn., **31**, 78-86, 2013.

Transcription activation of the proapoptotic target genes is a means by which the p53 protein implements its function of tumor suppression. Zn²⁺ is a known regulator of p53 binding to the target genes. We have previously obtained an evidence that amino acid substitutions in the p53 Zn²⁺-binding pocket can presumably exert an influence on Zn²⁺ position in the Zn²⁺-p53 complex and thereby affect p53 binding to DNA. With these background considerations, our aim was to estimate the effect of the putative changes in the Zn²⁺ position in its binding pocket due to the G245C and G245D substitutions on the conformation of the p53 DNA-binding motif.

DFT study of glucose based glycolipid crown ethers and their complexes with alkali metal cations Na⁺ and K⁺

Hockseng Nguan [University of Malaya], Sara Ahmadi, Rauzah Hashim

J. Mol.Mod., **18**, 5041-5050, 2012.

A theoretical study of a series of five glucose based glycolipid crown ethers and their complexes with Na⁺ and K⁺ was performed using the density functional theory with B3LYP/6-31 G* to obtain the optimized geometrical structures and electronic properties. The local nucleophilicity of the five molecules was investigated using Fukui function, while the global nucleophilicity was calculated from the ionization potential and electron affinity. The structures and coordination of the complexes were studied to identify the best match of the glycolipid crown ethers with cations.

Molecular Dynamics (Cont'd)

A fast parallel clustering algorithm for molecular simulation trajectories

Yutong Zhao, Fu Kit Sheong, Jian Sun, Pedro Sander and Xuhui Huang [The Hong Kong University of Science and Technology]

J. Comp. Chem. **33**, 95–104, 2013.

We implemented a GPU-powered parallel k-centers algorithm to perform clustering on the conformations of molecular dynamics (MD) simulations. The algorithm is up to two orders of magnitude faster than the CPU implementation. We tested our algorithm on four protein MD simulation datasets ranging from the small Alanine Dipeptide to a 370-residue Maltose Binding Protein (MBP). It is capable of grouping 250,000 conformations of the MBP into 4000 clusters within 40 seconds.

Initial Decomposition of the Condensed-Phase β -HMX under Shock Waves: Molecular Dynamics Simulations

Ni-Na Ge, Yong-Kai Wei, Guang-Fu Ji, Xiang-Rong Chen, Feng Zhao, and Dong-Qing Wei [Beijing Institute of Technology]

J. Phys. Chem. B., **116**, 13696–13704, 2012.

We have performed quantum-based multiscale simulations to study the initial chemical processes of condensed-phase octahydro-1,3,5,7-tetranitro-1,3,5,7-tetrazocine (HMX) under shock wave loading. A self-consistent charge density-functional tight-binding (SCC-DFTB) method was employed. The results show that the initial decomposition of shocked HMX is triggered by the N–NO₂ bond breaking under the low velocity impact (8 km/s). As the shock velocity increases (11 km/s), the homolytic cleavage of the N–NO₂ bond is suppressed under high pressure, the C–H bond dissociation becomes the primary pathway for HMX decomposition in its early stages.

QM and QM/MM

Electronic Absorption Spectra from MM and ab Initio QM/MM Molecular Dynamics: Environmental Effects on the Absorption Spectrum of Photoactive Yellow Protein

Christine M. Isborn, Andreas W. Götz, Matthew A. Clark, Ross C. Walker, and Todd J. Martínez [Stanford University, Stanford]

J. Chem. Theor. and Comp., **8**, 5092–5106, 2012.

We describe a new interface of the GPU parallelized Terachem electronic structure package and the Amber molecular dynamics package for quantum mechanical (QM) and mixed QM and molecular mechanical (MM) molecular dynamics simulations. This QM/MM interface is used for computation of the absorption spectra of the photoactive yellow protein (PYP) chromophore in vacuum, aqueous solution, and protein environments. The computed excitation energies of PYP require a very large QM region (hundreds of atoms) covalently bonded to the chromophore in order to achieve agreement with calculations that treat the entire protein quantum mechanically.

QM and QM/MM (Cont'd)

An assessment of pure, hybrid, meta, and hybrid-meta GGA density functional theory methods for open-shell systems: The case of the nonheme iron enzyme 8R-LOX

Eric A. C. Bushnell and James W. Gauld [University of Windsor, Windsor]

J. Comp. Chem. **33**, 141–148, 2013.

The performance of a range density functional theory functionals combined in a quantum mechanical (QM)/molecular mechanical (MM) approach was investigated in their ability to reliably provide geometries, electronic distributions, and relative energies of a multicentered open-shell mechanistic intermediate in the mechanism 8R-Lipoxygenase. With the use of large QM/MM active site chemical models, the smallest average differences in geometries between the catalytically relevant quartet and sextet complexes were obtained with the B3LYP* functional. Moreover, in the case of the relative energies between ⁴II and ⁶II, the use of the B3LYP* functional provided a difference of 0.0 kcal mol⁻¹.

Role of Tunneling in the Enzyme Glutamate Mutase

Judith B. Rommel, Yu Liu, Hans-Joachim Werner, and Johannes Kästner [University of Stuttgart, Pfaffenwaldring 55]

J. Phys. Chem. B., **116**, 13682–13689, 2012.

The role of quantum mechanical atom tunneling during the conversion of glutamate to methylaspartate catalyzed by glutamate mutase is investigated by quantum mechanical/molecular mechanical (QM/MM) simulations based on coupled cluster and density functional calculations. The use of instanton theory allows us to calculate the tunneling contributions of up to 78 atoms in the active site. We calculate kinetic isotope effects (KIEs) and compare them to experimental data.

Tautomerization in the UDP-Galactopyranose Mutase Mechanism: A DFT-Cluster and QM/MM Investigation

WenJuan Huang and James W. Gauld [University of Windsor, Windsor]

J. Phys. Chem. B., **116**, 14040–14050, 2012.

UDP-galactopyranose mutase (UGM) is a key flavoenzyme involved in cell wall biosynthesis of a variety of pathogenic bacteria and hence, integral to their survival. It catalyzes the interconversion of UDP-galactopyranose (UDP-Galp) and UDP-galactofuranose (UDP-Galf); interconversion of the galactose moieties six- and five-membered ring forms. We have synergistically applied both density functional theory (DFT)-cluster and ONIOM quantum mechanics/molecular mechanics (QM/MM) hybrid calculations to elucidate the mechanism of this important enzyme and to provide insight into its uncommon mechanism.

Comparative or Homology Modeling

Regulation of JAK2 Activation by Janus Homology 2: Evidence from Molecular Dynamics Simulations

Shunzhou Wan and Peter V. Coveney [University College London]

J.Chem. Infor. and Mod. **52**, 2992–3000, 2012.

Janus kinase 2 (JAK2) is a protein tyrosine kinase implicated in signaling by specific members of the cytokine receptor family. Although it has been established that the JAK2 tyrosine kinase is negatively regulated by the JAK homology 2 (JH2) pseudokinase domain, the underlying mechanism of JH2 mediated regulation remains elusive. To elucidate the regulation of JAK2 kinase, we have built a structural model for the kinase and pseudokinase domains of JAK2. An asymmetric dimer is proposed, in which the kinase domain JH1 occupies a position where it could not be activated. We investigate the dynamic and energetic properties of the dimer by molecular dynamics simulation.

Are Homology Models Sufficiently Good for Free-Energy Simulations?

Samuel Genheden [Lund University]

J.Chem. Infor. and Mod. **52**, 3013–3021, 2012.

In this paper, I evaluate the usefulness of protein homology models in rigorous free-energy simulations to determine ligand affinities. Two templates were used to create models of the factor Xa protein and one template was used for dihydrofolate reductase from *Plasmodium falciparum*. Then, the relative free energies for several pairs of ligands were estimated using thermodynamic integration with the homology models as starting point of the simulation. These binding affinities were compared to affinities obtained when using published crystal structures as starting point of the simulations.

Structure and functional features of olive pollen pectin methylesterase using homology modeling and molecular docking methods

Jose C. Jimenez-Lopez [Purdue University], Simeon O. Kotchoni, María I. Rodríguez-García, Juan D. Alché

J. Mol.Mod., **18**, 4965-4984, 2012.

Pectin methylesterases (PMEs), a multigene family of proteins with multiple differentially regulated isoforms, are key enzymes implicated in the carbohydrates (pectin) metabolism of cell walls. Olive pollen PME has been identified as a new allergen (Ole e 11) of potential relevance in allergy amelioration, since it exhibits high prevalence among atopic patients. In this work, the structural and functional characterization of two olive pollen PME isoforms and their comparison with other PME plants was performed by using different approaches.

Ligand Docking

GABA Binding to an Insect GABA Receptor: A Molecular Dynamics and Mutagenesis Study

Jamie A. Ashby, Ian V. McGonigle, Kerry L. Price, Netta Cohen, Federico Comitani, Dennis A. Dougherty, Carla Molteni, Sarah C.R. Lummis [Department of Biochemistry, Cambridge]

Biophysical Journal. **103**, 2071-2081, 2012.

RDL receptors are GABA-activated inhibitory Cys-loop receptors found throughout the insect CNS. They are a key target for insecticides. Here, we characterize the GABA binding site in RDL receptors using computational and electrophysiological techniques. A homology model of the extracellular domain of RDL was generated and GABA docked into the binding site. Molecular dynamics simulations predicted critical GABA binding interactions with aromatic residues F206, Y254, and Y109 and hydrophilic residues E204, S176, R111, R166, S176, and T251.

Coupled Flexibility Change in Cytochrome P450cam Substrate Binding Determined by Neutron Scattering, NMR, and Molecular Dynamics Simulation

Yinglong Miao, Zheng Yi, Carey Cantrell, Dennis C. Glass, Jerome Baudry, Nitin Jain [University of Tennessee-Knoxville], Jeremy C. Smith

Biophysical Journal. **103**, 2167-2176, 2012.

Neutron scattering and nuclear magnetic resonance relaxation experiments are combined with molecular dynamics (MD) simulations in a novel, to our knowledge, approach to investigate the change in internal dynamics on substrate (camphor) binding to a protein (cytochrome P450cam). The MD simulations agree well with both the neutron scattering, which furnishes information on global flexibility, and the nuclear magnetic resonance data, which provides residue-specific order parameters. Decreased fluctuations are seen in the camphor-bound form using all three techniques, dominated by changes in specific regions of the protein.

Application of a post-docking procedure based on MM-PBSA and MM-GBSA on single and multiple protein conformations

Miriam Sgobba, Fabiana Caporuscio, Andrew Anighoro, Corinne Portioli, Giulio Rastelli [Università di Modena e Reggio Emilia]

Europ. Jou. Med. Chem., **58**, 431-440, 2012.

In the last decades, molecular docking has emerged as an increasingly useful tool in the modern drug discovery process, but it still needs to overcome many hurdles and limitations such as how to account for protein flexibility and poor scoring function performance. For this reason, it has been recognized that in many cases docking results need to be post-processed to achieve a significant agreement with experimental activities. In this study, we have evaluated the performance of MM-PBSA and MM-GBSA scoring functions, implemented in our post-docking procedure BEAR, in rescoring docking solutions.

3. JOURNAL REVIEWS

Journal of Computational Chemistry, 34(1), January, 2013.

- 2–9 **Continuous symmetry analyses: C_{nv} and D_n measures of molecules, complexes, and proteins**, Mark Pinsky [The Lise Meitner Minerva Center for Computational Quantum Chemistry], Amir Zait, Maayan Bonjack and David Avnir

The continuous symmetry methodology has been developed to provide a quantitative estimation for the degree of a selected symmetry point-group in a molecular structure.

- 10–20 **Distance dependency and minimum amino acid alphabets for decoy scoring potentials**, Susanne Pape, Franziska Hoffgaard, Mirjam Dür and Kay Hamacher [TU Darmstadt]

The validity and accuracy of a proposed tertiary structure of a protein can be assessed in several ways. Although several parameterizations for such models have been derived over the course of time, improvements in accuracy by explicitly using continuous distance information have not been suggested yet. We close this methodological gap by formulating the parameterization of a protein structure model as a linear program.

- 21–26 **Consistent scheme for computing standard hydrogen electrode and redox potentials**, Toru Matsui, Yasutaka Kitagawa, Mitsutaka Okumura, Yasuteru Shigeta and Shigeyoshi Sakaki [Osaka University]

The standard hydrogen electrode (SHE) potential in aqueous solution was evaluated with new computational procedure that provides the Gibbs energy of a proton in aqueous solution from the experimental pK_a value and the Gibbs energy change by deprotonation reactions of several neutral alcohol molecules.

- 27–37 **Configuration space partitioning and matrix buildup scaling for the vibrational configuration interaction method**, Andriy Samsonyuk and Christoph Scheurer [Technische Universität München]

The accurate computation of anharmonic vibrational states for medium to large molecules is a requirement for the detailed understanding of nonlinear multidimensional infrared spectra and the dynamical information encoded in them. We analyze the scaling behavior of several well-known as well as some new approximate VCI schemes in detail, which are complementary to the class of configuration selection schemes developed recently.

- 38–48 **An efficient algorithm for complete active space valence bond self-consistent field calculation**, Jinshuai Song, Zhenhua Chen, Sason Shaik and Wei Wu [Xiamen University]

This article describes a novel algorithm for the optimization of valence bond self-consistent field (VBSCF) wave function for a complete active space (CAS), so-called VBSCF(CAS). This was achieved by applying the strategies adopted in the optimization of CASSCF wave functions to VBSCF(CAS) wave functions, using an auxiliary orthogonal orbital set that generates the same configuration space as the original nonorthogonal orbital set.

- 49–59 **Pseudopotentials for hybridized carbon atoms**, J. Drujon and Y. Carissan [Aix Marseille Université]

Pseudopotentials for hybridized atoms are extracted and combined. The study focuses on sp^2 carbon atoms and their combination to give rise to a π electronic system. As electrons of interest are treated explicitly, any ab initio method can be used, thus, configuration interaction methods and time-dependent density functional theory are used and compared.

- 60–66 **The role of water in the adsorption of oxygenated aromatics on Pt and Pd**, Jin Yang, Paul J. Dauenhauer and Ashwin Ramasubramaniam [University of Massachusetts Amherst]

Catalytic processing of biomass-derived oxygenates to valuable chemical products will contribute to a sustainable future. To provide insight into the conversion of processed sugars and lignin monomers, we present density functional theory studies of adsorption of phloroglucinol, a potentially valuable biomass derivative, on Pt(111) and Pd(111) surfaces.

- 67–75 **FIPSDock: A new molecular docking technique driven by fully informed swarm optimization algorithm**, Yu Liu, Lei Zhao, Wentao Li, Dongyu Zhao, Miao Song and Yongliang Yang [Dalian University of Technology]

See Applications / Membrane proteins and Lipid-Peptide Interactions.

Journal of Computational Chemistry, 34(2), January, 2013.

- 77–82 **Very efficient search for nucleotide alignments**, Milan Randić [Drake University, Des Moines]

See Applications / Nucleic Acids.

- 83–94 **GPGPU for orbital function evaluation with a new updating scheme**, Yutaka Uejima and Ryo Maezono [JAIST, Asahidai 1-1, Nomi]

We have accelerated an ab initio quantum Monte Carlo electronic structure calculation using general purpose computing on graphical processing units (GPGPU). The part of the code causing the bottleneck for extended systems is replaced by Compute Unified Device Architecture-GPGPU subroutine kernels which build up spline basis set expansions of electronic orbital functions at each Monte Carlo step.

- 95–104 **A fast parallel clustering algorithm for molecular simulation trajectories**, Yutong Zhao, Fu Kit Sheong, Jian Sun, Pedro Sander and Xuhui Huang [The Hong Kong University of Science and Technology]

See Methodology / Molecular Dynamics.

- 105–120 **An analytical method for computing atomic contact areas in biomolecules**, Paul Mach and Patrice Koehl [University of California]

We propose a new analytical method for detecting and computing contacts between atoms in biomolecules. It is based on the alpha shape theory and proceeds in three steps.

- 121–131 **Appropriate description of intermolecular interactions in the methane hydrates: An assessment of DFT methods**, Yuan Liu, Jijun Zhao, Fengyu Li and Zhongfang Chen [Dalian University of Technology]

Accurate description of hydrogen-bonding energies between water molecules and van der Waals interactions between guest molecules and host water cages is crucial for study of methane hydrates (MHs). Using high-level ab initio MP2 and CCSD(T) results as the reference, we carefully assessed the performance of a variety of exchange–correlation functionals and various basis sets in describing the noncovalent interactions in MH.

- 132–140 **A convective replica-exchange method for sampling new energy basins**, Yannick G. Spill, Guillaume Bouvier and Michael Nilges [Unité de Bioinformatique Structurale]

See Applications / Free energy calculations.

- 141–148 **An assessment of pure, hybrid, meta, and hybrid-meta GGA density functional theory methods for open-shell systems: The case of the nonheme iron enzyme 8R–LOX**, Eric A. C. Bushnell and James W. Gauld [University of Windsor, Windsor]

See Methodology / QM and QM/MM.

- 149–161 **Variationally determined electronic states for the theoretical analysis of intramolecular interaction. II. Qualitative nature of the P—O bond in phosphine oxides**, Kenta Yamada and Nobuaki Koga [Nagoya University]

We have developed a space-restricted wave function (SRW) method for the analysis of various types of intramolecular interactions. In this study, we demonstrate the applicability of our SRW method to the analysis of the nature of the P—O bond in phosphine oxide (R_3PO), one of the hypervalent molecules.

Journal of Molecular Modeling, 18(12), December, 2012.

- 4955–4963 **Ruthenium hydride-catalyzed regioselective addition of benzaldehyde to dienes leading to β,γ -unsaturated ketones: a DFT study**, Qingxi Meng [Shandong Agricultural University], Fen Wang, Ming Li

Density functional theory (DFT) was used to investigate the ruthenium hydride-catalyzed regioselective addition reactions of benzaldehyde to isoprene leading to the branched β,γ -unsaturated ketone.

- 4965–4984 **Structure and functional features of olive pollen pectin methylesterase using homology modeling and molecular docking methods**, Jose C. Jimenez-Lopez [Purdue University], Simeon O. Kotchoni, María I. Rodríguez-García, Juan D. Alché

See Methodology / Homology Modeling.

- 4985-4993 **Theoretical study on ion-pair recognition of M^+X^- ($M = \text{Li, Na, K}$ and $X = \text{F, Cl, Br}$) by formylaminocalix[4]arene derivatives**, Ju Xie [Yangzhou University], Guolian Jin, Long Sun, Wenling Feng, Pengfei Lu, Guowang Diao

DFT calculations were reported for calix[4]arene derivatives [i.e., formylaminocalix[4]arene (**1**) and formylaminocalix[4]bis-crown-3 (**2**)] binding cations M^+ (Li^+ , Na^+ , and K^+) and anions X^- (F^- , Cl^- , and Br^-) simultaneously.

- 4995-5003 **Identification of old drugs as potential inhibitors of HIV-1 integrase – human LEDGF/p75 interaction via molecular docking**, Guoping Hu, Xi Li, Xianqiang Sun, Weiqiang Lu, Guixia Liu, Jin Huang, Xu Shen, Yun Tang [East China University of Science and Technology]

See Applications / Medicinal Chemistry and Drug Design.

- 5005-5016 **Investigation of H-bonding and halogen-bonding effects in dichloroacetic acid: DFT calculations of NQR parameters and QTAIM analysis**, Mehdi D. Esrafil [University of Maragheh]

A theoretical study was performed to examine hydrogen and halogen bonds properties in gas phase and crystalline dichloroacetic acid (DCAA).

- 5017-5028 **Computational investigation on microsolvation of the osmolyte glycine betaine $[\text{GB}(\text{H}_2\text{O})_{1-7}]$** , Srinivasadesikan Venkatesan, Shyi-Long Lee [National Chung Cheng University]

The preferential interactions of glycine betaine (GB) with solvent components and the effect of solvent on its stability have been examined.

- 5029-5033 **Interaction between an icosahedron Li_{13} cluster and a graphene layer doped with a hydrogen atom**, Eduardo Rangel [Universidad Nacional Autónoma de México], Gerardo Vázquez, Fernando Magaña, Enrique Sansores

It is known that graphene reacts with atomic hydrogen to form a hydrogenated sheet of graphene. In order to understand the nature of the interaction between hydrogen and lithium in hydrogenated samples, we have carried out first principle calculations.

- 5035-5040 **First principles study of periodic size dependent band gap variation of Cu doped ZnO single-wall nanotube**, Dong Mei Song, Tong Hui Wang, Jian Chen Li [Jilin University]

In this contribution, the size dependent band gap variation of $(\text{Zn}_{4/6}\text{Cu}_{2/6}\text{O})_L/(\text{Zn}_{5/6}\text{Cu}_{1/6}\text{O})_L$ (L is the periodic size) superlattices are investigated with the change of L . The results show that the variation tendency of band gap appears a minimum in S_4 ($L = 4$) which is nearly a conductor.

- 5041-5050 **DFT study of glucose based glycolipid crown ethers and their complexes with alkali metal cations Na^+ and K^+** , Hockseng Nguan [University of Malaya], Sara Ahmadi, Rauzah Hashim

See Methodology / Molecular Dynamics.

- 5051-5063 **Selectivity and activation of dopamine D3R from molecular dynamics**, Zhiwei Feng, Tingjun Hou, Youyong Li [Soochow University]

See Applications / Medicinal Chemistry and Drug Design.

- 5065-5073 **Leishmania donovani pteridine reductase 1: comparative protein modeling and protein–ligand interaction studies of the leishmanicidal constituents isolated from the fruits of Piper longum**, Shakti Sahi, Parul Tewatia, Sabari Ghosal [Amity University]

See Applications / Medicinal Chemistry and Drug Design.

- 5075-5088 **A joint experimental and theoretical investigation of kinetics and mechanistic study in a synthesis reaction between triphenylphosphine and dialkyl acetylenedicarboxylates in the presence of benzhydrazide**, Mohammad Amin Kazemian, Sayyed Mostafa Habibi-Khorassani [University of Sistan and Baluchestan], Ali Ebrahimi, Malek Taher Maghsoodlou, Peyman Mohammadzadeh Jahani, Mahbobeh Ghahramaninezhad

Stable crystalline phosphorus ylides were obtained in excellent yields from the 1:1:1 addition reaction between triphenylphosphine (TPP) and dialkyl acetylenedicarboxylates, in the presence of NH-acids, such as benzhydrazide. To determine the kinetic parameters of the reactions, they were monitored by UV spectrophotometry.

- 5089-5095 **Bis-dibenzo[a.i]fluorenylidene, does it exist as stable 1,2-diradical?**, Basem Kanawati, Alexander Genest, Philippe Schmitt-Kopplin, Dieter Lenoir [Helmholtz Zentrum München]

The geometries, energies, and electronic properties of the two possible configurations of bis-[dibenzo[a.i]fluorenylidene] were investigated theoretically by density functional theory DFT B3LYP at the UB3LYP/6-311 + G(2d,p) // UB3LYP/6-31 + G(d,p) level of theory.

- 5097-5106 **Intensity enhancement in the molecular ionization and dissociation dynamics in the presence of noise**, Li-Qiang Feng, Tian-Shu Chu [Dalian Institute of Chemical Physics]

The ionization and the dissociation of the diatomic molecular ion H_2^+ have been investigated within a scheme where a noise field is added to an intense infrared laser field.

- 5107-5111 **Effect of surface hydroxyls on DME and methanol adsorption over γ -Al₂O₃ (hkl) surfaces and solvent effects: a density functional theory study**, Zhi-Jun Zuo, Pei-De Han, Jian-Shui Hu, Wei Huang [Technology of Ministry of Education and Shanxi Province]

Methanol and dimethyl ether (DME) adsorption over clean and hydrated γ -Al₂O₃(100) and (110) surfaces was studied by using density functional theory (DFT) combined with conductor-like solvent model (COSMO) in gas phase and liquid paraffin.

- 5113-5126 **An atomistic-based chemophysical environment for evaluating asphalt oxidation and antioxidants**, Tongyan Pan [The Catholic University of America], Lu Sun, Qifeng Yu

Asphalt binders in service conditions are subject to oxidative aging that involves the reactions between oxygen molecules and the component species of bulk asphalt. The current state of knowledge in asphalt oxidation and

antioxidant evaluation is centered on determining the degradation of asphalt physical properties, mainly the viscosity and ductility. From this standpoint, this study was initiated to study the chemical and physical bases of asphalt oxidation, as well as the anti-oxidation mechanisms of bio-based antioxidants using the coniferyl-alcohol lignin as an example.

- 5127-5132 **Insight into shock-induced chemical reaction from the perspective of ring strain and rotation of chemical bonds**, Bisheng Tan [China Academy of Engineering Physics], Xinping Long, Jinshan Li, Fude Nie, Jinglun Huang

Density functional theory BLYP/DNP and hyperhomodesmotic equations were employed to calculate ring strain energy, the bond dissociation energy of $X-NO_2$ ($X=C, N$) and the charges on the nitro groups of several four-membered and six-membered heterocycle compounds.

- 5133-5146 **Comparative study of the relaxation mechanisms of the excited states of cytosine and isocytosine**, Romyana I. Bakalska, Vassil B. Delchev [University of Plovdiv]

An experimental and theoretical investigation was performed to study the photostability of cytosine and isocytosine. The experimental UV irradiation of acetonitrile solutions of the two compounds showed that the amino-oxo tautomer of cytosine is photostable while the amino-oxo tautomer of isocytosine tautomerizes to the amino-hydroxy form.

Molecular Simulation, 39(1), 2013.

- 1-13 **The role of additional O–H...O intramolecular hydrogen bonds for acylphloroglucinols' conformational preferences in vacuo and in solution**, L. Mammino [University of Venda] & M. M. Kabanda

Acylphloroglucinols (ACPLs) are phloroglucinol derivatives characterised by the presence of a COR group and exhibiting a variety of biological activities, making them potentially interesting for drug development. This work studies the geometric characteristics and the stabilising effects of additional O–H...O IHBs, considering a selection of structures representative of the more common possibilities for their formation and comparing the results in vacuo, chloroform, acetonitrile and water.

- 14-24 **Gas adsorption and diffusion in a highly CO₂ selective metal–organic framework: molecular simulations**, Seda Keskin [Koc University]

Grand canonical Monte Carlo and equilibrium molecular dynamics simulations were used to assess the performance of an rht-type metal–organic framework (MOF), Cu-TDPAT, in adsorption-based and membrane-based separation of CH₄/H₂, CO₂/CH₄ and CO₂/H₂ mixtures.

- 25-48 **Generalised canonical–isokinetic ensemble: speeding up multiscale molecular dynamics and coupling with 3D molecular theory of solvation**, Igor Omelyan [University of Alberta] & Andriy Kovalenko

We have proposed a new canonical–isokinetic ensemble for efficient sampling of conformational space in molecular dynamics (MD) simulations which leads to the optimised isokinetic Nosé–Hoover (OIN) chain algorithm for atomic and molecular systems. We applied OIN to multiple time step (MTS) MD simulations of the rigid and flexible models of water to demonstrate its advantage over the standard canonical, isokinetic and canonical–isokinetic ensembles.

- 49-58 **Development of 3D-pharmacophore model followed by successive virtual screening, molecular docking and ADME studies for the design of potent CCR2 antagonists for inflammation-driven diseases**, Rajesh Singh [National Institute of Pharmaceutical Education and Research], Anand Balupuri & M. Elizabeth Sobhia

See Applications / Medicinal Chemistry and Drug Design.

- 59-63 **Internal carburisation of an industrial alloy: a quantum chemical study of microstructure's changes**, C. Lanz [Universidad Nacional del Sur], G. Brizuela & S. Simonetti

A quantum chemical theoretical study on the chemical bonding and electronic structure of the γ -FeNiCr–C interaction is performed using the Atom Superposition and Electron Delocalisation method in order to contribute to the understanding of the changes in the alloy microstructure caused by carburisation phenomenon.

- 64-71 **Liquid–vapour interface varying the softness and range of the interaction potential**, A. Martínez-Valencia [Universidad Autónoma del Estado de México], M. González-Melchor, P. Orea & J. López-Lemus

Molecular dynamics simulations in a canonical ensemble were carried out for simple fluids. The inter-particles interaction law is described by the Morse function plus a repulsive term. This kind of combination allows to tune the repulsive term of the interaction function by fitting the range of the attractive well and vice versa.

- 72-83 **Theoretical investigation of the conformational, electronic and antioxidant properties of azaleatin, isorhamnetin and quercetagenin**, K. Senthil kumar [Hindusthan College of Engineering and Technology] & R. Kumaresan

Gas phase and solvent phase reaction enthalpies related to the individual steps of three phenolic antioxidants in the view of action mechanisms – hydrogen atom transfer (HAT), single electron transfer–proton transfer (SET–PT) and sequential proton loss electron transfer (SPLET) – have been calculated using DFT/B3LYP/6-311++G** method.

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 Journal of Computational Chemistry, 33 (5), February, 2012.
 Journal of Molecular Modeling, 18 (1), January, 2012.

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1. APPLICATIONS

1.1. Small Molecules

Medicinal Chemistry and Drug Design

Quantitative structure–activity relationships of 1,3,4-thiadiazol-2(3H)-ones and 1,3,4-oxadiazol-2(3H)-ones as human protoporphyrinogen oxidase inhibitors

Yang Zuo, Sheng-Gang Yang, Li-Li Jiang, Ge-Fei Hao, Zhi-Fang Wang, Qiong-You Wu, Zhen Xi, Guang-Fu Yang
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Bioorg. and Med. Chem., **20**, 296-304, 2012.

Protoporphyrinogen oxidase (Protox, EC 1.3.3.4) has attracted great interest during the last decades due to its unique biochemical characteristics and biomedical significance. As a continuation of our research work on the development of new PPO inhibitors, 23 new 1,3,4-thiadiazol-2(3H)-ones bearing benzothiazole substructure were designed and synthesized. The in vitro assay indicated that the newly synthesized compounds **1a–w** displayed good inhibition activity against human PPO (hPPO) with K_i values ranging from 0.04 μ M to 245 μ M.

Molecular Dynamics Simulation Study Explaining Inhibitor Selectivity in Different Class of Histone Deacetylases

Sundarapandian Thangapandian, Shalini John, Keun Woo Lee
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J. Biomol. Stru. and Dyn., **29**, 677-698, 2012.

Histone deacetylases (HDACs) are key regulators of gene expression and thereby compelling targets in the treatment of various cancers. Class- and isoform-selective HDAC inhibitors targeting the particular isoform to treat cancers without affecting the normal expression of other isoforms are highly desirable. Molecular dynamics simulations were performed with the set of selective inhibitors and HDAC isoforms of three different classes. The results were compared both within and across the isoforms.



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Medicinal Chemistry and Drug Design (Cont'd)

Molecular Dynamics of HIV1-Integrase in Complex with 93del – A Structural Perspective on the Mechanism of Inhibition

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J. Biomol. Stru. and Dyn., **29**, 863-877, 2012.

HIV1 integrase is an important target for the antiviral therapy. Guanine-rich quadruplex, such as 93del, have been shown to be potent inhibitors of this enzyme and thus representing a new class of antiviral agents. Although X-ray and NMR structures of HIV1 integrase and 93del have been reported, there is no structural information of the complex and the mechanism of inhibition still remains unexplored. A number of computational methods including automated protein-DNA docking and molecular dynamics simulation in explicit solvent were used to model the binding of 93del to HIV1 integrase.

Denaturation of HIV-1 Protease (PR) Monomer by Acetic Acid: Mechanistic and Trajectory Insights from Molecular Dynamics Simulations and NMR

Aditi Borkar, Manoj Kumar Rout, Ramakrishna V. Hosur
[Tata Institute of Fundamental Research]

J. Biomol. Stru. and Dyn., **29**, 893-903, 2012.

Inside a living cell there can be a variety of interactions for any given protein, which serve to regulate denaturation and renaturation processes. Insights into some of them can be obtained by in vitro studies using various denaturing agents. In this study, all-atom MD simulations in explicit solvent and NMR relaxation studies were performed on HIV-1 Protease (PR) in 9 M acetic acid (AcOH) (the commonly used denaturant during PR preparation). Following previous reports that denaturation proceeds via dissociation of the dimer into monomers, unfolding of the monomer by acetic acid has been explicitly investigated here.

In silico Investigation of the Disease-Associated Retinoschisin C110Y and C219G Mutants

Josephine W. Wu, Hsuan-Liang Liu [National Taipei University of Technology]

J. Biomol. Stru. and Dyn., **29**, 937-959, 2012.

The juvenile X-linked retinoschisis (XLRS) is a retinal disease caused by mutations in the secretory protein, retinoschisin (RS1). Majority of the disease is resulted from single point mutations on the RS1 discoidin domain with cysteine mutations being related to some of the more severe cases of XLRS. Through homology modeling, bioinformatics predictions, molecular dynamics (MD) and docking simulations, we attempt to investigate the effects of these two mutations on the structure of the RS1 discoidin domain in relevance to the discrepancy found between structural stability and aggregation propensity.

Permeation Pathway of Homomeric Connexin 26 and Connexin 30 Channels Investigated by Molecular Dynamics

Francesco Zonta, Guido Polles, Giuseppe Zanotti, Fabio Mammano [University of Padua]

J. Biomol. Stru. and Dyn., **29**, 985-998, 2012.

Mutations in the genes GJB2 and GJB6 encoding human connexin26 (hCx26) and connexin30 (hCx30), respectively, are the leading cause of non-syndromic prelingual deafness in several human populations. In this work, we exploited the high degree (77%) of sequence similarity shared by hCx26 and hCx30 to create atomistic models of homomeric hCx26 and hCx30 connexons starting from the X-ray crystallographic structure of an intercellular channel formed by hCx26 protomers at 3.5-Å resolution. The equilibrium dynamics of the two protein complexes was followed for 40 ns each by Molecular Dynamics (MD) simulations.

Medicinal Chemistry and Drug Design (Cont'd)

Binding efficiencies of carbohydrate ligands with different genotypes of cholera toxin B: molecular modeling, dynamics and docking simulation studies

Mobashar Hussain Urf Turabe Fazil, Sunil Kumar, Rohit Farmer, Haushila Prasad Pandey and Durg Vijai Singh [Institute of Life Sciences, Bhubaneswar]

J. Mol.Mod., **18**, 1-10, 2012.

Vibrio cholerae produces cholera toxin (CT) that consists of two subunits, A and B, and is encoded by a filamentous phage CTXΦ. The A subunit carries enzymatic activity that ribosylates ADP, whereas the B subunit binds to monosialoganglioside (GM1) receptor in epithelial cells. Molecular analysis of toxigenic *V. cholerae* strains indicated the presence of multiple ctxB genotypes. In this study, we employed a comparative modeling approach to define the structural features of all known variants of ctxB found in O139 serogroup *V. cholerae*. Modeling, molecular dynamics and docking simulations studies suggested subtle variations in the binding ability of ctxB variants to carbohydrate ligands of GM1.

A comparative study of the hydrogen-bonding patterns and prototropism in solid 2-thiocyto sine (potential antileukemic agent) and cytosine, as studied by 1H-14N NQDR and QTAIM/ DFT

Jolanta N. Latosińska [Adam Mickiewicz University], Janez Seliger, Veselko Žagar and Dorota V. Burchardt

J. Mol.Mod., **18**, 11-26, 2012.

A potential antileukemic and anticancer agent, 2-thiocyto sine (2-TC), has been studied experimentally in the solid state by 1H-14N NMR-NQR double resonance (NQDR) and theoretically by the quantum theory of atoms in molecules (QTAIM)/density functional theory (DFT). Eighteen resonance frequencies on 14N were detected at 180 K and assigned to particular nitrogen sites (–NH2, –N=, and –NH–) in 2-thiocyto sine. Factors such as the nonequivalence of molecules (connected to the duplication of sites) and possible prototropic tautomerism (capable of modifying the type of site due to proton transfer) were taken into account during frequency assignment.

Molecular modeling, docking and dynamics simulations of GNA-related lectins for potential prevention of influenza virus (H1N1)

Huai-long Xu, Chun-yang Li, Xue-mei He, Ke-qin Niu and Hao Peng, Jin-ku Bao [Sichuan University], et al.

J. Mol.Mod., **18**, 27-37, 2012.

The *Galanthus nivalis* agglutinin (GNA)-related lectin family exhibit significant anti-HIV and anti-HSV properties that are closely related to their carbohydrate-binding activities. However, there is still no conclusive evidence that GNA-related lectins possess anti-influenza properties. The hemagglutinin (HA) of influenza virus is a surface protein that is involved in binding host cell sialic acid during the early stages of infection. Herein, we studied the 3D-QSARs (three-dimensional quantitative structure–activity relationships) of lectin– and HA–sialic acid by molecular modeling.

Computer-assisted design for paracetamol masking bitter taste prodrugs

Hatem Hejaz, Rafik Karaman [Al-Quds University] and Mustafa Khamis

J. Mol.Mod., **18**, 103-114, 2012.

It is believed that the bitter taste of paracetamol, a pain killer drug, is due to its hydroxyl group. Hence, it is expected that blocking the hydroxy group with a suitable linker could inhibit the interaction of paracetamol with its bitter taste receptor/s and hence masking its bitterness. Using DFT theoretical calculations we calculated proton transfers in ten different Kirby's enzyme models, 1–10. The calculation results revealed that the reaction rate is linearly correlated with the distance between the two reactive centers (rGM) and the angle of the hydrogen bonding (α) formed along the reaction pathway.

Medicinal Chemistry and Drug Design (Cont'd)

Virtual screening and in vitro assay of potential drug like inhibitors from spices against glutathione-S-transferase of filarial nematodes

Shamina Azeez [Indian Institute of Spices Research], Rosana O. Babu, Riju Aykkal and Reena Narayanan

J. Mol.Mod., **18**, 151-163, 2012.

Glutathione-S-transferase(s) (GST) enzyme from *Brugia malayi* has been exploited as a target in lymphatic filariasis therapeutics. The components of the glutathione (GSH) system, mainly GST enzymes, are critical antioxidant and detoxification system responsible for the long-term existence of filarial worms in mammalian host; hence they are major chemotherapeutic targets in filarial species. In the present study, 58 phytochemicals from 10 plants, predicted and reported to have potential nematicidal activity and ADMET satisfaction, have been docked to GST enzyme of *B. malayi* to assess their binding affinity and consequently their inhibitory activity.

Identification of novel, less toxic PTP-LAR inhibitors using in silico strategies: pharmacophore modeling, SADMET-based virtual screening and docking

Dara Ajay and M. Elizabeth Sobhia [National Institute of Pharmaceutical Education and Research (NIPER)]

J. Mol.Mod., **18**, 187-201, 2012.

Human leukocyte antigen-related (PTP-LAR) is a receptor-like transmembrane phosphatase and a potential target for diabetes, obesity and cancer. In the present study, a sequence of in silico strategies (pharmacophore mapping, a 3D database searching, SADMET screening, and docking and toxicity studies) was performed to identify eight novel nontoxic PTP-LAR inhibitors. Twenty different pharmacophore hypotheses were generated using two methods; the best (hypothesis 2) consisted of three hydrogen-bond acceptor (A), one ring aromatic (R), and one hydrophobic aliphatic (Z) features.

Noscapinoids with anti-cancer activity against human acute lymphoblastic leukemia cells (CEM): a three dimensional chemical space pharmacophore modeling and electronic feature analysis

Pradeep K. Naik [Emory University School of Medicine], Seneha Santoshi and Harish C. Joshi

J. Mol.Mod., **18**, 307-318, 2012.

We have identified a new class of microtubule-binding compounds—noscapinoids—that alter microtubule dynamics at stoichiometric concentrations without affecting tubulin polymer mass. Noscapinoids show great promise as chemotherapeutic agents for the treatment of human cancers. To investigate the structural determinants of noscapinoids responsible for anti-cancer activity, we tested 36 structurally diverse noscapinoids in human acute lymphoblastic leukemia cells (CEM).

Molecular dynamics simulation and density functional theory studies on the active pocket for the binding of paclitaxel to tubulin

Sichuan Xu [Yunnan University], Shaoming Chi, Yi Jin, Qiang Shi and Maofa Ge, et al.

J. Mol.Mod., **18**, 377-391, 2012.

Paclitaxel (PTX) is used to treat various cancers, but it also causes serious side effects and resistance. To better design similar compounds with less toxicity and more activity against drug-resistant tumors, it is important to clearly understand the PTX-binding pocket formed by the key residues of active sites on β -tubulin. Using a docking method, molecular dynamics (MD) simulation and density functional theory (DFT), we identified some residues (such as Arg278, Asp26, Asp226, Glu22, Glu27, His229, Arg369, Lys218, Ser277 and Thr276) on β -tubulin that are the active sites responsible for interaction with PTX.

Quantitative Structure-Activity Relations

QSAR study and synthesis of new phenyltropanes as ligands of the dopamine transporter (DAT)

Sylvie Mavel [Université François-Rabelais], Zoya Mincheva, Nathalie Méheux, Yvan Carcenac, Denis Guilloteau, Mohamed Abarbri, Patrick Emond

Bioorg. and Med.Chem., **20**, 1388-1395, 2012.

The dopamine transporter (DAT) plays a pivotal role in the regulation of dopamine neurotransmission, and is involved in a number of physiological functions and brain disorders. Furthermore the DAT analysis by molecular imaging techniques is a useful tool for the diagnosis and follow up treatment of diseases involving the DAT. In order to predict the affinity of new derivatives for the DAT, different QSAR molecular modeling models based on cocaine were compared. We have evaluated in these models tropane derivatives synthesized with original synthons which coupled properties of both fluorine and iodine atoms.

QSAR studies for prediction of cross- β sheet aggregate binding affinity and selectivity

Katryna Cisek, Jeff Kuret [The Ohio State University College of Medicine]

Bioorg. and Med.Chem., **20**, 1434-1441, 2012.

Protein aggregates that accumulate in neurodegenerative diseases are important targets of radiotracer discovery efforts. Although multiple scaffold classes have been reported to bind cross- β sheet structure, their mechanism of binding and their ability to interact selectively with aggregates of varying protein composition are not well understood. Here we take a ligand-based quantitative structure-activity relationship approach to identify descriptors of binding affinity and selectivity for a series of 50 closely related benzothiazole derivatives reported to displace Thioflavin T fluorescent probe from synthetic aggregates composed of β -amyloid peptide and insulin.

Structural determinants of benzodiazepinedione/peptide-based p53-HDM2 inhibitors using 3D-QSAR, docking and molecular dynamics

Fangfang Wang, Yan Li, Zhi Ma, Xia Wang and Yonghua Wang [Northwest A&F University]

J. Mol.Mod., **18**, 295-306, 2012.

As a tumor suppressor, p53 protein regulates the cell cycle and is involved in preventing tumorigenesis. The protein level of p53 is under the tight control of its negative regulator human double minute 2 (HDM2) via ubiquitination. Therefore, the design of inhibitors of HDM2 has attracted much interest of research on developing novel anticancer drugs. Presently, two classes of molecules, i.e., the 1,4-benzodiazepine-2,5-diones (BDPs) and N-Acylpolyamine (NAPA) derivatives were studied by 3D-QSAR modeling approaches including the CoMFA and CoMSIA as promising p53-HDM2 inhibitors.

Host Guest Systems

A model for the shuttle motions of puerarin and daidzin inside the cavity of β -cyclodextrin in aqueous acetic acid: insights from molecular dynamics simulations

Haiyang Zhang, Wei Feng, Cong Li, Yongqin Lv and Tianwei Tan [Beijing University of Chemical Technology]

J. Mol. Mod., **18**, 221-227, 2012.

Acetic acid acts as one component of the mobile phase to influence separation of puerarin from daidzin when using β -cyclodextrin-substituted media. In this work considering an explicit acetic acid solution, host-guest complexes of β -cyclodextrin (β -CD) with puerarin and daidzin were investigated by molecular dynamics simulations. Computational results indicate different shuttle motions of puerarin and daidzin inside the cavity of β -CD. A model detailing the shuttle motion was constructed, and the relationships between shuttle depth and guest rotation angles, hydrogen bonds, and host-guest interaction energies were analyzed.

Molecular Dynamics Simulations of the Supramolecular Assembly between an Azobenzene-Containing Surfactant and α -Cyclodextrin: Role of Photoisomerization

Xiaoyan Zheng, Dong Wang [Tsinghua University], Zhigang Shuai, and Xi Zhang

J. Phys. Chem. B., **116**, 823-832, 2012.

Control of the self-assembly and disassembly at the molecular level has become a subject of increasing activity. The supramolecular assembly between a photoswitchable azobenzene-containing surfactant, AzoC10, and α -cyclodextrin that combines photochemistry and host-guest chemistry for a stimulus-responsive vesicle has been recently reported. To clarify the role of photoisomerization in the reversible assembly and disassembly, we present in this work atomistic molecular dynamics simulations of the host-guest complexation of AzoC10 with α -cyclodextrin.

Carbon Nanoparticles

Insights in the Plasma-Assisted Growth of Carbon Nanotubes through Atomic Scale Simulations: Effect of Electric Field

Erik C. Neyts [University of Antwerp], Adri C. T. van Duin, and Annemie Bogaerts

J. Am. Chem. Soc., **134**, 1256-1260, 2012.

Carbon nanotubes (CNTs) are nowadays routinely grown in a thermal CVD setup. State-of-the-art plasma-enhanced CVD (PECVD) growth, however, offers advantages over thermal CVD. A lower growth temperature and the growth of aligned freestanding single-walled CNTs (SWNTs) makes the technique very attractive. The atomic scale growth mechanisms of PECVD CNT growth, however, remain currently entirely unexplored. In this contribution, we employed molecular dynamics simulations to focus on the effect of applying an electric field on the SWNT growth process, as one of the effects coming into play in PECVD.

Biomimetic Design of a Brush-Like Nanopore: Simulation Studies

Prapasiri Pongprayoon, Oliver Beckstein, and Mark S. P. Sansom [University of Oxford]

J. Phys. Chem. B., **116**, 462-468, 2012.

Combining a high degree of selectivity and nanoscale dimensions, biological pores are attractive potential components for nanotechnology devices and applications. Biomimetic design will facilitate production of stable synthetic nanopores with defined functionality. Bacterial porins offer a good source of possible templates for such nanopores as they form stable, selective pores in lipid bilayers. Molecular dynamics simulations have been used to design simple model nanopores with permeation free energy profiles that can be made to mimic a template protein, the OprP porin, which forms pores selective for anions.

Carbon Nanoparticles (Cont'd)

Simulation Study of Structural, Transport, and Thermodynamic Properties of TIP4P/2005 Water in Single-Walled Carbon Nanotubes

Christa Guse and Reinhard Hentschke [Bergische Universität]

J. Phys. Chem. B., **116**, 751–762, 2012.

Because carbon nanotubes lack a strong interaction with water, its hydrogen bond network is altered mainly by the confining geometry alone, allowing one to study its influence on the structure of water. Here structural, transport, and thermodynamic properties are investigated for TIP4P/2005 water confined in single-walled carbon nanotubes, possessing diameters from 11 to 50 Å. Temperatures range from 220 to 600 K for the two pressures studied, 1 and 1000 atm.

1.2. Biopolymers

Bioinformatics and Cheminformatics

MTBindingSim: simulate protein binding to microtubules

Julia T. Philip [University of Notre Dame], Charles H. Pence, and Holly V. Goodson

Bioinformatics. **28**, 3002-3009, 2012.

Many protein–protein interactions are more complex than can be accounted for by 1:1 binding models. However, biochemists have few tools available to help them recognize and predict the behaviors of these more complicated systems, making it difficult to design experiments that distinguish between possible binding models. MTBindingSim provides researchers with an environment in which they can rapidly compare different models of binding for a given scenario.

Protein Secondary Structure

Characterization of an alternative low energy fold for bovine α -lactalbumin formed by disulfide bond shuffling

Sarah Lewney and Lorna J. Smith [University of Oxford]

Proteins: Stru. Fun. & Bioinf. **80**, 913–919, 2012.

Bovine α -lactalbumin (α LA) forms a misfolded disulfide bond shuffled isomer, X- α LA. This X- α LA isomer contains two native disulfide bridges (Cys 6–Cys 120 and Cys 28–Cys 111) and two non-native disulfide bridges (Cys 61–Cys 73 and Cys 77–Cys 91). MD simulations have been used to characterize the X- α LA isomer and its formation via disulfide bond shuffling and to compare it with the native fold of α LA. In the simulations of the X- α LA isomer the structure of the α -domain of native α LA is largely retained in agreement with experimental data.

Comparative or Homology Modeling

Structural models of CFTR-AMPK and CFTR-PKA interactions: R-domain flexibility is a key factor in CFTR regulation

Marian Siwiak, Aleksander Edelman and Piotr Zielenkiewicz
[Polish Academy of Sciences]

J. Mol.Mod., **18**, 83-90, 2012.

Cystic fibrosis (CF), the most common lethal genetic disease among Caucasians, is caused by mutations in cystic fibrosis transmembrane conductance regulator (CFTR). However, the exact role of CFTR in cellular processes is not yet fully understood. The important kinases regulating CFTR are cAMP-dependent protein kinase A (PKA) and 5'-AMP-activated protein kinase (AMPK). Utilizing homology modeling, in silico mutagenesis and literature mining, we supplement available information regarding the atomic-resolution structures of PKA, AMPK and CFTR, and the complexes CFTR-PKA and CFTR-AMPK.

A selectivity study on mTOR/PI3K α inhibitors by homology modeling and 3D-QSAR

Ting Ran, Tao Lu, Haoliang Yuan, Haichun Liu and Jian Wang, Yadong Chen [China Pharmaceutical University], et al.

J. Mol.Mod., **18**, 171-186, 2012.

The phosphatidylinositol-3-kinase (PI3K)/Akt/mammalian target of rapamycin (mTOR) signaling pathway plays a critical role in the regulation of cellular growth, survival and proliferation. These kinases belong to the phosphatidylinositol-3-kinase-related kinase (PIKK) family and therefore have considerable homology in their active sites. To accelerate the discovery of inhibitors with selective activity against mTOR and PI3K as cancer targets, in this work, a homology model of mTOR was developed to identify the structural divergence in the active sites between mTOR and PI3K α .

Receptor recognition mechanism of human influenza A H1N1 (1918), avian influenza A H5N1 (2004), and pandemic H1N1 (2009) neuraminidase

Nipa Jongkon and Chak Sangma [Kasetsart University]

J. Mol.Mod., **18**, 285-293, 2012.

Influenza A neuraminidase (NA) is a target for anti-influenza drugs. The function of this enzyme is to cleave a glycosidic linkage of a host cell receptor that links sialic acid (Sia) to galactose (Gal), to allow the virus to leave an infected cell and propagate. The receptor is an oligosaccharide on the host cell surface. Some researchers believe that NAs from different viruses show selectivity for each type of linkage, but there is limited information available to confirm this hypothesis. To see if the linkage type is more specific to any particular NA, a number of NA-receptor complexes of human influenza A H1N1 (1918), avian influenza A H5N1 (2004), and a pandemic strain of H1N1 (2009) were constructed using homology modeling and molecular dynamics simulation.

Protein Confirmation Analysis

Investigating How Peptide Length and a Pathogenic Mutation Modify the Structural Ensemble of Amyloid Beta Monomer

Yu-Shan Lin, Gregory R. Bowman, Kyle A. Beauchamp, Vijay S. Pande [Stanford University]

Biophysical Journal. **102**, 315-324, 2012.

The aggregation of amyloid beta (A β) peptides plays an important role in the development of Alzheimer's disease. Despite extensive effort, it has been difficult to characterize the secondary and tertiary structure of the A β monomer, the starting point for aggregation, due to its hydrophobicity and high aggregation propensity. Here, we employ extensive molecular dynamics simulations with atomistic protein and water models to determine structural ensembles for A β ₄₂, A β ₄₀, and A β ₄₂-E22K (the Italian mutant) monomers in solution.

Unveiling the Unfolding Pathway of F5F8D Disorder-Associated D81H/V100D Mutant of MCFD2 via Multiple Molecular Dynamics Simulations

Adel Hamza [University of Kentucky], Ning-Ning Wei, Trudy Johnson-Scalise, Frederick Naftolin, Hoon Cho, Chang-Guo Zhan

J. Biomol. Stru. and Dyn., **29**, 677-698, 2012.

Combined factor deficiency (F5F8D) is a rare autosomal recessive disorder caused by mutations in the LMAN1 or MCFD2 genes. It has been proposed that this pathogenic process occurs via a multi-step pathway involving metal loss, EF-hand-Ca21 dissociation and assembly of misfolded MCFD2-LMAN1 complex. Here, we have investigated the solution conformations of the MCFD2^(D81H,V100D) protein mutant through extensive molecular dynamics (MD) simulations. The V100D, one of the many MCFD2 mutations known to be associated to F5F8D, is difficult to be reconciled with the pathway model because it is located far from the metal sites and the MCFD2/LMAN1 interface.

Dynamics of Noncovalent Interactions in All- α and All- β Class Proteins: Implications for the Stability of Amyloid Aggregates

Alok Jain and Ramasubbu Sankararamakrishnan [Indian Institute of Technology Kanpur]

J.Chem. Infor. and Mod. **51**, 3208–3216, 2011.

A fully folded functional protein is stabilized by several noncovalent interactions. When a protein undergoes conformational motions, the existing noncovalent interactions may be maintained. They may also break or new interactions may be formed. Knowledge of the dynamical nature of the different types of noncovalent interactions is extremely important to understand the structural stability, function, and folding of a protein. We have carried out molecular dynamics simulations on four different proteins, two belonging to all- α class proteins and the other two are representatives of all- β class proteins.

Searching the “Biologically Relevant” Conformation of Dopamine: A Computational Approach

Sebastian A. Andujar, Rodrigo D. Tosso, Fernando D. Suvire, Emilio Angelina, Nelida Peruchena, Nuria Cabedo, Diego Cortes, and Ricardo D. Enriz [Universidad Nacional de San Luis]

J.Chem. Infor. and Mod. **52**, 99–112, 2012.

We report here an exhaustive and complete conformational study on the conformational potential energy hypersurface (PEHS) of dopamine (DA) interacting with the dopamine D2 receptor (D2–DR). A reduced 3D model for the binding pocket of the human D2–DR was constructed on the basis of the theoretical model structure of bacteriorhodopsin. In our reduced model system, only 13 amino acids were included to perform the quantum mechanics calculations. To obtain the different complexes of DA/D2–DR, we combined semiempirical (PM6), DFT (B3LYP/6-31G(d)), and QTAIM calculations.

Protein Conformational Analysis (Cont'd)

Molecular dynamics simulation of conformational heterogeneity in transportin 1

Xia Wang, Xue Xu, Shanna Zhu, Zhengtao Xiao, Zhi Ma, Yan Li and Yonghua Wang [Northwest A&F University]

Proteins: Stru. Fun. & Bioinf. **80**, 382–397, 2012.

Transportin 1 (Trn1), as a typical transport receptor of the karyopherin- β family, mediates numerous RNA binding proteins into the nucleus by recognizing proline-tyrosine nuclear localization signals (PY-NLSs). Such process is regulated by RanGTP through its nucleotide cycle, which is associated with ligand dissociation. Here, we use molecular dynamics simulations to probe the conformational dynamics of the apo-Trn1 and Trn1 in complex with ligand and Ran.

Analysis on folding of misgurin using two-dimensional HP model

Shaomin Yan and Guang Wu [Guangxi Academy of Sciences]

Proteins: Stru. Fun. & Bioinf. **80**, 764–773, 2012.

Misgurin is an antimicrobial peptide from the loach, while the hydrophobic-polar (HP) model is a way to study the folding conformations and native states in peptide and protein although several amino acids cannot be classified either hydrophobic or polar. Practically, the HP model requires extremely intensive computations, thus it has yet to be used widely. In this study, we use the two-dimensional HP model to analyze all possible folding conformations and native states of misgurin with conversion of natural amino acids according to the normalized amino acid hydrophobicity index as well as the shortest benchmark HP sequence.

Computational protein design with explicit consideration of surface hydrophobic patches

Ron Jacak, Andrew Leaver-Fay and Brian Kuhlman [University of North Carolina]

Proteins: Stru. Fun. & Bioinf. **80**, 825–838, 2012.

De novo protein design requires the identification of amino-acid sequences that favor the target-folded conformation and are soluble in water. One strategy for promoting solubility is to disallow hydrophobic residues on the protein surface during design. A less restrictive approach for surface design that is used by the modeling program Rosetta is to parameterize the energy function so that the number of hydrophobic amino acids designed on the protein surface is similar to what is observed in naturally occurring monomeric proteins. Here, we describe a new score term that explicitly detects and penalizes the formation of hydrophobic patches during computational protein design.

Protein Dynamics

Investigating the Mechanism of Substrate Uptake and Release in the Glutamate Transporter Homologue Glt_{Ph} through Metadynamics Simulations

Giovanni Grazioso, Vittorio Limongelli, Davide Branduardi, Ettore Novellino, Carlo De Micheli, Andrea Cavalli, and Michele Parrinello [Eidgenössische Technische Hochschule]

J. Am. Chem. Soc., **134**, 453–463, 2012.

A homeostatic concentration of glutamate in the synaptic cleft ensures a correct signal transduction along the neuronal network. An unbalance in this concentration can lead to neuronal death and to severe neurodegenerative diseases such as Alzheimer's or Parkinson's. Glutamate transporters play a crucial role in this respect. Structural studies have shown that this transporter can assume at least three conformations, thus suggesting a pronounced dynamical behavior. Here, using metadynamics simulations, we investigate the substrate uptake from the synaptic cleft and its release in the intracellular medium.

Protein Dynamics (Cont'd)

Dynamics of Pyrophosphate Ion Release and Its Coupled Trigger Loop Motion from Closed to Open State in RNA Polymerase II

Lin-Tai Da, Dong Wang, and Xuhui Huang [The Hong Kong University of Science and Technology]

J. Am. Chem. Soc., **134**, 2399–2406, 2012.

Pyrophosphate ion (PP_i) release after nucleotide incorporation is a necessary step for RNA polymerase II (pol II) to enter the next nucleotide addition cycle during transcription elongation. However, the role of pol II residues in PP_i release and the mechanistic relationship between PP_i release and the conformational change of the trigger loop remain unclear. In this study, we constructed a Markov state model (MSM) from extensive all-atom molecular dynamics (MD) simulations in the explicit solvent to simulate the PP_i release process along the pol II secondary channel.

Microsecond Time-Scale Conformational Exchange in Proteins: Using Long Molecular Dynamics Trajectory To Simulate NMR Relaxation Dispersion Data

Yi Xue, Joshua M. Ward, Tairan Yuwen, Ivan S. Podkorytov, and Nikolai R. Skrynnikov [Purdue University]

J. Am. Chem. Soc., **134**, 2555–2562, 2012.

With the advent of ultra-long MD simulations it becomes possible to model microsecond time-scale protein dynamics and, in particular, the exchange broadening effects (R^{ex}) as probed by NMR relaxation dispersion measurements. This new approach allows one to identify the exchanging species, including the elusive “excited states”. It further helps to map out the exchange network, which is potentially far more complex than the commonly assumed 2- or 3-site schemes. In this study, recent millisecond-long MD trajectory of protein BPTI (Shaw et al. *Science***2010**, 330, 341) is employed to simulate the time variation of amide ¹⁵N chemical shifts.

Insight into the Common Mechanism of the Chromophore Formation in the Red Fluorescent Proteins: The Elusive Blue Intermediate Revealed

Ksenia B. Bravaya, Oksana M. Subach, Nadezhda Korovina, Vladislav V. Verkhusha, and Anna I. Krylov [University of Southern California]

J. Am. Chem. Soc., **134**, 2807–2814, 2012.

Understanding the chromophore maturation process in fluorescent proteins is important for the design of proteins with improved properties. Here, we present the results of electronic structure calculations identifying the nature of a blue intermediate, a key species in the process of the red chromophore formation in DsRed, TagRFP, fluorescent timers, and PAmCherry. Ab initio and QM/MM calculations of the isolated model and protein-bound (mTagBFP) chromophores identify the anionic form of HIMA as the only structure that has absorption that is consistent with the experiment and is stable in the protein binding pocket.

Molecular Dynamics Simulations on Pars Intercerebralis Major Peptide-C (PMP-C) Reveal the Role of Glycosylation and Disulfide Bonds in its Enhanced Structural Stability and Function

Sandeep Kaushik, Debasisa Mohanty [National Institute of Immunology, New Delhi], Avadhesh Surolia

J. Biomol. Stru. and Dyn., **29**, 905-920, 2012.

Fucosylation of Thr 9 in pars intercerebralis major peptide-C (PMP-C) enhances its structural stability and functional ability as a serine protease inhibitor. In order to understand the role of disulfide bonds and glycosylation on the structure and function of PMP-C, we have carried out multiple explicit solvent molecular dynamics (MD) simulations on fucosylated and non-fucosylated forms of PMP-C, both in the presence and absence of the disulfide bonds. Our simulations revealed that there were no significant structural changes in the native disulfide bonded forms of PMP-C due to fucosylation.

Protein Dynamics (Cont'd)

Role of Hydrophobic Core on the Thermal Stability of Proteins – Molecular Dynamics Simulations on a Single Point Mutant of Sso7d Abstract

U. Deva Priyakumar [International Institute of Information Technology, Hyderabad]

J. Biomol. Stru. and Dyn., **29**, 961-971, 2012.

The role of salt bridges in chromatin protein Sso7d, from *S. solfataricus* has previously been shown to be crucial for its unusual high thermal stability. Experimental studies have shown that single site mutation of Sso7d (F31A) leads to a substantial decrease in the thermal stability of this protein due to distortion of the hydrophobic core. In the present study, we have performed a total of 0.2 μ s long molecular dynamics (MD) simulations on F31A at room temperature, and at 360 K, close to the melting temperature of the wild type (WT) protein to investigate the role of hydrophobic core on protein stability.

Study of the betulin molecule in a water environment; ab initio and molecular simulation calculations

Miroslav Pospíšil [Charles University in Prague], Petr Kovář, Robert Vácha and Michal Svoboda

J. Mol.Mod., **18**, 367-376, 2012.

Ab initio and molecular simulation methods were used in calculations of the neutral individual betulin molecule, and molecular simulations were used to optimize the betulin molecule immersed in various amounts of water. Individual betulin was optimized in different force fields to find the one exhibiting best agreement with ab initio calculations obtained in the Gaussian03 program. Dihedral torsions of active groups of betulin were determined for both procedures, and related calculated structures were compared successfully.

Key Structural Features of the Actin Filament Arp2/3 Complex Branch Junction Revealed by Molecular Simulation

Jim Pfandtner, Niels Volkman, Dorit Hanein, Paul Dalhaimer, Thomas D. Pollard, Gregory A. Voth [The University of Chicago]

J. Molec. Bio. **415**, 148-161, 2012.

We investigated the structure, properties and dynamics of the actin filament branch junction formed by actin-related protein (Arp) 2/3 complex using all-atom molecular dynamics (MD) simulations based on a model fit to a reconstruction from electron tomograms. Simulations of the entire structure consisting of 31 protein subunits together with solvent molecules containing ~ 3 million atoms were performed for an aggregate time of 175 ns. One 75-ns simulation of the original reconstruction was compared to two 50-ns simulations of alternate structures, showing that the hypothesized branch junction structure is very stable.

Assessment of the Intrinsic Conformational Preferences of Dipeptide Amino Acids in Aqueous Solution by Combined Umbrella Sampling/MBAR Statistics. A Comparison with Experimental Results

Victor L. Cruz [BIOPHYM], Javier Ramos, and Javier Martinez-Salazar

J. Phys. Chem. B., **116**, 469–475, 2012.

The propensities of 19 amino acid dipeptides have been calculated by a distributed umbrella sampling molecular dynamics simulation procedure using the OPLS-AA force field. The potential of mean force maps was estimated with the multiple Bennett acceptance ratio statistics. The resulting propensities compare satisfactorily well with very recently published experimental data on equivalent systems. In particular, α conformation-probabilities for all of the dipeptides remain much lower than either β or P_{II} propensities. This result is in agreement with most experimental data for dipeptides.

Protein Dynamics (Cont'd)

Conformational Study of the Hydroxyproline–O–Glycosidic Linkage: Sugar–Peptide Orientation and Prolyl Amide Isomerization in (α/β)–Galactosylated 4(R/S)–Hydroxyproline

Emmanuel B. Naziga, Frank Schweizer, and Stacey D. Wetmore [University of Lethbridge]

J. Phys. Chem. B., **116**, 860–871, 2012.

Glycosylation is a frequent post-translational modification of proteins that has been shown to influence protein structure and function. Glycosylation of hydroxyproline occurs widely in plants, but is absent in humans and animals. In this work, molecular dynamics simulations in explicit water and implicit solvent DFT optimizations are used to examine the structure of the hydroxyproline–O–galactosyl linkage and the effect of glycosylation on the structure and cis/trans isomerization of the peptide backbone.

Theoretical Studies of Chromophore Maturation in the Wild-Type Green Fluorescent Protein: ONIOM(DFT:MM) Investigation of the Mechanism of Cyclization

Yingying Ma, Qiao Sun, Zhen Li, Jian-Guo Yu [Beijing Normal University], and Sean C. Smith

J. Phys. Chem. B., **116**, 1426–1436, 2012.

The availability of a gene encoding green fluorescence immediately stimulates interest in the puzzle of autocatalytic formation of the green fluorescent protein (GFP) chromophore. Numerous experimental and theoretical studies have indicated that cyclization is the first and most important step in the maturation process of the GFP. In our previous paper based on cluster models, two possible mechanisms have been investigated. In this paper, we investigated the two possible mechanisms with inclusion of protein environmental effects by using molecular dynamics (MD) and combined quantum mechanics/molecular mechanics (QM/MM) calculations.

Free Energy Calculations

Computing Free Energy of a Large-Scale Allosteric Transition in Adenylate Kinase Using All Atom Explicit Solvent Simulations

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J. Phys. Chem. B., **116**, 1709–1715, 2012.

During allosteric motions proteins navigate rugged energy landscapes. Hence, mapping of these multidimensional landscapes into lower dimensional manifolds is important for gaining deeper insights into allosteric dynamics. Using a recently developed computational technique, we calculated the free energy difference between the open and closed states of adenylate kinase, an allosteric protein which was extensively studied previously using both experimental and theoretical approaches. Two independent simulations indicate reasonable convergence of the computed free energy profiles.

Ligand Binding/Docking

Importance of V3 Loop Flexibility and Net Charge in the Context of Co-Receptor Recognition. A Molecular Dynamics Study on HIV gp120

Balasubramanian Chandramouli, Giovanni Chillemi, Isabella Abbate, Maria R. Capobianchi, Gabriella Rozera, Alessandro Desideri [University of Rome Tor Vergata]

J. Biomol. Stru. and Dyn., **29**, 879-891, 2012.

The entry of HIV-1 into a host cell requires the interaction of envelope glycoprotein gp120 with CD4 receptor as well as a co-receptor, which can be either CCR5 or CXCR4. The third variable loop (V3) of HIV-1 gp120 plays an important role in co-receptor selection (CCR5 or CXCR4) and also acts as an epitope for neutralizing antibodies against gp120. Here we have performed long time molecular dynamics simulations of two gp120 structures that are representatives of a R5 and X4 strains in the CD4-free and CD4-bound states.

Molecular Dynamics Simulation and Free Energy Calculation Studies of the Binding Mechanism of Allosteric Inhibitors with p38 α MAP Kinase

Ying Yang, Yulin Shen, Huanxiang Liu, and Xiaojun Yao [Lanzhou University]

J.Chem. Infor. and Mod. **51**, 3235–3246, 2011.

p38 MAP kinase is a promising target for anti-inflammatory treatment. The classical kinase inhibitors imatinib and sorafenib as well as BI-1 and BIRB-796 were reported to bind in the DFG-out form of human p38 α , known as type II or allosteric kinase inhibitors. As allosteric inhibition is important to the selectivity of kinase inhibitor, herein the binding modes of imatinib, sorafenib, BI-1 and BIRB-796 to p38 α were investigated by molecular dynamics simulation. Binding free energies were calculated by molecular mechanics/Poisson–Boltzmann surface area method.

Molecular Dynamic Behavior and Binding Affinity of Flavonoid Analogues to the Cyclin Dependent Kinase 6/cyclin D Complex

Wasinee Khuntawee, Thanyada Rungrotmongkol [Chulalongkorn University], and Supot Hannongbua

J.Chem. Infor. and Mod. **52**, 76–83, 2012.

The cyclin dependent kinases (CDKs), each with their respective regulatory partner cyclin that are involved in the regulation of the cell cycle, apoptosis, and transcription, are potentially interesting targets for cancer therapy. The CDK6 complex with cyclin D (CDK6/cycD) drives cellular proliferation by phosphorylation of specific key target proteins. To understand the flavonoids that inhibit the CDK6/cycD functions, molecular dynamics simulations (MDSs) were performed on three inhibitors, fisetin (FST), apigenin (AGN), and chrysin (CHS), complexed with CDK6/cycD, including the two different binding orientations of CHS: FST-like (CHS_A) and deschloro-flavopiridol-like (CHS_B).

Effects of point mutations in pVHL on the binding of HIF-1 α

Carmen Domene [University of Oxford] and Christopher J. R. Illingworth

Proteins: Stru. Fun. & Bioinf. **80**, 733–746, 2012.

The von Hippel-Lindau tumor suppressor protein (pVHL) has an essential role in the regulation of the hypoxia response pathway in animal cells. Under normoxic conditions, the hypoxia-inducible factor (HIF) undergoes trans-4-prolyl hydroxylation and is subsequently recognised by the β -domain of pVHL, leading to the ubiquitination and degradation of HIF. Mutations of pVHL alter the binding of HIF. Here, we present computational studies analyzing the interaction of HIF with mutant forms of pVHL, describing at atomic detail the local structural reorganization caused by substitution of certain residues of pVHL.

Enzyme Catalysis

QM/MM Analysis Suggests That Alkaline Phosphatase (AP) and Nucleotide Pyrophosphatase/Phosphodiesterase Slightly Tighten the Transition State for Phosphate Diester Hydrolysis Relative to Solution: Implication for Catalytic Promiscuity in the AP Superfamily

Guanhua Hou and Qiang Cui [University of Wisconsin]

J. Am. Chem. Soc., **134**, 229–246, 2012.

Several members of the Alkaline Phosphatase (AP) superfamily exhibit a high level of catalytic proficiency and promiscuity in structurally similar active sites. A thorough characterization of the nature of transition state for different substrates in these enzymes is crucial for understanding the molecular mechanisms that govern those remarkable catalytic properties. In this work, we study the hydrolysis of a phosphate diester, MpNPP^- , in solution, two experimentally well-characterized variants of AP (R166S AP, R166S/E322Y AP) and wild type Nucleotide pyrophosphatase/phosphodiesterase (NPP) by QM/MM calculations in which the QM method is an approximate density functional theory previously parametrized for phosphate hydrolysis (SCC-DFTBPR).

Large-Scale Domain Conformational Change Is Coupled to the Activation of the Co–C Bond in the B₁₂-Dependent Enzyme Ornithine 4,5-Aminomutase: A Computational Study

Jiayun Pang, Xin Li, Keiji Morokuma, Nigel S. Scrutton, and Michael J. Sutcliffe [University of Manchester]

J. Am. Chem. Soc., **134**, 2367–2377, 2012.

We present here an energetic and atomistic description of how d-ornithine 4,5-aminomutase (OAM), an adenosylcobalamin (AdoCbl; coenzyme B₁₂)-dependent isomerase, employs a large-scale protein domain conformational change to orchestrate the homolytic rupture of the Co–C bond. Our results suggest that in going from the open form (catalytically inactive) to the closed form (catalytically active), the Rossmann domain of OAM effectively approaches the active site as a rigid body. It undergoes a combination of a $\sim 52^\circ$ rotation and a $\sim 14 \text{ \AA}$ translation to bring AdoCbl—initially positioned $\sim 25 \text{ \AA}$ away—into the active-site cavity.

Quantum Mechanical/Molecular Mechanical Study on the Mechanism of the Enzymatic Baeyer–Villiger Reaction

Iakov Polyak, Manfred T. Reetz, and Walter Thiel [Max-Planck-Institut für Kohlenforschung]

J. Am. Chem. Soc., **134**, 2732–2741, 2012.

We report a combined quantum mechanical/molecular mechanical (QM/MM) study on the mechanism of the enzymatic Baeyer–Villiger reaction catalyzed by cyclohexanone monooxygenase (CHMO). In QM/MM geometry optimizations and reaction path calculations, density functional theory (B3LYP/TZVP) is used to describe the QM region consisting of the substrate (cyclohexanone), the isoalloxazine ring of C4a-peroxyflavin, the side chain of Arg-329, and the nicotinamide ring and the adjacent ribose of NADP^+ , while the remainder of the enzyme is represented by the CHARMM force field.

Enzyme Catalysis (Cont'd)

Potential Human Cholesterol Esterase Inhibitor Design: Benefits from the Molecular Dynamics Simulations and Pharmacophore Modeling Studies

Shalini John, Sundarapandian Thangapandian, Keun Woo Lee [Gyeongsang National University]

J. Biomol. Stru. and Dyn., **29**, 921-936, 2012.

Human pancreatic cholesterol esterase (hCEase) is one of the lipases found to involve in the digestion of large and broad spectrum of substrates including triglycerides, phospholipids, cholesteryl esters, etc. The presence of bile salts is found to be very important for the activation of hCEase. Molecular dynamic simulations were performed for the apoform and bile salt complexed form of hCEase using the co-ordinates of two bile salts from bovine CEase. The stability of the systems throughout the simulation time was checked and two representative structures from the highly populated regions were selected using cluster analysis.

A Negative Cooperativity Mechanism of Human CYP2E1 Inferred from Molecular Dynamics Simulations and Free Energy Calculations

Jue Li, Dong-Qing Wei [Shanghai Jiao Tong University], Jing-Fang Wang, and Yi-Xue Li

J.Chem. Infor. and Mod. **51**, 3217–3225, 2011.

Human cytochrome P450 2E1 (CYP2E1) participates in the metabolism of over 2% of all the oral drugs. A hallmark peculiar feature of this enzyme is that it exhibits a pronounced negative cooperativity in substrate binding. However the mechanism by which the negative cooperativity occurs is unclear. Here, we performed molecular dynamics simulations and free energy calculations on human CYP2E1 to examine the structural differences between the substrate-free and the enzymes with one and two aniline molecules bound.

Ligand-induced formation of transient dimers of mammalian 12/15-lipoxygenase: A key to allosteric behavior of this class of enzymes?

Igor Ivanov [Charité-Universitätsmedizin Berlin], Weifeng Shang, Lea Toledo, Laura Masgrau, Dmitri I. Svergun, Sabine Stehling, Hansel Gómez, Almerinda Di Venere, Giampiero Mei, José M. Lluch, Ewa Skrzypczak-Jankun, Angels González-Lafont and Hartmut Kühn

Proteins: Stru. Fun. & Bioinf. **80**, 703–712, 2012.

Mammalian lipoxygenases (LOXs) have been implicated in cellular defense response and are important for physiological homeostasis. Because the allosteric character of the enzyme can hardly be explained using a single ligand binding-site model, we proposed that the binding of allosteric effectors may shift the monomer–dimer equilibrium toward dimer formation. To test this hypothesis, we explored the impact of an allosteric effector [13(S)-hydroxyoctadeca-9(Z),11(E)-dienoic acid] on the structural properties of rabbit 12/15-LOX by small-angle X-ray scattering. Our data indicate that the enzyme undergoes ligand-induced dimerization in aqueous solution, and molecular dynamics simulations suggested that LOX dimers may be stable in the presence of substrate fatty acids.

Protein-Protein Interactions

Virtual screening for compounds that mimic protein–protein interface epitopes

Tim Geppert, Felix Reisen, Max Pillong, Volker Hähnke, Yusuf Tanrikulu, Christian P. Koch, Anna Maria Perna, Tatiana Batista Perez, Petra Schneider and Gisbert Schneider [Swiss Federal Institute of Technology]

J. Comp. Chem. **33**, 573–579, 2012.

Modulation of protein–protein interactions (PPI) has emerged as a new concept in rational drug design. Here, we present a computational protocol for identifying potential PPI inhibitors. Relevant regions of interfaces (epitopes) are predicted for three-dimensional protein models and serve as queries for virtual compound screening. We present a computational screening protocol that incorporates two different pharmacophore models. One model is based on the mathematical concept of autocorrelation vectors and the other utilizes fuzzy labeled graphs.

Protein–Protein Binding Sites Prediction by 3D Structural Similarities

Fei Guo, Shuai Cheng Li, and Lusheng Wang [City University of Hong Kong]

J.Chem. Infor. and Mod. **51**, 3287–3294, 2011.

Identifying the location of binding sites on proteins is of fundamental importance for a wide range of applications including molecular docking, de novo drug design, structure identification, and comparison of functional sites. In this paper, we develop an efficient approach for finding binding sites between proteins. Our approach consists of four steps: local sequence alignment, protein surface detection, 3D structure comparison, and candidate binding site selection.

Hot Spots and Transient Pockets: Predicting the Determinants of Small-Molecule Binding to a Protein–Protein Interface

Alexander Metz, Christopher Pfleger, Hannes Kopitz, Stefania Pfeiffer-Marek, Karl-Heinz Baringhaus, and Holger Gohlke [Heinrich-Heine-University]

J.Chem. Infor. and Mod. **52**, 120–133, 2012.

Protein–protein interfaces are considered difficult targets for small-molecule protein–protein interaction modulators (PPIMs). Here, we present for the first time a computational strategy that simultaneously considers aspects of energetics and plasticity in the context of PPIM binding to a protein interface. The strategy aims at identifying the determinants of small-molecule binding, hot spots, and transient pockets, in a protein–protein interface in order to make use of this knowledge for predicting binding modes of and ranking PPIMs with respect to their affinity. When applied to interleukin-2 (IL-2), the computationally inexpensive constrained geometric simulation method FRODA outperforms molecular dynamics simulations in sampling hydrophobic transient pockets.

Temperature-dependent study reveals that dynamics of hydrophobic residues plays an important functional role in the mitochondrial Tim9–Tim10 complex

Ekaterina Ivanova, Jiayun Pang, Thomas A. Jowitt, Guanhua Yan, Jim Warwicker, Michael J. Sutcliffe and Hui Lu [University of Manchester]

Proteins: Stru. Fun. & Bioinf., **80**, 602–615, 2012.

Protein–protein interaction is a fundamental process in all major biological processes. The hexameric Tim9–Tim10 (translocase of inner membrane) complex of the mitochondrial intermembrane space plays an essential chaperone-like role during import of mitochondrial membrane proteins. This study investigates how electrostatic and hydrophobic interactions affect the conformation and function of the complex at physiological temperatures, using both experimental and computational methods.

Membrane Proteins and Lipid Peptide Interactions

Predicting Three-Dimensional Structures of Transmembrane Domains of β -Barrel Membrane Proteins

Hammad Naveed, Yun Xu, Ronald Jackups, Jr., and Jie Liang
[University of Illinois at Chicago]

J. Am. Chem. Soc., **134**, 1775–1781, 2012.

β -Barrel membrane proteins are found in the outer membrane of gram-negative bacteria, mitochondria, and chloroplasts. They are important for pore formation, membrane anchoring, and enzyme activity. These proteins are also often responsible for bacterial virulence. We have developed a computational method for predicting structures of the transmembrane (TM) domains of β -barrel membrane proteins. Based on physical principles, our method can predict structures of the TM domain of β -barrel membrane proteins of novel topology, including those from eukaryotic mitochondria.

α -Synuclein Induces Both Positive Mean Curvature and Negative Gaussian Curvature in Membranes

Anthony R. Braun, Eva Sevcsik, Pamela Chin, Elizabeth Rhoades, Stephanie Tristram-Nagle, and Jonathan N. Sachs
[University of Minnesota]

J. Am. Chem. Soc., **134**, 453–463, 2012.

Using a combination of X-ray scattering, fluorescence correlation spectroscopy, coarse-grained molecular dynamics (MD) simulations and potential of mean force calculations, we have explored the membrane remodeling effects of monomeric α -synuclein (α S). Our initial findings from multiple approaches are that α S (1) causes a significant thinning of the bilayer and (2) stabilizes positive mean curvature, such that the maximum principle curvature matches that of synaptic vesicles, α S-induced tubules, and the synthetic lipid vesicles to which the protein binds most tightly. This suggests that α S binding to synaptic vesicles likely stabilizes their intrinsic curvature.

Statistical Potential for Modeling and Ranking of Protein–Ligand Interactions

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J. Chem. Infor. and Mod. **51**, 3078–3092, 2011.

Applications in structural biology and medicinal chemistry require protein–ligand scoring functions for two distinct tasks: (i) ranking different poses of a small molecule in a protein binding site and (ii) ranking different small molecules by their complementarity to a protein site. Using probability theory, we developed two atomic distance-dependent statistical scoring functions: PoseScore was optimized for recognizing native binding geometries of ligands from other poses and RankScore was optimized for distinguishing ligands from nonbinding molecules.

Scattering Density Profile Model of POPG Bilayers As Determined by Molecular Dynamics Simulations and Small-Angle Neutron and X-ray Scattering Experiments

Norbert Kučerka [Canadian Neutron Beam Centre], Bryan W. Holland, Chris G. Gray, Bruno Tomberli, and John Katsaras

J. Phys. Chem. B., **116**, 232–239, 2012.

We combine molecular dynamics (MD) simulations and experiment, both small-angle neutron (SANS) and small-angle X-ray scattering (SAXS), to determine the precise structure of bilayers composed of 1-palmitoyl-2-oleoyl-sn-glycero-3-phosphatidylglycerol (POPG), a lipid commonly encountered in bacterial membranes. Experiment and simulation are used to develop a one-dimensional scattering density profile (SDP) model suitable for the analysis of experimental data. The joint refinement of such data (i.e., SANS and SAXS) results in the area per lipid that is then used in the fixed-area simulations.

Membrane Proteins and Lipid Peptide Interactions (Cont'd)

Molecular Dynamics Simulations of Membranes Composed of Glycolipids and Phospholipids

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J. Phys. Chem. B., **116**, 244–252, 2012.

Lipid membranes composed of 1,2-di-(9Z,12Z,15Z)-octadecatrienoyl-3-O- β -D-galactosyl-sn-glycerol or monogalactosyldiacylglycerol (MGDG) and 1,2-dimyristoyl-sn-glycero-3-phosphocholine (DMPC) were studied by means of molecular dynamics (MD) computer simulations. Three lipid compositions were considered: 0%, 20%, and 45% MGDG (by mole) denoted as MG-0, MG-20, and MG-45, respectively. The article is focused on the calculation of NMR dipolar interactions, which were confronted with previously reported experimental couplings.

Cationic Dimyristoylphosphatidylcholine and Dioleoyltrimethylammonium Propane Lipid Bilayers: Atomistic Insight for Structure and Dynamics

Wei Zhao, Andrey A. Gurtovenko, Ilpo Vattulainen, and Mikko Karttunen [University of Waterloo]

J. Phys. Chem. B., **116**, 269–276, 2012.

We performed atomistic molecular dynamics simulations of lipid bilayers consisting of a mixture of cationic dioleoyltrimethylammonium propane (DOTAP) and zwitterionic dimyristoylphosphatidylcholine (DMPC) lipids at different DOTAP fractions. Our primary focus was the specific effects of unsaturated lipid chains on structural and dynamic properties of mixed cationic bilayers. The bilayer area, as well as the ordering of lipid tails, shows a pronounced nonmonotonic behavior when TAP lipid fraction increases.

Destabilization of Lipid Membranes by a Peptide Derived from Glycoprotein gp36 of Feline Immunodeficiency Virus: A Combined Molecular Dynamics/Experimental Study

Antonello Merlino, Giuseppe Vitiello, Manuela Grimaldi, Filomena Sica, Elena Busi, Riccardo Basosi, Anna Maria D'Ursi, Giovanna Fragneto, Luigi Paduano, and Gerardino D'Errico [University of Naples "Federico II"]

J. Phys. Chem. B., **116**, 401–412, 2012.

Viral fusion glycoproteins present a membrane-proximal external region (MPER) which is usually rich in aromatic residues and exhibits a marked tendency to stably reside at the membrane interfaces, leading, through unknown mechanisms, to a destabilization of the bilayer structure. This step has been proposed to be fundamental for the fusion process between target membrane and viral envelope. In the present work, we investigate the interaction between an octapeptide (C8) deriving from the MPER domain of gp36 of feline immunodeficiency virus and POPC bilayers by combining experimental results obtained by neutron reflectivity, electron spin resonance, circular dichroism, and fluorescence spectroscopy with molecular dynamics simulations.

Molecular Dynamics Simulation Study of the Effect of DMSO on Structural and Permeation Properties of DMPC Lipid Bilayers

Jieqiong Lin, Brian Novak, and Dorel Moldovan [Louisiana State University]

J. Phys. Chem. B., **116**, 1299–1308, 2012.

We present molecular dynamics simulations of dimyristoylphosphatidylcholine (DMPC) lipid bilayers in the presence of dimethyl sulfoxide (DMSO). The MD simulations focus on understanding the effect of 3 mol % DMSO on structural and permeation properties of DMPC bilayers. The potential of mean force (PMF) and the diffusivity profiles along the normal direction to the bilayer were calculated for water and DMSO molecules in systems containing 0 and 3 mol % DMSO.

Membrane Proteins and Lipid Peptide Interactions (Cont'd)

Positioning of Antioxidant Quercetin and Its Metabolites in Lipid Bilayer Membranes: Implication for Their Lipid-Peroxidation Inhibition

Pavlna Košinová, Karel Berka, Michael Wykes, Michal Otyepka, and Patrick Trouillas [Université de Limoges]

J. Phys. Chem. B., **116**, 1309–1318, 2012.

Among numerous biological activities, natural polyphenols are antioxidants widely distributed in plants capable of inhibiting lipid peroxidation, which belongs to the most serious degenerative cell processes. Positioning of antioxidants in lipid bilayers can provide an insight to the lipid-peroxidation inhibition at the molecular level. This work aims at determining the location and orientation of quercetin and its most representative (glucuronidated, methylated, and sulfated) metabolites in lipid bilayer via molecular dynamic simulations.

Understanding the Phase Behavior of Coarse-Grained Model Lipid Bilayers through Computational Calorimetry

Jocelyn M. Rodgers [Lawrence Berkeley National Laboratory], Jesper Sørensen, Frédérick J.-M. de Meyer, Birgit Schiøtt, and Berend Smit

J. Phys. Chem. B., **116**, 1551–1569, 2012.

We study the phase behavior of saturated lipids as a function of temperature and tail length for two coarse-grained models: the soft-repulsive model typically employed with dissipative particle dynamics (DPD) and the MARTINI model. We characterize the simulated transitions through changes in structural properties, and we introduce a computational method to monitor changes in enthalpy, as is done experimentally with differential scanning calorimetry. The lipid system experimentally presents four different bilayer phases — subgel, gel, ripple, and fluid — and the DPD model describes all of these phases structurally while MARTINI describes a single order–disorder transition between the gel and the fluid phases.

Protein Folding

50 Years of Lifson–Roig Models: Application to Molecular Simulation Data

Andreas Vitalis [University of Zurich] and Amedeo Caflisch

J. Chem. Theor. and Comp., **8**, 363–373, 2012.

Simple helix–coil transition theories have been indispensable tools in the analysis of data reporting on the reversible folding of α -helical polypeptides. They provide a transferable means to not only characterize different systems but to also compare different techniques, viz., experimental probes monitoring helix–coil transitions in vitro or biomolecular force fields in silico. This article addresses several issues with the application of Lifson–Roig theory to helix–coil transition data. We use computer simulation to generate two sets of ensembles for the temperature-controlled, reversible folding of the 21-residue, alanine-rich FS peptide.

Protein Folding (Cont'd)

How Hydrophobicity and the Glycosylation Site of Glycans Affect Protein Folding and Stability: A Molecular Dynamics Simulation

Diannan Lu, Cheng Yang, and Zheng Liu [Tsinghua University]

J. Phys. Chem. B., **116**, 390–400, 2012.

Glycosylation is one of the most common post-translational modifications in the biosynthesis of protein, but its effect on the protein conformational transitions underpinning folding and stabilization is poorly understood. In this study, we present a coarse-grained off-lattice 46- β barrel model protein glycosylated by glycans with different hydrophobicity and glycosylation sites to examine the effect of glycans on protein folding and stabilization using a Langevin dynamics simulation, in which an H term was proposed as the index of the hydrophobicity of glycan. Compared with its native counterpart, introducing glycans of suitable hydrophobicity ($0.1 < H < 0.4$) at flexible peptide residues of this model protein not only facilitated folding of the protein but also increased its conformation stability significantly.

Kinetic consequences of native state optimization of surface-exposed electrostatic interactions in the Fyn SH3 domain

Arash Zarrine-Afsar, Zhuqing Zhang, Katrina L. Schweiker, George I. Makhataдзе, Alan R. Davidson [University of Toronto] and Hue Sun Chan

Proteins: Stru. Fun. & Bioinf. **80**, 858–870, 2012.

Optimization of surface exposed charge–charge interactions in the native state has emerged as an effective means to enhance protein stability; but the effect of electrostatic interactions on the kinetics of protein folding is not well understood. To investigate the kinetic consequences of surface charge optimization, we characterized the folding kinetics of a Fyn SH3 domain variant containing five amino acid substitutions that was computationally designed to optimize surface charge–charge interactions. Our results demonstrate that this optimized Fyn SH3 domain is stabilized primarily through an eight-fold acceleration in the folding rate.

Protein-Nucleic acid Interactions

Dynamic and Structural Changes in the Minimally Restructuring EcoRI Bound to a Minimally Mutated DNA Chain

Vigneshwar Ramakrishnan [National University of Singapore], Srivatsan Jagannathan, Abdul Rajjak Shaikh, Raj Rajagopalan

J. Biomol. Stru. and Dyn., **29**, 743–756, 2012.

The dynamics of a protein plays an important role in protein functionality. Here, we examine the differences in the dynamics of a minimally restructuring protein, EcoRI, when it is bound to its cognate DNA and to a noncognate sequence which differs by just a single basepair. Molecular dynamics simulations of the complexes and essential dynamics analyses reveal that the overall dynamics of the protein subunits change from a coordinated motion in the cognate complex to a scrambled motion in the noncognate complex. This dynamical difference extends to the protein-DNA interface where EcoRI tries to constrict the DNA in the cognate complex.

Molecular Dynamics of Anthraquinone DNA Intercalators with Polyethylene Glycol Side Chains

Shirlene Jackson Beckford, Dabney W. Dixon [Georgia State University]

J. Biomol. Stru. and Dyn., **29**, 1065-1080, 2012.

The interactions of a homologous series of four anthraquinone (AQ) intercalators with increasing lengths of polyethylene glycol (PEG) side chains with DNA have been studied via molecular dynamics (MD) simulations. The geometry, conformation, interactions, and hydration of the complexes were examined. The geometries of the four ligands were similar with parallel stacking to the long axis of the adjacent DNA base pairs. Hydrogen bonding between the AQ amide and DNA led to a preference for the trans-syn conformer.

Molecular mechanism of HIV-1 integrase-vDNA interactions and strand transfer inhibitor action: A molecular modeling perspective

Weiwei Xue, Huanxiang Liu and Xiaojun Yao [Lanzhou University]

J. Comp. Chem. **33**, 527–536, 2012.

Human immunodeficiency virus type 1 (HIV-1) integrase (IN) is an essential enzyme for splicing a viral DNA (vDNA) replica of its genome into host cell chromosomal DNA (hDNA) and has been recently recognized as a promising therapeutic target for developing anti-AIDS agents. In the present work, a molecular modeling study by combining homology modeling, molecular dynamics (MD) simulations with molecular mechanics Poisson–Boltzmann surface area (MM-PBSA), and molecular mechanics Generalized-Born surface area (MM-GBSA) calculations was performed to investigate the molecular mechanism of HIV-1 IN–vDNA interactions and the inhibition action of vDNA strand transfer inhibitor (INSTI) RAL.

Nucleic Acids

Insights into Intrastrand Cross-Link Lesions of DNA from QM/MM Molecular Dynamics Simulations

Julian Garrec, Chandan Patel, Ursula Rothlisberger, and Elise Dumont [Université de Lyon]

J. Am. Chem. Soc., **134**, 2111–2119, 2012.

DNA damages induced by oxidative intrastrand cross-links have been the subject of intense research during the past decade. Yet, the currently available experimental protocols used to isolate such lesions only allow to get structural information about linked dinucleotides. In this study we generated in silico the most frequent oxidative intrastrand cross-link adduct, G[8,5-Me]T, embedded in a solvated DNA dodecamer by means of quantum mechanics/molecular mechanics (QM/MM) Car–Parrinello simulations.

Molecular electrostatic potentials of DNA base–base pairing and mispairing

Ivonne Otero-Navas and Jorge M. Seminario [Texas A&M University]

J. Mol.Mod., **18**, 91-101, 2012.

An understanding of why adenine (A) pairs with thymine (T) and cytosine (C) with guanine (G) in DNA is very useful in the design of sensors and other related devices. We report the use of dissociation energies, geometries and molecular electrostatic potentials (MEPs) to justify the canonical (AT and CG) Watson-Crick pairs. We also analyze all mismatches in both configurations—cis and trans—with respect to their glycoside bonds. As expected, we found that the most stable pair configuration corresponds to CG, providing an energy criterion for that preferred configuration.

Nucleic Acids (Cont'd)

Constant pH Molecular Dynamics Simulations of Nucleic Acids in Explicit Solvent

Garrett B. Goh, Jennifer L. Knight, and Charles L. Brooks [University of Michigan]

J. Chem. Theor. and Comp., **8**, 36–46, 2012.

The nucleosides of adenine and cytosine have pK_a values of 3.50 and 4.08, respectively, and are assumed to be unprotonated under physiological conditions. However, evidence from recent NMR and X-ray crystallography studies has revealed the prevalence of protonated adenine and cytosine in RNA macromolecules. With the work presented here, we establish the framework and demonstrate the first constant pH MD simulations (CPHMD) for nucleic acids in explicit solvent, in which the protonation state is coupled to the dynamical evolution of the RNA system via λ -dynamics.

Understanding the Sequence Preference of Recurrent RNA Building Blocks Using Quantum Chemistry: The Intrastrand RNA Dinucleotide Platform

Arnošt Mládek [Academy of Sciences of the Czech Republic], Judit E. Šponer, Petr Kulhánek, Xiang-Jun Lu, Wilma K. Olson, and Jiří Šponer

J. Chem. Theor. and Comp., **8**, 6–16, 2012.

Folded RNA molecules are shaped by an astonishing variety of highly conserved noncanonical molecular interactions and backbone topologies. The dinucleotide platform is a widespread recurrent RNA modular building submotif formed by the side-by-side pairing of bases from two consecutive nucleotides within a single strand, with highly specific sequence preferences. The present study investigates the gas-phase intrinsic stabilities of the three most common RNA dinucleotide platforms—5'-GpU-3', ApA, and UpC—via state-of-the-art quantum-chemical (QM) techniques.

Surfaces, Catalysts, and Materials Subjects

Structure–Behavior–Property Relationship Study of Surfactants as Foam Stabilizers Explored by Experimental and Molecular Simulation Approaches

Xiaoying Hu [Shandong University], Ying Li, Xiujuan He, Chunxiu Li, Zhengquan Li, Xulong Cao, Xia Xin, and P. Somasundaran

J. Phys. Chem. B., **116**, 160–167, 2012.

A multiscale stability study of foams stabilized by sodium dodecyl sulfate (SDS), sodium dodecylbenzene sulfonate (SDBS), and sodium polyoxyethylene alkylether sulfate (AES) was conducted, to investigate the relationship of surfactant molecular behavior and interfacial monolayer configuration of foam film to the foam film properties. Molecular dynamic (MD) simulations using a full-atom model was utilized to explore the microscopic features of the air/liquid interface layer. Several parameters such as the distribution of surfactant head groups and the order degree of surfactant hydrophobic tails were used to describe the molecular adsorption behavior.

Use of a Short Peptide as a Building Block in the Layer-by-Layer Assembly of Biomolecules on Polymeric Surfaces

Dewi P. Go, Andrew Hung, Sally L. Gras [University of Melbourne], and Andrea J. O'Connor

J. Phys. Chem. B., **116**, 1120–1133, 2012.

The incorporation of low molecular weight drugs and therapeutic peptides into multilayer films assembled via the layer-by-layer technique can potentially provide means to deliver small molecules to target sites. This study describes the use of both hydrophobic and electrostatic interactions to incorporate a tridecapeptide antiinflammatory hormone, α -melanocyte stimulating hormone (α -MSH), as a building block at the base of a multilayer assembly of hyaluronic acid and chitosan (CS) on poly(lactic-co-glycolic acid) (PLGA) surfaces.

2. METHODOLOGY

Quantitative Structure-Activity Relations

Design of Novel FLT-3 Inhibitors Based on Dual-Layer 3D-QSAR Model and Fragment-Based Compounds in Silico

Kuei-Chung Shih, Chun-Yuan Lin, Hsiao-Chieh Chi, Chrong-Shiong Hwang, Ting-Shou Chen, Chuan-Yi Tang [National Tsing Hua University], and Nai-Wan Hsiao

J.Chem. Infor. and Mod. **52**, 146–155, 2012.

FMS-like tyrosine kinase 3 (FLT-3) is strongly correlated with acute myeloid leukemia, but no FLT-3-inhibitor cocomplex structure is available to assist the design of therapeutic inhibitors. Hence, we propose a dual-layer 3D-QSAR model for FLT-3 that integrates the pharmacophore, CoMFA, and CoMSIA. We then coupled the model with the fragment-based design strategy to identify novel FLT-3 inhibitors. In the first layer, the previously established model, Hypo02, was evaluated in terms of its correlation coefficient (*r*), RMS, cost difference, and configuration cost, with values of 0.930, 1.24, 106.45, and 16.44, respectively.

Potentials and Parameters

Parameterization of PACE Force Field for Membrane Environment and Simulation of Helical Peptides and Helix–Helix Association

Cheuk-Kin Wan [The Hong Kong University of Science and Technology], Wei Han, and Yun-Dong Wu

J. Chem. Theor. and Comp. **8**, 300–313, 2012.

The recently developed PACE force field was further parametrized so that it can be applied to the studies of membrane systems. Parameters for the interactions between united-atom protein particles and lipid hydrophobic tails were developed by reproducing the solvation free energies of small organic molecules in hexadecane. Interactions between protein particles and lipid heads were parametrized by fitting the potential of mean force of the corresponding all-atom simulation. The force field was applied to the study of five helical peptides in membrane environments.

Molecular Dynamics

Tracing Cytoplasmic Ca²⁺ Ion and Water Access Points in the Ca²⁺-ATPase

Maria Musgaard, Lea Thøgersen, Birgit Schiøtt [Aarhus University], Emad Tajkhorshid

Biophysical Journal. **102**, 268–277, 2012.

Sarco(endo)plasmic reticulum Ca²⁺-ATPase (SERCA) transports two Ca²⁺ ions across the membrane of the sarco(endo)plasmic reticulum against the concentration gradient, harvesting the required energy by hydrolyzing one ATP molecule during each transport cycle. Although SERCA is one of the best structurally characterized membrane transporters, it is still largely unknown how the transported Ca²⁺ ions reach their transmembrane binding sites in SERCA from the cytoplasmic side. Here, we performed extended all-atom molecular dynamics simulations of SERCA.

Molecular Dynamics (Cont'd)

Insights into the Mechanism of Proton Transport in Cytochrome c Oxidase

Takefumi Yamashita and Gregory A. Voth [University of Chicago]

J. Am. Chem. Soc., **134**, 1147–1152, 2012.

Cytochrome c oxidase (CcO), known as complex IV of the electron transport chain, plays several important roles in aerobic cellular respiration. Electrons transferred from cytochrome c to CcO's catalytic site reduce molecular oxygen and produce a water molecule. In this work, it is shown why the reduction of heme a is essential for proton pumping. This is demonstrated via novel reactive molecular dynamics (MD) simulations that can describe the Grotthuss shuttling associated with the PT as well as the dynamic delocalization of the excess proton electronic charge defect.

Thermodynamics and kinetics of large-time-step molecular dynamics

Francesco Rao [Freiburg Institute for Advanced Studies] and Martin Spichty

J. Comp. Chem. **33**, 475–483, 2012.

Molecular dynamics (MD) simulations provide essential information about the thermodynamics and kinetics of proteins. Technological advances in both hardware and algorithms have seen this method accessing timescales that used to be unreachable only few years ago. The quest to simulate slow, biologically relevant macromolecular conformational changes, is still open. Here, we present an approximate approach to increase the speed of MD simulations by a factor of ~4.5.

Overcoming the Barrier on Time Step Size in Multiscale Molecular Dynamics Simulation of Molecular Liquids

Igor P. Omelyan and Andriy Kovalenko [University of Alberta]

J. Chem. Theor. and Comp. **8**, 6–16, 2012.

We propose and validate a new multiscale technique, the extrapolative isokinetic Nosé–Hoover chain orientational (EINO) motion multiple time step algorithm for rigid interaction site models of molecular liquids. It nontrivially combines the multiple time step decomposition operator method with a specific extrapolation of intermolecular interactions, complemented by an extended isokinetic Nosé–Hoover chain approach in the presence of translational and orientational degrees of freedom. The EINO algorithm obviates the limitations on time step size in molecular dynamics simulations.

Protecting High Energy Barriers: A New Equation to Regulate Boost Energy in Accelerated Molecular Dynamics Simulations

William Sinko [University of California San Diego], César Augusto F. de Oliveira, Levi C. T. Pierce, and J. Andrew McCammon

J. Chem. Theor. and Comp. **8**, 17–23, 2012.

Molecular dynamics (MD) is one of the most common tools in computational chemistry. Recently, our group has employed accelerated molecular dynamics (aMD) to improve the conformational sampling over conventional molecular dynamics techniques. In the original aMD implementation, sampling is greatly improved by raising energy wells below a predefined energy level. Recently, our group presented an alternative aMD implementation where simulations are accelerated by lowering energy barriers of the potential energy surface. When coupled with thermodynamic integration simulations, this implementation showed very promising results.

Molecular Dynamics (Cont'd)

Improving Sampling by Exchanging Hamiltonians with Efficiently Configured Nonequilibrium Simulations

Robert M. Dirks, Huafeng Xu, and David E. Shaw [D. E. Shaw Research]

J. Chem. Theor. and Comp. **8**, 6–16, 2012.

Molecular simulations aim to sample all of the thermodynamically important states; when the sampling is inadequate, inaccuracy follows. A widely used technique to enhance sampling in simulations is Hamiltonian exchange. This technique introduces auxiliary Hamiltonians under which sampling is computationally efficient and attempts to exchange the molecular states among the auxiliary and the original Hamiltonians. We show that properly configured nonequilibrium simulations can modestly increase the overall efficiency of Hamiltonian exchange.

Molecular Dynamics Simulations of a Hyperthermophilic and a Mesophilic Protein L30e

Kuei-Jen Lee [Asia University, Taichung]

J. Chem. Infor. and Mod. **52**, 7–15, 2012.

Molecular dynamics (MD) simulations were used to study the hyperthermophilic ribosomal protein L30e from archaeon *Thermococcus celer* at 300 and 350 K, and its mesophilic homologue, yeast L30e, at 300 K in explicit solvent for a period of 5.0 ns. Three trajectories obtained from the MD simulations were stable throughout the simulation period, such as total potential energy, radius of gyration, root-mean-square deviation, and secondary structures assignment. At 300 K, *T. celer* L30e is less flexible than its mesophilic homologue, and this difference becomes more pronounced at 350 K. Salt bridge networks, one triad and one hexad, are present at the surface of *T. celer* L30e.

QM and QM/MM

On the effect of a variation of the force field, spatial boundary condition and size of the QM region in QM/MM MD simulations

Katharina Meier, Walter Thiel and Wilfred F. van Gunsteren [Swiss Federal Institute of Technology Zürich]

J. Comp. Chem. **33**, 363–378, 2012.

During the past years, the use of combined quantum–classical, QM/MM, methods for the study of complex biomolecular processes, such as enzymatic reactions and photocycles, has increased considerably. The quality of the results obtained from QM/MM calculations is largely dependent on five aspects to be considered when setting up a molecular model: the QM Hamiltonian, the MM Hamiltonian or force field, the boundary and coupling between the QM and MM regions, the size of the QM region and the boundary condition for the MM region. In this study, we systematically investigate the influence of a variation of the molecular mechanics force field and the size of the QM region in QM/MM MD simulations on properties of the photoactive part of the blue light photoreceptor protein AppA.

QM and QM/MM (Cont'd)

Understanding cross-boundary events in ONIOM QM:QM' calculations

Marcus Lundberg [Kyoto University]

J. Comp. Chem. **33**, 406–415, 2012.

QM:QM' models, where QM' is a fast molecular orbital method, offers advantages over standard quantum mechanics: molecular mechanics (QM:MM) models, especially in the description of charge transfer and mutual polarization between layers. The ONIOM QM:QM' scheme also allows for reactions across the layer boundary, but the understanding of these events is limited. To explain the factors that affect cross-boundary events, a set of proton transfer processes, including the acylation reaction in serine protease, have been investigated.

Bathochromic Shift in Green Fluorescent Protein: A Puzzle for QM/MM Approaches

Claudia Filippi [University of Twente], Francesco Buda, Leonardo Guidoni, and Adalgisa Sinicropi

J. Chem. Theor. and Comp. **8**, 112–124, 2012.

We present an extensive investigation of the vertical excitations of the anionic and neutral forms of wild-type green fluorescent protein using time-dependent density functional theory (TDDFT), multiconfigurational perturbation theory (CASPT2), and quantum Monte Carlo (QMC) methods within a quantum mechanics/molecular mechanics (QM/MM) scheme. The protein models are constructed via room-temperature QM/MM molecular dynamics simulations based on DFT and are representative of an average configuration of the chromophore–protein complex.

QM/MM Reweighting Free Energy SCF for Geometry Optimization on Extensive Free Energy Surface of Enzymatic Reaction

Takahiro Kosugi and Shigehiko Hayashi [Kyoto University]

J. Chem. Theor. and Comp. **8**, 322–334, 2012.

We developed a QM/MM free energy geometry optimization method by which the geometry of a quantum chemically treated (QM) molecule is optimized on a free energy surface defined with thermal distribution of the surrounding molecular environment obtained by molecular dynamics simulation with a molecular mechanics (MM) force field. The method called QM/MM reweighting free energy self-consistent field combines a mean field theory of QM/MM free energy geometry optimization developed by Yamamoto with a reweighting scheme for updating the MM distribution introduced by Hu et al. and features high computational efficiency suitable for exploring the reaction free energy surface of extensive protein conformational space.

Computational Studies of Bacterial Resistance to β -Lactam Antibiotics: Mechanism of Covalent Inhibition of the Penicillin-Binding Protein 2a (PBP2a)

Nguyen Hoa My, Hajime Hirao [Nanyang Technological University], Dang Ung Van, and Keiji Morokuma

J. Chem. Infor. and Mod. **51**, 3226–3234, 2011.

β -Lactam resistance of methicillin-resistant *Staphylococcus aureus* (MRSA), a pathogenic bacterium that causes staph infections, represents a serious threat to public health. To gain fundamental insights into the mode of covalent inhibition of the enzyme, we have carried out computational studies of the acylation reactions between small β -lactam molecules (methicillin and nitrocefin) and PBP2a using the B3LYP/6-31G* and ONIOM(B3LYP/6-31G*:AMBER) hybrid quantum mechanical/molecular mechanical methods.

QM and QM/MM (Cont'd)

Assessment of Weak Intermolecular Interactions Across QM/MM Noncovalent Boundaries

Sadhana Kumbhar, Frank D. Fischer, and Mark P. Waller
[Organisch-Chemisches Institut der Universität Münster]

J.Chem. Infor. and Mod. **52**, 93–98, 2012.

An assessment of a number of quantum mechanical/molecular mechanical (QM/MM) combinations was performed for weak intermolecular interactions across noncovalent QM/MM ‘boundaries’. The popular S22 data set, comprising of a number of weak hydrogen-bonded, dispersion-bound and complexes with mixed interactions was used for the assessment. A range of QM methods was combined with a number of popular MM force fields. The single-point interaction energies, at reference geometries, are presented as deviations to accurate CCSD(T)/CBS reference values.

Direct Hydride Shift Mechanism and Stereoselectivity of P450_{nor} Confirmed by QM/MM Calculations

Balázs Krámos, Dóra K. Menyhárd, and Julianna Oláh
[Budapest University of Technology and Economics]

J. Phys. Chem. B., **116**, 872–885, 2012.

Nitric oxide reductase (P450_{nor}) found in *Fusarium oxysporum* catalyzes the reduction of nitric oxide to N₂O in a multistep process. The reducing agent, NADH, is bound in the distal pocket of the enzyme, and direct hydride transfer occurs from NADH to the nitric oxide bound heme enzyme, forming intermediate I. Here we studied the possibility of hydride transfer from NADH to both the nitrogen and oxygen of the heme-bound nitric oxide, using quantum chemical and combined quantum mechanics/molecular mechanics (QM/MM) calculations, on two different protein models, representing both possible stereochemistries, a syn- and an anti-NADH arrangement.

Aqueous Solvation of Polyalanine α -Helices with Specific Water Molecules and with the CPCM and SM5.2 Aqueous Continuum Models Using Density Functional Theory

Mateusz Marianski and J. J. Dannenberg [City University of New York–Hunter College]

J. Phys. Chem. B., **116**, 1437–1445, 2012.

We present density functional theory (DFT) calculations at the X3LYP/D95(d,p) level on the solvation of polyalanine α -helices in water. The study includes the effects of discrete water molecules and the CPCM and AMSOL SM5.2 solvent continuum model both separately and in combination. We find that individual water molecules cooperatively hydrogen-bond to both the C- and N-termini of the helix, which results in increases in the dipole moment of the helix/water complex to more than the vector sum of their individual dipole moments.

Comparative or Homology Modeling

Two-Component Coarse-Grained Molecular-Dynamics Model for the Human Erythrocyte Membrane

He Li, George Lykotrafitis [University of Connecticut]

Biophysical Journal. **102**, 75–84, 2012.

We present a two-component coarse-grained molecular-dynamics model for simulating the erythrocyte membrane. The proposed model possesses the key feature of combining the lipid bilayer and the erythrocyte cytoskeleton, thus showing both the fluidic behavior of the lipid bilayer and the elastic properties of the erythrocyte cytoskeleton. In this model, three types of coarse-grained particles are introduced to represent clusters of lipid molecules, actin junctions, and band-3 complexes, respectively.

Comparative or Homology Modeling (Cont'd)

Coarse-Grained Modeling of Mucus Barrier Properties

Pawel Gniewek, Andrzej Kolinski [University of Warsaw]

Biophysical Journal. **102**, 195-200, 2012.

We designed a simple coarse-grained model of the glycocalyx layer, or adhesive mucus layer (AML), covered by mucus gel (luminal mucus layer) using a polymer lattice model and stochastic sampling (replica exchange Monte Carlo) for canonical ensemble simulations. We assumed that mucin MUC16 is responsible for the structural properties of the AML. Other mucins that are much smaller in size and less relevant for layer structure formation were not included.

Homology modeling, molecular dynamics, e-pharmacophore mapping and docking study of Chikungunya virus nsP2 protease

Kh. Dhanachandra Singh, Palani Kirubakaran, Shanthi Nagarajan, Sugunadevi Sakthiah and Karthikeyan Muthusamy, Jeyaraman Jeyakanthan [Alagappa University], et al.

J. Mol.Mod., **18**, 39-51, 2012.

To date, no suitable vaccine or specific antiviral drug is available to treat Chikungunya viral (CHIKV) fever. Hence, it is essential to identify drug candidates that could potentially impede CHIKV infection. Here, we present the development of a homology model of nsP2 protein based on the crystal structure of the nsP2 protein of Venezuelan equine encephalitis virus (VEEV). The protein modeled was optimized using molecular dynamics simulation; the junction peptides of a nonstructural protein complex were then docked in order to investigate the possible protein-protein interactions between nsP2 and the proteins cleaved by nsP2.

Comparative modeling of UDP-N-acetylmuramoyl-glycyl-D-glutamate-2, 6-diaminopimelate ligase from Mycobacterium leprae and analysis of its binding features through molecular docking studies

Anusuya Shanmugam [Vinayaka Missions University] and Jeyakumar Natarajan

J. Mol.Mod., **18**, 115-125, 2012.

Leprosy is an infectious disease caused by Mycobacterium leprae. The increasing drug and multi-drug resistance of M. leprae enforce the importance of finding new drug targets. Peptidoglycan is an important component of the cell wall of M. leprae. UDP-N-acetylmuramoyl-glycyl-D-glutamate-2, 6-diaminopimelate ligase (MurE) plays a crucial role in the peptidoglycan biosynthesis and hence it could be considered as a potential drug target for leprosy. Structure of this enzyme for M. leprae has not yet been elucidated. We modeled the three-dimensional structure of MurE from M. leprae using comparative modeling methods based on the X-ray crystal structure of MurE from E. coli and validated.

Microscopic Binding of M5 Muscarinic Acetylcholine Receptor with Antagonists by Homology Modeling, Molecular Docking, and Molecular Dynamics Simulation

Xiaoqin Huang, Guangrong Zheng, and Chang-Guo Zhan [University of Kentucky]

J. Phys. Chem. B., **116**, 532-541, 2012.

By performing homology modeling, molecular docking, and molecular dynamics (MD) simulations, we have developed three-dimensional (3D) structural models of the M5 muscarinic acetylcholine receptor (mAChR) and two complexes for M5 mAChR binding with antagonists SVT-40776 and solifenacin in the environment of lipid bilayer and solvent water. According to the simulated results, each of the antagonists is oriented horizontally in the binding pocket formed by transmembrane helices 2, 3, and 5-7. The cationic headgroup of each of the antagonists interacts with a negatively charged residue, Asp110, through electrostatic and hydrogen-bonding interactions.

Ligand Docking

Specific Material Recognition by Small Peptides Mediated by the Interfacial Solvent Structure

Julian Schneider and Lucio Colombi Ciacchi [University of Bremen]

J. Am. Chem. Soc., **134**, 2407–2413, 2012.

We present evidence that specific material recognition by small peptides is governed by local solvent density variations at solid/liquid interfaces, sensed by the side-chain residues with atomic-scale precision. In particular, we unveil the origin of the selectivity of the binding motif RKLPDA for Ti over Si using a combination of metadynamics and steered molecular dynamics simulations, obtaining adsorption free energies and adhesion forces in quantitative agreement with corresponding experiments.

Identification of the Structural Features that Mediate Binding Specificity in the Recognition of STAT Proteins by Dual-Specificity Phosphatases

Christophe Jardin [Universität Erlangen-Nürnberg], Heinrich Sticht

J. Biomol. Stru. and Dyn., **29**, 777-792, 2012.

Inactivation of signal transducers and activators of transcription (STAT) proteins is regulated by dual-specificity phosphatases (DSPs) with high substrate specificity. Although experiments have provided useful information about the phosphatase activity and the specificity for STATs, there is up-to-date no data at a molecular level to explain the specific recognition of STAT substrates by this subfamily of phosphatases. Here, a combined approach of molecular modeling, docking and molecular dynamics simulations was used to address the binding between DSPs and their STAT substrates.

An Integrated Study of Tyrosinase Inhibition by Rutin: Progress Using a Computational Simulation

Yue-Xiu Si, Shang-Jun Yin, Sangho Oh, Zhi-Jiang Wang, Sen Ye, Li Yan, Jun-Mo Yang, Yong-Doo Park, Jinhyuk Lee, Guo-Ying Qian [Korean Bioinformation Center]

J. Biomol. Stru. and Dyn., **29**, 999-1012, 2012.

Tyrosinase inhibition studies have recently gained the attention of researchers due to their potential application values. We simulated docking (binding energies for AutoDock Vina: -9.1 kcal/mol) and performed a molecular dynamics simulation to verify docking results between tyrosinase and rutin. The docking results suggest that rutin mostly interacts with histidine residues located in the active site. A 10ns molecular dynamics simulation showed that one copper ion at the tyrosinase active site was responsible for the interaction with rutin.

Computer-aided de novo ligand design and docking/molecular dynamics study of Vitamin D receptor agonists

Xiu-Long Shen, Midori Takimoto-Kamimura, Jing Wei [Tianjin University] and Qing-Zhi Gao

J. Mol.Mod., **18**, 203-212, 2012.

1 α ,25(OH)2D3, which is directly mediated by the vitamin D receptor (VDR), exerts a wide variety of biological actions. However, the treatment with 1 α ,25(OH)2D3 is limited because of its side effects. Many analogs and several nonsteroidal mimics with potent biological activity have been reported so far, and our rationale for designing the VDR agonists was on the basis of computer-aided drug design method by de novo design of A-ring and C/D-ring position of 1 α ,25(OH)2D3.

Ligand Docking (Cont'd)

Rationalizing Tight Ligand Binding through Cooperative Interaction Networks

Bernd Kuhn [F. Hoffmann-La Roche AG], Julian E. Fuchs, Michael Reutlinger, Martin Stahl, and Neil R. Taylor

J.Chem. Infor. and Mod. **51**, 3180–3198, 2011.

Small modifications of the molecular structure of a ligand sometimes cause strong gains in binding affinity to a protein target, rendering a weakly active chemical series suddenly attractive for further optimization. Our goal in this study is to better rationalize and predict the occurrence of such interaction hot-spots in receptor binding sites. First, we take a broader view of noncovalent interactions and describe protein–ligand binding with a set of favorable and unfavorable contact types. Second, we go beyond the commonly used pairwise additive treatment of atomic interactions and use a small world network approach to describe how interactions are modulated by their environment.

Binding Conformation of 2-Oxoamide Inhibitors to Group IVA Cytosolic Phospholipase A₂ Determined by Molecular Docking Combined with Molecular Dynamics

Varnavas D. Mouchlis, Vasiliki Michopoulou, Violetta Constantinou-Kokotou, Thomas Mavromoustakos, Edward A. Dennis, and George Kokotos [University of Athens]

J.Chem. Infor. and Mod. **52**, 243–254, 2012.

The group IVA cytosolic phospholipase A₂ (GIVA cPLA₂) plays a central role in inflammation. Long chain 2-oxoamides constitute a class of potent GIVA cPLA₂ inhibitors that exhibit potent in vivo anti-inflammatory and analgesic activity. We have now gained insight into the binding of 2-oxoamide inhibitors in the GIVA cPLA₂ active site through a combination of molecular docking calculations and molecular dynamics simulations. The combination of molecular docking calculations and molecular dynamics simulations is useful in defining the binding of small-molecule inhibitors and provides a valuable tool for the design of new compounds with improved inhibitory activity against GIVA cPLA₂.

Molecular Mechanism of the Effects of Salt and pH on the Affinity between Protein A and Human Immunoglobulin G1 Revealed by Molecular Simulations

Bo Huang, Fu-Feng Liu, Xiao-Yan Dong, and Yan Sun [Tianjin University]

J. Phys. Chem. B., **116**, 424–433, 2012.

Protein A from the bacterium *Staphylococcus aureus* (SpA) has been widely used as an affinity ligand for purification of immunoglobulin G (IgG). The affinity between SpA and IgG is affected differently by salt and pH, but their molecular mechanisms still remain unclear. In this work, molecular dynamics simulations and molecular mechanics Poisson–Boltzmann surface area analysis were performed to investigate the salt (NaCl) and pH effects on the affinity between SpA and human IgG1 (hIgG1). It is found that salt and pH affect the interactions of the hot spots of SpA by different mechanisms.

Molecular Insight into the Ligand–IgG Interactions for 4-Mercaptoethyl-pyridine Based Hydrophobic Charge-Induction Chromatography

Dong-Qiang Lin [Zhejiang University], Hong-Fei Tong, Hong-Yin Wang, and Shan-Jing Yao

J. Phys. Chem. B., **116**, 1393–1400, 2012.

Hydrophobic charge-induction chromatography (HCIC) with 4-mercaptoethyl-pyridine (MEP) as the ligand is a novel technology for antibody purification. In the present work, the molecular simulation methods were used to investigate the interactions between MEP ligand and Fc fragment of IgG (Fc-A). Six ligands with different structures of spacer arm were studied with molecular docking and dynamics simulation at neutral and acidic pH. The binding modes and the interaction energies were analyzed.

Ligand Docking (Cont'd)

Probing the Effect of Conformational Constraint on Phosphorylated Ligand Binding to an SH2 Domain Using Polarizable Force Field Simulations

Yue Shi, Crystal Z. Zhu, Stephen F. Martin, and Pengyu Ren
[The University of Texas at Austin]

J. Phys. Chem. B., **116**, 1716–1727, 2012.

Preorganizing a ligand in the conformation it adopts upon binding to a protein has long been considered to be an effective way to improve affinity by making the binding entropy more favorable. However, recent thermodynamic studies of a series of complexes of the Grb2 SH2 domain with peptide analogues having constrained and flexible replacements for a phosphotyrosine residue revealed that less favorable binding entropies may result from constraining ligands in their biologically active conformations. Toward probing the origin of this unexpected finding, we examined the complexes of four phosphotyrosine-derived analogues with the Grb2 SH2 domain using MD simulations with a polarizable force field.

PDB-scale analysis of known and putative ligand-binding sites with structural sketches

Jun-Ichi Ito, Yasuo Tabei, Kana Shimizu, Kentaro Tomii [The University of Tokyo] and Koji Tsuda

Proteins: Stru. Fun. & Bioinf., **80**, 747–763, 2012.

Computational investigation of protein functions is one of the most urgent and demanding tasks in the field of structural bioinformatics. Given the vast amounts of data available now, existing 3D structural comparison methods are not adequate due to their computation time complexity. In this article, we propose a new bit string representation of binding sites called structural sketches, which is obtained by random projections of triplet descriptors.

3. JOURNAL REVIEWS

Journal of Computational Chemistry, 33(4), February, 2012.

355–362 **Complex configuration interaction calculations of the cross section for the dissociative electron**

attachment process $e^- + F_2 \rightarrow F \rightarrow F + F^-$ using the complex basis function method, Michael Honigmann [Bergische Universität Wuppertal], Robert J. Buenker and Heinz-Peter Liebermann

In the context of the Born-Oppenheimer approximation, one of the best theoretical descriptions of the electronic states involves the use of complex basis functions together with configuration interaction (CI) methods. In this work, multireference CI calculations using the complex basis function method have been carried out for the autoionizing ground state of the F_2 molecule.

363–378 **On the effect of a variation of the force field, spatial boundary condition and size of the QM region in QM/MM MD simulations,** Katharina Meier, Walter Thiel and Wilfred F. van Gunsteren [Swiss Federal Institute of Technology Zürich]

See Methodology / QM and QM/MM.

379–390 **Direct evaluation of individual hydrogen bond energy in situ in intra- and intermolecular multiple hydrogen bonds system,** Cui Liu, Dong-Xia Zhao and Zhong-Zhi Yang [Liaoning Normal University]

The results of evaluating the individual hydrogen bond (H-bond) strength are expected to be helpful for the rational design of new strategies for molecular recognition or supramolecular assemblies. We present a local analytic model, ABEEM $\sigma\pi$ H-bond energy (HBE) model based on ab initio calculations (MP2) as benchmark, to directly and rapidly evaluate the individual HBE in situ in inter- and intramolecular multiple H-bonds system.

391–400 **Development and optimization of a novel genetic algorithm for identifying nanoclusters from scanning transmission electron microscopy images,** Andrew J. Logsdail, Z. Y. Li and Roy L. Johnston [University of Birmingham]

Whilst technological advancements have allowed imaging at atomic resolution using scanning transmission electron microscopy (STEM), identification of nanocluster structures has proven difficult due to their low thermal stability, and often resultant low-symmetry. In this work, we look at a novel solution to this problem using a genetic algorithm (GA). GAs are search methods for the minimization of statistical problems based on natural evolution.

401–405 **Ab Initio direct classical trajectory investigation on the S_N2 reaction of F^- with NH_2F : Nonstatistical central barrier recrossing dynamics,** Feng Yu [Xi'an Technological University]

The bimolecular nucleophilic substitution (S_N2) reaction of F_a^- with NH_2F_b has been investigated with the ab initio direct classical trajectory method. According to our trajectory calculations, a dynamic behavior of nonstatistical central barrier recrossing is revealed.

- 406–415 **Understanding cross-boundary events in ONIOM QM:QM' calculations**, Marcus Lundberg [Kyoto University]

See Methodology / QM and QM/MM.

- 416–424 **Structure and properties of the aluminum borates $Al(BO_2)_n$ and $Al(BO_2)_n^-$, ($n = 1-4$)**, Gennady L. Gutsev [Florida A&M University], Charles A. Weatherford, Lewis E. Johnson and Purusottam Jena

The geometrical and electronic structures of $Al(BO_2)_n$ and $Al(BO_2)_n^-$ ($n = 1-4$) clusters are computed at different levels of theory including density functional theory (DFT), hybrid DFT, double-hybrid DFT, and second-order perturbation theory.

- 425–434 **A computational study on the hydrogen adsorption capacity of various lithium—Doped boron hydrides**, Sudip Pan, Santanab Giri and Pratim K. Chattaraj [Indian Institute of Technology, Kharagpur]

An aromatic boron hydride $B_3H_3^{2-}$ and its various Li/Li^+ doped isomers have been studied at the B3LYP/6-311+G(d) and M06/6-311+G(d) levels of theory to assess their hydrogen storage potential.

- 435–441 **Path-integral calculations of heavy atom kinetic isotope effects in condensed phase reactions using higher-order trotter factorizations**, Alexandra Vardi-Kilshtain, Asaf Azuri and Dan Thomas Major [Bar-Ilan University]

A convenient approach to compute kinetic isotope effects (KIEs) in condensed phase chemical reactions is via path integrals (PIs). Usually, the primitive approximation is used in PI simulations, although such quantum simulations are computationally demanding.

- 442–452 **On the use of big-bang method to generate low-energy structures of atomic clusters modeled with pair potentials of different ranges**, J. M. C. Marques [Universidade de Coimbra], A. A. C. C. Pais and P. E. Abreu

The efficiency of the so-called big-bang method for the optimization of atomic clusters is analysed in detail for Morse pair potentials with different ranges; here, we have used Morse potentials with four different ranges, from long- $\rho = 3$) to short-ranged $\rho = 14$) interactions.

- 453–465 **Convergence and error estimation in free energy calculations using the weighted histogram analysis method**, Fangqiang Zhu [National Institutes of Health, Bethesda] and Gerhard Hummer

The weighted histogram analysis method (WHAM) has become the standard technique for the analysis of umbrella sampling simulations. In this article, we address the challenges (1) of obtaining fast and accurate solutions of the coupled nonlinear WHAM equations, (2) of quantifying the statistical errors of the resulting free energies, (3) of diagnosing possible systematic errors, and (4) of optimally allocating of the computational resources.

- 466–470 **Modeling nonlinear optics of nanosystems with sum-over-states model**, Wei Quan Tian [Harbin Institute of Technology]

Three-stage strategies (ladder rule, few state model (FSM), and parallelization) were proposed to improve the computational efficiency of the sum-over-states (SOS) model in nonlinear optics (NLO) modeling.

Journal of Computational Chemistry, 33(5), February, 2012.

- 475–483 **Thermodynamics and kinetics of large-time-step molecular dynamics**, Francesco Rao [Freiburg Institute for Advanced Studies] and Martin Spichty

See **Methodology / Molecular Dynamics**.

- 484–489 **Theoretical calculation about the valence and rydberg excited states of hydrogen cyanide**, Bu-Tong Li, Lu-Lin Li and Hai-Shun Wu [Shanxi Normal University]

The singlet and triplet excited states of hydrogen cyanide have been computed by using the complete active space self-consistent field and completed active space second order perturbation methods with the atomic natural orbital (ANO-L) basis set.

- 490–501 **Interaction and protection mechanism between Li@C_{60} and nucleic acid bases (NABs): Performance of PM6-DH2 on noncovalent interaction of NABs- Li@C_{60}** , Wenming Sun, Yuxiang Bu [Shandong University] and Yixuan Wang

To discuss the protection mechanism of DNA from radiation as well as assess the performance of PM6-DH2 on noncovalent interactions, the interaction of four nucleic acid bases (NABs) such as adenine (A), cytosine (C), guanine (G), and thymine (T), with Li@C_{60} was extensively investigated with the-state-of-art theoretical methods describing noncovalent systems, like M06-2x, PBE-D, and PM6-DH2 methods.

- 502–508 **Identifying clusters as low-lying minima—efficiency of stochastic and genetic algorithms using inexpensive electronic structure levels**, Fabrice Avaltroni and Clemence Corminboeuf [Ecole Polytechnique Fédérale de Lausanne]

Molecular candidates possessing unconventional chemical bonding paradigms (e.g., boron wheels, molecular stars, and multicenter bonding) have attracted a great deal of attention by the computational community. The simple random search and genetic algorithm (GA) are among these: but how do these approaches perform on typical isomeric searches? The performance of three specific variants for the ab initio exploration of the PES of prototype planar tetracoordinated and hypercoordinated carbon-containing systems C_2Al_4 and CB_6^{2-} are compared.

- 509–516 **Alder-ene reaction: Aromaticity and activation-strain analysis**, Israel Fernández [Universidad Complutense] and F. Matthias Bickelhaupt

We have computationally explored the trend in reactivity of the Alder-ene reactions between propene and a series of seven enophiles using density functional theory at M06-2X/def2-TZVPP.

- 517–526 **A reliable and efficient first principles-based method for predicting pK_a values. III. Adding explicit water molecules: Can the theoretical slope be reproduced and pK_a values predicted more accurately?**, Shuming Zhang [University of Arkansas]

A popular method for predicting pK_a values for organic molecules in aqueous solution is to establish empirical linear least-squares fits between calculated deprotonation energies and known experimental pK_a values. A popular method for predicting pK_a values for organic molecules in aqueous solution is to establish empirical linear least-squares fits between calculated deprotonation energies and known experimental pK_a values. The most likely cause for the strange behavior of the fitted slope is explicit solute–solvent (water) interactions, especially involving the ions, which cannot be described accurately by continuum solvation models. We used our previously developed pK_a protocol (OLYP/6-311+G(d,p)//3-21G(d) with the COSMO solvation model) to investigate the effect of adding one or two explicit water molecules to the system.

- 527–536 **Molecular mechanism of HIV-1 integrase–vDNA interactions and strand transfer inhibitor action: A molecular modeling perspective**, Weiwei Xue, Huanxiang Liu and Xiaojun Yao [Lanzhou University]

See Applications / Protein-Nucleic acid Interactions.

- 537–549 **The bergman cyclizations of the enediyne and its N-substituted analogs using multiconfigurational second-order perturbation theory**, Hua Dong, Bo-Zhen Chen [Graduate University of Chinese Academy of Sciences], Ming-Bao Huang and Roland Lindh

The Bergman cyclizations of the enediyne and its four N-substituted analogs [(Z)-pent-2-en-4-ynenitrile, 3-azahex-3-en-1,5-diyne, malenitrile, and 3,4-azahex-3-en-1,5-diyne] have been studied using the complete active space self-consistent field and multiconfigurational second-order perturbation theory methods in conjunction with the atomic natural orbital basis sets.

- 550–560 **Evaluation of protein-ligand binding free energy focused on its entropic components**, Shuntaro Chiba, Yuich Harano, Roland Roth, Masahiro Kinoshita and Minoru Sakurai [Tokyo Institute of Technology]

The binding free energy for FK506-binding protein-ligand systems is evaluated as a sum of two entropic components, the water-entropy gain, and the configurational-entropy loss for the protein and ligand molecules upon the binding. The two entropic components are calculated using morphometric thermodynamics combined with a statistical-mechanical theory for molecular liquids and the normal mode analysis, respectively.

- 561–572 **In Silico screening for agonists and blockers of the β_2 adrenergic receptor: Implications of inactive and activated state structures**, Stefano Costanzi [National Institutes of Health, DHHS, Bethesda] and Santiago Vilar

Ten crystal structures of the β_2 adrenergic receptor have been published, reflecting different signaling states. Here, through controlled-docking experiments, we examined the implications of using inactive or activated structures on the in silico screening for agonists and blockers of the receptor.

- 573–579 **Virtual screening for compounds that mimic protein–protein interface epitopes**, Tim Geppert, Felix Reisen, Max Pillong, Volker Hähnke, Yusuf Tanrikulu, Christian P. Koch, Anna Maria Perna, Tatiana Batista Perez, Petra Schneider and Gisbert Schneider [Swiss Federal Institute of Technology]

See Applications / Protein Protein Interactions.

Journal of Molecular Modeling, 18(1), January, 2012.

- 1-10 **Binding efficiencies of carbohydrate ligands with different genotypes of cholera toxin B: molecular modeling, dynamics and docking simulation studies**, Mobashar Hussain Urf Turabe Fazil, Sunil Kumar, Rohit Farmer, Haushila Prasad Pandey and Durg Vijai Singh [Institute of Life Sciences, Bhubaneswar]

See Applications / Medicinal Chemistry and Drug Design.

- 11-26 **A comparative study of the hydrogen-bonding patterns and prototropism in solid 2-thiocytosine (potential antileukemic agent) and cytosine, as studied by 1H-14N NQDR and QTAIM/ DFT**, Jolanta N. Latosińska [Adam Mickiewicz University], Janez Seliger, Veselko Žagar and Dorota V. Burchardt

See Applications / Medicinal Chemistry and Drug Design.

- 27-37 **Molecular modeling, docking and dynamics simulations of GNA-related lectins for potential prevention of influenza virus (H1N1)**, Huai-long Xu, Chun-yang Li, Xue-mei He, Ke-qin Niu and Hao Peng, Jin-ku Bao [Sichuan University], et al.

See Applications / Medicinal Chemistry and Drug Design.

- 39-51 **Homology modeling, molecular dynamics, e-pharmacophore mapping and docking study of Chikungunya virus nsP2 protease**, Kh. Dhanachandra Singh, Palani Kirubakaran, Shanthi Nagarajan, Sugunadevi Sakkiyah and Karthikeyan Muthusamy, Jeyaraman Jeyakanthan [Alagappa University], et al.

See Methodology / Homology Modeling.

- 53-64 **Solvation counteracts coulombic repulsion in the binding of two cations to a model hexapeptide**, Hongqi Ai [University of Jinan], Chong Zhang, Wei He, Kwaichow Chan and Qiang Li

In the present paper we employ a series of dicationized (K^+ & C^+ ; $C^+=CH$, Li, Na, or K) hexapeptide ($G6C^+K^+x$, $x=1, 2, \dots$ or 5) complexes in gas phase (GP) and aqueous phase (AP) as models to mimic the key characteristics of the real biosystems.

- 65-82 **Application of electron conformational-genetic algorithm approach to 1,4-dihydropyridines as calcium channel antagonists: pharmacophore identification and bioactivity prediction**, Nazmiye Geçen, Emin Sarıpınar [Erciyes University], Ersin Yanmaz and Kader Şahin

Two different approaches, namely the electron conformational and genetic algorithm methods (EC-GA), were combined to identify a pharmacophore group and to predict the antagonist activity of 1,4-dihydropyridines (known calcium channel antagonists) from molecular structure descriptors.

- 83-90 **Structural models of CFTR-AMPK and CFTR-PKA interactions: R-domain flexibility is a key factor in CFTR regulation**, Marian Siwiak, Aleksander Edelman and Piotr Zielenkiewicz [Polish Academy of Sciences]

See Applications / Homology Modeling.

- 91-101 **Molecular electrostatic potentials of DNA base–base pairing and mispairing**, Ivonne Otero-Navas and Jorge M. Seminario [Texas A&M University]

See Applications / Nucleic Acids.

- 103-114 **Computer-assisted design for paracetamol masking bitter taste prodrugs**, Hatem Hejaz, Rafik Karaman [Al-Quds University] and Mustafa Khamis

See Applications / Medicinal Chemistry and Drug Design.

- 115-125 **Comparative modeling of UDP-N-acetylmuramoyl-glycyl-D-glutamate-2, 6-diaminopimelate ligase from Mycobacterium leprae and analysis of its binding features through molecular docking studies**, Anusuya Shanmugam [Vinayaka Missions University] and Jeyakumar Natarajan

See Methodology / Homology Modeling.

- 127-135 **Interference of H-bonding and substituent effects in nitro- and hydroxy-substituted salicylaldehydes**, Aneta Jezierska-Mazzarello [University of Wrocław], Halina Szatyłowicz and Tadeusz Marek Krygowski

Two intramolecular interactions, i.e., (1) hydrogen bond and (2) substituent effect, were analyzed and compared. For this purpose, the geometry of 4- and 5-X-substituted salicylaldehyde derivatives ($X = \text{NO}_2$, H or OH) was optimized by means of B3LYP/6-311++G(d,p) and MP2/aug-cc-pVDZ methods.

- 137-144 **DFT studies of the phenol adsorption on boron nitride sheets**, Jose Mario Galicia Hernández, Gregorio Hernández Cocoltzi and Ernesto Chigo Anota [Ciudad Universitaria]

We perform first principles total energy calculations to investigate the atomic structures of the adsorption of phenol ($\text{C}_6\text{H}_5\text{OH}$) on hexagonal boron nitride (BN) sheets. Calculations are done within the density functional theory as implemented in the DMOL code.

- 145-150 **Brønsted-Evans-Polanyi relationships for C–C bond forming and C–C bond breaking reactions in thiamine-catalyzed decarboxylation of 2-keto acids using density functional theory**, Rajeev Surendran Assary [Northwestern University], Linda J. Broadbelt and Larry A. Curtiss

The concept of generalized enzyme reactions suggests that a wide variety of substrates can undergo enzymatic transformations, including those whose biotransformation has not yet been realized. In this work, we propose a structure/activity relationship based on the free energy of binding or reaction of non-native substrates to evaluate the catalysis relative to that of native substrates.

- 151-163 **Virtual screening and in vitro assay of potential drug like inhibitors from spices against glutathione-S-transferase of filarial nematodes**, Shamina Azeez [Indian Institute of Spices Research], Rosana O. Babu, Riju Aykkal and Reena Narayanan

See Applications / Medicinal Chemistry and Drug Design.

- 165-170 **Theoretical investigations of a high density cage compound 10-(1-nitro-1, 2, 3, 4-tetraazol-5-yl) methyl-2, 4, 6, 8, 12-hexanitrohexaazaisowurtzitane**, Jian-ying Zhang [Nanjing University of Science and Technology], Hong-chen Du, Fang Wang, Xue-dong Gong and Yin-sheng Huang

A new polynitro cage compound with the framework of HNIW and a tetrazole unit, i.e., 10-(1-nitro-1, 2, 3, 4-tetraazol-5-yl) methyl-2, 4, 6, 8, 12-hexanitrohexaazaisowurtzitane (NTz-HNIW) has been proposed and studied by density functional theory (DFT) and molecular mechanics methods.

- 171-186 **A selectivity study on mTOR/PI3K α inhibitors by homology modeling and 3D-QSAR**, Ting Ran, Tao Lu, Haoliang Yuan, Haichun Liu and Jian Wang, Yadong Chen [China Pharmaceutical University], et al.

See Applications / Homology Modeling.

- 187-201 **Identification of novel, less toxic PTP-LAR inhibitors using in silico strategies: pharmacophore modeling, ADMET-based virtual screening and docking**, Dara Ajay and M. Elizabeth Sobhia [National Institute of Pharmaceutical Education and Research (NIPER)]

See Applications / Medicinal Chemistry and Drug Design.

- 203-212 **Computer-aided de novo ligand design and docking/molecular dynamics study of Vitamin D receptor agonists**, Xiu-Long Shen, Midori Takimoto-Kamimura, Jing Wei [Tianjin University] and Qing-Zhi Gao

See Methodology / Ligand Docking.

- 213-220 **Simulated Q-annealing: conformational search with an effective potential**, Won-joon Son, Soonmin Jang and Seokmin Shin [Seoul National University]

We have tested a version of the generalized simulated annealing algorithm based on molecular dynamics simulations with effective potential suggested by Tsallis statistics.

- 221-227 **A model for the shuttle motions of puerarin and daidzin inside the cavity of β -cyclodextrin in aqueous acetic acid: insights from molecular dynamics simulations**, Haiyang Zhang, Wei Feng, Cong Li, Yongqin Lv and Tianwei Tan [Beijing University of Chemical Technology]

See Applications / Host-Guest Systems.

- 229-237 **Fuzzy oil drop model to interpret the structure of antifreeze proteins and their mutants**, Mateusz Banach, Katarzyna Prymula, Wiktor Jurkowski, Leszek Konieczny and Irena Roterman [Jagiellonian University]

Mutations in proteins introduce structural changes and influence biological activity: the specific effects depend on the location of the mutation. The simple method proposed in the present paper is based on a two-step model of in silico protein folding.

- 239-250 **Theoretical study of the surface properties of poly(dimethylsiloxane) and poly(tetrafluoroethylene)**, Andrea Michalkova, Sonia Tulyani, James Beals and Jerzy Leszczynski [Jackson State University]

Molecular dynamics (MD) simulations of poly(dimethylsiloxane) (PDMS) and poly(tetrafluoroethylene) (PTFE) were carried out to determine their surface properties and energies.

- 251-256 **Elucidation of specific aspects of dielectric constants of conjugated organic compounds: a QSPR approach**, Areum Lee, Daejin Kim, Kyung-Hyun Kim, Seung-Hoon Choi and Kihang Choi, Dong Hyun Jung [Insilicotech Co. Ltd] , et al.

The characteristic aspects of dielectric constants of π -conjugated compounds are elucidated by a quantitative structure property relationship (QSPR) study.

- 257-263 **Electron-topological, energetic and π -electron delocalization analysis of ketoenamine-enolimine tautomeric equilibrium**, Agata Martyniak, Pawel Lipkowski, Noel Boens and Aleksander Filarowski [University of Wrocław]

The ketoenamine-enolimine tautomeric equilibrium has been studied by the analysis of aromaticity and electron-topological parameters. The influence of substituents on the energy of the transition state and of the tautomeric forms has been investigated for different positions of chelate chain.

- 265-274 **Microsolvation effect and hydrogen-bonding pattern of taurine-water TA-(H₂O)_n (n = 1–3) complexes**, Yumei Dai, Yuhua Wang, Zhengguo Huang [Tianjin Normal University], Hongke Wang and Lei Yu

The microsolvation of taurine (TA) with one, two or three water molecules was investigated by a density functional theory (DFT) approach. Quantum theory of atoms in molecules (QTAIM) analyses were employed to elucidate the hydrogen bond (H-bond) interaction characteristics in TA-(H₂O)_n (n = 1–3) complexes.

- 275-283 **Ab initio calculation of the geometries, stabilities, and electronic properties for the bimetallic Be₂Au_n (n = 1–9) clusters: comparison with pure gold clusters**, Ya-Ru Zhao, Xiao-Yu Kuang [Sichuan University], Bao-Bing Zheng, Su-Juan Wang and Yan-Fang Li

Ab initio methods based on density functional theory at BP86 level were applied to the study of the geometrical structures, relative stabilities, and electronic properties of small bimetallic Be₂Au_n (n = 1–9) clusters.

- 285-293 **Receptor recognition mechanism of human influenza A H1N1 (1918), avian influenza A H5N1 (2004), and pandemic H1N1 (2009) neuraminidase**, Nipa Jongkon and Chak Sangma [Kasetsart University]

See Applications / Homology Modeling.

- 295-306 **Structural determinants of benzodiazepinedione/peptide-based p53-HDM2 inhibitors using 3D-QSAR, docking and molecular dynamics**, Fangfang Wang, Yan Li, Zhi Ma, Xia Wang and Yonghua Wang [Northwest A&F University]

See Applications / QSAR.

- 307-318 **Noscapinoids with anti-cancer activity against human acute lymphoblastic leukemia cells (CEM): a three dimensional chemical space pharmacophore modeling and electronic feature analysis**, Pradeep K. Naik [Emory University School of Medicine], Seneha Santoshi and Harish C. Joshi

See Applications / Medicinal Chemistry and Drug Design.

- 319-328 **A density functional theory approach toward substituent effect in Meerwein–Eschenmoser–Claisen rearrangement**, Rahim Ghadari and Ahmad Shaabani [Shahid Beheshti University]

B3LYP/6-31 G(d) level of theory has been used for the examination of substituent effect in the concerted step of the Meerwein-Eschenmoser-Claisen rearrangement. In this regard, the effect of NO₂ and NH₂ groups in different positions has been investigated.

- 329-338 **A DFT study on equilibrium geometries, stabilities, and electronic properties of small bimetallic Na-doped Au_n (n = 1-9) clusters: comparison with pure gold clusters**, Yan-Fang Li [Sichuan University], Xiao-Yu Kuang, Ai-Jie Mao, Yang Li and Ya-Ru Zhao

A systematic study on the geometric structures, relative stabilities, and electronic properties of small bimetallic Au_n Na (n = 1-9) clusters has been performed by means of first-principle density functional theory calculations at the PW91PW91 level.

- 339-350 **Ab initio and DFT conformational study on N-nitrosodiethylamine, (C₂H₅)₂N-N=O**, Silmar A. do Monte [Universidade Federal da Paraíba], Railton B. de Andrade, Elizete Ventura and Sidney R. de Santana

Ab initio (MP2) and DFT (B3LYP) calculations, using the cc-pVTZ and aug-cc-pVTZ basis sets, have been performed to characterize some stationary points on the ground state potential energy surface of the title molecules.

- 351-358 **Gas adsorption on the Zn-, Pd- and Os-doped armchair (5,5) single-walled carbon nanotubes**, Chanukorn Tabtimsai, Somchai Keawwangchai, Banchob Wanno and Vithaya Ruangpornvisuti [Chulalongkorn University]

The adsorption of NO₂, NH₃, H₂O, CO₂ and H₂ gases on the undoped, Zn-, Pd- and Os-doped armchair (5,5) single-walled carbon nanotubes (SWCNTs) were studied using density functional method.

- 359-365 **Quantum chemical investigation of the thermal pyrolysis reactions of the carboxylic group in a brown coal model**, Shengyu Liu [Taiyuan University of Technology], Zhiqiang Zhang and Huifang Wang

Different reaction pathways of the carboxylic group in a brown coal model were investigated by applying density function quantum chemical theory, examining the possible cross-linking and decomposition reactions between the hydrogen bonded carboxylic group–carboxylic group and the carboxylic group–hydroxyl group during the thermal pyrolysis process.

- 367-376 **Study of the betulin molecule in a water environment; ab initio and molecular simulation calculations**, Miroslav Pospíšil [Charles University in Prague], Petr Kovář, Robert Vácha and Michal Svoboda

See Applications / Protein Dynamics.

- 377-391 **Molecular dynamics simulation and density functional theory studies on the active pocket for the binding of paclitaxel to tubulin**, Sichuan Xu [Yunnan University], Shaoming Chi, Yi Jin, Qiang Shi and Maofa Ge, et al.

See Applications / Medicinal Chemistry and Drug Design.

- 393-404 **Computational study of the electronic structures, UV-Vis spectra and static second-order nonlinear optical susceptibilities of macrocyclic thiophene derivatives**, Shuang Huang, Ai-Min Ren [Jilin University], Lu-Yi Zou, Yang Zhao and Jing-Fu Guo, et al.

Using thiophene (which has a moderate resonance energy) as a spacer rather than benzene permits better π -electron delocalization and leads to a large nonlinear optical response. Thus, the nonlinear optical coefficients of a series of macrocyclic thiophene derivatives (C[3T_{DA}]_n with C_n symmetry) were studied, and their electronic structures, UV-Vis spectra and static second-order nonlinear optical susceptibilities (β 0) were computed.

- 405-418 **Architecture, electronic structure and stability of TM@Ge(n) (TM = Ti, Zr and Hf; n = 1-20) clusters: a density functional modeling**, Manish Kumar, Nilanjana Bhattacharyya and Debashis Bandyopadhyay [Institute of Technology and Science, Pilani]

The present study reports the geometry, electronic structure and properties of neutral and anionic transition metal (TM = Ti, Zr and Hf) doped germanium clusters containing 1 to 20 germanium atoms within the framework of linear combination of atomic orbitals density functional theory under spin polarized generalized gradient approximation.

4. ADDRESSES OF PRINCIPAL AUTHORS

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1. APPLICATIONS

1.1. Small Molecules

General and Model Systems

Potential of mean force of water-proton bath and molecular dynamic simulation of proteins at constant pH

Yury N. Vorobjev [Institute of Chemical Biology and Fundamental Medicine of the Siberian Branch of the Russian Academy of Science]

J. Comp. Chem. **33**, 832–842, 2012.

An advanced implicit solvent model of water-proton bath for protein simulations at constant pH is presented. The implicit water-proton bath model approximates the potential of mean force of a protein in water solvent in a presence of hydrogen ions. Accurate and fast computational implementation of the implicit water-proton bath model is developed using the continuum electrostatic Poisson equation model for calculation of ionization equilibrium and the corrected MSR6 generalized Born model for calculation of the electrostatic atom-atom interactions and forces.

Medicinal Chemistry and Drug Design

Asymmetrical 2,6-bis(benzylidene)cyclohexanones: Synthesis, cytotoxic activity and QSAR study

Maryam Nakhjiri, Maliheh Safavi, Eskandar Alipour, Saeed Emami, Amir Farzin Atash, Mona Jafari-Zavareh, Sussan K. Ardestani, Mehdi Khoshneviszadeh, Alireza Foroumadi, Abbas Shafiee [Tehran University of Medical Sciences]

Europ. Jou. Med. Chem., **50**, 113-123, 2012.

In order to develop novel anti-cancer agents, a series of asymmetrical 2,6-bis (benzylidene)cyclohexanone derivatives containing nitrobenzylidene moiety were synthesized and their cytotoxic activity were determined in vitro against MDA-MB 231, MCF-7 and SK-N-MC cell lines using MTT assay. Among the tested compounds, the highest activity against MDA-MB 231 cells was achieved by 2-(3-bromo-5-methoxy-4-propoxybenzylidene)-6-(2-nitrobenzylidene) cyclohexanone (compound **5d**).



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Medicinal Chemistry and Drug Design (Cont'd)

Insights from ligand and structure based methods in virtual screening of selective Ni-peptide deformylase inhibitors

Ravi Shekar Ananthula [GVKBIO S-1], Muttineni Ravikumar, S. K. Mahmood and M. N. S. Pavan Kumar

J. Mol.Mod., **18**, 693-708, 2012

In recent years, there has been a growing interest in developing bacterial peptide deformylase (PDF) inhibitors as novel antibiotics. The purpose of the study is to generate a three-dimensional (3D) pharmacophore model by using diverse PDF inhibitors which is useful for designing of potential antibiotics. Twenty one structurally diverse compounds were considered for the generation of quantitative pharmacophore model using HypoGen of Catalyst, further model was validated using 78 compounds.

CYP isoform specificity toward drug metabolism: analysis using common feature hypothesis

M. Ramesh and Prasad V. Bharatam [National Institute of Pharmaceutical Education and Research]

J. Mol.Mod., **18**, 709-720, 2012

Three dimensional pharmacophoric maps were generated for each isoforms of CYP2C9, CYP2D6 and CYP3A4 separately using independent training sets consist of highly potent substrates (seven substrates for each isoform). HipHop module of CATALYST software was used in the generation of pharmacophore models. The best pharmacophore model was chosen out of the several models on the basis of (i) highest ranking score, (ii) better fit value among training set, (iii) capability to screen substrates from data set and (iv) efficiency to identify the isoform specificity.

Four-component pharmacophore model for endomorphins toward μ opioid receptor subtypes

Yng-Ching Wu, Tim Jaglinski, Jin-Yuan Hsieh, Jia-Jyun Chiu and Tzen-Yuh Chiang, Chi-Chuan Hwang [National Cheng Kung University]

J. Mol.Mod., **18**, 825-834, 2012

In the present work, a series of simulation tools were used to determine structure-activity relationships for the endomorphins (EMs) and derive μ -pharmacophore models for these peptides. Potential lowest energy conformations were determined in vacuo by systematically varying the torsional angles of the Tyr1-Pro2 (ω_1) and Pro2-Trp3/Phe3 (ω_2) as tuning parameters in AM1 calculations. These initial models were then exposed to aqueous conditions via molecular dynamics simulations.

Fighting High Molecular Weight in Bioactive Molecules with Sub-Pharmacophore-Based Virtual Screening

Modest von Korff [Department of Research Informatics, Gewerbestrasse 16], Joel Freyss, Thomas Sander, Christoph Boss, and Claire-Lise Ciana

J.Chem. Infor. and Mod. **52**, 380-390, 2012.

A new subpharmacophore-based virtual screening method is introduced. Subpharmacophores are derived from large active molecules to detect small bioactive molecules as seeds for starting points in medicinal chemistry programs. A large data set was assembled from the ChEMBL database to check the validity of this approach. Molecules for 133 targets with molecular weights between 450 and 850 were selected as queries. For the query molecules, the pharmacophore descriptors were calculated. Up to 56,000 subpharmacophore descriptors with five to seven pharmacophore points were derived from the query pharmacophores.

Medicinal Chemistry and Drug Design (Cont'd)

HIV-1 Protease and Substrate Coevolution Validates the Substrate Envelope As the Substrate Recognition Pattern

Ayşegül Özen, Türkan Haliloğlu, and Celia A. Schiffer
[University of Massachusetts Medical School]

J. Chem. Theor. and Comp., **8**, 703–714, 2012.

Drug resistance of HIV-1 protease alters the balance in the molecular recognition events in favor of substrate processing versus inhibitor binding. To develop robust inhibitors targeting ensembles of drug-resistant variants, the code of this balance needs to be cracked. For this purpose, the principles governing the substrate recognition are required to be revealed. In this study, three coevolved protease–substrate complexes (^{AP2V}NC-p1_{V82A}, ^{LP1F}p1-p6_{D30N/N88D}, and ^{SP3N}p1-p6_{D30N/N88D}) were investigated for structural and dynamic properties by molecular modeling and dynamics simulations.

Quantitative Structure-Activity Relations

Developing consensus 3D-QSAR and pharmacophore models for several beta-secretase, farnesyl transferase and histone deacetylase inhibitors

Hsin-Yuan Wei[National Tsing Hua University], Guan-Ju Chen, Chih-Lun Chen and Thy-Hou Lin

J. Mol.Mod., **18**, 675-692, 2012

Three consensus 3D-QSAR (c-3D-QSAR) models were built for 38, 34, and 78 inhibitors of β -secretase, histone deacetylase, and farnesyltransferase, respectively. To build an individual 3D-QSAR model, the structures of an inhibitor series are aligned through docking of a protein receptor into the active site using the program GOLD. CoMFA, CoMSIA, and Catalyst are then performed for the training set of each structurally aligned inhibitor series to obtain a 3D-QSAR model. Each c-3D-QSAR pharmacophore model built was examined visually and compared with that obtained by simultaneous mapping of the corresponding 3D-QSAR pharmacophores built onto a selected inhibitor structure.

Carbon Nanoparticles

Instability of C60 fullerene interacting with lipid bilayer

Duangkamon Baowan [Mahidol University], Barry J. Cox and James M. Hill

J. Mol.Mod., **18**, 549-557, 2012

Due to the large number of possible applications of nanoparticles in cosmetic and medical products, the possible hazards of nanoparticles in the human body are a major concern. A worst-case scenario is that nanoparticles might cause health issues such as skin damage or even induce cancer. As a first step to study the toxicity of nanoparticles, we investigate the energy behaviour of a C60 fullerene interacting with a lipid bilayer. Using the 6–12 Lennard-Jones potential function and the continuous approximation, the equilibrium spacing between the two layers of a bilayer is predicted to be 3.36 Å.

Carbon Nanoparticles (Cont'd)

Noncovalent and covalent functionalization of a (5, 0) single-walled carbon nanotube with alanine and alanine radicals

Muthusivarajan Rajarajeswari, Kombiah Iyakutti [Madurai Kamaraj University] and Yoshiyuki Kawazoe

J. Mol.Mod., **18**, 771-781, 2012

We have systematically investigated the noncovalent and covalent adsorption of alanine and alanine radicals, respectively, onto a (5, 0) single-walled carbon nanotube using first-principles calculation. It was found that $XH\cdots\pi$ ($X=\text{N, O, C}$) interactions play a crucial role in the non-ovalent adsorption and that the functional group close to the carbon nanotube exhibits a significant influence on the binding strength. Noncovalent functionalization of the carbon nanotube with alanine enhances the conductivity of the metallic (5, 0) nanotube.

Structural, Dynamical, and Thermodynamical Properties of Carbon Nanotube Polycarbonate Composites: A Molecular Dynamics Study

Souvik Chakraborty and Sudip Roy [National Chemical Laboratory, Pune]

J. Phys. Chem. B., **116**, 3083–3091, 2012.

All-atom molecular dynamics simulations are performed on pure monomer and trimer of polycarbonate and their mixtures with different molecular weight percentages of embedded single walled carbon nanotubes at different temperatures to study the structural and dynamical properties of the composite system. The diffusion behaviors of monomer, trimer of polycarbonate and carbon nanotubes in composite matrices are investigated and compared with pure matrices in details.

1.2. Biopolymers

Bioinformatics and Cheminformatics

COPICAT: a software system for predicting interactions between proteins and chemical compounds

Yasubumi Sakakibara [Keio University], Tsuyoshi Hachiya, Miho Uchida, Nobuyoshi Nagamine, Yohei Sugawara, Masahiro Yokota, Masaomi Nakamura, Kris Pendorf, Takashi Komori, and Kengo Sato

Bioinformatics. **28**, 745-746, 2012.

Since tens of millions of chemical compounds have been accumulated in public chemical databases, fast comprehensive computational methods to predict interactions between chemical compounds and proteins are needed for virtual screening of lead compounds. Previously, we proposed a novel method for predicting protein–chemical interactions using two-layer Support Vector Machine classifiers that require only readily available biochemical data. In this article, the method has been implemented as the COPICAT web service, with an easy-to-use front-end interface.

Bioinformatics and Cheminformatics (Cont'd)

In silico investigations of possible routes of assembly of ORF 3a from SARS-CoV

Hao-Jen Hsu and Wolfgang B. Fischer [National Yang-Ming University]

J. Mol.Mod., **18**, 501-514, 2012

ORF 3a of human severe acute respiratory syndrome corona virus (SARS-CoV) has been identified as a 274 amino acid membrane protein. When expressed in *Xenopus* oocytes the protein forms channels. Based on bioinformatics approaches the topology has been identified to include three transmembrane domains (TMDs). Since structural models from experiments are still lacking, computational methods can be challenged to generate such models. In this study, a 'sequential approach' for the assembly is proposed in which the individual TMDs are assembled one by one. This protocol is compared with a concerted protocol in which all TMDs are assembled simultaneously.

SiteBinder: An Improved Approach for Comparing Multiple Protein Structural Motifs

David Sehnal, Radka Svobodová Vařeková, Heinrich J. Huber, Stanislav Geidl, Crina-Maria Ionescu, Michaela Wimmerová, and Jaroslav Koča [Masaryk University Brno]

J.Chem. Infor. and Mod. **52**, 343–359, 2012.

There is a paramount need to develop new techniques and tools that will extract as much information as possible from the ever growing repository of protein 3D structures. We report here on the development of a software tool for the multiple superimposition of large sets of protein structural motifs. Our superimposition methodology performs a systematic search for the atom pairing that provides the best fit. This approach guarantees that the best fit will be found and can be applied even when sequence similarity is low or does not exist at all.

Design of Combinatorial Libraries for the Exploration of Virtual Hits from Fragment Space Searches with LoFT

Uta Lessel [Boehringer Ingelheim Pharma GmbH & Co. KG], Bernd Wellenzohn, J. Robert Fischer, and Matthias Rarey

J.Chem. Infor. and Mod. **52**, 373–379, 2012.

A case study is presented illustrating the design of a focused CDK2 library. The scaffold of the library was detected by a feature trees search in a fragment space based on reactions from combinatorial chemistry. For the design the software LoFT (Library optimizer using Feature Trees) was used. The special feature called FTMatch was applied to restrict the parts of the queries where the reagents are permitted to match. This way a 3D scoring function could be simulated. Results were compared with alternative designs by GOLD docking and ROCS 3D alignments.

AsteriX: A Web Server To Automatically Extract Ligand Coordinates from Figures in PDF Articles

V. Lounnas [CMBI NCMLS Radboud University] and G. Vriend

J.Chem. Infor. and Mod. **52**, 568–576, 2012.

Coordinates describing the chemical structures of small molecules that are potential ligands for pharmaceutical targets are used at many stages of the drug design process. The coordinates of the vast majority of ligands can be obtained from either publicly accessible or commercial databases. However, interesting ligands sometimes are only available from the scientific literature, in which case their coordinates need to be reconstructed manually—a process that consists of a series of time-consuming steps. We present a Web server that helps reconstruct the three-dimensional (3D) coordinates of ligands for which a two-dimensional (2D) picture is available in a PDF file

Protein Secondary Structure

Protein Secondary Structure Prediction with SPARROW

Francesco Bettella, Dawid Rasinski, and Ernst Walter Knapp
[Freie Universität Berlin]

J.Chem. Infor. and Mod. **52**, 545–556, 2012.

A first step toward predicting the structure of a protein is to determine its secondary structure. The secondary structure information is generally used as starting point to solve protein crystal structures. In the present study, a machine learning approach based on a complete set of two-class scoring functions was used. Such functions discriminate between two specific structural classes or between a single specific class and the rest. The approach uses a hierarchical scheme of scoring functions and a neural network. The parameters are determined by optimizing the recall of learning data.

Structures of the Amyloid β -Peptides $A\beta_{1-40}$ and $A\beta_{1-42}$ as Influenced by pH and a d-Peptide

Olujide O. Olubiyi and Birgit Strodel [Research Centre Jülich]

J. Phys. Chem. B., **116**, 3280–3291, 2012.

In this simulation study, we present a comparison of the secondary structure of the two major alloforms of the Alzheimer's peptide ($A\beta_{1-40}$ and $A\beta_{1-42}$) on the basis of molecular dynamics (MD) simulations on the microsecond time scale using the two GROMOS96 force fields ffG43a2 and ffG53a6. We observe peptide and force-field related differences in the sampled conformations of $A\beta_{1-40}$ and $A\beta_{1-42}$, which we characterize in terms of NMR chemical shifts calculated from the MD trajectories and validate against the corresponding experimental NMR results.

Folding of a Helix Is Critically Stabilized by Polarization of Backbone Hydrogen Bonds: Study in Explicit Water

Li L. Duan, Ya Gao, Ye Mei, Qing G. Zhang, Bo Tang, and John Z. H. Zhang [East China Normal University]

J. Phys. Chem. B., **116**, 3430–3435, 2012.

Multiple single-trajectory molecular dynamics (MD) simulation at room temperature (300 K) in explicit water was carried out to study the folding dynamics of an α -helix (PDB 2I9M) using a polarized charge scheme that includes electronic polarization of backbone hydrogen bonds. Starting from an extended conformation, the 17-residue peptide was successfully folded into the native structure (α -helix) between 80 and 130 ns with a root-mean-square deviation of ≈ 1.0 Å. Analysis of the time-dependent trajectories revealed that helix formation of the peptide started at the terminals and progressed toward the center of the peptide.

Protein Structure Prediction

Prospects for Tertiary Structure Prediction of RNA Based on Secondary Structure Information

Satoshi Yamasaki [National Institute of Advanced Industrial Science and Technology (AIST), 2-4-7 Aomi], Shugo Nakamura, and Kazuhiko Fukui

J.Chem. Infor. and Mod. **52**, 557–567, 2012.

We developed a method, called RNA Assembler using Secondary Structure Information Effectively (RASSIE), for predicting RNA tertiary structures using known secondary structure information. We attempted a fragment assembly-based method that uses a secondary structure-based fragment library. For several typical target structures such as stem-loops, bulge-loops, and 2-way junctions, our method provided numerous good quality candidate structures in less computational time than previously proposed methods.

Comparative or Homology Modeling

Comparative modeling of 25-hydroxycholesterol-7 α -hydroxylase (CYP7B1): ligand binding and analysis of hereditary spastic paraplegia type 5 CYP7B1 mutations

Afraa Siam, Andrea Brancale and Claire Simons [Cardiff University]

J. Mol.Mod., **18**, 441-453, 2012

CYP7B1 mutations have been linked directly with the neurodegenerative disease hereditary spastic paraplegia (HSP), with mutations in the CYP7B1 gene identified as being directly responsible for autosomal recessive HSP type 5A (SPG5). To evaluate the potential impact of CYP7B1 mutations identified in SPG5 on binding and protein function, a comparative model of cytochrome P450 7B1 (CYP7B1) was constructed using human CYP7A1 as a template during model construction.

Building a Model of the Blue Cone Pigment Based on the Wild Type Rhodopsin Structure with QM/MM Methods

Jan S. Frähmcke, Marius Wanko, and Marcus Elstner [Institute for Physical and Theoretical Chemistry, TU Braunschweig]

J. Phys. Chem. B., **116**, 3313–3321, 2012.

Understanding the mechanism of color tuning of the retinal chromophore by its host protein became one of the key issues in the research on rhodopsins. While early mutation studies addressed its genetic origin, recent studies advanced to investigate its structural origin, based on X-ray crystallographic structures. . In this theoretical study, we take a different route to establish a structural model for human blue. Starting from the well-resolved structure of bovine rhodopsin, we derive multiple mutant models by stepwise mutation and equilibration using molecular dynamics simulations in a hybrid quantum mechanics/molecular mechanics framework.

Protein Structure Analysis

Characterization of the Conformational Equilibrium between the Two Major Substates of RNase A Using NMR Chemical Shifts

Carlo Camilloni, Paul Robustelli, Alfonso De Simone, Andrea Cavalli, and Michele Vendruscolo [University of Cambridge]

J. Am. Chem. Soc., **134**, 3968–3971, 2012.

Following the recognition that NMR chemical shifts can be used for protein structure determination, rapid advances have recently been made in methods for extending this strategy for proteins and protein complexes of increasing size and complexity. A remaining major challenge is to develop approaches to exploit the information contained in the chemical shifts about conformational fluctuations in native states of proteins. In this work we show that it is possible to determine an ensemble of conformations representing the free energy surface of RNase A using chemical shifts as replica-averaged restraints in molecular dynamics simulations.

Protein Confirmation Analysis

Multiscale simulation of small peptides: Consistent conformational sampling in atomistic and coarse-grained models

Olga Bezkorovaynaya, Alexander Lukyanov, Kurt Kremer and Christine Peter [Max Planck Institute for Polymer Research]

J. Comp. Chem. **33**, 937–949, 2012.

A bottom–up coarse-graining procedure for peptides in aqueous solution is presented, where the interactions in the coarse-grained (CG) model are determined such that the CG peptide samples conformations according to a high-resolution (atomistic) model. It is shown that important aspects of conformational sampling, such as correlated degrees of freedom (DOF) which play an important role in secondary structure formation, can be reproduced in the CG description. It is possible to link an existing all-atom model of a biomolecular system with a CG description such that after inverse mapping one can recover structures at high resolution with the correctly sampled (according to the atomistic model) conformational properties.

Insights into the Conformational Switching Mechanism of the Human Vascular Endothelial Growth Factor Receptor Type 2 Kinase Domain

Matteo Chioccioli, Simone Marsili, Claudia Bonaccini, Piero Procacci, and Paola Gratteri [University of Firenze]

J.Chem. Infor. and Mod. **52**, 483–491, 2012.

Human vascular endothelial growth factor receptor type 2 (h-VEGFR2) is a receptor tyrosine kinase involved in the angiogenesis process and regarded as an interesting target for the design of anticancer drugs. Its activation/inactivation mechanism is related to conformational changes in its cytoplasmatic kinase domain, involving first among all the α C-helix in N-lobe and the A-loop in C-lobe. In this view, a detailed knowledge of the conformational landscape of KDR domain is of central relevance to rationalize the efficiency and selectivity of kinase inhibitors.

Structural and Thermodynamic Characteristics That Seed Aggregation of Amyloid- β Protein in Water

Song-Ho Chong, Mirae Park, and Sihyun Ham [Sookmyung Women's University]

J. Chem. Theor. and Comp. **8**, 724–734, 2012.

Amyloid- β (A β) proteins undergo conformational transitions leading to aggregation-prone structures, which can initiate self-assembly to form soluble oligomers and eventually insoluble amyloid fibrils when transferred from the transmembrane phase to the physiological aqueous phase. Yet, how A β proteins acquire an aggregation-prone nature during the conformational transitions in water remains elusive. Here, we investigate key structural and thermodynamic features of a 42-residue A β (A β 42) protein that seed aggregation based on the fully atomistic, explicit-water molecular dynamics simulations as well as on the integral-equation theory of liquids for solvation thermodynamic analysis.

Differential role of calmodulin and calcium ions in the stabilization of the catalytic domain of adenyl cyclase CyaA from *Bordetella pertussis*

Edithe Selwa, Elodie Laine and Thérèse E. Malliavin [Unité de Bioinformatique Structurale]

Proteins: Stru. Fun. & Bioinf. **80**, 1028–1040, 2012.

The catalytic adenyl cyclase (AC) domain of the protein CyaA from *Bordetella pertussis* is activated by interaction with the C terminal lobe of calmodulin (C-CaM). The AC/C-CaM complex displays an elongated shape, but hydrodynamics measurements on the isolated AC domain allowed to characterize the shape of the protein as spherical. Here, we study by molecular dynamics simulations the complexes between AC and the apo and Ca²⁺-loaded C-CaM, as well as the isolated AC, to characterize the features of AC conformational variability and of AC/C-CaM interaction.

Protein Conformational Analysis (Cont'd)

Alternative Interdomain Configurations of the Full-Length MMP-2 Enzyme Explored by Molecular Dynamics Simulations

Natalia Díaz [Universidad de Oviedo] and Dimas Suárez

J. Phys. Chem. B., **116**, 2677–2686, 2012.

Conformational freedom between the different domains of the matrix metalloproteinase family of enzymes has been repeatedly invoked to explain the mechanism of hydrolysis of some of their most complex macromolecular substrates. This proposed interdomain motion has been experimentally confirmed to occur in solution for matrix metalloproteinases MMP-1, MMP-9, and MMP-12. In this work, we computationally assess the likely conformational freedom in aqueous solution of the full-length form of the MMP-2 enzyme in the absence of its pro-peptide domain.

Protein Dynamics

Membrane Clustering and the Role of Rebinding in Biochemical Signaling

Andrew Mugler, Aimee Gotway Bailey, Koichi Takahashi, Pieter Rein ten Wolde [FOM Institute AMOLF]

Biophysical Journal. **102**, 1069-1078, 2012.

In many cellular signaling pathways, key components form clusters at the cell membrane. Although much work has focused on the mechanisms behind such cluster formation, the implications for downstream signaling remain poorly understood. Here, motivated by recent experiments, we use particle-based simulation to study a covalent modification network in which the activating component is either clustered or randomly distributed on the membrane. We find that whereas clustering reduces the response of a single-modification network, it can enhance the response of a double-modification network.

Functional Domain Motions in Proteins on the ~1–100 ns Timescale: Comparison of Neutron Spin-Echo Spectroscopy of Phosphoglycerate Kinase with Molecular-Dynamics Simulation

N. Smolin, R. Biehl, G.R. Kneller, D. Richter, J.C. Smith [Oak Ridge National Laboratory]

Biophysical Journal. **102**, 1108-1117, 2012.

Protein function often requires large-scale domain motion. An exciting new development in the experimental characterization of domain motions in proteins is the application of neutron spin-echo spectroscopy (NSE). NSE directly probes coherent (i.e., pair correlated) scattering on the ~1–100 ns timescale. Here, we report on all-atom molecular-dynamics (MD) simulation of a protein, phosphoglycerate kinase, from which we calculate small-angle neutron scattering (SANS) and NSE scattering properties. The simulation-derived and experimental-solution SANS results are in excellent agreement.

Mechanical Anisotropy of Ankyrin Repeats

Whasil Lee, Xiancheng Zeng, Kristina Rotolo, Ming Yang, Christopher J. Schofield, Vann Bennett, Weitao Yang, Piotr E. Marszalek [Duke University]

Biophysical Journal. **102**, 1118-1126, 2012.

Red blood cells are frequently deformed and their cytoskeletal proteins such as spectrin and ankyrin-R are repeatedly subjected to mechanical forces. While the mechanics of spectrin was thoroughly investigated in vitro and in vivo, little is known about the mechanical behavior of ankyrin-R. In this study, we combine coarse-grained steered molecular dynamics simulations and atomic force spectroscopy to examine the mechanical response of ankyrin repeats (ARs) in a model synthetic AR protein NI6C, and in the D34 fragment of native ankyrin-R when these proteins are subjected to various stretching geometry conditions.

Protein Dynamics (Cont'd)

Charge-State Dependent Compaction and Dissociation of Protein Complexes: Insights from Ion Mobility and Molecular Dynamics

Zoe Hall, Argyris Politis, Matthew F. Bush, Lorna J. Smith, and Carol V. Robinson [University of Oxford]

J. Am. Chem. Soc., **134**, 3429–3438, 2012.

Collapse to compact states in the gas phase, with smaller collision cross sections than calculated for their native-like structure, has been reported previously for some protein complexes although not rationalized. Here we combine experimental and theoretical studies to investigate the gas-phase structures of four multimeric protein complexes during collisional activation. Importantly, using ion mobility–mass spectrometry (IM–MS), we find that all four macromolecular complexes retain their native-like topologies at low energy. To simulate the collision-induced dissociation (CID) of different charge states of SAP, we used MS to measure the charge state of the ejected monomer and assigned this charge to one subunit, distributing the residual charges evenly among the remaining four subunits.

Structure and Dynamics of an Unfolded Protein Examined by Molecular Dynamics Simulation

Kresten Lindorff-Larsen, Nikola Trbovic, Paul Maragakis, Stefano Piana, and David E. Shaw [D. E. Shaw Research]

J. Am. Chem. Soc., **134**, 3787–3791, 2012.

The accurate characterization of the structure and dynamics of proteins in disordered states is a difficult problem whose solution promises to further our understanding of protein folding and intrinsically disordered proteins. MD simulations have added considerably to our understanding of folded proteins, but the accuracy with which the force fields used in such simulations can describe disordered proteins is unclear. In this work, using a modern force field, we performed a 200 μ s unrestrained MD simulation of the acid-unfolded state of an experimentally well-characterized protein, ACBP, to explore the extent to which state-of-the-art simulation can describe the structural and dynamical features of a disordered protein.

Hydrophobic Core Flexibility Modulates Enzyme Activity in HIV-1 Protease

Seema Mittal, Yufeng Cai, Madhavi N. L. Nalam, Daniel N. A. Bolon, and Celia A. Schiffer [University of Massachusetts Medical School]

J. Am. Chem. Soc., **134**, 4163–4168, 2012.

Human immunodeficiency virus Type-1 (HIV-1) protease is crucial for viral maturation and infectivity. Studies of protease dynamics suggest that the rearrangement of the hydrophobic core is essential for enzyme activity. Many mutations in the hydrophobic core are also associated with drug resistance and may modulate the core flexibility. To test the role of flexibility in protease activity, pairs of cysteines were introduced at the interfaces of flexible regions remote from the active site. Molecular dynamics simulations showed that altered dynamics propagated throughout the enzyme from the engineered disulfide.

Protein Dynamics (Cont'd)

Effects of external electromagnetic fields on the conformational sampling of a short alanine peptide

Gleb Y. Solomentsev, Niall J. English and Damian A. Mooney [University College Dublin]

J. Comp. Chem. **33**, 917–923, 2012.

Non-equilibrium molecular dynamics simulations of a solvated 21-residue polyalanine (A21) peptide, featuring a high propensity for helix formation, have been performed at 300 K and 1 bar in the presence of external electromagnetic (e/m) fields in the microwave region (2.45 GHz) and an r.m.s. electric field intensity range of 0.01–0.05 V/Å. To investigate how the field presence affects transitions between the conformational states of a protein, we report 16 independent 40 ns-trajectories of A21 starting from both extended and fully folded states.

Comparison of Cellulose I β Simulations with Three Carbohydrate Force Fields

James F. Matthews [National Renewable Energy Laboratory], Gregg T. Beckham, Malin Bergenstr hle-Wohlert, John W. Brady, Michael E. Himmel, and Michael F. Crowley

J. Chem. Theor. and Comp. **8**, 735–748, 2012.

Molecular dynamics simulations of cellulose have recently become more prevalent due to increased interest in renewable energy applications, and many atomistic and coarse-grained force fields exist that can be applied to cellulose. However, to date no systematic comparison between carbohydrate force fields has been conducted for this important system. To that end, we present a molecular dynamics simulation study of hydrated, 36-chain cellulose I β microfibrils at room temperature with three carbohydrate force fields (CHARMM35, GLYCAM06, and Gromos 45a4) up to the near-microsecond time scale.

The Role of Hydration in Protein Stability: Comparison of the Cold and Heat Unfolded States of Yfh1

Miquel Adrover, Gabriel Martorell, Stephen R. Martin, Dunja Urosev, Petr V. Konarev, Dmitri I. Svergun, Xavier Daura, Pierandrea Temussi, Annalisa Pastore [National Institute for Medical Research, The Ridgeway]

J. Molec. Bio. **415**, 413–424, 2012.

Protein unfolding occurs at both low and high temperatures, although in most cases, only the high-temperature transition can be experimentally studied. A pressing question is how much the low- and high-temperature denatured states, although thermodynamically equivalent, are structurally and kinetically similar. We have combined experimental and computational approaches to compare the high- and low-temperature unfolded states of Yfh1, a natural protein that, at physiologic pH, undergoes

Insights into internal dynamics of 6-phosphogluconolactonase from *Trypanosoma brucei* studied by nuclear magnetic resonance and molecular dynamics

Paolo A. Calligari, Gilmar F. Salgado [INSERM U869 - Universit  Bordeaux Segalen], Philippe Pelupessy, Philippe Lopes, Jamal Ouazzani, Geoffrey Bodenhausen and Daniel Abergel

Proteins: Stru. Fun. & Bioinf. **80**, 1196–1210, 2012.

Nuclear magnetic resonance is used to investigate the backbone dynamics in 6-phosphogluconolactonase from *Trypanosoma brucei* (Tb6PGL) with (holo-) and without (apo-) 6-phosphogluconic acid as ligand. Relaxation data were analyzed using the model-free approach and reduced spectral density mapping. Comparison of predictions, based on 77 ns molecular dynamics simulations, with the observed relaxation rates gives insight into dynamical properties of the protein and their alteration on ligand binding.

Protein Dynamics (Cont'd)

Molecular Dynamics Simulation Studies of the Interactions between Ionic Liquids and Amino Acids in Aqueous Solution

Luciana I. N. Tomé, Miguel Jorge, José R. B. Gomes, and João A. P. Coutinho [Universidade de Aveiro]

J. Phys. Chem. B., **116**, 1831–1842, 2012.

Although the understanding of the influence of ionic liquids (ILs) on the solubility behavior of biomolecules in aqueous solutions is relevant for the design and optimization of novel biotechnological processes, the underlying molecular-level mechanisms are not yet consensual or clearly elucidated. In order to contribute to the understanding of the molecular interactions established between amino acids and ILs in aqueous media, classical molecular dynamics (MD) simulations were performed for aqueous solutions of five amino acids with different structural characteristics (glycine, alanine, valine, isoleucine, and glutamic acid) in the presence of 1-butyl-3-methylimidazolium bis(trifluoromethyl)sulfonyl imide.

Molecular Origin of Piezo- and Pyroelectric Properties in Collagen Investigated by Molecular Dynamics Simulations

Harish Kumar Ravi, Fabio Simona, Jürg Hulliger, and Michele Cascella [Universität Bern]

J. Phys. Chem. B., **116**, 1901–1907, 2012.

Molecular dynamics simulations were used to study the effect of mechanical and thermal stimuli on the electrostatic properties of collagen model helices. Our model sequences were based on glycine proline and hydroxyproline amino acids. We find that longitudinal mechanical strain induces significant variation of the polarization of the collagen fibril. Such a phenomenon is determined by reorientation of the backbone polar groups, which are free to respond to the mechanical solicitation.

Protein Dynamics in Organic Media at Varying Water Activity Studied by Molecular Dynamics Simulation

Rasmus Wedberg, Jens Abildskov, and Günther H. Peters [Technical University of Denmark]

J. Phys. Chem. B., **116**, 2575–2585, 2012.

In nonaqueous enzymology, control of enzyme hydration is commonly approached by fixing the thermodynamic water activity of the medium. In this work, we present a strategy for evaluating the water activity in molecular dynamics simulations of proteins in water/organic solvent mixtures. The method relies on determining the water content of the bulk phase and uses a combination of Kirkwood–Buff theory and free energy calculations to determine corresponding activity coefficients.

Molecular Dynamics Simulations of the Bacterial ABC Transporter SAV1866 in the Closed Form

Jean-François St-Pierre, Alex Bunker, Tomasz Róg, Mikko Karttunen, and Normand Mousseau [Université de Montréal]

J. Phys. Chem. B., **116**, 2934–2942, 2012.

The ATP binding cassette (ABC) transporter family of proteins contains members involved in ATP-mediated import or export of ligands at the cell membrane. For the case of exporters, the translocation mechanism involves a large-scale conformational change that involves a clothespin-like motion from an inward-facing open state, able to bind ligands and adenosine triphosphate (ATP), to an outward-facing closed state. Our work focuses on SAV1866, a bacterial member of the ABC transporter family for which the structure is known for the closed state.

Protein Dynamics (Cont'd)

Insights into Structural Properties of Denatured Human Prion 121-230 at Melting Temperature Studied by Replica Exchange Molecular Dynamics

Jaw-Luen Tang, Po-Jen Wu, Shing-Chuen Wang, and Cheng-I Lee [National Chung Cheng University]

J. Phys. Chem. B., **116**, 3305–3312, 2012.

Misfolding and aggregation of the prion protein (PrP) is responsible for the development of fatal transmissible neurodegenerative diseases. PrP undergoes structural conversion from a natively folded state into a misfolded state, resulting in aggregated amyloid fibrils. Partial unfolding has been recognized as an essential step in fibrillation, especially at the middle point of unfolding. To study the possible aggregation-prone states, we characterized the structure of the C-terminal globular domain of human prion (huPrP) 121-230 near extended conformation at melting temperature by replica exchange molecular dynamics (REMD) simulation.

Free Energy Calculations

Determination of Membrane-Insertion Free Energies by Molecular Dynamics Simulations

James Gumbart [Argonne National Laboratory], Benoît Roux

Biophysical Journal. **102**, 795-801, 2012.

The accurate prediction of membrane-insertion probability for arbitrary protein sequences is a critical challenge to identifying membrane proteins and determining their folded structures. Although algorithms based on sequence statistics have had moderate success, a complete understanding is needed. However, for a recently resolved water-to-bilayer scale, it is found that MD simulations that carefully mimic the conditions of the experiment can reproduce experimental free energies, even when using the same force field as previous computational studies that were cited as evidence of this disagreement. Therefore, it is suggested that experimental and simulation-based scales can both be accurate and that discrepancies stem from disparities in the microscopic processes being considered rather than methodological errors.

Computation of the binding affinities of catechol-O-methyltransferase inhibitors: Multisubstate relative free energy calculations

P. Nuno Palma [BIAL, Department of Research and Development], Maria João Bonifácio, Ana Isabel Loureiro and Patrício Soares-da-Silva

J. Comp. Chem. **33**, 970–986, 2012.

Alchemical free energy simulations are amongst the most accurate techniques for the computation of the free energy changes associated with noncovalent protein–ligand interactions. A procedure is presented to estimate the relative binding free energies of several ligands to the same protein target where multiple, low-energy configurational substates might coexist, as opposed to one unique structure. The contributions of all individual substates were estimated, explicitly, with the free energy perturbation method, and combined in a rigorous fashion to compute the overall relative binding free energies and dissociation constants.

Free Energy Calculations (Cont'd)

On the electronic properties of two-dimensional honeycomb GaInN and GaAlN alloys: a molecular analysis

Ernesto Chigo Anotá [Benemérita Universidad Autónoma de Puebla] and Heriberto Hernández Cocoltzi

J. Mol.Mod., **18**, 591-596, 2012

We have performed first principles total energy calculations to investigate the structural and the electronic properties of two-dimensional honeycomb GaAlN and GaInN alloys. Calculations were done using a coronene-like (C₂₄H₁₂) cluster and for different numbers of Ga, Al, and In atoms. The exchange and correlation potential energies were treated within the generalized gradient approximation (GGA). The bond length, dipole moment, binding energy, and gap between the HOMO and the LUMO are reported as a function of x.

Cocaine Esterase–Cocaine Binding Process and the Free Energy Profiles by Molecular Dynamics and Potential of Mean Force Simulations

Xiaoqin Huang, Xinyun Zhao, Fang Zheng, and Chang-Guo Zhan [University of Kentucky]

J. Phys. Chem. B., **116**, 3361–3368, 2012.

The combined molecular dynamics (MD) and potential of mean force (PMF) simulations have been performed to determine the free energy profiles for the binding process of (–)-cocaine interacting with wild-type cocaine esterase (CocE) and its mutants (T172R/G173Q and L119A/L169K/G173Q). According to the MD simulations, the general protein–(–)-cocaine binding mode is not affected by the mutations; e.g., the benzoyl group of (–)-cocaine is always bound in a subsite composed of aromatic residues W151, W166, F261, and F408 and hydrophobic residue L407, while the carbonyl oxygen on the benzoyl group of (–)-cocaine is hydrogen-bonded with the oxyanion-hole residues Y44 and Y118.

Ligand Binding/Docking

Conformational switch of a flexible loop in human laminin receptor determines laminin-1 interaction

Carmen Di Giovanni, Alessandro Grottesi and Antonio Lavecchia [University of Naples “Federico II”]

Europ. Biophys. Jou., **41**, 353-358, 2012.

The 37/67-kDa human laminin receptor (LamR) is a cell surface protein that interacts with molecules located in the extra-cellular matrix. The exact interaction mode of laminin-1 and LamR is not fully understood. Laminin-1 is thought to bind to LamR through interaction with the so-called peptide G (residues 161–180) and the C-terminal helix (residues 205–229). Here we performed 100-ns atomistic force field-based molecular dynamics simulations to explore the structure and dynamics of LamR related to laminin-1 interactions.

Tetrahydroisoquinolines acting as dopaminergic ligands. A molecular modeling study using MD simulations and QM calculations

Sebastián Andujar, Fernando Suvire, Inmaculada Berenguer, Ricardo D. Enriz [Universidad Nacional de San Luis], Nuria Cabedo and Paloma Marín, et al.

J. Mol.Mod., **18**, 419-431, 2012

A molecular modeling study on 16 1-benzyl tetrahydroisoquinolines (BTHIQs) acting as dopaminergic ligands was carried out. By combining molecular dynamics simulations with ab initio and density functional theory (DFT) calculations, a simple and generally applicable procedure to evaluate the binding energies of BTHIQs interacting with the human dopamine D2 receptor (D2 DR) is reported here, providing a clear picture of the binding interactions of BTHIQs from both structural and energetic viewpoints.

Ligand Binding / Docking (Cont'd)

Binding of BIS like and other ligands with the GSK-3 β kinase: a combined docking and MM-PBSA study

Nihar R. Jena [Indian Institute of Science]

J. Mol.Mod., **18**, 631-644, 2012

Binding of several bisindolylmaleimide (BIS) like (BIS-3, BIS-8 and UCN1) and other ligands (H89, SB203580 and Y27632) with the glycogen synthase kinase-3 (GSK-3 β) has been studied using combined docking, molecular dynamics and Poisson-Boltzmann surface area analysis approaches. The study generated novel binding modes of these ligands that can rationalize why some ligands inhibit GSK-3 β while others do not. The relative binding free energies associated with these binding modes are in agreement with the corresponding measured specificities.

Interaction of I50V Mutant and I50L/A71V Double Mutant HIV-Protease with Inhibitor TMC114 (Darunavir): Molecular Dynamics Simulation and Binding Free Energy Studies

Biswa Ranjan Meher and Yixuan Wang [Albany State University]

J. Phys. Chem. B., **116**, 1884–1900, 2012.

In the present work, the binding of inhibitor TMC114 (darunavir) to wild-type (WT), single (I50V) as well as double (I50L/A71V) mutant HIV-proteases (HIV-pr) was investigated with all-atom molecular dynamics (MD) simulations as well as molecular mechanic-Poisson-Boltzmann surface area (MM-PBSA) calculation. For both the apo and complexed HIV-pr, many intriguing effects due to double mutant, I50L/A71V, are observed. The I50L/A71V mutant directly increases the binding affinity by approximately -0.88 (Ile50 to Leu50) and -0.90 (Ile50' to Leu50') kcal/mol, accounting 45% for the total gain of the binding affinity.

Rigid Body Brownian Dynamics as a Tool for Studying Ion Channel Blockers

Dan Gordon [Australian National University], Rong Chen, Junming Ho, Michelle L. Coote, and Shin-Ho Chung

J. Phys. Chem. B., **116**, 1933–1941, 2012.

Using a novel rigid body Brownian dynamics algorithm, we investigate how a spherically asymmetrical polyamine molecule, a branched analogue of spermine, interacts with the external vestibule of the voltage-gated potassium channel, Kv1.2. Simulations reveal that the blocker, with a charge of +4e, inserts one of its charged amine groups into the selectivity filter, while another forms a salt bridge with an aspartate residue located just outside the entrance of the pore. This binding mode mimics features of the binding of polypeptides such as the scorpion venom charybdotoxin to the channel.

Enzyme Catalysis

Docking and molecular dynamics simulation studies on glycation-induced conformational changes of human paraoxonase 1

Ammara Saleem, S. Sikander Azam and Shamshad Zarina [University of Karachi]

Europ. Biophys. Jou., **41**, 241-248, 2012.

Human paraoxonase 1 (huPON1) is a calcium-dependent esterase responsible for hydrolysis of a wide variety of substrates including organophosphates, esters, lactones, and paraoxon. Although its natural substrate is unknown, the action of PON as an antioxidant is well documented. Because recent reports have suggested glycation may induce reduced PON activity in diabetes, we investigated the structural features of huPON1 and its glycated mutant by template-based modeling, docking, and molecular dynamics (MD) simulations.

Enzyme Catalysis (Cont'd)

Combining molecular dynamics and docking simulations of the cytidine deaminase from *Mycobacterium tuberculosis* H37Rv

Luis Fernando Saraiva Macedo Timmers, Rodrigo Gay Ducati, Zilpa Adriana Sánchez-Quitian, Walter Filgueira de Azevedo [Pontificia Universidade Católica do Rio Grande do Sul], Luiz Augusto Basso and Diógenes Santiago Santos, et al.

J. Mol.Mod., **18**, 467-479, 2012

Cytidine Deaminase (CD) is an evolutionarily conserved enzyme that participates in the pyrimidine salvage pathway recycling cytidine and deoxycytidine into uridine and deoxyuridine, respectively. Here, our goal is to apply computational techniques in the pursuit of potential inhibitors of *Mycobacterium tuberculosis* CD (MtCDA) enzyme activity. Molecular docking simulation was applied to find the possible hit compounds. Molecular dynamics simulations were also carried out to investigate the physically relevant motions involved in the protein-ligand recognition process, aiming at providing estimates for free energy of binding.

Investigation of the acylation mechanism of class C beta-lactamase: pKa calculation, molecular dynamics simulation and quantum mechanical calculation

Smriti Sharma and Pradipta Bandyopadhyay [Jawaharlal Nehru University]

J. Mol.Mod., **18**, 481-492, 2012

β -Lactamases are bacterial enzymes that act as a bacterial defense system against β -lactam antibiotics. β -Lactamase cleaves the β -lactam ring of the antibiotic by a two step mechanism involving acylation and deacylation steps. Although class C β -lactamases have been investigated extensively, the details of their mechanism of action are not well understood at the molecular level. In this study, we investigated the mechanism of the acylation step of class C β -lactamase using pKa calculations, molecular dynamics (MD) simulations and quantum mechanical (QM) calculations.

Insight into the reaction mechanism of cis,cis-muconate lactonizing enzymes: a DFT QM/MM study

Tuanjai Somboon, Matthew Paul Gleeson [Kasetsart University] and Supa Hannongbua

J. Mol.Mod., **18**, 525-531, 2012

MLEs derived from *mycobacterium smegmatis* and *seudomonas fluorescens* share ~76% identity and have a very similar arrangement of catalytic residues in their active site configuration. However, while they catalyze the conversion of cis,cis-muconate to the same achiral product, muconolactone, studies in deuterated solvent surprisingly show that the cyclo-isomerization proceeds with the formation of a chiral product. In this paper we discuss the application of DFT QM/MM calculations on both MLEs, to our knowledge the first reported in the literature on this protein.

Identification of new potential *Mycobacterium tuberculosis* shikimate kinase inhibitors through molecular docking simulations

Carolina Pasa Vianna and Walter F. de Azevedo [Pontificia Universidade Católica do Rio Grande do Sul (PUCRS)]

J. Mol.Mod., **18**, 755-764, 2012

Tuberculosis (TB) is the major cause of human mortality from a curable infectious disease, attacking mainly in developing countries. Among targets identified in *Mycobacterium tuberculosis* genome, enzymes of the shikimate pathway deserve special attention, since they are essential to the survival of the microorganism and absent in mammals. The object of our study is shikimate kinase (SK), the fifth enzyme of this pathway. We applied virtual screening methods in order to identify new potential inhibitors for this enzyme. In this work we employed MOLDOCK program in all molecular docking simulations.

Enzyme Catalysis (Cont'd)

Analyzing the Molecular Basis of Enzyme Stability in Ethanol/Water Mixtures Using Molecular Dynamics Simulations

Diana Lousa, António M. Baptista, and Cláudio M. Soares [Universidade Nova de Lisboa]

J.Chem. Infor. and Mod. **52**, 465–473, 2012.

One of the drawbacks of nonaqueous enzymology is the fact that enzymes tend to be less stable in organic solvents than in water. There are, however, some enzymes that display very high stabilities in nonaqueous media. In order to take full advantage of the use of nonaqueous solvents in enzyme catalysis, it is essential to elucidate the molecular basis of enzyme stability in these media. Toward this end, we performed μ s-long molecular dynamics simulations using two homologous proteases, pseudolysin, and thermolysin, which are known to have considerably different stabilities in solutions containing ethanol.

Exploring Inhibitor Release Pathways in Histone Deacetylases Using Random Acceleration Molecular Dynamics Simulations

Subha Kalyaanamoorthy and Yi-Ping Phoebe Chen [La Trobe University]

J.Chem. Infor. and Mod. **52**, 589–603, 2012.

Molecular channel exploration perseveres to be the prominent solution for eliciting structure and accessibility of active site and other internal spaces of macromolecules. Histone deacetylases (HDACs) are metal-dependent enzymes that are involved in the cell growth, cell cycle regulation, and progression, and their deregulations have been linked with different types of cancers. The class I HDACs are known to possess two different protein channels, an 11 Å and a 14 Å, of which the former is a ligand or substrate occupying tunnel that leads to the buried active site zinc ion and the latter is speculated to be involved in product release. We have carried out random acceleration MD simulations coupled with the classical molecular dynamics to explore the release of the ligand, N-(2-aminophenyl) benzamide (LLX) from the active sites of the recently solved X-ray crystal structure of HDAC2 and the computationally modeled HDAC1 proteins.

Internal Diffusion-Controlled Enzyme Reaction: The Acetylcholinesterase Kinetics

Sangyun Lee, Ji-Hyun Kim, and Sangyoub Lee [Seoul National University]

J. Chem. Theor. and Comp. **8**, 715–723, 2012.

Acetylcholinesterase is an enzyme with a very high turnover rate; it quenches the neurotransmitter, acetylcholine, at the synapse. We have investigated the kinetics of the enzyme reaction by calculating the diffusion rate of the substrate molecule along an active site channel inside the enzyme from atomic-level molecular dynamics simulations. In contrast to the previous works, we have found that the internal substrate diffusion is the determinant of the acetylcholinesterase kinetics in the low substrate concentration limit.

Enzyme Catalysis (Cont'd)

The Structural Role of Mg^{2+} Ions in a Class I RNA Polymerase Ribozyme: A Molecular Simulation Study

Jacopo Sgrignani and Alessandra Magistrato [CNR-IOM-Democritos National Simulation Center]

J. Phys. Chem. B., **116**, 2259–2268, 2012.

According to the RNA world hypothesis, self-replicating ribozymes, storing the genetic information and being able to perform catalysis, were the constituents of the first living organisms. Polymerase catalysis is usually assisted by Mg^{2+} ions, but it is not always trivial to find out experimentally the number of Mg^{2+} ions placed in the active site as well as the identity and the number of their coordination ligands. Here, we addressed this issue in an artificial class I ligase ribozyme. On the basis of a recently solved crystal structure, we constructed computational models of reactant and product states of this ribozyme, considering monometallic and bimetallic species.

Proton Transport Pathways in [NiFe]-Hydrogenase

Isaiah Sumner and Gregory A. Voth [University of Chicago]

J. Phys. Chem. B., **116**, 2917–2926, 2012.

Hydrogenases reversibly catalyze the production of molecular hydrogen. Current interest in these enzymes is focused on understanding the catalysis, since this may prove useful for hydrogen-based fuel cell and photosynthetic hydrogen production cell technologies. A key step in the hydrogenase catalytic cycle and the focus of this work is proton transport (PT) to and from the active site. The PT mechanism of the enzyme is studied using reactive molecular dynamics simulations of the full protein and the excess proton transfers via the multistate empirical valence bond (MS-EVB) method.

Effects of Organic Solvent and Crystal Water on γ -Chymotrypsin in Acetonitrile Media: Observations from Molecular Dynamics Simulation and DFT Calculation

Lijuan Zhu, Wei Yang, Yan Yan Meng, Xiuchan Xiao, Yanzhi Guo, Xuemei Pu, and Menglong Li [Sichuan University]

J. Phys. Chem. B., **116**, 3292–3304, 2012.

The use of enzymes in nonaqueous solvent has been one of the most exciting facets of enzymology in recent times; however, the mechanism of how organic solvent and essential water influence on structure and function of enzyme has been not satisfactorily explained in experiments, which limit its further application. Herein, we used molecular dynamics (MD) simulation to study γ -chymotrypsin in two types of media (viz., acetonitrile media with inclusion of 151 crystal water molecules and aqueous solution).

Protein-Protein Interactions

Monte Carlo Simulation on Complex Formation of Proteins and Polysaccharides

Yunqi Li, Tongfei Shi, Lijia An, and Qingrong Huang [Rutgers University]

J. Phys. Chem. B., **116**, 3045–3053, 2012.

In protein–polysaccharide complex systems, how nonspecific interactions such as electrostatic and van der Waals interactions affect complex formation has not been clearly understood. On the basis of a coarse-grained model with the specificity of a target system, we have applied Monte Carlo (MC) simulation to illustrate the process of complex coacervate formation from the association of proteins and polysaccharides. The coarse-grained model is based on serum albumin and a polycation system, and the MC simulation of pH impact on complex coacervation has been carried out.

Membrane Proteins and Lipid Peptide Interactions

Tuning Membrane Phase Separation Using Nonlipid Amphiphiles

Hari S. Muddana, Homer H. Chiang, Peter J. Butler [The Pennsylvania State University]

Biophysical Journal. **102**, 489-497, 2012.

Lipid phase separation may be a mechanism by which lipids participate in sorting membrane proteins and facilitate membrane-mediated biochemical signaling in cells. To provide new tools for membrane lipid phase manipulation that avoid direct effects on protein activity and lipid composition, we studied phase separation in binary and ternary lipid mixtures under the influence of three nonlipid amphiphiles, vitamin E (VE), Triton-X (TX)-100, and benzyl alcohol (BA).

α -Synuclein Induces Both Positive Mean Curvature and Negative Gaussian Curvature in Membranes

Anthony R. Braun, Eva Sevesik, Pamela Chin, Elizabeth Rhoades, Stephanie Tristram-Nagle, and Jonathan N. Sachs [University of Minnesota]

J. Am. Chem. Soc., **134**, 2613–2620, 2012.

Using a combination of X-ray scattering, fluorescence correlation spectroscopy, coarse-grained molecular dynamics (MD) simulations and potential of mean force calculations, we have explored the membrane remodeling effects of monomeric α -synuclein (α S). Our initial findings from multiple approaches are that α S (1) causes a significant thinning of the bilayer and (2) stabilizes positive mean curvature, such that the maximum principle curvature matches that of synaptic vesicles, α S-induced tubules, and the synthetic lipid vesicles to which the protein binds most tightly.

Molecular Dynamics Simulations Reveal Specific Interactions of Post-translational Palmitoyl Modifications with Rhodopsin in Membranes

Bjoern E. S. Olausson, Alan Grossfield, Michael C. Pitman, Michael F. Brown, Scott E. Feller, and Alexander Vogel [Martin-Luther-University Halle-Wittenberg]

J. Am. Chem. Soc., **134**, 4324–4331, 2012.

We present a detailed analysis of the behavior of the highly flexible post-translational lipid modifications of rhodopsin from multiple-microsecond all-atom molecular dynamics simulations. Rhodopsin was studied in a realistic membrane environment that includes cholesterol, as well as saturated and polyunsaturated lipids with phosphocholine and phosphoethanolamine headgroups. The simulation reveals striking differences between the palmitoylations at Cys322 and Cys323 as well as between the palmitoyl chains and the neighboring lipids.

Molecular dynamics simulations of nafion and sulfonated poly ether sulfone membranes II. Dynamic properties of water and hydronium

Takahiro Ohkubo [Chiba University], Koh Kidena, Naohiko Takimoto and Akihiro Ohira

J. Mol.Mod., **18**, 533-540, 2012

We measured the self-diffusion coefficients of water in a Nafion membrane and two sulfonated polyethersulfone (SPES) membranes with varying ion-exchange capacities (IEC) in terms of relative humidity using the pulse field gradient NMR (PFG-NMR) technique. The self-diffusion coefficients were plotted against the number of water molecules per sulfonic acid group, λ , and compare these values with the results of molecular dynamics (MD) simulations. Classical MD simulations for all membranes were carried out using a consistent force field at $\lambda = 3, 6, 9, 12$, and 15 .

Membrane Proteins and Lipid Peptide Interactions (Cont'd)

Modification of Lipid Bilayer Structure by Diacylglycerol: A Comparative Study of Diacylglycerol and Cholesterol

Mohammad Alwarawrah, Jian Dai, and Juyang Huang [Texas Tech University]

J. Chem. Theor. and Comp., **8**, 749–758, 2012.

Diacylglycerols (DAGs) are important second messengers in biomembranes, and they can activate protein kinase C and many other enzymes and receptors. However, their interactions with cholesterol and other lipids have not been previously studied using molecular dynamics (MD) simulation. In this study, nine independent atomistic MD simulations were performed to specifically investigate the interactions between di16:0DAG, 16:0,18:1-phosphatidylcholine (POPC), and cholesterol.

Membrane Protein Simulations Using AMBER Force Field and Berger Lipid Parameters

Arnau Cordoní [Universitat Autònoma de Barcelona], Gianluigi Caltabiano, and Leonardo Pardo

J. Chem. Theor. and Comp., **8**, 948–958, 2012.

AMBER force fields are among the most commonly used in molecular dynamics (MD) simulations of proteins. Unfortunately, they lack a specific set of lipid parameters, thus limiting its use in membrane protein simulations. In order to overcome this limitation we assessed whether the widely used united-atom lipid parameters described by Berger and co-workers could be used in conjunction with AMBER force fields in simulations of membrane proteins. Thus, free energies of solvation in water and in cyclohexane, and free energies of water to cyclohexane transfer, were computed by thermodynamic integration procedures for neutral amino acid side-chains employing AMBER99, AMBER03, and OPLS-AA amino acid force fields.

Molecular Dynamics Investigations of PRODAN in a DLPC Bilayer

William K. Nitschke, Cintia C. Vequi-Suplicy, Kaline Coutinho, and Hubert Stassen [UFRGS Av. Bento Gonçalves 9500]

J. Phys. Chem. B., **116**, 2713–2721, 2012.

Molecular dynamics computer simulations have been performed to identify preferred positions of the fluorescent probe PRODAN in a fully hydrated DLPC bilayer in the fluid phase. In addition to the intramolecular charge-transfer first vertical excited state, we considered different charge distributions for the electronic ground state of the PRODAN molecule by distinct atomic charge models corresponding to the probe molecule in vacuum as well as polarized in a weak and a strong dielectric solvent (cyclohexane and water).

Difference between Magainin-2 and Melittin Assemblies in Phosphatidylcholine Bilayers: Results from Coarse-Grained Simulations

Kolattukudy P. Santo and Max L. Berkowitz [University of North Carolina at Chapel Hill]

J. Phys. Chem. B., **116**, 3021–3030, 2012.

We performed coarse-grained computer simulations using MARTINI force field to study the difference in the self-assembly and possible pore creation in DPPC phospholipid membranes by two different antimicrobial peptides: magainin-2 and melittin. Simulations showed that magainin-2 peptides create large sized disordered toroidal pores that allow easy water permeation across them. Melittin assemblies contain peptides in U-shaped conformations that, although creating holes in membranes, block effectively the passage of water.

Protein Folding

Adsorption, Folding, and Packing of an Amphiphilic Peptide at the Air/Water Interface

Ozge Engin and Mehmet Sayar [Koç University]

J. Phys. Chem. B., **116**, 2198–2207, 2012.

Peptide oligomers play an essential role as model compounds for identifying key motifs in protein structure formation and protein aggregation. Here, we present our results, based on extensive molecular dynamics simulations, on adsorption, folding, and packing within a surface monolayer of an amphiphilic peptide at the air/water interface. Experimental results suggest that these molecules spontaneously form ordered monolayers at the interface, adopting a β -hairpin-like structure within the surface layer.

Simulations of Tryptophan Fluorescence Dynamics during Folding of the Villin Headpiece

Jose R. Tusell and Patrik R. Callis [Montana State University]

J. Phys. Chem. B., **116**, 2586–2594, 2012.

Protein folding kinetics is commonly monitored by changes in tryptophan (Trp) fluorescence intensity. Considerable recent discussion has centered on whether the fluorescence of the single Trp in the much-studied, fast-folding villin headpiece C-terminal domain (HP35) accurately reflects folding kinetics, given the general view that quenching is by a histidine cation (His^+) one turn away in an α -helix (helix III) that forms early in the folding process, according to published MD simulations. To help answer this question, we ran 1.0 μs MD simulations on HP35 (N27H) and a faster-folding variant in its folded form at 300 K.

Protein-Nucleic acid Interactions

Study of intermolecular contacts in the proline-rich homeodomain (PRH)–DNA complex using molecular dynamics simulations

Seifollah Jalili [K. N. Toosi University of Technology] and Leila Karami

Europ. Biophys. Jou., **41**, 329–340, 2012.

The proline-rich homeodomain (PRH)–DNA complex consists of a protein with 60 residues and a 13-base-pair DNA. The PRH protein is a transcription factor that plays a key role in the regulation of gene expression. PRH is a significant member of the Q50 class of homeodomain proteins. The homeodomain section of PRH is essential for binding to DNA and mediates sequence-specific DNA binding. Three 20-ns molecular dynamics (MD) simulations (free protein, free DNA and protein–DNA complex) in explicit solvent water were performed to elucidate the intermolecular contacts in the PRH–DNA complex and the role of dynamics of water molecules forming water-mediated contacts.

Interactions between Al12X (X = Al, C, N and P) nanoparticles and DNA nucleobases/base pairs: implications for nanotoxicity

Peng Jin [Chinese Academy of Sciences], Yongsheng Chen, Shengbai B. Zhang and Zhongfang Chen

J. Mol.Mod., **18**, 559–568, 2012

The interactions between neutral Al12X(I h) (X = Al, C, N and P) nanoparticles and DNA nucleobases, namely adenine (A), thymine (T), guanine (G) and cytosine (C), as well as the Watson–Crick base pairs (BPs) AT and GC, were investigated by means of density functional theory computations. The Al12X clusters can tightly bind to DNA bases and BPs to form stable complexes with negative binding Gibbs free energies at room temperature, and considerable charge transfers occur between the bases/BPs and the Al12X clusters.

Protein-Nucleic acid Interactions (Cont'd)

Molecular Dynamics Simulations for Complexation of DNA with 2 kDa PEI Reveal Profound Effect of PEI Architecture on Complexation

Chongbo Sun, Tian Tang[University of Alberta], and Hasan Uludağ

J. Phys. Chem. B., **116**, 2405–2413, 2012.

A series of all-atom molecular dynamics (MD) simulations of the complexation between DNA and 2 kDa branched and linear polyethylenimines (PEIs) are reported in this study. The simulations revealed distinct binding modes of branched and linear PEIs to DNA, with branched PEIs adhering to the DNA surface like beads and linear PEIs adhering to the DNA surface like cords. The dynamics of each PEI's binding state to the DNA during the simulations and how the PEIs neutralize the DNA were quantified. For both branched and linear PEIs, the addition of salt ions similar to physiological conditions were found to have only a small effect on DNA/PEI complexation compared to salt-free conditions.

Nucleic Acids

Molecular Dynamics of a DNA Holliday Junction: The Inverted Repeat Sequence d(CCGGTACCGG)₄

Elizabeth G. Wheatley, Susan N. Pieniazek, Ishita Mukerji, D.L. Beveridge [Wesleyan University]

Biophysical Journal. **102**, 552-560, 2012.

All-atom molecular dynamics (MD) computer simulations have been applied successfully to duplex DNA structures in solution for some years and found to give close accord with observed results. However, the MD force fields have generally not been parameterized against unusual DNA structures, and their use to obtain dynamical models for this class of systems needs to be independently validated. To characterize the accuracy of MD modeling on 4WJ, we report a set of explicit solvent MD simulations of ~100 ns on the repeat sequence d(CCGGTACCGG)₄ starting from the STX structure (PDB code 1dcw), and an OPN structure built for the same sequence.

Minimalist Model for Force-Dependent DNA Replication

Eva X. Nong, Stephen J. DeVience [Harvard University], Dudley Herschbach

Biophysical Journal. **102**, 810-818, 2012.

In experiments using optical or magnetic tweezers, investigators have monitored the rate at which polymerase enzymes catalyze DNA replication when the template strand is subjected to a stretching force. For T7, Klenow, and Sequenase polymerases, the replication rate increases modestly at low tension and then decreases markedly at higher tension. Molecular-dynamics (MD) simulations using x-ray structure data for the open and closed complexes of the Taq enzyme with DNA revealed that the dependence of replication rate on tension could be accounted for in terms of the induced enthalpy changes for the two DNA segments adjacent to the site of the added nucleotide.

Nucleic Acids (Cont'd)

RNA and Its Ionic Cloud: Solution Scattering Experiments and Atomically Detailed Simulations

Serdal Kirmizialtin, Suzette A. Pabit, Steve P. Meisburger, Lois Pollack, Ron Elber [The University of Texas at Austin]

Biophysical Journal. **102**, 819-828, 2012.

RNA molecules play critical roles in many cellular processes. Traditionally viewed as genetic messengers, RNA molecules were recently discovered to have diverse functions related to gene regulation and expression. Metal ions are an integral part of RNA structure and should be considered in any experimental or theoretical study of RNA. Here, we report a multidisciplinary approach that combines anomalous small-angle x-ray scattering and molecular-dynamics (MD) simulations with explicit solvent and ions around RNA.

The Ionic Atmosphere around A-RNA: Poisson-Boltzmann and Molecular Dynamics Simulations

Serdal Kirmizialtin [The University of Texas at Austin], Alexander R.J. Silalahi, Ron Elber, Marcia O. Fenley

Biophysical Journal. **102**, 829-838, 2012.

The distributions of different cations around A-RNA are computed by Poisson-Boltzmann (PB) equation and replica exchange molecular dynamics (MD). Both the nonlinear PB and size-modified PB theories are considered. The number of ions bound to A-RNA, which can be measured experimentally, is well reproduced in all methods. On the other hand, the radial ion distribution profiles show differences between MD and PB. We showed that PB results are sensitive to ion size and functional form of the solvent dielectric region but not the solvent dielectric boundary definition.

Unwrapping of Nucleosomal DNA Ends: A Multiscale Molecular Dynamics Study

Karine Voltz, Joanna Trylska, Nicolas Calimet, Jeremy C. Smith, Jörg Langowski [German Cancer Research Center]

Biophysical Journal. **102**, 849-858, 2012.

To permit access to DNA-binding proteins involved in the control and expression of the genome, the nucleosome undergoes structural remodeling including unwrapping of nucleosomal DNA segments from the nucleosome core. Here we examine the mechanism of DNA dissociation from the nucleosome using microsecond timescale coarse-grained molecular dynamics simulations. The simulations exhibit short-lived, reversible DNA detachments from the nucleosome and long-lived DNA detachments not reversible on the timescale of the simulation.

Effects of Hofmeister Ions on the α -Helical Structure of Proteins

Alvaro H. Crevenna [Max Planck Institute of Biochemistry], Nikolaus Naredi-Rainer, Don C. Lamb, Roland Wedlich-Söldner, Joachim Dzubiella

Biophysical Journal. **102**, 907-915, 2012.

The molecular conformation of proteins is sensitive to the nature of the aqueous environment. In particular, the presence of ions can stabilize or destabilize (denature) protein secondary structure. The underlying mechanisms of these actions are still not fully understood. Here, we combine circular dichroism (CD), single-molecule Förster resonance energy transfer, and atomistic computer simulations to elucidate salt-specific effects on the structure of three peptides with large α -helical propensity.

Nucleic Acids (Cont'd)

Rolling Circle Amplification-Templated DNA Nanotubes Show Increased Stability and Cell Penetration Ability

Graham D. Hamblin, Karina M. M. Carneiro, Johans F. Fakhoury, Katherine E. Bujold, and Hanadi F. Sleiman [McGill University]

J. Am. Chem. Soc., **134**, 2888–2891, 2012.

DNA nanotubes hold promise as scaffolds for protein organization, as templates of nanowires and photonic systems, and as drug delivery vehicles. We present a new DNA-economic strategy for the construction of DNA nanotubes with a backbone produced by rolling circle amplification (RCA), which results in increased stability and templated length. These nanotubes are more resistant to nuclease degradation, capable of entering human cervical cancer (HeLa) cells with significantly increased uptake over double-stranded DNA, and are amenable to encapsulation and release behavior.

Structural and electronic property responses to the arsenic/phosphorus exchange in GC-related DNA of the B-form

Jiande Gu, Jing Wang, Yaoming Xie, Jerzy Leszczynski and Henry F. Schaefer III [Chinese Academy of Sciences]

J. Comp. Chem. **33**, 817–821, 2012.

The suggestion that phosphorus/arsenic replacement in DNA can play a role in living things has generated great controversy (Wolfe-Simon et al., *Science* 2011, 332, 1163). Examined here theoretically are substitution effects on Watson–Crick base pairing and base stacking patterns in realistic DNA subunits. Using duplex DNA models deoxyguanylyl-3',5'-deoxycytidine ([dGpdC]₂) and deoxycytidylyl-3',5'-deoxyguanosine ([dCpdG]₂), this research reveals that the geometric variations caused by the As/P exchange are small and are limited to the phosphate/arsenate groups.

QM/MM Molecular Dynamics Study of Purine-Specific Nucleoside Hydrolase

Ruibo Wu, Wengjin Gong, Ting, Liu, Yingkai Zhang, and Zexing Cao [Xiamen University]

J. Phys. Chem. B., **116**, 1984–1991, 2012.

Although various *T. vivax* purine-specific inosine–adenosine–guanosine nucleoside hydrolase (IAG-NH) crystal structures were determined in recent years, the mechanistic details for the cleavage of N-glycosidic bond and the release of base are still unclear. Herein, the irreversible hydrolysis reaction has been studied by ab initio QM/MM MD simulations, and the results indicate a highly dissociative and concerted mechanism.

Surfaces, Catalysts, and Materials Subjects

2. METHODOLOGY

Quantitative Structure-Activity Relations

Identification of cytochrome P450 2D6 and 2C9 substrates and inhibitors by QSAR analysis

Svava Ósk Jónsdóttir [Technical University of Denmark],
Tine Ringsted, Nikolai G. Nikolov, Marianne Dybdahl, Eva
Bay Wedebye, Jay R. Niemelä

Bioorg. and Med.Chem., **20**, 2042-2053, 2012.

This paper presents four new QSAR models for CYP2C9 and CYP2D6 substrate recognition and inhibitor identification based on human clinical data. The models were used to screen a large data set of environmental chemicals for CYP activity, and to analyze the frequency of CYP activity among these compounds. A large fraction of these chemicals were found to be CYP active, and thus potentially capable of affecting human physiology. 20% of the compounds within applicability domain of the models were predicted to be CYP2C9 substrates, and 17% to be inhibitors.

Synthesis and biological validation of novel pyrazole derivatives with anticancer activity guided by 3D-QSAR analysis

Ines Vujasinović, Andrea Paravić-Radičević, Kata Mlinarić-Majerski, Karmen Brajša, Branimir Bertoša [Ruđer Bošković Institute]

Bioorg. and Med.Chem., **20**, 2101-2110, 2012.

Using literature data on anticancer activity of pyrazole derivatives, 3D-QSAR models were developed and 3D-QSAR analysis was performed. The 3D-QSAR analysis enabled identification of molecular properties that have the highest impact on antitumor activity against lung cancer cells. The results of 3D-QSAR analysis were taken into account while new compounds were designed. Obtained 3D-QSAR models were used for prediction of activity of new compounds. In this way, design of new compounds was guided by 3D-QSAR analysis which was performed on literature data.

Potentials and Parameters

Ab initio parameterization of YFF1, a universal force field for drug-design applications

Olexandr Ya Yakovenko [BC Cancer Agency], Yvonne Y. Li, Alexander A. Oliferenko, Ganna M. Vashchenko and Volodymyr G. Bdzhola, et al.

J. Mol.Mod., **18**, 663-673, 2012

The YFF1 is a new universal molecular mechanic force field designed for drug discovery purposes. The electrostatic part of YFF1 has already been parameterized to reproduce ab initio calculated dipole and quadrupole moments. Now we report a parameterization of the van der Waals interactions (vdW) for the same atom types that were previously defined. The 6-12 Lennard-Jones potential terms were parameterized against homodimerization energies calculated at the MP2/6-31 G* level of theory.

Molecular Dynamics

Microsecond Time-Scale Conformational Exchange in Proteins: Using Long Molecular Dynamics Trajectory To Simulate NMR Relaxation Dispersion Data

Yi Xue, Joshua M. Ward, Tairan Yuwen, Ivan S. Podkorytov, and Nikolai R. Skrynnikov [Purdue University]

J. Am. Chem. Soc., **134**, 2555–2562, 2012.

With the advent of ultra-long MD simulations it becomes possible to model microsecond time-scale protein dynamics and, in particular, the exchange broadening effects (R^{ex}) as probed by NMR relaxation dispersion measurements. This new approach allows one to identify the exchanging species, including the elusive “excited states”. In this study, recent millisecond-long MD trajectory of protein BPTI (Shaw et al. *Science***2010**, 330, 341) is employed to simulate the time variation of amide ^{15}N chemical shifts.

Fast Atomistic Molecular Dynamics Simulations from Essential Dynamics Samplings

Oliver Carrillo, Charles A. Laughton, and Modesto Orozco [Barcelona Supercomputing Center]

J. Chem. Theor. and Comp., **8**, 792–799, 2012.

We present a new method for fast molecular dynamics simulations in cases where the new trajectories can be considered a perturbation or a combination of previously stored ones. The method is designed for the postgenomic scenario, where databases such as MoDEL will store curated equilibrium trajectories of all biomolecules (proteins, nucleic acids, etc.) of human interest. The method can work simultaneously with low- and high-resolution pictures of the macromolecule, allowing the level of detail to be matched to that required for obtaining the information of biological interest.

Kinetics of the Terminal Electron Transfer Step in Cytochrome c Oxidase

Varomyalin Tipmanee and Jochen Blumberger [University of Cambridge]

J. Phys. Chem. B., **116**, 1876–188, 2012.

Cytochrome c oxidase (cco) catalyzes the oxygen reduction reaction in most aerobically respiring organisms. Decades of research have uncovered many aspects relating to structure and function of this enzyme. However, the origin of the unusually fast terminal electron transfer step from heme a to heme a₃ in cco has been the subject of intense discussions over recent years. Carrying out large-scale molecular dynamics simulation of the protein embedded in a solvated membrane, we obtain a reorganization free energy $\lambda = 0.57$ eV.

Monte Carlo

Bayesian Functional Integral Method for Inferring Continuous Data from Discrete Measurements

William J. Heuett [Marymount University], Bernard V. Miller, Susan B. Racette, John O. Holloszy, Carson C. Chow, Vipul Periwal

Biophysical Journal. **102**, 399–406, 2012.

Inference of the insulin secretion rate (ISR) from C-peptide measurements as a quantification of pancreatic β -cell function is clinically important in diseases related to reduced insulin sensitivity and insulin action. ISR derived from C-peptide concentration is an example of nonparametric Bayesian model selection where a proposed ISR time-course is considered to be a “model”. We propose a computationally tractable method that uses the exact solution of an associated likelihood function as a prior probability distribution for a Markov-chain Monte Carlo evaluation of the posterior for the full model.

Monte Carlo (Cont'd)

An information-carrying and knowledge-producing molecular machine. A Monte-Carlo simulation

Christoph Kuhn [University Hospital Zürich]

J. Mol.Mod., **18**, 607-609, 2012

The concept called Knowledge is a measure of the quality of genetically transferred information. Its usefulness is demonstrated quantitatively in a Monte-Carlo simulation on critical steps in a origin of life model. The model describes the origin of a bio-like genetic apparatus by a long sequence of physical-chemical steps: it starts with the presence of a self-replicating oligomer and a specifically structured environment in time and space that allow for the formation of aggregates.

QM and QM/MM

Mechanical Force Can Fine-Tune Redox Potentials of Disulfide Bonds

Ilona B. Baldus, Frauke Gräter [Heidelberg Institute for Theoretical Studies]

Biophysical Journal. **102**, 622-629, 2012.

Mechanical force applied along a disulfide bond alters its rate of reduction. We here aimed at quantifying the direct effect of force onto the chemical reactivity of a sulfur-sulfur bond in contrast to indirect, e.g., steric or mechanistic, influences. To this end, we evaluated the dependency of a disulfide bond's redox potential on a pulling force applied along the system. Our QM/MM simulations of cystine as a model system take conformational dynamics and explicit solvation into account and show that redox potentials increase over the whole range of forces probed here (30–3320 pN), and thus even in the absence of a significant disulfide bond elongation (<500 pN).

A Single-Site Mutation (F429H) Converts the Enzyme CYP 2B4 into a Heme Oxygenase: A QM/MM Study

Dandamudi Usharani, Costantino Zazza, Wenzhen Lai, Mukesh Chourasia, Lucy Waskell, and Sason Shaik [The Hebrew University of Jerusalem]

J. Am. Chem. Soc., **134**, 4053–4056, 2012.

The intriguing deactivation of the cytochrome P450 (CYP) 2B4 enzyme induced by mutation of a single residue, Phe429 to His, is explored by quantum mechanical/molecular mechanical calculations of the O–OH bond activation of the $(\text{Fe}^{3+}\text{OOH})^-$ intermediate. Thus, the mutant acquires the following characteristics of a heme oxygenase enzyme: (a) donation by His429 of an additional NH---S H-bond to the cysteine ligand combined with the presence of the substrate retards the heterolytic cleavage and gives rise to homolytic O–OH cleavage, and (b) the Thr302/water cluster orients nascent $\text{OH}^\bullet$ and ensures efficient meso hydroxylation.

Recent performance improvements to the DFT and TDDFT in GAMESS

Michael E. Lasinski [High Performance Technologies, Inc.], Nichols A. Romero, Shawn T. Brown and Jean-Philippe Blaudeau

J. Comp. Chem. **33**, 723–731, 2012.

The general atomic and molecular electronic structure system (GAMESS) is a quantum chemistry package used in the first-principles modeling of complex molecular systems using density functional theory (DFT) as well as a number of other post-Hartree-Fock methods. Both DFT and time-dependent DFT (TDDFT) are of particular interest to the materials modeling community. As part of this work, three areas for improvement were identified: (1) the exchange-correlation (XC) integration grid, (2) profiling and optimization of the DFT code, and (3) TDDFT parallelization.

QM and QM/MM (Cont'd)

Multiple receptor conformation docking and dock pose clustering as tool for CoMFA and CoMSIA analysis – a case study on HIV-1 protease inhibitors

Sree Kanth Sivan and Vijjulatha Manga [Osmania University]

J. Mol.Mod., **18**, 569-582, 2012

Multiple receptors conformation docking (MRCD) and clustering of dock poses allows seamless incorporation of receptor binding conformation of the molecules on wide range of ligands with varied structural scaffold. The accuracy of the approach was tested on a set of 120 cyclic urea molecules having HIV-1 protease inhibitory activity using 12 high resolution X-ray crystal structures and one NMR resolved conformation of HIV-1 protease extracted from protein data bank. A cross validation was performed on 25 non-cyclic urea HIV-1 protease inhibitor having varied structures.

Intermolecular interactions between gold clusters and selected amino acids cysteine and glycine: a DFT study

Hu-Jun Xie [Zhejiang Gongshang University], Qun-Fang Lei and Wen-Jun Fang

J. Mol.Mod., **18**, 645-652, 2012

The intermolecular interactions between Aun ($n = 3-4$) clusters and selected amino acids cysteine and glycine have been investigated by means of density functional theory (DFT). Present calculations show that the complexes possessing Au-NH₂ anchoring bond are found to be energetically favored. The results of NBO and frontier molecular orbitals analysis indicate that for the complex with anchoring bonds, lone pair electrons of sulfur, oxygen, and nitrogen atoms are transferred to the antibonding orbitals of gold, while for the complex with the nonconventional hydrogen bonds (Au...H-O), the lone pair electrons of gold are transferred to the antibonding orbitals of O-H bonds during the interaction.

Understanding Product Specificity of Protein Lysine Methyltransferases from QM/MM Molecular Dynamics and Free Energy Simulations: The Effects of Mutation on SET7/9 beyond the Tyr/Phe Switch

Jianzhuang Yao, Yuzhuo Chu, Ran An, and Hong Guo [University of Tennessee]

J.Chem. Infor. and Mod. **52**, 449–456, 2012.

The results of hybrid quantum mechanical/molecular mechanical (QM/MM) free energy (potential of mean force) simulations for methyl-transfer processes in SET7/9 and its Y245A mutant are compared to address the question concerning the change of the product specificity as well as catalytic efficiency due to the mutation. One of the key questions is whether or not the free energy profiles of methyl transfers may be used to predict the change of the product specificity as a result of the mutations for the residues that are not located at the Tyr/Phe switch position.

Robust and Efficient Constrained DFT Molecular Dynamics Approach for Biochemical Modeling

Jan Řezáč, Bernard Lévy, Isabelle Demachy, and Aurélien de la Lande [Université Paris-Sud. Bât. 349]

J. Chem. Theor. and Comp., **8**, 418–427, 2012.

Constrained density functional theory (cDFT) is a powerful tool to investigate the dynamics of the electrons accompanying various physical–chemical processes. In this article we present our recent progresses in the implementation of the method in the parallelized version of the DFT program deMon2k. We take advantage of the possibility to express atomic densities in terms of linear combination of Hermite Gaussian functions to improve the computation of the cDFT integration weights within the Hirshfeld and Voronoi deformation density electronic population approaches.

QM and QM/MM (Cont'd)

Detailed QM/MM study of the Electron Paramagnetic Resonance Parameters of Nitrosyl Myoglobin

Mahesh Sundararajan and Frank Neese [Max-Planck Institut für Bioanorganische Chemie]

J. Chem. Theor. and Comp., **8**, 563–574, 2012.

A number of popular density functionals are calibrated against high-resolution EPR data for low spin iron-nitrosyls present in nitric oxide bound myoglobin. The model incorporates both electrostatic and steric effects using a combined quantum mechanics/molecular mechanics (QM/MM) approach. Compared to the most recent experimental data, the calculated EPR parameters using GGA functionals are distinctly more accurate than those predicted by hybrid functionals.

A Polarizable QM/MM Explicit Solvent Model for Computational Electrochemistry in Water

Lee-Ping Wang and Troy Van Voorhis [Massachusetts Institute of Technology]

J. Chem. Theor. and Comp., **8**, 610–617, 2012.

We present a QM/MM explicit solvent model for the computation of standard reduction potentials E_0 . The QM/MM model uses DFT to model the solute and a polarizable MM force field to describe the solvent. The linear response approximation is applied to estimate E_0 from the thermally averaged electron attachment/detachment energies computed in the oxidized and reduced states. Using the QM/MM model, we calculated one-electron E_0 values for several aqueous transition-metal complexes and found substantially improved agreement with experiment compared to values obtained from implicit solvent models.

Comparative or Homology Modeling

Protein-protein docking on molecular models of *Aspergillus niger* RNase and human actin: novel target for anticancer therapeutics

Ravi Kumar Gundampati [Banaras Hindu University], Rajasekhar Chikati, Moni Kumari, Anurag Sharma and Daliparthi Devi Pratyush, et al.

J. Mol. Mod., **18**, 653–662, 2012

The 3D models of human actin protein and *A.niger* RNase were designed using the templates ACTBIND (PDB ID: 3D3Z) and crystalline profilin-beta-actin (PDB ID: 2BTF), respectively in Modeller9v5. These models are testified using several validation methods including PROCHECK, ERRAT, WHAT-IF, PROSA2003 and VERIFY-3D. The stereo-chemical quality of the models was judged by Ramachandran plot with PROCHECK. The total quality G-factor –0.2, shows a good quality model.

Effect of the methylation of uracil and/or glycine on their mutual interaction

Hongqi Ai [University of Jinan], Dejie Li, Yongping Zhao, Chong Zhang and Qiang Li, et al.

J. Mol. Mod., **18**, 791–802, 2012

In order to simulate the hydrogen bonding and proton transfer (PT) in protein-DNA/RNA interactions, a series of simplified models were employed and investigated in the gas phase. These models included various neutral, anionic and cationic glycine-uracil dimers, and their methylated derivatives generated by the mono- or dimethylation of glycine and/or uracil moieties of the dimer. The results reveal that the only process that can occur in the neutral complexes is a double-PT process leading to proton exchange between the two moieties (i.e., point mutation).

Comparative or Homology Modeling (Cont'd)

Homology Model-Guided 3D-QSAR Studies of HIV-1 Integrase Inhibitors

Horrick Sharma, Xiaolin Cheng, and John K. Buolamwini
[University of Tennessee Health Science Center]

J.Chem. Infor. and Mod. **52**, 515–544, 2012.

In the present study, we report the exploration of binding modes of potent HIV-1 integrase (IN) inhibitors MK-0518 (raltegravir) and GS-9137 (elvitegravir) as well as chalcone and related amide IN inhibitors we recently synthesized and the development of 3D-QSAR models for integrase inhibition. Homology models of DNA-bound HIV-1 IN were constructed on the basis of the X-ray crystal structure of the foamy virus IN-DNA complex (PDB ID: 3L2T) and used for docking. The binding modes of raltegravir and elvitegravir in our homology models are in accordance with those in the foamy virus structure revealing interactions important for inhibitor-IN binding.

Charge Transfer in Model Peptides: Obtaining Marcus Parameters from Molecular Simulation

Alexander Heck, P. Benjamin Woiczikowski, Tomáš Kubař, Bernd Giese, Marcus Elstner, and Thomas B. Steinbrecher
[Karlsruhe Institute of Technology]

J. Phys. Chem. B., **116**, 2284–2293, 2012.

Charge transfer within and between biomolecules remains a highly active field of biophysics. Due to the complexities of real systems, model compounds are a useful alternative to study the mechanistic fundamentals of charge transfer. In recent years, such model experiments have been underpinned by molecular simulation methods as well. In this work, we study electron hole transfer in helical model peptides by means of molecular dynamics simulations. A theoretical framework to extract Marcus parameters of charge transfer from simulations is presented.

Structure Refinement of Protein Low Resolution Models Using the GNEIMO Constrained Dynamics Method

In-Hee Park, Vamshi Gangupomu, Jeffrey Wagner, Abhinandan Jain, and Nagarajan Vaidehi [Beckman Research Institute of the City of Hope]

J. Phys. Chem. B., **116**, 2365–2375, 2012.

The challenge in protein structure prediction using homology modeling is the lack of reliable methods to refine the low resolution homology models. Unconstrained all-atom molecular dynamics (MD) does not serve well for structure refinement due to its limited conformational search. We have developed and tested the constrained MD method, based on the generalized Newton–Euler inverse mass operator (GNEIMO) algorithm for protein structure refinement. In this method, the high-frequency degrees of freedom are replaced with hard holonomic constraints and a protein is modeled as a collection of rigid body clusters connected by flexible torsional hinges.

Ligand Docking

A Hot-Spot Motif Characterizes the Interface between a Designed Ankyrin-Repeat Protein and Its Target Ligand

Luthur Siu-Lun Cheung, Manu Kanwar, Marc Ostermeier [The Johns Hopkins University], Konstantinos Konstantopoulos

Biophysical Journal. **102**, 407-416, 2012.

Nonantibody scaffolds such as designed ankyrin repeat proteins (DARPin) can be rapidly engineered to detect diverse target proteins with high specificity and offer an attractive alternative to antibodies. Using molecular simulations, we predicted that the binding interface between DARPin off7 and its ligand is characterized by a hot-spot motif in which binding energy is largely concentrated on a few amino acids. To experimentally test this prediction, we fused MBP to a transmembrane domain to properly orient the protein into a polymer-cushioned lipid bilayer, and characterized its interaction with off7 using force spectroscopy.

Nuclear Inelastic Scattering and Mössbauer Spectroscopy as Local Probes for Ligand Binding Modes and Electronic Properties in Proteins: Vibrational Behavior of a Ferriheme Center inside a β -Barrel Protein

Beate Moeser, Adam Janoschka, Juliusz A. Wolny, Hauke Paulsen, Igor Filippov, Robert E. Berry, Hongjun Zhang, Aleksandr I. Chumakov, F. Ann Walker, and Volker Schünemann [Technische Universität Kaiserslautern]

J. Am. Chem. Soc., **134**, 4216–4228, 2012.

In this work, we present a study of the influence of the protein matrix on its ability to tune the binding of small ligands such as NO, cyanide (CN⁻), and histamine to the ferric heme iron center in the NO-storage and -transport protein Nitrophorin 2 (NP2) from the salivary glands of the blood-sucking insect *Rhodnius prolixus*. The change in the vibrational signature of the protein upon ligand binding has been monitored by Nuclear Inelastic Scattering (NIS), also called Nuclear Resonant Vibrational Spectroscopy (NRVS). The NIS data thus obtained have also been calculated by quantum mechanical (QM) density functional theory (DFT) coupled with molecular mechanics (MM) methods.

A 3D-QSAR-Driven Approach to Binding Mode and Affinity Prediction

Paolo Tosco [University of Turin] and Thomas Balle

J.Chem. Infor. and Mod. **52**, 302–307, 2012.

A method for predicting the binding mode of a series of ligands is proposed. The procedure relies on 3D-QSAR and does not require structural knowledge of the binding site. Candidate alignments are automatically built and ranked according to a consensus scoring function. 3D-QSAR analysis based on the selected binding mode enables affinity prediction of new drug candidates having less than 10 rotatable bonds.

Molecular Dynamics Simulations for Human CAR Inverse Agonists

Johanna Jyrkkärinne, Jenni Küblbeck, Juha Pulkkinen, Paavo Honkakoski, Reino Laatikainen, Antti Poso, and Tuomo Laitinen [University of Eastern Finland]

J.Chem. Infor. and Mod. **52**, 457–464, 2012.

Constitutive androstane receptor (CAR), along with pregnane x receptor (PXR), is an important metabolic sensor in the hepatocytes. Like all other nuclear receptors (NRs), CAR works in concert with coregulator proteins, coactivators, and corepressors which bind to the NRs. The main basis for the receptor to distinguish between coactivators and corepressors is the position of the C-terminal helix 12 (H12), which is determined by the bound NR ligand. Here, we have run a series of MD simulations to study the movement of H12 in the presence of both activating and repressing ligands as well as a corepressor peptide.

3. JOURNAL REVIEWS

Journal of Computational Chemistry, 33(7), March, 2012.

- 715–722 **Mechanisms of the cascade synthesis of substituted 4-amino-1,2,4-triazol-3-one from huisgen zwitterion and aldehyde hydrazone: A DFT study**, Wenjing Zhang, Yanyan Zhu, Donghui Wei and Mingsheng Tang [Zhengzhou University]

The detailed reaction mechanisms of the title reaction are shed light on by using the density functional theory (DFT). The calculated results have demonstrated that the whole reaction takes place via four processes (processes (I–IV)), among which, three possible reaction mechanisms are proposed for process (II) (channels 1–3) and two for process (IV) (channels 4–5).

- 723–731 **Recent performance improvements to the DFT and TDDFT in GAMESS**, Michael E. Lasinski [High Performance Technologies, Inc.], Nichols A. Romero, Shawn T. Brown and Jean-Philippe Blaudeau

See Methodology / QM and QM/MM.

- 732–747 **Highlighting and trying to overcome a serious drawback with qspr studies; data collection in different experimental conditions**, Abolghasem Beheshti, Siavash Riahi [University of Tehran], Mohammad Reza Ganjali and Parviz Norouzi

The experimental conditions in quantitative structure–property relationship (QSPR) studies need to be the same for each dataset in case one wishes to relate the property, only to the structure. This major drawback limits QSPR studies due to two reasons: (1) Gathering of physicochemical data obtained under the same experimental condition is difficult. (2) The obtained model is just useful to predict the physicochemical properties under the specific experimental condition. In this article, we report an attempt to highlight the shortcoming of QSPR studies for a property that was measured under different experimental conditions.

- 748–756 **Nature of the ring-closure process along the rearrangement of octa-1,3,5,7-tetraene to cycloocta-1,3,5-triene from the perspective of the electron localization function and catastrophe theory**, J. Andrés [Universitat Jaume I], S. Berski, L. R. Domingo and P. González-Navarrete

We analyze the behavior of the energy profile of the ring-closure process for the transformation of (3Z,5Z)-octa-1,3,5,7-tetraene **5** to (1Z,3Z,5Z)-cycloocta-1,3,5-triene **6** through a combination of electron localization function (ELF) and catastrophe theory (CT).

- 757–766 **“First-Principles” kinetic monte carlo simulations revisited: CO oxidation over RuO₂(110)**, Franziska Hess, Attila Farkas, Ari P. Seitsonen and Herbert Over [Justus-Liebig-University]

First principles-based kinetic Monte Carlo (kMC) simulations are performed for the CO oxidation on RuO₂(110) under steady-state reaction conditions.

- 767–778 **Ab initio calculation of structure and transport properties of He...X (X = Zn, Cd, Hg) van der Waals complexes**, Vladimír Sládek [Slovak University of Technology], Vladimír Lukeš, Michal Ilčín and Stanislav Biskupič

The ground state ab initio CCSD(T) potential curves using various basis sets (aug-cc-pVXZ-PP (X = D, T, Q, 5)) is obtained for the dimers of helium with IIb group metals.

- 779–790 **Interactive quantum chemistry: A divide-and-conquer ASED-MO method**, Mäel Bosson [NANO-D - INRIA Grenoble - Rhône-Alpes/CNRS Laboratoire Jean Kuntzmann], Caroline Richard, Antoine Plet, Sergei Grudinín and Stephane Redon

We present interactive quantum chemistry simulation at the atom superposition and electron delocalization molecular orbital (ASED-MO) level of theory. Our method is based on the divide-and-conquer (D&C) approach, which we show is accurate and efficient for this non-self-consistent semiempirical theory.

- 791–799 **A discriminative Ramachandran potential of mean force aimed at minimizing secondary structure bias**, Sampath Koppole and Michael Schaefer [Novartis Institutes for Biomedical Research]

We introduce PMF*, a novel potential of mean force (PMF) for the Ramachandran ϕ/ψ dihedral plot of the 20 standard amino acids and assess its relevance to the conformation of polypeptides by scoring structures in the protein data bank and decoy datasets.

- 800–809 **Electronic structure and thermochemical properties of silicon-doped lithium clusters $\text{Li}_n\text{Si}^{0/+}$, n = 1–8: New insights on their stability**, Truong Ba Tai and Minh Tho Nguyen [Katholieke Universiteit Leuven]

A theoretical investigation on small silicon-doped lithium clusters Li_nSi with n = 1–8, in both neutral and cationic states is performed using the high accuracy CCSD(T)/complete basis set (CBS) method.

Journal of Computational Chemistry, 33(8), March, 2012.

- 817–821 **Structural and electronic property responses to the arsenic/phosphorus exchange in GC-related DNA of the B-form**, Jiande Gu, Jing Wang, Yaoming Xie, Jerzy Leszczynski and Henry F. Schaefer III [Chinese Academy of Sciences]

Applications / Nucleic Acids.

- 822–831 **Evaluation of the electron momentum density of crystalline systems from ab initio linear combination of atomic orbitals calculations**, Alessandro Erba [Università di Torino] and Cesare Pisan

Alternative techniques are presented for the evaluation of the electron momentum density (EMD) of crystalline systems from ab initio linear combination of atomic-orbitals calculations performed in the frame of one-electron self-consistent-field Hamiltonians.

- 832–842 **Potential of mean force of water–proton bath and molecular dynamic simulation of proteins at constant pH**, Yury N. Vorobjev [Institute of Chemical Biology and Fundamental Medicine of the Siberian Branch of the Russian Academy of Science]

See Applications / General and Model Systems.

- 843–852 **Voids and necks in liquid ammonia and their roles in diffusion of ions of varying size**, Debashree Chakraborty and Amalendu Chandra [Indian Institute of Technology, Kanpur]

Voids in a medium are defined as the regions that are located outside an appropriately defined occupied space associated with molecules. This work deals with an analysis of voids and diffusion in liquid ammonia.

- 853–860 **MolecularNetworks: An integrated graph theoretic and data mining tool to explore solvent organization in molecular simulation**, Barbara Logan Mooney, L.René Corrales and Aurora E. Clark [University of Arizona]

This work discusses scripts for processing molecular simulations data written using the software package R: A Language and Environment for Statistical Computing.

- 861–867 **Chemically modified fullerene derivatives as photosensitizers in photodynamic therapy: A first-principles study**, Cai-Hua Zhou and Xiang Zhao [Xi'an Jiaotong University]

The first-principles density functional theory (DFT) and its time-dependent approach (TD-DFT) are used to characterize the electronic structures and optical spectra properties of five chemically modified fullerenes.

Journal of Computational Chemistry, 33(9), April, 2012.

- 917–923 **Effects of external electromagnetic fields on the conformational sampling of a short alanine peptide**, Gleb Y. Solomentsev, Niall J. English and Damian A. Mooney [University College Dublin]

See Applications / Protein Dynamics.

- 924–936 **Fourier transform general formula for systematic potentials**, Kazuhiro Ishida [Tokyo University of Science]

For calculating molecular integrals of systematic potentials, a three-dimensional (3D) Fourier transform general formula can be derived, by the use of the Abel summation method.

- 937–949 **Multiscale simulation of small peptides: Consistent conformational sampling in atomistic and coarse-grained models**, Olga Bezkorovaynaya, Alexander Lukyanov, Kurt Kremer and Christine Peter [Max Planck Institute for Polymer Research]

See Applications / Protein Conformational Analysis.

- 950–957 **Core-shell potential-derived point charges**, Jeffrey S. Tan [Eli Lilly and Company], Stephan X. M. Boerrigter, Raymond P. Scaringe and Kenneth R. Morris

The present work details the development of a core-shell model for the purposes of obtaining potential-derived point charges from the ab initio molecular electrostatic potential.

- 958–969 **Quantum molecular mechanics—a noniterative procedure for the fast Ab Initio calculation of closed shell systems**, Gustavo L. C. Moura and Alfredo M. Simas [Universidade Federal de Pernambuco]

In this article, we advance the foundations of a strategy to develop a molecular mechanics method based not on classical mechanics and force fields but entirely on quantum mechanics and localized electron-pair orbitals, which we call quantum molecular mechanics (QMM).

- 970–986 **Computation of the binding affinities of catechol-O-methyltransferase inhibitors: Multisubstate relative free energy calculations**, P. Nuno Palma [BIAL, Department of Research and Development], Maria João Bonifácio, Ana Isabel Loureiro and Patricio Soares-da-Silva

See Applications / Free Energy Calculations.

- 987–997 **Density functional study of electronic, bonding, and vibrational properties of Ca (NH₂BH₃)₂**, Ch. Bheema Lingam, K. Ramesh Babu, Surya P. Tewari and G. Vaitheeswaran [University of Hyderabad]

We present structural, electronic, bonding and vibrational properties of new type hydrogen storage material calcium amidoborane **Ca(NH₂BH₃)₂** by first principles density functional theory using plane wave pseudopotential method.

- 998–1003 **Liquid properties of dimethyl ether from molecular dynamics simulations using Ab Initio force fields**, Shi-Bao Wang, Arvin Huang-Te Li and Sheng D. Chao [National Taiwan University]

We have used molecular dynamic simulations to study the structural and dynamical properties of liquid dimethyl ether (DME) with a newly constructed ab initio force field in this article. The ab initio potential energy data were calculated at the second order Møller-Plesset (MP2) perturbation theory with Dunning's correlation consistent basis sets (up to aug-cc-pVQZ).

- 1004–1013 **Influence of the solvent representation on vibrational entropy calculations: Generalized born versus distance-dependent dielectric model**, Hannes Kopitz, Daniel A. Cashman, Stefania Pfeiffer-Marek and Holger Gohlke [Heinrich-Heine-University]

The harmonic model is the most popular approximation for estimating the “configurational” entropy of a solute in molecular mechanics/Poisson-Boltzmann solvent accessible surface area (MM/PBSA)-type binding free energy calculations. Here, we investigate the influence of the solvent representation in the harmonic model by comparing estimates of changes in the vibrational entropies for 30 trypsin/ligand complexes on ligand binding.

Journal of Molecular Modeling, 18(2), February, 2012.

- 419-431 **Tetrahydroisoquinolines acting as dopaminergic ligands. A molecular modeling study using MD simulations and QM calculations**, Sebastián Andujar, Fernando Suvire, Inmaculada Berenguer, Ricardo D. Enriz [Universidad Nacional de San Luis], Nuria Cabedo and Paloma Marín, et al.

See Applications / Ligand Binding.

- 433-440 **Triethanolammonium acetate as a multifunctional ionic liquid in the palladium-catalyzed green Heck reaction**, Zorica D. Petrović, Svetlana Marković [University of Kragujevac], Vladimir P. Petrović and Dušica Simijonović

An efficient green Heck reaction protocol was performed using a triethanolammonium acetate ionic liquid–palladium(II) catalytic system.

- 441-453 **Comparative modeling of 25-hydroxycholesterol-7 α -hydroxylase (CYP7B1): ligand binding and analysis of hereditary spastic paraplegia type 5 CYP7B1 mutations**, Afraa Siam, Andrea Brancale and Claire Simons [Cardiff University]

See Applications / Homology Modeling.

- 455-466 **Geometric distortions on a three-coordinated T1 Cu site model as a potential strategy to modulate redox potential. A theoretical study**, Hugo Vázquez-Lima, Patricia Guadarrama [Universidad Nacional Autónoma de México] and Claudia Martínez-Anaya

A model of the three-coordinated T1 Cu site from *Trametes versicolor* was considered to evaluate the effect on redox potential of geometrical distortions in the copper coordination sphere.

- 467-479 **Combining molecular dynamics and docking simulations of the cytidine deaminase from *Mycobacterium tuberculosis* H37Rv**, Luís Fernando Saraiva Macedo Timmers, Rodrigo Gay Ducati, Zilpa Adriana Sánchez-Quitian, Walter Filgueira de Azevedo [Pontificia Universidade Católica do Rio Grande do Sul], Luiz Augusto Basso and Diógenes Santiago Santos, et al.

See Applications / Enzyme Catalysis.

- 481-492 **Investigation of the acylation mechanism of class C beta-lactamase: pKa calculation, molecular dynamics simulation and quantum mechanical calculation**, Smriti Sharma and Pradipta Bandyopadhyay [Jawaharlal Nehru University]

See Applications / Enzyme Catalysis.

- 493-500 **Study of the interaction between 8-azaguanine and bovine serum albumin using optical spectroscopy and molecular modeling methods**, Qiao-Ling Gong, Xin-Gen Hu [Wenzhou University], Guo-Yong Fang and Xin-Hua Li

The interaction between 8-azaguanine (8-Azan) and bovine serum albumin (BSA) in Tris-HCl buffer solutions at pH 7.4 was investigated by means of fluorescence and ultraviolet-visible (UV-Vis) spectroscopy.

- 501-514 **In silico investigations of possible routes of assembly of ORF 3a from SARS-CoV**, Hao-Jen Hsu and Wolfgang B. Fischer [National Yang-Ming University]

See Applications / Bioinformatics.

- 515-523 **A Curtin–Hammett mechanism for the copolymerization of ethylene and methyl acrylate monomer using a PymNox nickel catalyst as revealed by DFT computational studies**, Javier Ramos [Instituto de Estructura de la Materia, CSIC], Sonia Martínez, Víctor L. Cruz and Javier Martínez-Salazar

In this work, the copolymerization of ethylene and methyl acrylate (MA) as catalyzed by a new Ni-based PymNox organometallic compound was studied computationally.

- 525-531 **Insight into the reaction mechanism of cis,cis-muconate lactonizing enzymes: a DFT QM/MM study**, Tuanjai Somboon, Matthew Paul Gleeson [Kasetsart University] and Supa Hannongbua

See Applications / Enzyme Catalysis.

- 533-540 **Molecular dynamics simulations of nafion and sulfonated poly ether sulfone membranes II. Dynamic properties of water and hydronium**, Takahiro Ohkubo [Chiba University], Koh Kidena, Naohiko Takimoto and Akihiro Ohira

See Applications / Membrane proteins and Lipid-Peptide Interactions.

- 541-548 **σ -Holes, π -holes and electrostatically-driven interactions**, Jane S. Murray [CleveTheoComp], Pat Lane, Timothy Clark, Kevin E. Riley and Peter Politzer

A positive π -hole is a region of positive electrostatic potential that is perpendicular to a portion of a molecular framework. In this work, the complexes of 13 π -hole-containing molecules with the nitrogen lone pairs of HCN and NH₃ have been characterized computationally using the MP2, M06-2X and B3PW91 procedures.

- 549-557 **Instability of C60 fullerene interacting with lipid bilayer**, Duangkamon Baowan [Mahidol University], Barry J. Cox and James M. Hill

See Applications / Carbon NanoParticles

- 559-568 **Interactions between Al₁₂X (X = Al, C, N and P) nanoparticles and DNA nucleobases/base pairs: implications for nanotoxicity**, Peng Jin [Chinese Academy of Sciences], Yongsheng Chen, Shengbai B. Zhang and Zhongfang Chen

See Applications / Protein –Nucleic acid Interactions.

- 569-582 **Multiple receptor conformation docking and dock pose clustering as tool for CoMFA and CoMSIA analysis – a case study on HIV-1 protease inhibitors**, Sree Kanth Sivan and Vijjulatha Manga [Osmania University]

See Methodology / QM and QM/MM.

- 583-589 **An important factor in relation to shock-induced chemistry: resonance energy**, Bisheng Tan [Southwest University of Science and Technology, Mianyang], Rufang Peng, Xinpeng Long, Hongbo Li and Bo Jin, et al.

With density function theory BLYP/DNP method, together with homodesmotic reactions and isodesmic reactions, we calculated the resonance energies of some explosives, including eight nitro compounds which contains benzene rings, three nitro compounds which contains azaheterocycles (2,4-dinitroimidazole (2,4-DNI), 2,6-diamino-3,5-dinitropyrazine-1-oxide (LLM-105) and 2,4,6-trinitro-1,3,5-triazine) and one nitrogen-rich energetic compound of 3,3'-azobis(6-amino-s-tetrazine) (DAAT).

- 591-596 **On the electronic properties of two-dimensional honeycomb GaInN and GaAlN alloys: a molecular analysis**, Ernesto Chigo Anotá [Benemérita Universidad Autónoma de Puebla] and Heriberto Hernández Cocoletzi

See Applications / Free energy.

- 597-605 **A DFT study of aminonitroimidazoles**, P. Ravi [University of Hyderabad], Girish M. Gore, Surya P. Tewari and Arun K. Sikder

Density functional theory (DFT) calculations at the B3LYP/aug-cc-pVDZ level were performed to explore the geometric and electronic structures, band gaps, thermodynamic properties, densities and performances of aminonitroimidazoles.

- 607-609 **An information-carrying and knowledge-producing molecular machine. A Monte-Carlo simulation**, Christoph Kuhn [University Hospital Zürich]

See Methodology / Monte Carlo.

- 611-621 **Ab initio study of electron transport in 4-(3-nitro-4-tetrafluorophenylthiolate-ethynyl, phenylethynyl) benzenethiolate**, Lilia Serrato-Villegas, Marco Gallo [Universidad Autónoma de San Luis Potosí], Marcos Delgado-Ríos, María Teresa Romero and Daniel Glossman-Mitnik

The electron transport of the 4-(3-nitro-4-tetrafluorophenylthiolate-ethynyl, phenylethynyl) benzenethiolate (S-FNPPB-o) molecule assembled in two Au (111) electrodes, was studied using two approaches: in the first approximate approach an electric field was applied to the pure molecule attached to two thiolate ends fixed, and in the second approach we used the nonequilibrium Green's function formalism (NEGF) coupled to DFT to calculate the I-V curve and the voltage dependence of the transmission function in the extended system, molecule plus electrodes.

- 623-629 **Polaron binding energy in polymers: poly[methyl(phenyl)silylene]**, Juraj Nožár [ASCR], Stanislav Nešpůrek and Jakub Šebera

This paper presents a theoretical approach to the evaluation of polaron binding energy in polymers. Quantum chemical calculations were performed on a model polymer, poly[methyl(phenyl)silylene], employing the B3LYP and CAM-B3LYP method.

- 631-644 **Binding of BIS like and other ligands with the GSK-3 β kinase: a combined docking and MM-PBSA study**, Nihar R. Jena [Indian Institute of Science]

See Applications / Lignad Binding.

645-652 **Intermolecular interactions between gold clusters and selected amino acids cysteine and glycine: a DFT study**, Hu-Jun Xie [Zhejiang Gongshang Universty], Qun-Fang Lei and Wen-Jun Fang

See Methodology / QM and QM/MM.

653-662 **Protein-protein docking on molecular models of Aspergillus niger RNase and human actin: novel target for anticancer therapeutics**, Ravi Kumar Gundampati [Banaras Hindu University], Rajasekhar Chikati, Moni Kumari, Anurag Sharma and Daliparthi Devi Pratyush, et al.

See Methodology / Homology Modeling.

663-673 **Ab initio parameterization of YFF1, a universal force field for drug-design applications**, Olexandr Ya Yakovenko [BC Cancer Agency], Yvonne Y. Li, Alexander A. Oliferenko, Ganna M. Vashchenko and Volodymyr G. Bdzhola, et al.

See Methodology / Potentilas and Parameters.

675-692 **Developing consensus 3D-QSAR and pharmacophore models for several beta-secretase, farnesyl transferase and histone deacetylase inhibitors**, Hsin-Yuan Wei[National Tsing Hua University], Guan-Ju Chen, Chih-Lun Chen and Thy-Hou Lin

See Applications / QSAR.

693-708 **Insights from ligand and structure based methods in virtual screening of selective Ni-peptide deformylase inhibitors**, Ravi Shekar Ananthula [GVKBIO S-1], Muttineni Ravikumar, S. K. Mahmood and M. N. S. Pavan Kumar

See Applications / Medicinal Chemmistry and Drug Design.

709-720 **CYP isoform specificity toward drug metabolism: analysis using common feature hypothesis**, M. Ramesh and Prasad V. Bharatam [National Institute of Pharmaceutical Education and Research]

See Applications / Medicinal Chemmistry and Drug Design.

721-736 **Signal mass and Ca²⁺ kinetics in local calcium events: a modeling study**, Irina Baran [“Carol Davila” University of Medicine and Pharmacy], Constanta Ganea, Raluca Ungureanu and Ioana Teodora Tofolean

We use a detailed modeling formalism based on numerical simulations of local calcium release events where the blurring of the image, the presence of diffusional barriers provided by large organelles situated close to the release site, as well as the variable position of the scan line with respect to the release site are taken into consideration.

737-749 **Chemisorptions effect of oxygen on the geometries, electronic and magnetic properties of small size Nin (n = 1-6) clusters**, Debashis Bandyopadhyay [Birla Institute of Technology and Science, Pilani]

The present study reports the effect of oxygen addition on small size Ni_n ($n=1-6$) clusters in different spin states within the framework of linear combination of atomic orbital (LCAO) density functional theory (DFT) under spin polarized generalized gradient approximation (GGA) functional.

- 751-754 **Theoretical study of the hydroboration reaction of cyclopropane with borane**, Satya Prakash Singh and Pompozhi Protasis Thankachan [Indian Institute of Technology Roorkee]

The hydroboration of cyclopropane has been investigated using the B3LYP density functional method employing several split-valence basis sets.

- 755-764 **Identification of new potential Mycobacterium tuberculosis shikimate kinase inhibitors through molecular docking simulations**, Carolina Pasa Vianna and Walter F. de Azevedo [Pontificia Universidade Católica do Rio Grande do Sul (PUCRS)]

See Applications / Enzyme Catalysis.

- 765-770 **A MP2 and DFT study of the influence of complexation on the aromatic character of phosphole**, Angeles Peña-Gallego [Universidade de Santiago de Compostela], Jesús Rodríguez-Otero and Enrique M. Cabaleiro-Lago

This work is focused in three topical subjects: intermolecular interactions, metal ions, and aromaticity. A comprehensive MP2/6-31G* and B3LYP/6-31G* study of the influence of cation- π interactions on the aromatic character of phosphole was conducted.

- 771-781 **Noncovalent and covalent functionalization of a (5, 0) single-walled carbon nanotube with alanine and alanine radicals**, Muthusivarajan Rajarajeswari, Kombiah Iyakutti [Madurai Kamaraj University] and Yoshiyuki Kawazoe

See Applications / Carbon NanoParticles

- 783-790 **Density functional theory study of small nickel clusters**, Satyender Goel [Northwestern University] and Artem E. Masunov

The stable geometries and atomization energies for the clusters Ni_n ($n=2-5$) are predicted with all-electron density functional theory (DFT), using the BMK hybrid functional and a Gaussian basis set.

- 791-802 **Effect of the methylation of uracil and/or glycine on their mutual interaction**, Hongqi Ai [University of Jinan], Dejie Li, Yongping Zhao, Chong Zhang and Qiang Li, et al.

See Methodology / Homology Modeling.

- 803-813 **Theoretical study on chiral recognition mechanism of methyl mandelate enantiomers on permethylated β -cyclodextrin**, Jie-hua Shi [Zhejiang University of Technology], Zuo-jing Ding and Ying Hu

Host-guest interactions of permethylated β -cyclodextrin (PM- β -CD) with methyl mandelate enantiomers ((R/S)-MMA) were simulated using semiempirical PM3 and ONIOM (B3LYP/6-31G(d):PM3) method. The chiral recognition mechanism of (R/S)-MMA enantiomers on PM- β -CD was investigated.

- 815-824 **XRD and DFT-modeled structures of a pteridine-2,4(1H,3H)-dithione/N,N'-dimethylformamide H-bonded cluster (2:2). MO study of the coordination ability**, Nuria A. Illán-Cabeza, Tomás Peña-Ruiz and Miguel N. Moreno-Carretero [Universidad de Jaén]

The title compound, C₆H₄N₄S₂•C₃H₇NO, crystallizes in the monoclinic space group C 2/c with $a = 26.673(5)$, $b = 5.397(1)$, $c = 16.522(3)$ Å, $\beta = 95.49(3)^\circ$, $Z = 8$, $R = 0.0461$ for 1891 reflections with $I > 2\sigma(I)$ and 174 parameters (4 restraints). MO study of the coordination ability

- 825-834 **Four-component pharmacophore model for endomorphins toward μ opioid receptor subtypes**, Yng-Ching Wu, Tim Jaglinski, Jin-Yuan Hsieh, Jia-Jyun Chiu and Tzen-Yuh Chiang, Chi-Chuan Hwang [National Cheng Kung University]

See Applications / Medicinal Chemistry and Drug Design.

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1. APPLICATIONS

1.1. Small Molecules

Medicinal Chemistry and Drug Design

Molecular modeling studies on phosphonic acid-containing thiazole derivatives: design for fructose-1,6-bisphosphatase inhibitors

Ping Lan, Zhi-Wei Wu, Wan-Na Chen, Ping-Hua Sun and Wei-Min Chen [Jinan University]

J. Mol.Mod., **18**, 973-990, 2012

Presently, an in silico modeling was carried out on a series of 63 phosphonic acid-containing thiazole derivatives as fructose-1,6-bisphosphatase (FBPase) inhibitors using CoMFA/CoMSIA and molecular docking methods. The CoMFA and CoMSIA models using 51 molecules in the training set gave r^2 values of 0.675 and 0.619, r^2 values of 0.985 and 0.979, respectively. The systemic external validation indicated that our CoMFA and CoMSIA models possessed high predictive powers with r^2 values of 0.995 and 0.994, r^2 (test) values of 0.887 and 0.860, respectively.

Studies of H4R antagonists using 3D-QSAR, molecular docking and molecular dynamics

Jing Liu, Yan Li [Dalian University of Technology], Hui-Xiao Zhang, Shu-Wei Zhang and Ling Yang

J. Mol.Mod., **18**, 991-1001, 2012

3D-QSAR relationship studies were performed on a series of 88 histamine receptor 4 (H4R) antagonists in an attempt to elucidate the 3D structural features required for activity. Several in silico modeling approaches, including comparative molecular field analysis (CoMFA), comparative similarity indices analysis (CoMSIA), molecular docking, and molecular dynamics (MD), were carried out. The results show that both the ligand-based CoMFA model ($Q^2 = 0.548$, $R_{ncv2} = 0.870$, $R_{pre2} = 0.879$, $SEE = 0.410$, $SEP = 0.386$) and the CoMSIA model ($Q^2 = 0.526$, $R_{ncv2} = 0.866$, $R_{pre2} = 0.848$, $SEE = 0.416$, $SEP = 0.413$) are acceptable, as they show good predictive capabilities.



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Medicinal Chemistry and Drug Design (Cont'd)

Predicting the potency of hERG K⁺ channel inhibition by combining 3D-QSAR pharmacophore and 2D-QSAR models

Yayu Tan, Yadong Chen, Qidong You [China Pharmaceutical University], Haopeng Sun and Manhua Li

J. Mol.Mod., **18**, 1023-1036, 2012

Blockade of the hERG K⁺ channel has been identified as the most important mechanism of QT interval prolongation and thus inducing cardiac risk. In this work, an ensemble of 3D-QSAR pharmacophore models was constructed to provide insight into the determinants of the interactions between the hERG K⁺ channel and channel inhibitors. To predict hERG inhibitory activities, the predicted values from the ensemble of models were averaged, and the results thus obtained showed that the predictive ability of the combined 3D-QSAR pharmacophore model was greater than those of the individual models.

Probing the structural requirements of A-type Aurora kinase inhibitors using 3D-QSAR and molecular docking analysis

Hui-xiao Zhang, Yan Li, Xia Wang and Yong-hua Wang [Northwest A&F University]

J. Mol.Mod., **18**, 1107-1122, 2012

Aurora-A, the most widely studied isoform of Aurora kinase overexpressed aberrantly in a wide variety of tumors, has been implicated in early mitotic entry, degradation of natural tumor suppressor p53 and centrosome maturation and separation; hence, potent inhibitors of Aurora-A may be therapeutically useful drugs in the treatment of various forms of cancer. Here, we report an in silico study on a group of 220 reported Aurora-A inhibitors with six different substructures. 3D-QSAR studies were carried out using CoMFA and CoMSIA techniques on this series of molecules.

Controlling the aggregation and rate of release in order to improve insulin formulation: molecular dynamics study of full-length insulin amyloid oligomer models

Workalemahu Mikre Berhanu and Artëm E. Masunov [University of Central Florida]

J. Mol.Mod., **18**, 1129-1142, 2012

Insulin is a hormone that regulates the physiological glucose level in human blood. The central fragments of the A and B chains (LYQLENY and LVEALYL) have recently been identified as β -sheet-forming regions, and their microcrystalline structures have been used to build a high-resolution amyloid fibril model of insulin. Here we report on a molecular dynamics (MD) study of single-layer oligomers of the full-length insulin which aimed to identify the structural elements that are important for amyloid stability, and to suggest single glycine mutants in the β -sheet region that may improve the formulation.

Molecular docking and 3D-QSAR study on 4-(1H-indazol-4-yl) phenylamino and aminopyrazolopyridine urea derivatives as kinase insert domain receptor (KDR) inhibitors

Xiaoyun Wu [Southern Medical University, Guangzhou], Shuguang Wu and Wen-Hua Chen

J. Mol.Mod., **18**, 1207-1218, 2012

Vascular endothelial growth factor (VEGF) and its receptor tyrosine kinase VEGFR-2 or kinase insert domain receptor (KDR) have been identified as new promising targets for the design of novel anticancer agents. It is reported that 4-(1H-indazol-4-yl)phenylamino and aminopyrazolopyridine urea derivatives exhibit potent inhibitory activities toward KDR. To investigate how their chemical structures relate to the inhibitory activities and to identify the key structural elements that are required in the rational design of potential drug candidates of this class, molecular docking simulations and 3D-QSAR methods were performed on 78 4-(1H-indazol-4-yl)phenylamino and aminopyrazolopyridine urea derivatives as KDR inhibitors.

Medicinal Chemistry and Drug Design (Cont'd)

In silico screening of epidermal growth factor receptor (EGFR) in the tyrosine kinase domain through a medicinal plant compound database

Orathai Sawatdichaikul, Supa Hannongbua, Chak Sangma, Peter Wolschann and Kiattawee Choowongkamon [Kasetsart University]

J. Mol.Mod., **18**, 1241-1254, 2012

The unregulated epidermal growth factor receptor tyrosine kinase (ErbB1-TK or EGFR-TK) protein is involved in the proliferation of more than 50% of all cancer types. The reduction of EGFR-TK activity by small or medium-sized molecules has been proven to be an effective treatment for cancer. There is a widespread belief that Chinese medicinal herbs are active against several diseases, including various types of cancer. In this study, 29,960 compounds from the Chemiebase medicinal compound database were virtually screened against the EGFR-TK using AutoDock4.0, GOLD and GLIDE (XP).

Molecular Modeling on Pyrimidine-Urea Inhibitors of TNF- α Production: An Integrated Approach Using a Combination of Molecular Docking, Classification Techniques, and 3D-QSAR CoMSIA

Varnavas D. Mouchlis, Georgia Melagraki, Thomas Mavromoustakos, George Kollias, and Antreas Afantitis [NovaMechanics, Ltd.]

J.Chem. Infor. and Mod. **52**, 711–723, 2012.

Molecular docking, classification techniques, and 3D-QSAR CoMSIA were combined in a multistep framework with the ultimate goal of identifying potent pyrimidine-urea inhibitors of TNF- α production. Using the crystal structure of p38 α , all the compounds were docked into the enzyme active site. The docking pose of each compound was subsequently used in a receptor-based alignment for the generation of the CoMSIA fields. “Active” and “inactive” compounds were used to build a Random Tree classification model using the docking score and the CoMSIA fields as input parameters.

Identification of Novel S-Adenosyl-L-Homocysteine Hydrolase Inhibitors through Homology-Model-Based Virtual Screening, Synthesis, and Biological Evaluation

Prashant Khare, Amit K. Gupta, Praveen K. Gajula, Krishna Y. Sunkari, Anil K. Jaiswal, Sanchita Das, Preeti Bajpai, Tushar K. Chakraborty, Anuradha Dube [C.S.I.R.-Central Drug Research Institute], and Anil K. Saxena

J.Chem. Infor. and Mod. **52**, 777–791, 2012.

The present study describes a successful application of computational approaches to identify novel *Leishmania donovani* (Ld) AdoHcyase inhibitors utilizing the differences for Ld AdoHcyase NAD⁺ binding between human and Ld parasite. The development and validation of the three-dimensional (3D) structures of Ld AdoHcyase using the L. major AdoHcyase as template has been carried out. At the same time, cloning of the Ld AdoHcyase gene from clinical strains, its overexpression and purification have been performed. The most potent inhibitor, compound **5**, may serve as a “lead” for developing more potent Ld AdoHcy hydrolase inhibitors as potential antileishmanial agents.

Computer-aided design of novel antibacterial 3-hydroxypyridine-4-ones: application of QSAR methods based on the MOLMAP approach

Razieh Sabet, Afshin Fassihi [Isfahan University of Medical Sciences], Bahram Hemmateenejad, Lotfollah Saghaei and Ramin Miri, et al.

J. Comp. Aided Mol. Des. **26**, 349-361, 2011.

3-Hydroxypyridine-4-one derivatives have shown good inhibitory activity against bacterial strains. In this work we report the application of MOLMAP descriptors based on empirical physicochemical properties with genetic algorithm partial least squares (GA-PLS) and counter propagation artificial neural networks (CP-ANN) methods to propose some novel 3-hydroxypyridine-4-one derivatives with improved antibacterial activity against *Staphylococcus aureus*. A large collection of 302 novel derivatives of this chemical scaffold was selected for this purpose.

Medicinal Chemistry and Drug Design (Cont'd)

The adenosine deaminases of *Plasmodium vivax* and *Plasmodium falciparum* exhibit surprising differences in ligand specificity

Andrei Ivanov, Ichiro Matsumura [Emory University School of Medicine]

J. Mol. Graph. and Mod., **35**, 43-48, 2012.

Plasmodium vivax and *Plasmodium falciparum* cause malaria, so proteins essential for their survival in vivo are potential anti-malarial drug targets. Adenosine deaminases (ADA) catalyze the irreversible conversion of adenosine into inosine, and play a critical role in the purine salvage pathways of Plasmodia and their mammalian hosts. Currently, the number of selective inhibitors of Plasmodium ADAs is limited. One potent and widely used inhibitor of the human ADA (hADA), erythro-9-(2-hydroxy-3-nonyl)adenine (EHNA), is a very weak inhibitor ($K_i = 120 \mu\text{M}$) of *P. falciparum* ADA (pfADA).

Validation of a Novel Molecular Dynamics Simulation Approach for Lipophilic Drug Incorporation into Polymer Micelles

Aliya O. Kasimova, Giovanni M. Pavan, Andrea Danani, Karine Mondon, Andrea Cristiani, Leonardo Scapozza, Robert Gurny, and Michael Möller [University of Geneva and University of Lausanne]

J. Phys. Chem. B., **116**, 4338–4345, 2012.

Polymer micelles can be used to facilitate the aqueous solubilization of lipophilic, poorly water-soluble compounds and drugs. Even if the evaluation of the efficiency of drug incorporation into such micelles can be tested experimentally, a theoretical approach based on molecular simulation can constitute a useful tool that reduces time and cost. Here we present a promising method, based on molecular dynamics simulation, for the calculation of the Flory–Huggins interaction parameters as a measure of the potential for drug incorporation into polymer micelles.

Quantitative Structure-Activity Relations

Quantitative structure activity relationships of some pyridine derivatives as corrosion inhibitors of steel in acidic medium

El Sayed H. El Ashry [Alexandria University], Ahmed El Nemr and Safaa Ragab

J. Mol. Mod., **18**1173-1188, 2012

Quantum chemical calculations using the density functional theory (B3LYP/6-31G* DFT) and semi-empirical AM1 methods were performed on ten pyridine derivatives used as corrosion inhibitors for mild steel in acidic medium to determine the relationship between molecular structure and their inhibition efficiencies. Quantum chemical parameters such as total negative charge (TNC) on the molecule, energy of highest occupied molecular orbital (E HOMO), energy of lowest unoccupied molecular orbital (E LUMO) and dipole moment (μ) as well as linear solvation energy terms, molecular volume (V_i) and dipolar-polarization (π^*) were correlated to corrosion inhibition efficiency of ten pyridine derivatives.

Host-Guest Systems

Insight into the Structural Deformations of Beta-Cyclodextrin Caused by Alcohol Cosolvents and Guest Molecules

Haiyang Zhang, Chunling Ge, David van der Spoel, Wei Feng, and Tianwei Tan [Beijing University of Chemical Technology]

J. Phys. Chem. B., **116**, 3880–3889, 2012.

Beta-cyclodextrin (β -CD) is an ideal candidate for a host molecule, and it is used as such in drug delivery and separation technology. The structural behavior of free β -CD and host-guest complexes of β -CD with two isoflavonoid isomers (puerarin and daidzin) in aqueous alcohol solutions, covering methanol, ethanol, 2-propanol, and 1-propanol, was investigated through molecular dynamics (MD) simulations. The MD results highlighted aspects of the structural flexibility and rigidity of β -CD in different alcohol solutions.

Carbon Nanoparticles

Molecular Structure of Membrane Tethers

Svetlana Baoukina, Siewert J. Marrink, D. Peter Tieleman [University of Calgary, Calgary]

Biophysical Journal. **102**, 1866-1871, 2012.

Membrane tethers are nanotubes formed by a lipid bilayer. They play important functional roles in cell biology and provide an experimental window on lipid properties. Tethers have been studied extensively in experiments and described by theoretical models, but their molecular structure remains unknown due to their small diameters and dynamic nature. We used molecular dynamics simulations to obtain molecular-level insight into tether formation.

Adsorption Mechanism and Collapse Propensities of the Full-Length, Monomeric A β_{1-42} on the Surface of a Single-Walled Carbon Nanotube: A Molecular Dynamics Simulation Study

Asis K. Jana, Neelanjana Sengupta [National Chemical Laboratory, Pune]

Biophysical Journal. **102**, 1889-1896, 2012.

Though nanomaterials such as carbon nanotubes have gained recent attention in biology and medicine, there are few studies at the single-molecule level that explore their interactions with disease-causing proteins. Using atomistic molecular-dynamics simulations, we have investigated the interactions of the monomeric A β_{1-42} peptide with a single-walled carbon nanotube of small diameter. Starting with peptide-nanotube complexes that delineate the interactions of different segments of the peptide, we find rapid convergence in the peptide's adsorption behavior on the nanotube surface, manifested in its arrested movement.

1.2. Biopolymers

Bioinformatics and Cheminformatics

SiteComp: a server for ligand binding site analysis in protein structures

Yingjie Lin, Seungyeul Yoo, and Roberto Sanchez [Mount Sinai School of Medicine]

Bioinformatics, **28**, 1172-1173, 2012.

Computational characterization of ligand-binding sites in proteins provides preliminary information for functional annotation, protein design and ligand optimization. SiteComp implements binding site analysis for comparison of binding sites, evaluation of residue contribution to binding sites and identification of sub-sites with distinct molecular interaction properties. The SiteComp server and tutorials are freely available at <http://sitecomp.sanchezlab.org>

Comparative or Homology Modeling

Homology modeling, molecular dynamics and QM/MM study of the regulatory protein PhoP from *Corynebacterium pseudotuberculosis*

Gleiciane Moraes, Vasco Azevedo, Marcília Costa, Jerônimo Lameira [Universidade Federal do Pará], Anderson Miyoshi and Artur Silva, et al.

J. Mol.Mod., **18**, 1219-1227, 2012

Corynebacterium pseudotuberculosis is a facultatively intracellular Gram-positive bacterium that causes caseous lymphadenitis, principally in sheep and goats, though sometimes in other species of animals, leading to considerable economic losses. This pathogen has a TCS known as PhoPR, which consists of a sensory histidine kinase protein (PhoR) and an intracellular response regulator protein (PhoP). This system is involved in the regulation of proteins present in various processes, including virulence. The regulation is activated by PhoP protein phosphorylation, an event that requires a magnesium (Mg²⁺) ion. Here we describe the 3D structure of the regulatory response protein (PhoP) of *C. pseudotuberculosis* through molecular modeling by homology.

Dynamic Modeling of Human 5-Lipoxygenase-Inhibitor Interactions Helps To Discover Novel Inhibitors

Yiran Wu, Chong He, Yang Gao, Shan He, Ying Liu, and Luhua Lai [Peking University]

J.Med.Chem., **55**, 2597-2605, 2012.

Human 5-lipoxygenase (5-LOX) is one of the key anti-inflammatory drug targets due to its key role in leukotrienes biosynthesis. We have built a model for the active conformation of human 5-LOX using comparative modeling, docking of known inhibitors, and molecular dynamics simulation. Using this model, novel 5-LOX inhibitors were identified by virtual screen. Of the 105 compounds tested in a cell-free assay, 30 have IC₅₀ values less than 100 μM and 11 less than 10 μM with the strongest inhibition of 620 nM. Compounds **4**, **7**, and **11** showed strong inhibition activity in the human whole blood (HWB) assay with IC₅₀ values of 8.6, 9.7, 8.1 μM, respectively.

Protein Conformational Analysis

Sequence-Dependent Stability Test of a Left-Handed β -Helix Motif

Natha R. Hayre [University of California, Davis], Rajiv R.P. Singh, Daniel L. Cox

Biophysical Journal. **102**, 1443-1452, 2012.

The left-handed β -helix (LHBH) is an intriguing, rare structural pattern in polypeptides that has been implicated in the formation of amyloid aggregates. We used accurate all-atom replica-exchange molecular dynamics (REMD) simulations to study the relative stability of diverse sequences in the LHBH conformation. Ensemble-average coordinates from REMD served as a scoring criterion to identify sequences and threadings optimally suited to the LHBH, as in a fold recognition paradigm.

Substituent Effect on the Structural Behavior of Modified Cyclodextrin: A Molecular Dynamics Study on Methylated β -CDs

Wan-Sheung Li, San-Chi Wang, Tsong-Song Hwang, and Ito Chao [Academia Sinica]

J. Phys. Chem. B., **116**, 3477-3489, 2012.

A series of methylated and non-methylated β -cyclodextrin (β -CD) structures in three macrocyclic configurations (a-c) were studied with molecular dynamics (MD) simulations to elucidate the dynamic behavior of the different CD structures using a continuum water model with the AMBER* force field. A set of parameters were defined to describe the geometric dimensions of the CD, such as its cavity shape, the upper and lower rim sizes, and the tilting of each of the glucose rings. Correlation analyses between the different parameters were carried out, and they have provided insights into the different dynamic behaviors for the different CD structures.

Conformational selection through electrostatics: Free energy simulations of gtp and gdp binding to archaeal initiation factor 2

Priyadarshi Satpati and Thomas Simonson [Laboratoire de Biochimie (CNRS UMR7654)]

Proteins: Stru. Fun. & Bioinf. **80**, 1264-1282, 2012.

Archaeal Initiation Factor 2 is a GTPase involved in protein biosynthesis. In its GTP-bound, "ON" conformation, it binds an initiator tRNA and carries it to the ribosome. In its GDP-bound, "OFF" conformation, it dissociates from tRNA. To understand the specific binding of GTP and GDP and their dependence on the conformational state, molecular dynamics free energy simulations were performed. The ON state specificity was predicted to be weak, with a GTP/GDP binding free energy difference of -1 kcal/mol, favoring GTP. The OFF state specificity is larger, 4 kcal/mol, favoring GDP.

Protein Dynamics

Dimerization of Helical β -Peptides in Solution

Michael McGovern [University of Wisconsin-Madison], Nicholas Abbott, Juan J. de Pablo

Biophysical Journal. **102**, 1435-1442, 2012.

Molecular simulations are used to examine the aggregation behavior of several β -peptides in explicit water. The particular peptides considered here adopt a helical, rodlike conformation in aqueous solution. Four distinct molecular sequences are considered. Earlier experimental studies have revealed the formation of ordered and disordered aggregates for such molecules, depending on sequence. The simulations reported here, which are conducted by resorting to metadynamics techniques, lead to free energy surfaces for dimerization of the peptides in water as a function of separation and relative orientation.

Protein Dynamics (Cont'd)

Charge Effects on the Fibril-Forming Peptide KTVHIE: A Two-Dimensional Replica Exchange Simulation Study

Joohyun Jeon, M. Scott Shell [University of California, Santa Barbara]

Biophysical Journal. **102**, 1952-1960, 2012.

The assembly of peptides into ordered nanostructures is increasingly recognized as both a bioengineering tool for generating new materials and a critical aspect of aggregation processes that underlie neurological diseases such as Alzheimer's disease, Parkinson's disease, and Huntington's disease. We develop a methodology to quantify and compare the propensity of different peptide sequences to form small oligomers during early self-assembly stages. This umbrella-sampling replica exchange molecular dynamics method performs a replica exchange MD simulation along peptide association reaction coordinates using umbrella restraints.

Effect of the A30P mutation on the structural dynamics of micelle-bound α Synuclein released in water: a molecular dynamics study

Prathit Chatterjee and Neelanjana Sengupta [National Chemical Laboratory, Pune]

Europ. Biophys. Jou., **41**, 483-489, 2012.

Atomistic MD simulation has been used to probe the effect of the A30P mutation on the structural dynamics of micelle-bound, helical α Synuclein when released in an aqueous environment. On the timescales simulated, the effect of the mutation on the secondary structure is restricted to local changes close to the mutation site in the N-terminal helical domain. The changes are transient, and all residues except Lys23 recover their initial structure. The local behavior due to the mutation gives rise to a global difference in the A30P mutant in the form of a permanent kink in the N-terminal helical domain.

Protein Crowding Affects Hydration Structure and Dynamics

Ryuhei Harada, Yuji Sugita, and Michael Feig [RIKEN Quantitative Biology Center]

J. Am. Chem. Soc., **134**, 4842-4849, 2012.

The effect of protein crowding on the structure and dynamics of water was examined from explicit solvent MD simulations of a series of protein G and protein G/villin systems at different protein concentrations. Hydration structure was analyzed in terms of radial distribution functions, three-dimensional hydration sites, and preservation of tetrahedral coordination. Analysis of hydration dynamics focused on self-diffusion rates and dielectric constants as a function of crowding. The results show significant changes in both structure and dynamics of water under highly crowded conditions.

Ab initio simulation of the effect of the potential of water on the electronic structure of arginine

Xingrong Wang and Haoping Zheng [Tongji University]

J. Mol.Mod., **18**, 859-870, 2012

As a part of the task of constructing the equivalent potential of water in order to obtain a reliable electronic structure for a protein, the equivalent potential of water for an arginine molecule was constructed by performing first-principles, all-electron, ab initio calculations. The process consisted of three steps. First, the electronic structure of arginine was calculated using a free cluster calculation. Then, the minimum-energy geometric structure of the system Arg++9H₂O was found using free cluster calculations. Then, based on the optimized geometric structure of the Arg++9H₂O system, the electronic structure of Arg+ in the potential of water was calculated using the SCCE method.

Protein Dynamics (Cont'd)

Unique example of amyloid aggregates stabilized by main chain H-bond instead of the steric zipper: molecular dynamics study of the amyloidogenic segment of amylin wild-type and mutants

Workalemahu Mikre Berhanu and Artëm E. Masunov
[University of Central Florida]

J. Mol.Mod., **18**, 891-903, 2012

Most proteins do not aggregate while in their native functional states. However, they may be disturbed from their native conformation by certain change in the environment, and form unwanted oligomeric or polymeric aggregates. Recent experimental data demonstrate that soluble oligomers of amyloidogenic proteins are responsible for amyloidosis and its cytotoxicity. Human islet amyloid polypeptide (IAPP or amylin) is a 37-residue hormone found as fibrillar deposits in pancreatic extracts of nearly all type II diabetics. In this study we performed in silico mutation analysis to examine the stability of the double layer five strand aggregates formed by heptapeptide NNFGAIL segment from amyline peptide.

Interactions of uranyl ion with cytochrome b5 and its His39Ser variant as revealed by molecular simulation in combination with experimental methods

Dun Wan, Li-Fu Liao [University of South China], Min-Min Zhao, Min-Long Wu and Yi-Mou Wu, et al.

J. Mol.Mod., **18**, 1009-1013, 2012

The biological toxicity of uranyl ion (UO₂²⁺) lies in interacting with proteins and disrupting their native functions. The structural and functional consequences of UO₂²⁺ interacting with cytochrome b 5 (cyt b 5), a small membrane heme protein, and its heme axial ligand His39Ser variant, cyt b 5 H39S, were investigated both experimentally and theoretically. In experiments, although cyt b 5 was only slightly affected, UO₂²⁺ binding to cyt b 5 H39S with a K_D of 2.5 μM resulted in obvious alteration of the heme active site, and led to a decrease in peroxidase activity.

Computational Prediction of Metabolism: Sites, Products, SAR, P450 Enzyme Dynamics, and Mechanisms

Johannes Kirchmair, Mark J. Williamson, Jonathan D. Tyzack, Lu Tan, Peter J. Bond, Andreas Bender, and Robert C. Glen [University of Cambridge]

J.Chem. Infor. and Mod. **52**, 617–648, 2012.

Metabolism of xenobiotics remains a central challenge for the discovery and development of drugs, cosmetics, nutritional supplements, and agrochemicals. Experimental investigation of the metabolism of small organic molecules is particularly resource demanding; hence, computational methods are of considerable interest to complement experimental approaches. This review provides a broad overview of structure- and ligand-based computational methods for the prediction of xenobiotic metabolism. This review attempts to survey the range and scope of computational methods applied to metabolism prediction and also to compare and contrast their applicability and performance.

Protein Dynamics (Cont'd)

Determination of Effective Potentials for the Stretching of $C^\alpha \cdots C^\alpha$ Virtual Bonds in Polypeptide Chains for Coarse-Grained Simulations of Proteins from ab Initio Energy Surfaces of N-Methylacetamide and N-Acetylpyrrolidine

Adam K. Sieradzan, Harold A. Scheraga, and Adam Liwo
[University of Gdańsk]

J. Chem. Theor. and Comp., **8**, 1334–1343, 2012.

The potentials of mean force (PMFs) for the deformation of the $C^\alpha \cdots C^\alpha$ virtual bonds in polypeptide chains were determined from the diabatic energy surfaces of N-methylacetamide (modeling regular peptide groups) and N-acetylpyrrolidine (modeling the peptide groups preceding proline), calculated at the Møller–Plesset (MP2) ab initio level of theory with the 6-31G(d,p) basis set. The energy surfaces were expressed in the $C^\alpha \cdots C^\alpha$ virtual-bond length (d) and the $H-N-C^\alpha \cdots C'$ improper dihedral angle (α) that describes the pyramidity of the amide nitrogen, or in the $C^\alpha-C'(O)-N-C^\alpha$ dihedral angle (ω) and the angle α . For each grid point, the potential energy was minimized with respect to all remaining degrees of freedom.

Cavity Closure Dynamics of Peracetylated β -Cyclodextrins in Supercritical Carbon Dioxide

Muhannad Altarsha, Francesca Ingrosso, and Manuel F. Ruiz-López [University of Lorraine]

J. Phys. Chem. B., **116**, 3982–3990, 2012.

Structural properties of peracetylated β -cyclodextrin in supercritical carbon dioxide were investigated by means of MD simulations. The study indicated a strong reduction of the cavity accessibility to guest molecules, compared to native β -cyclodextrin in water. Indeed, the cavity is self-closed during the largest part of the simulation, which agrees well with suggestions made on the basis on high-pressure NMR experiments. Self-closure happens because one glucose unit undergoes a main conformational change (from chair to skew) that brings one of the acetyl groups in the wide rim of the cyclodextrin to the cavity interior.

Atomistic Simulations of Dilute Polyelectrolyte Solutions

Soohyung Park, Xiao Zhu, and Arun Yethiraj [University of Wisconsin, Madison]

J. Phys. Chem. B., **116**, 4319–4327, 2012.

The properties of short chains of poly-(styrene)-co-(styrene sulfonate) are studied using atomistic MD simulations with explicit solvent. We study single 8-mers and 16-mers with two species of counterions, Na^+ and Mg^{2+} , and for various degrees of sulfonation, f . We find that single trajectories do not efficiently sample configurational space, even for fairly long 100-ns simulations, because of rotational barriers caused by nonbonded interactions. Hamiltonian replica exchange MD simulations or averages over multiple trajectories are required in order to obtain equilibrium properties.

Dimerization of the Full-Length Alzheimer Amyloid β -Peptide (A β 42) in Explicit Aqueous Solution: A Molecular Dynamics Study

Xiaoxia Zhu, Ram Prasad Bora, Arghya Barman, Rajiv Singh, and Rajeev Prabhakar [University of Miami]

J. Phys. Chem. B., **116**, 4405–4416, 2012.

In this study, the mechanism of dimerization of the full-length Alzheimer amyloid beta (A β 42) peptide and structural properties of the three most stable dimers have been elucidated through 0.8 μs classical molecular dynamics (MD) simulations. The A β 42 dimer has been reported to be the smallest neurotoxic species that adversely affects both memory and synaptic plasticity. On the basis of interactions between the distinct regions of the A β 42 monomer, 10 different starting configurations were developed from their native folded structures.

Protein Dynamics (Cont'd)

Melting of Hydrogen Bonds in Uracil Derivatives Probed by Infrared Spectroscopy and ab Initio Molecular Dynamics

Zsolt Szekrényes [Wigner Research Centre for Physics], Katalin Kamarás, György Tarczay, Anna Llanes-Pallás, Tomas Marangoni, Maurizio Prato, Davide Bonifazi, Jonas Björk, Felix Hanke, and Mats Persson

J. Phys. Chem. B., **116**, 4626–4633, 2012.

The thermal response of hydrogen bonds is a crucial aspect in the self-assembly of molecular nanostructures. To gain a detailed understanding of their response, we investigated infrared spectra of monomers and hydrogen-bonded dimers of two uracil-derivative molecules, supported by density functional theory calculations. Matrix isolation spectra of monomers, temperature dependence in the solid state, and ab initio molecular dynamics calculations give a comprehensive picture about the dimer structure and dynamics of such systems as well as a proper assignment of hydrogen-bond affected bands.

Free Energy Calculations

Free-Energy Simulations Reveal that Both Hydrophobic and Polar Interactions Are Important for Influenza Hemagglutinin Antibody Binding

Zhen Xia, Tien Huynh, Seung-gu Kang, Ruhong Zhou [IBM Thomas J. Watson Research Center]

Biophysical Journal. **102**, 1453–1461, 2012.

Antibodies binding to conserved epitopes can provide a broad range of neutralization to existing influenza subtypes and may also prevent the propagation of potential pandemic viruses by fighting against emerging strands. Here we propose a computational framework to study structural binding patterns and detailed molecular mechanisms of viral surface glycoprotein hemagglutinin (HA) binding with a broad spectrum of neutralizing monoclonal antibody fragments (Fab). We used rigorous free-energy perturbation (FEP) methods to calculate the antigen-antibody binding affinities, with an aggregate underlying molecular-dynamics simulation time of several microseconds ($\sim 2 \mu\text{s}$) using all-atom, explicit-solvent models.

Improving the Efficiency of Protein–Ligand Binding Free-Energy Calculations by System Truncation

Samuel Genheden and Ulf Ryde [Lund University]

J. Chem. Theor. and Comp., **8**, 1449–1458, 2012.

We have studied whether the efficiency of alchemical free-energy calculations with the Bennett acceptance ratio method of protein–ligand binding energies can be improved by simulating only part of the protein. To this end, we solvated the full protein in a spherical droplet with a radius of 46 Å, surrounded by a vacuum. Then, we systematically reduced the size of the droplet and at the same time ignored protein residues that were outside the droplet. Radii of 40–15 Å were tested. Ten inhibitors of the blood clotting factor Xa were studied, and the results were compared to an earlier study in which the protein was solvated in a periodic box, showing complete agreement between the two sets of calculations within statistical uncertainty.

Free Energy Calculations (Cont'd)

Construction of the Free Energy Landscape of Peptide Aggregation from Molecular Dynamics Simulations

Laura Riccardi, Phuong H. Nguyen, and Gerhard Stock
[Albert Ludwigs University]

J. Chem. Theor. and Comp. **8**, 1471–1479, 2012.

To describe the structure and dynamics of oligomers during peptide aggregation, a method is proposed that considers both the intramolecular and intermolecular structures of the multimolecule system and correctly accounts for its degeneracy. The approach is based on the “by-parts” strategy, which partitions a complex molecular system into parts, determines the metastable conformational states of each part, and describes the overall conformational state of the system in terms of a product basis of the states of the parts. Based on these states, a transition network reflecting the free energy landscape of the aggregation process can be constructed that facilitates the identification of the aggregation pathways.

Stability and free energy calculation of LNA modified quadruplex: a molecular dynamics study

Amit Kumar Chaubey, Kshatresh Dutta Dubey and Rajendra Prasad Ojha [DDU Gorakhpur University]

J. Comp. Aided Mol. Des. **26**, 289–299, 2011.

Telomeric ends of chromosomes, which comprise noncoding repeat sequences of guanine-rich DNA, which are the fundamental in protecting the cell from recombination and degradation. Telomeric DNA sequences can form four stranded quadruplex structures, which are involved in the structure of telomere ends. The formation and stabilization of telomeric quadruplexes has been shown to inhibit the activity of telomerase, thus establishing telomeric DNA quadruplex as an attractive target for cancer therapeutic intervention. Here we report the relative stabilities of these structures under K⁺ ion conditions and binding interaction between the strands, as determined by molecular dynamic simulations followed by energy calculation.

Ligand Binding/Docking

A semiempirical approach to ligand-binding affinities: Dependence on the Hamiltonian and corrections

Paulius Mikulskis, Samuel Genheden, Karin Wichmann and Ulf Ryde [Lund University]

J. Comp. Chem. **33**, 1179–1189, 2012.

We present a combination of semiempirical quantum-mechanical (SQM) calculations in the conductor-like screening model with the MM/GBSA (molecular-mechanics with generalized Born and surface-area solvation) method for ligand-binding affinity calculations. We test three SQM Hamiltonians, AM1, RM1, and PM6, as well as hydrogen-bond corrections and two different dispersion corrections. As test cases, we use the binding of seven biotin analogues to avidin, nine inhibitors to factor Xa, and nine phenol-derivatives to ferritin.

Ligand Binding / Docking (Cont'd)

Molecular modeling of hair keratin/peptide complex: Using MM-PBSA calculations to describe experimental binding results

Nuno G. Azoia, Margarida M. Fernandes, Nuno M. Micaêlo, Cláudio M. Soares and Artur Cavaco-Paulo [Universidade do Minho]

Proteins: Stru. Fun. & Bioinf. **80**, 1409–1417, 2012.

Molecular dynamics simulations of a keratin/peptide complex have been conducted to predict the binding affinity of four different peptides toward human hair. Free energy calculations on the peptides' interaction with the keratin model demonstrated that electrostatic interactions are believed to be the main driving force stabilizing the complex. The molecular mechanics–Poisson-Boltzmann surface area methodology used for the free energy calculations demonstrated that the dielectric constant in the protein's interior plays a major role in the free energy calculations.

Enzyme Catalysis

Retaining Glycosyltransferase Mechanism Studied by QM/MM Methods: Lipopolysaccharyl- α -1,4-galactosyltransferase C Transfers α -Galactose via an Oxocarbenium Ion-like Transition State

Hansel Gómez, Iakov Polyak, Walter Thiel, José M. Lluch, and Laura Masgrau [Universitat Autònoma de Barcelona]

J. Am. Chem. Soc., **134**, 4743–4752, 2012.

Glycosyltransferases (GTs) catalyze the highly specific biosynthesis of glycosidic bonds and, as such, are important both as drug targets and for biotechnological purposes. Despite their broad interest, fundamental questions about their reaction mechanism remain to be answered. In the present work, we focus on the reaction catalyzed by lipopolysaccharyl- α -1,4-galactosyltransferase C (LgtC) from *Neisseria meningitidis*. We study and compare the different proposed mechanisms (S_Ni , S_{Ni} -like, and double displacement mechanism via a covalent glycosyl-enzyme intermediate, CGE) by using density functional theory (DFT) and quantum mechanics/molecular mechanics (QM/MM) calculations on the full enzyme.

Virtual screening for potential inhibitors of bacterial MurC and MurD ligases

Tihomir Tomašić, Andreja Kovač, Gerhard Klebe, Lucija Peterlin Mašič [University of Ljubljana], Didier Blanot and Stanislav Gobec, et al.

J. Mol.Mod., **18**, 1063-1072, 2012

Mur ligases are bacterial enzymes involved in the cytoplasmic steps of peptidoglycan biosynthesis and are viable targets for antibacterial drug discovery. We have performed virtual screening for potential ATP-competitive inhibitors targeting MurC and MurD ligases, using a protocol of consecutive hierarchical filters. Selected compounds were evaluated for inhibition of MurC and MurD ligases, and weak inhibitors possessing dual inhibitory activity have been identified. These compounds represent new scaffolds for further optimisation towards multiple Mur ligase inhibitors with improved inhibitory potency.

Enzyme Catalysis (Cont'd)

Insight into the binding interactions of CYP450 aromatase inhibitors with their target enzyme: a combined molecular docking and molecular dynamics study

Roberta Galeazzi [Università Politecnica delle Marche] and Luca Massaccesi

J. Mol.Mod., **18**, 1153-1166, 2012

CYP450 aromatase catalyzes the terminal and rate-determining step in estrogen synthesis, the aromatization of androgens, and its inhibition is an efficient approach to treating estrogen-dependent breast cancer. Insight into the molecular basis of the interaction at the catalytic site between CYP450 aromatase inhibitors and the enzyme itself is required in order to design new and more active compounds. Hence, a combined molecular docking–molecular dynamics study was carried out to obtain the structure of the lowest energy association complexes of aromatase with some third-generation aromatase inhibitors (AIs) and with other novel synthesized letrozole-derived compounds which showed high in vitro activity.

Homology modeling of the structure of acyl-CoA:isopenicillin N-acyltransferase (IAT) from *Penicillium chrysogenum*. IAT interaction studies with isopenicillin-N, combining molecular dynamics simulations and docking

Liliana Moreno-Vargas, Jose Correa-Basurto, Rachid C. Maroun and Francisco J. Fernández [Universidad Autónoma Metropolitana-Iztapalapa]

J. Mol.Mod., **18**, 1189-1205, 2012

In the last step of penicillin biosynthesis, acyl-CoA:isopenicillin N acyltransferase (IAT) (E.C. 2.3.1.164) catalyzes the conversion of isopenicillin N (IPN) to penicillin G. IAT substitutes the α -aminoadipic acid side chain of IPN by a phenylacetic acid phenolate group (from phenylacetyl-CoA). Having a three-dimensional (3D) structure of IAT helps to determine the steps involved in side chain exchange by identifying the atomic details of substrate recognition. We predicted the IAT 3-D structure (α - and β -subunits), as well as the manner of IPN and phenylacetyl-CoA bind to the mature enzyme (β -subunit). The 3D IAT prediction was achieved by homology modeling and molecular docking in different snapshots, and refined by molecular dynamic simulations.

Gas-Phase Chemical Dynamics Simulations on the Bifurcating Pathway of the Pimaradienyl Cation Rearrangement: Role of Enzymatic Steering in Abietic Acid Biosynthesis

Matthew R. Siebert, Paranjothy Manikandan, Rui Sun, Dean J. Tantillo, and William L. Hase [Texas Tech University]

J. Chem. Theor. and Comp., **8**, 1212–1222, 2012.

The biosynthesis of abietadiene is the first biosynthetically relevant process shown to involve a potential energy surface with a bifurcating reaction pathway. Herein, we use gas-phase, enzyme-free direct dynamics simulations to study the behavior of the key reaction (bifurcating) step, which is conversion of the C₂₀ pimaradienyl cation to the abietadienyl cation. In a previous study (*J. Am. Chem. Soc.* **2011**, 133, 8335), a truncated C₁₀ model was used to investigate this reaction. The current work finds that the complete C₂₀ pimaradienyl cation gives reaction dynamics similar to that reported for the truncated C₁₀ model.

Enzyme Catalysis (Cont'd)

Reaction Pathway and Free Energy Profile for Cocaine Hydrolase-Catalyzed Hydrolysis of (–)-Cocaine

Junjun Liu and Chang-Guo Zhan [University of Kentucky]

J. Chem. Theor. and Comp., **8**, 1426–1435, 2012.

The reaction pathway of (–)-cocaine hydrolysis catalyzed by our recently discovered, most efficient cocaine hydrolase, which is the A199S/F227A/S287G/A328W/Y332G mutant of human butyrylcholinesterase (BChE), and the corresponding free energy profile have been studied by performing first-principles pseudobond QM/MM-free energy (FE) calculations. On the basis of the QM/MM-FE results, the catalytic hydrolysis process consists of four major reaction steps, including the nucleophilic attack on the carbonyl carbon of the (–)-cocaine benzoyl ester by the hydroxyl group of S198, dissociation of the (–)-cocaine benzoyl ester, nucleophilic attack on the carbonyl carbon of the (–)-cocaine benzoyl ester by water, and finally the dissociation between the (–)-cocaine benzoyl group and S198 of the enzyme.

Molecular dynamics simulations of the coenzyme induced conformational changes of Mycobacterium tuberculosis L-alanine dehydrogenase

Baoping Ling, Min Sun, Siwei Bi, Zhihong Jing, Yongjun Liu [Chinese Academy of Sciences]

J. Mol. Graph. and Mod., **35**, 1-9, 2012.

Mycobacterium tuberculosis l-alanine dehydrogenase (l-MtAlaDH) catalyzes the NADH-dependent reversible oxidative deamination of l-alanine to pyruvate and ammonia. l-MtAlaDH has been proposed to be a potential target in the treatment of tuberculosis. Based on the crystal structures of this enzyme, molecular dynamics simulations were performed to investigate the conformational changes of l-MtAlaDH induced by coenzyme NADH. The results show that the presence of NADH in the binding domain restricts the motions and conformational distributions of l-MtAlaDH.

Relationship between the structure and the enzymatic activity of crotoxin complex and its phospholipase A₂ subunit: An in silico approach

Jaime Andrés Pereañez [Universidad de Antioquia], Iván Dario Gómez, Arley Camilo Patiño

J. Mol. Graph. and Mod., **35**, 36-42, 2012.

Crotoxin, one of the major toxins of South American rattlesnake *Crotalus durissus* subspecies, is an heterodimeric complex composed of two distinct subunits: a basic phospholipase A₂ (PLA₂, CB) and an acidic nontoxic catalytically inactive protein, crotapotin (CA). It's well known that CB has a high enzymatic activity; however the molecular aspects that determine this fact remain unknown. In this study, an in silico approach was used to predict the CA structure by homology modeling, and the crotoxin structure by means of molecular docking. CA structure was built using the software Modeller taking *Crotalus atrox* PLA₂ (1PP2:R) as a template.

Membrane Proteins and Lipid Peptide Interactions

Determining the Gaussian Curvature Modulus of Lipid Membranes in Simulations

Mingyang Hu, John J. Briguglio, Markus Deserno [Carnegie Mellon University]

Biophysical Journal. **102**, 1403-1410, 2012.

The Gaussian curvature modulus κ^- of lipid bilayers likely contributes more than 100 kcal/mol to every cellular fission or fusion event. This huge impact on membrane remodeling energetics might be a factor that codetermines the complex lipid composition of biomembranes through tuning of κ^- . Yet, its value has been measured only for a handful of simple lipids, and no simulation has so far determined it better than a factor of two, rendering a systematic investigation of such enticing speculations impossible. Here we propose a highly accurate method to determine κ^- in computer simulations.

Influence of Hydrophobic Mismatch on Structures and Dynamics of Gramicidin A and Lipid Bilayers

Taehoon Kim, Kyu Il Lee, Phillip Morris, Richard W. Pastor, Olaf S. Andersen, Wonpil Im [The University of Kansas]

Biophysical Journal. **102**, 1551-1560, 2012.

Gramicidin A (gA) is a 15-amino-acid antibiotic peptide with an alternating L-D sequence, which forms (dimeric) bilayer-spanning, monovalent cation channels in biological membranes and synthetic bilayers. We performed MD simulations of gA dimers and monomers in all-atom, explicit dilauroyl phosphatidylcholine (DLPC), dimyristoyl phosphatidylcholine (DMPC), dioleoyl phosphatidylcholine (DOPC), and 1-palmitoyl-2-oleoyl-phosphatidylcholine (POPC) bilayers. The lipid behaviors in the first shell around gA dimers are more complex than predicted from a simple mismatch model, which has implications for understanding the energetics of membrane protein-lipid interactions.

Large Influence of Cholesterol on Solute Partitioning into Lipid Membranes

Christian L. Wennberg, David van der Spoel, and Jochen S. Hub [Uppsala University, Husargatan]

J. Am. Chem. Soc., **134**, 5351-5361, 2012.

Cholesterol plays an important role in maintaining the correct fluidity and rigidity of the plasma membrane of all animal cells, and hence, it is present in concentrations ranging from 20 to 50 mol %. Here we apply systematic molecular dynamics simulations to study the partitioning of solutes between water and membranes. The simulations indicate that the cost of breaking van der Waals interactions between the lipid tails of cholesterol-containing membranes account for the reduced partitioning rather than the surface area per phospholipid, which has been frequently suggested as a determinant for solute partitioning.

Computer-Aided Drug Design of Falcipain Inhibitors: Virtual Screening, Structure-Activity Relationships, Hydration Site Thermodynamics, and Reactivity Analysis

Falgun Shah, Jiri Gut, Jennifer Legac, Devleena Shivakumar, Woody Sherman, Philip J. Rosenthal, and Mitchell A. Avery [University of Mississippi]

J.Chem. Infor. and Mod. **52**, 696-710, 2012.

Falcipains (FPs) are hemoglobins of *Plasmodium falciparum* that are validated targets for the development of antimalarial chemotherapy. A combined ligand- and structure-based virtual screening of commercial databases was performed to identify structural analogs of virtual screening hits previously discovered in our laboratory. A total of 28 low micromolar inhibitors of FP-2 and FP-3 were identified and the structure-activity relationship (SAR) in each series was elaborated. The present study highlights the importance of considering energetic contributors to binding beyond traditional ligand-protein interactions.

Membrane Proteins and Lipid Peptide Interactions (Cont'd)

Convergence of Free Energy Profile of Coumarin in Lipid Bilayer

Markéta Paloncýová, Karel Berka, and Michal Otyepka
[Palacky University]

J. Chem. Theor. and Comp., **8**, 1200–1211, 2012.

Atomistic molecular dynamics (MD) simulations of druglike molecules embedded in lipid bilayers are of considerable interest as models for drug penetration and positioning in biological membranes. Here we analyze partitioning of coumarin in dioleoylphosphatidylcholine (DOPC) bilayer, based on both multiple, unbiased 3 μ s MD simulations (total length) and free energy profiles along the bilayer normal calculated by biased MD simulations (~ 7 μ s in total). The convergences in time of free energy profiles calculated by both umbrella sampling and z-constraint techniques are thoroughly analyzed.

Replica exchange Monte-Carlo simulations of helix bundle membrane proteins: rotational parameters of helices

H.-H. Wu, C.-C. Chen [National Taiwan Normal University] and C.-M. Chen

J. Comp. Aided Mol. Des., **26**, 363–374, 2011.

We propose a united-residue model of membrane proteins to investigate the structures of helix bundle membrane proteins (HBMPs) using coarse-grained (CG) replica exchange Monte-Carlo (REMC) simulations. To demonstrate the method, it is used to identify the ground state of HBMPs in a CG model, including bacteriorhodopsin (BR), halorhodopsin (HR), and their subdomains. The rotational parameters of transmembrane helices (TMHs) are extracted directly from the simulations, which can be compared with their experimental measurements from site-directed dichroism.

Comparison of Ternary Bilayer Mixtures with Asymmetric or Symmetric Unsaturated Phosphatidylcholine Lipids by Coarse Grained Molecular Dynamics Simulations

C. Rosetti [Centro Atómico Constituyentes CNEA] and C. Pastorino

J. Phys. Chem. B., **116**, 3525–3537, 2012.

We studied the phase behavior of various ternary bilayer mixtures composed of cholesterol, an unsaturated lipid, and a fully saturated lipid, by means of molecular dynamics simulations of the MARTINI(1) coarse grain model. We aimed at comparing lateral organization and local properties of bilayers containing phosphatidylcholine (PC) lipids, either with two unsaturated tails (symmetric), or one unsaturated and one saturated tail (asymmetric), as the low-melting component of the mixture. Membranes with a symmetric or an asymmetric unsaturated lipid, with the same kind of unsaturated chain, show different phase behavior.

Structure and Elasticity of Lipid Membranes with Genistein and Daidzein Bioflavonoids Using X-ray Scattering and MD Simulations

Mohit Raghunathan, Yuriy Zubovski, Richard M. Venable, Richard W. Pastor, John F. Nagle, and Stephanie Tristram-Nagle [Carnegie Mellon University]

J. Phys. Chem. B., **116**, 3918–3927, 2012.

This work reports the effects of the bioflavonoids genistein and daidzein on lipid bilayers as determined by volume measurements, X-ray scattering, and molecular dynamics simulations. The experimental and simulated total molecular volumes were found to be in outstanding agreement with each other before the addition of genistein and daidzein and also after their addition. Both bioflavonoids inserted into the hydrocarbon region of both DOPC and diphytanoylPC near the carbonyls of the lipids and both decreased the bilayer thicknesses.

Membrane Proteins and Lipid Peptide Interactions (Cont'd)

Molecular Dynamics Simulation of PEGylated Bilayer Interacting with Salt Ions: A Model of the Liposome Surface in the Bloodstream

Aniket Magarkar, Esra Karakas, Michał Stepniewski, Tomasz Róg, and Alex Bunker [University of Helsinki]

J. Phys. Chem. B., **116**, 4212–4219, 2012.

PEGylation is an effective mechanism to prolong the bloodstream lifetime, and thus efficacy, of drug delivery liposomes. The mechanism through which poly(ethylene glycol) (PEG) increases bloodstream lifetime is, however, not completely understood. The interaction with salt ions found in the bloodstream is known to play a role in this. We have used all-atom molecular dynamics simulation to study the effect of PEGylated lipid density, salt concentration, and the interaction with KCl and CaCl₂ salts in addition to NaCl. This work expands on our previous work where we studied the gel and liquid crystalline membranes in physiological salt concentration.

Molecular Dynamics Study of the Interaction of Arginine with Phosphatidylcholine and Phosphatidylethanolamine Bilayers

Fernando E. Herrera [Institut Pasteur de Montevideo], Ana Bouchet, Fabiana Lairion, E. Anibal Disalvo, and Sergio Pantano

J. Phys. Chem. B., **116**, 4476–4483, 2012.

In this work, the differential interaction of zwitterionic arginines with fully hydrated dimyristoylphosphatidylcholine (DMPC) and dimyristoylphosphatidylethanolamine (DMPE) bilayers was analyzed by molecular dynamics simulations. In both systems, arginine binds to lipids with the carboxylate moiety oriented toward the aqueous phase, in agreement with previous experimental determinations of ζ potential of DMPC and DMPE liposomes. The guanidinium groups are found at different depths within the bilayers indicating that some arginines are buried, especially in DMPE.

Mixing Properties of Sphingomyelin Ceramide Bilayers: A Simulation Study

Rainer Metcalf and Sagar A. Pandit [University of South Florida]

J. Phys. Chem. B., **116**, 4500–4509, 2012.

Ceramide is the simplest molecule in the class of glycosphingolipids composed of a sphingosine backbone and acyl moiety. It plays significant roles in cell signaling; apoptosis; binding of hormones, toxins, and viruses; and many other biologically important functions. Sphingomyelin, ceramide with a phosphatidylcholine headgroup, is another biologically vital lipid present in the myelin sheath of nerve cell axons. To better understand the biophysical and thermodynamic properties of these molecules and their mixtures, we have performed NPT molecular dynamics simulations of hydrated 16:0 sphingomyelin bilayers with increasing concentrations of 16:0 ceramide at 323, 332, 340, and 358 K.

Protein Folding

Residue-Specific α -Helix Propensities from Molecular Simulation

Robert B. Best [University of Cambridge, Cambridge], David de Sancho, Jeetain Mittal

Biophysical Journal. **102**, 1462-1467, 2012.

Formation of α -helices is a fundamental process in protein folding and assembly. By studying helix formation in molecular simulations of a series of alanine-based peptides, we obtain the temperature-dependent α -helix propensities of all 20 naturally occurring residues with two recent additive force fields, Amber ff03w and Amber ff99SB*. Encouragingly, we find that the overall helix propensity of many residues is captured well by both energy functions, with Amber ff99SB* being more accurate.

Low Folding Cooperativity of Hp35 Revealed by Single-Molecule Force Spectroscopy and Molecular Dynamics Simulation

Chunmei Lv, Cheng Tan, Meng Qin, Dawei Zou, Yi Cao, Wei Wang [Nanjing University, Nanjing]

Biophysical Journal. **102**, 1944-1951, 2012.

Some small proteins, such as HP35, fold at submicrosecond timescale with low folding cooperativity. Although these proteins have been extensively investigated, still relatively little is known about their folding mechanism. Here, using single-molecule force spectroscopy and steered molecule dynamics simulation, we study the unfolding of HP35 under external force. Our results show that HP35 unfolds at extremely low forces without a well-defined unfolding transition state. Subsequently, we probe the structure of unfolded HP35 using the persistence length obtained in the force spectroscopy.

Replica exchange molecular dynamics simulation of structure variation from $\alpha/4\beta$ -fold to 3α -fold protein

Raudah Lazim, Ye Mei and Dawei Zhang [Nanyang Technological University]

J. Mol.Mod., **18**, 1087-1095, 2012

Replica exchange molecular dynamics (REMD) simulation provides an efficient conformational sampling tool for the study of protein folding. In this study, we explore the mechanism directing the structure variation from $\alpha/4\beta$ -fold protein to 3α -fold protein after mutation by conducting REMD simulation on 42 replicas with temperatures ranging from 270 K to 710 K. The simulation began from a protein possessing the primary structure of GA88 but the tertiary structure of GB88, two G proteins with "high sequence identity."

For the Sequence YKGQ, the Turn and Extended Conformational Forms Are Separated by Small Barriers and the Turn Propensity Persists Even at High Temperatures: Implications for Protein Folding

Harpreet Kaur and Yellamraju U. Sasidhar [Indian Institute of Technology Bombay]

J. Phys. Chem. B., **116**, 3850-3860, 2012.

The folding of the sequence ²¹DTVKLMYKGQPM³⁵TFR from staphylococcal nuclease into a β -hairpin, nucleated by the turn region YKGQ, is known to be an early folding event. With YKGQ being the shortest sequence for a β -turn model and in view of its importance to the folding of staphylococcal nuclease, we investigated the thermodynamics of turn formation at a range of temperatures from 280 to 380 K, with a regular interval of 10 K. Eleven independent molecular dynamics simulations (under NPT conditions) were performed using the GROMACS package of programs and the OPLS-AA/L all-atom force field, each for a time period of 1 μ s.

Protein Folding (Cont'd)

Distinct Dimerization for Various Alloforms of the Amyloid-Beta Protein: $A\beta_{1-40}$, $A\beta_{1-42}$, and $A\beta_{1-40}(D23N)$

Sébastien Côté, Rozita Laghaei, Philippe Derreumaux, and Normand Mousseau [Université de Montréal]

J. Phys. Chem. B., **116**, 4043–4055, 2012.

The Amyloid-beta protein is related to Alzheimer's disease, and various experiments have shown that oligomers as small as the dimer are cytotoxic. Two alloforms are mainly produced: $A\beta_{1-40}$ and $A\beta_{1-42}$. They have very different oligomer distributions, and it was recently suggested, from experimental studies, that this variation may originate from structural differences in their dimer structures. Little structural information is available on the $A\beta$ dimer, however, and to complement experimental observations, we simulated the folding of the wild-type $A\beta_{1-40}$ and $A\beta_{1-42}$ dimers as well as the mutated $A\beta_{1-40}(D23N)$ dimer using an accurate coarse-grained force field coupled to Hamiltonian-temperature replica exchange molecular dynamics.

Nucleic Acids

RNA Unwinding from Reweighted Pulling Simulations

Francesco Colizzi [SISSA – Scuola Internazionale Superiore di Studi Avanzati] and Giovanni Bussi

J. Am. Chem. Soc., **134**, 5173–5179, 2012.

The forming and melting of complementary base pairs in RNA duplexes are conformational transitions required to accomplish a plethora of biological functions. Yet the dynamic steps of these transitions have not been quantitatively characterized at the molecular level. In this work, the base opening process was first enforced by atomistic pulling simulations and then analyzed with a novel reweighting scheme, which allowed the free-energy profile along any suitable reaction coordinate, for example, solvation, to be reconstructed.

Monomeric adenine decay dynamics influenced by the DNA environment

You Lu, Zhenggang Lan and Walter Thiel [Max-Planck-Institut für Kohlenforschung]

J. Comp. Chem. **33**, 1225–1235, 2012.

We report on-the-fly surface-hopping dynamics simulations of single adenine embedded in solvated DNA oligomers, $(dA)_{10}$ and $(dA)_{10} \cdot (dT)_{10}$. Both model systems are found to decay from the S_1 to the S_0 state via distinct monomeric channels, on account of the strong hydrogen-bonding interactions between the Watson–Crick pair in the double-stranded oligomer. Surprisingly, the decay times (several picoseconds) for the current models are 10 times longer than those of adenine in the gas or aqueous phase, while matching one of the time constants observed experimentally.

2. METHODOLOGY

Quantitative Structure-Activity Relations

Insights into the permeability of drugs and drug-likemolecules from MI-QSAR and HQSAR studies

Ranajit N. Shinde, K. Srikanth and M. Elizabeth Sobhia [NIPER]

J. Mol.Mod., **18**, 947-962, 2012

Membrane-interaction QSAR (MI-QSAR) and Holographic QSAR (HQSAR) analyses have been performed on a diverse set of drugs and drug-like molecules. MI-QSAR combines a set of membrane-solute interaction properties calculated during molecular dynamics simulation with the set of classical solute descriptors to predict the biological behavior of drugs and drug-like molecules. HQSAR is a technique which employs fragment fingerprints or molecular holograms as predictive variables of biological activity. A data set of 60 structurally diverse molecules with permeability coefficients were used to construct significant MI-QSAR and HQSAR models of Caco-2 cell permeation.

Potentials and Parameters

Determination of best-fit potential parameters for a reactive force field using a genetic algorithm

Poonam Pahari [Bhabha Atomic Research Centre, Visakhapatnam] and Shashank Chaturvedi

J. Mol.Mod., **18**, 1049-1061, 2012

The ReaxFF interatomic potential, used for organic materials, involves more than 600 adjustable parameters, the best-fit values of which must be determined for different materials. A new method of determining the set of best-fit parameters for specific molecules containing carbon, hydrogen, nitrogen and oxygen is presented, based on a parameter reduction technique followed by genetic algorithm (GA) minimization. In this work, GA has been used to optimize the parameter set to determine best-fit parameters that can reproduce molecular properties to within a given accuracy.

Molecular Dynamics

Thermodynamic Coupling of Protonation and Conformational Equilibria in Proteins: Theory and Simulation

Chuanyin Shi, Jason A. Wallace, Jana K. Shen [University of Oklahoma, Norman]

Biophysical Journal. **102**, 1590-1597, 2012.

Ionization-coupled conformational phenomena are ubiquitous in biology. However, quantitative characterization of the underlying thermodynamic cycle comprised of protonation and conformational equilibria has remained an elusive goal. Here we use theory and continuous constant pH MD (CpHMD) simulations to provide a thermodynamic description for the coupling of proton titration and conformational exchange between two distinct states of a protein. CpHMD simulations with a hybrid-solvent scheme and the pH-based replica-exchange protocol are applied to obtain the equilibrium constants and atomic details of the ionization-coupled conformational exchange between open and closed states of an engineered mutant of staphylococcal nuclease.

Molecular Dynamics (Cont'd)

Suitability of the MARTINI Force Field for Use with Gas-Phase Protein Complexes

Sarah K. Fegan and Mark Thachuk [University of British Columbia]

J. Chem. Theor. and Comp., **8**, 1304–1313, 2012.

The MARTINI coarse-grained force field [Monticelli, L. et al. *J. Chem. Theory Comput.* **2008**, 4, 819–834] is examined for use in molecular dynamics simulations of the dissociation of gas-phase protein complexes. Coarse-grained force fields allow longer time scales and larger systems to be treated compared with all-atom force fields. In this work, results for the dissociation of the cytochrome c' dimer using MARTINI are compared with published studies using the OPLS-AA/L all-atom force field.

Magnesium Ion–Water Coordination and Exchange in Biomolecular Simulations

Olof Allnér, Lennart Nilsson, and Alessandra Villa [Karolinska Institutet]

J. Chem. Theor. and Comp., **8**, 1493–1502, 2012.

Magnesium ions have an important role in the structure and folding mechanism of ribonucleic acid systems. To properly simulate these biophysical processes, the applied molecular models should reproduce, among other things, the kinetic properties of the ions in water solution. Here, we have studied the kinetics of the binding of magnesium ions with water molecules and nucleic acid systems using molecular dynamics simulation in detail. We have validated the parameters used in biomolecular force fields, such as AMBER and CHARMM, for Mg^{2+} ions and also for the biologically relevant ions Na^+ , K^+ , and Ca^{2+} together with three different water models (TIP3P, SPC/E, and TIP5P).

Understanding the mechanism of cellulose dissolution in 1-butyl-3-methylimidazolium chloride ionic liquid via quantum chemistry calculations and molecular dynamics simulations

Hao Xu, Wenxiao Pan, Ruoxi Wang, Dongju Zhang [Key Laboratory of Colloid and Interface Chemistry, Ministry of Education, Jinan] and Chengbu Liu

J. Comp. Aided Mol. Des. **26**, 329–337, 2011.

While N,N'-dialkylimidazolium ionic liquids (ILs) have been well-established as effective solvents for dissolution and processing of cellulose, the detailed mechanism at the molecular level still remains unclear. In this work, we present a combined quantum chemistry and molecular dynamics simulation study on how the ILs dissolve cellulose. On the basis of calculations on 1-butyl-3-methylimidazolium chloride, one of the most effective ILs dissolving cellulose, we further studied the molecular behavior of cellulose models (i.e. cellulose oligomers with degrees of polymerization $n = 2, 4$, and 6) in the IL, including the structural features and hydrogen bonding patterns.

Predicting and Improving the Membrane Permeability of Peptidic Small Molecules

Salma B. Rafi, Brian R. Hearn, Punitha Vedantham, Matthew P. Jacobson, and Adam R. Renslo [University of California, San Francisco]

J. Med. Chem., **55**, 3163–3169, 2012.

We evaluate experimentally and computationally the membrane permeability of matched sets of peptidic small molecules bearing natural or bioisosteric unnatural amino acids. We find that the intentional introduction of hydrogen bond acceptor–donor pairs in such molecules can improve membrane permeability while retaining or improving other favorable drug-like properties. We employ an all-atom force field based method to calculate changes in free energy associated with the transfer of the peptidic molecules from water to membrane.

Molecular Dynamics (Cont'd)

Microsolvation and hydrogen bond interactions in Glycine Dipeptide: Molecular dynamics and density functional theory studies

Balasubramaniam Yogeswari, Ramasamy Kanakaraju, Subramaniam Boopathi, Ponmalai Kolandaivel [Bharathiar University]

J. Mol. Graph. and Mod., **35**, 11-20, 2012.

Molecular dynamics (MD) simulations were carried out to study the conformational characteristics of Glycine Dipeptide (GD) in the presence of explicit water molecules for over 10 ns with a MD time step of 2 fs. The density functional theory (DFT) methods with 6-311G** basis set have been employed to study the effects of microsolvation on the conformations of GD with 5–10 water molecules. The interaction energy with BSSE corrections and the strength of the intermolecular hydrogen bond interactions have been analyzed. The Bader's Atoms in Molecules (AIM) theory has been employed to investigate H-bonding patterns in water interacting complexes.

The Enolization Chemistry of a Thioester-Dependent Racemase: The 1.4 Å Crystal Structure of a Reaction Intermediate Complex Characterized by Detailed QM/MM Calculations

Satyan Sharma, Prasenjit Bhaumik, Werner Schmitz, Rajaram Venkatesan, J. Kalervo Hiltunen, Ernst Conzelmann, André H. Juffer, and Rik K. Wierenga [University of Oulu]

J. Phys. Chem. B., **116**, 3619–3629, 2012.

In the active site of the bacterial α -methylacyl-CoA racemase of *Mycobacterium tuberculosis* (MCR), the chirality of the 2-methyl branched C2-atom is interconverted between (S) and (R) isomers. Protein crystallographic data and quantum mechanics/molecular mechanics (QM/MM) computational approaches show that this interconversion is achieved via a planar enolate intermediate. The crystal structure, at 1.4 Å, visualizes the mode of binding of a reaction intermediate analogue, 2-methylacetoacetyl-CoA, in a well-defined planar enolate form. The computational studies confirm that in the conversion from (S) to (R), first a proton is abstracted by N δ 1 (His126), and subsequently the planar enolate form is reprotonated by O δ 2 (Asp156).

Simulating the Dynamics and Orientations of Spin-Labeled Side Chains in a Protein–DNA Complex

Jessica L. Sarver, Jacqueline E. Townsend, Gayathri Rajapakse, Linda Jen-Jacobson, and Sunil Saxena [University of Pittsburgh]

J. Phys. Chem. B., **116**, 4024–4033, 2012.

Site-directed spin labeling, wherein a nitroxide side chain is introduced into a protein at a selected mutant site, is increasingly employed to investigate biological systems by electron spin resonance (ESR) spectroscopy. An understanding of the packing and dynamics of the spin label is needed to extract the biologically relevant information about the macromolecule from ESR measurements. In this work, molecular dynamics (MD) simulations were performed on the spin-labeled restriction endonuclease, EcoRI in complex with DNA. Mutants of this homodimeric enzyme were previously constructed, and distance measurements were performed using the double electron electron resonance experiment.

Molecular Dynamics (Cont'd)

Molecular Dynamics Simulation of Nitric Oxide in Myoglobin

Myung Won Lee and Markus Meuwly [University of Basel]

J. Phys. Chem. B., **116**, 4154–4162, 2012.

The infrared (IR) spectroscopy and ligand migration of photodissociated nitric oxide (NO) in and around the active sites in myoglobin (Mb) are investigated. A distributed multipolar model for open-shell systems is developed and used, which allows one to realistically describe the charge distribution around the diatomic probe molecule. The IR spectra were computed from the trajectories for two conformational substates at various temperatures. Contrary to full quantum mechanical calculations, however, the force field and mixed QM/MM simulations do not correctly describe the relative shifts between the B- and C-states relative to gas-phase NO. Free energy simulations establish that NO preferably localizes in the distal site and the barrier for migration to the neighboring Xe4 pocket is $\Delta G_{B \rightarrow C}^{\ddagger} = 1.7\text{--}2.0$ kcal/mol.

QM and QM/MM

Density functional theory studies on the inclusion complexes of cyclic decapeptide with 1-phenyl-1-propanol enantiomers

Hongge Zhao, Yanyan Zhu [Zhengzhou University], Mingqiong Tong, Juan He and Chunmei Liu, et al

J. Mol.Mod., **18**, 851-858, 2012

Cyclic peptides are exciting novel hosts for chiral and molecular recognition. In this work, the inclusion complexes of cyclic decapeptide (CDP) with the 1-phenyl-1-propanol enantiomers (E-PP) are firstly studied using the density functional theory (DFT) B3LYP method. Our calculated results indicated that S(-)-1-phenyl-1-propanol (S-PP) could form a more stable inclusion complex with CDP than that of R(+)-1-phenyl-1-propanol (R-PP). The obvious differences in binding energy and thermodynamics data suggest that the cyclic decapeptide could differentiate the two enantiomers.

Ab initio DFT study of bisphosphonate derivatives as a drug for inhibition of cancer: NMR and NQR parameters

Hussein Aghabozorg, Beheshteh Sohrabi [Iran University of Science and Technology], Sara Mashkouri and Hamid Reza Aghabozorg

J. Mol.Mod., **18**, 929-936, 2012

DFT computations were carried out to characterize the ^{17}O and ^2H electric field gradient, EFG, in various bisphosphonate derivatives. The computations were performed at the B3LYP level with 6-311++G (d,p) standard basis set. Calculated EFG tensors were used to determine the ^{17}O and ^2H nuclear quadrupole coupling constant, χ and asymmetry parameter, η . For better understanding of the bonding and electronic structure of bisphosphonates, isotropic and anisotropic NMR chemical shieldings were calculated for the ^{13}C , ^{17}O and ^{31}P nuclei using GIAO method for the optimized structure of intermediate bisphosphonates at B3LYP level of theory using 6-311++G (d, p) basis set.

Comparative or Homology Modeling

Molecular docking and structural analysis of cofactor-protein interaction between NAD⁺ and 11 β -hydroxysteroid dehydrogenase type 2

Hideaki Yamaguchi [Meijo University], Tatsuo Akitaya, Tao Yu, Yumi Kidachi and Katsuyoshi Kamiie, et al.

J. Mol.Mod., **18**, 1037-1048, 2012

Molecular docking and structural analysis of the cofactor-protein interaction between NAD⁺ and human (h) or mouse (m) 11 β -hydroxysteroid dehydrogenase type 2 (11 β HSD2) were performed with the molecular operating environment (MOE). 11 β HSD1 (PDB code: 3HFG) was selected as a template for the 3D structure modeling of 11 β HSD2. The MOE docking (MOE-dock) and the alpha sphere and excluded volume-based ligand-protein docking (ASE-dock) showed that both NAD⁺-h11 β HSD2 and NAD⁺-m11 β HSD2 models have a similar binding orientation to the template cofactor-protein model.

Substrate binding and translocation of the serotonin transporter studied by docking and molecular dynamics simulations

Mari Gabrielsen, Aina Westrheim Ravna, Kurt Kristiansen and Ingebrigt Sylte [University of Tromsø]

J. Mol.Mod., **18**, 1073-1085, 2012

The serotonin (5-HT) transporter (SERT) plays an important role in the termination of 5-HT-mediated neurotransmission by transporting 5-HT away from the synaptic cleft and into the presynaptic neuron. In addition, SERT is the main target for antidepressant drugs, including the selective serotonin reuptake inhibitors (SSRIs). The three-dimensional (3D) structure of SERT has not yet been determined. In this study, a homology model of SERT was constructed based on the 3D structure of a prokaryotic homologous leucine transporter (LeuT) (PDB id: 2A65).

Design of β -Amyloid Aggregation Inhibitors from a Predicted Structural Motif

Paul A. Novick [Stanford University], Dahabada H. Lopes, Kim M. Branson, Alexandra Esteras-Chopo, Isabella A. Graef, Gal Bitan, and Vijay S. Pande

J.Med.Chem., **55**, 3002–3010, 2012.

Drug design studies targeting one of the primary toxic agents in Alzheimer's disease, soluble oligomers of amyloid β -protein (A β), have been complicated by the rapid, heterogeneous aggregation of A β and the resulting difficulty to structurally characterize the peptide. To address this, we have developed [Nle³⁵, d-Pro³⁷]A β ₄₂, a substituted peptide inspired from molecular dynamics simulations which forms structures stable enough to be analyzed by NMR. We report herein that [Nle³⁵, d-Pro³⁷]A β ₄₂ stabilizes the trimer and prevents mature fibril and β -sheet formation.

Ligand Docking

Conformational Transition and Energy Landscape of ErbB4 Activated by Neuregulin1 β : One Microsecond Molecular Dynamics Simulations

Yun Du, Huaiyu Yang [Shanghai Institute of Materia Medica], Yechun Xu, Xiaohui Cang, Cheng Luo, Yanyan Mao, Yuanyuan Wang, Guangrong Qin, Xiaomin Luo, and Hualiang Jiang

J. Am. Chem. Soc., **134**, 6720–6731, 2012.

ErbB4, a receptor tyrosine kinase of the ErbB family, plays crucial roles in cell growth and differentiation, especially in the development of the heart and nervous system. Ligand binding to its extracellular region could modulate the activation process. To understand the mechanism of ErbB4 activation induced by ligand binding, we performed one microsecond MD simulations on the ErbB4 extracellular region (ECR) with and without its endogenous ligand neuregulin1 β (NRG1 β). On the basis of the simulation results, an atomic mechanism for the ligand-induced activation of ErbB4 was postulated.

Ligand Docking (Cont'd)

Visualizing the Induced Binding of SH2-Phosphopeptide

T. Giorgino, I. Buch, and G. De Fabritiis [Universitat Pompeu Fabra]

J. Chem. Theor. and Comp., **8**, 1171–1175, 2012.

Approximately 100 proteins in the human genome contain an SH2 domain recognizing small flexible phosphopeptides. It is therefore important to understand in atomistic detail the way these peptides bind and the conformational changes that take place upon binding. Here, we obtained several spontaneous binding events between the p56 lck SH2 domain and the pYEEI peptide within 2 Å RMSD from the crystal structure and with kinetic rates compatible with experiments using high-throughput molecular dynamics simulations.

Modeling Structural Coordination and Ligand Binding in Zinc Proteins with a Polarizable Potential

Jiajing Zhang, Wei Yang, Jean-Philip Piquemal, and Pengyu Ren [The University of Texas at Austin]

J. Chem. Theor. and Comp., **8**, 1314–1324, 2012.

As the second most abundant cation in the human body, zinc is vital for the structures and functions of many proteins. Zinc-containing matrix metalloproteinases (MMPs) have been widely investigated as potential drug targets in a range of diseases ranging from cardiovascular disorders to cancers. However, it remains a challenge in theoretical studies to treat zinc in proteins with classical mechanics. In this study, we examined Zn^{2+} coordination with organic compounds and protein side chains using a polarizable atomic multipole-based electrostatic model.

Role of Denaturation in Maltose Binding Protein Translocation Dynamics

Marco Bacci, Mauro Chinappi, Carlo Massimo Casciola, and Fabio Cecconi [Istituto dei Sistemi Complessi (CNR)]

J. Phys. Chem. B., **116**, 4255–4262, 2012.

We present a computational study on the driven transport of the Maltose Binding Protein (MBP) across nanochannels in the framework of coarse-grained modeling. The work is motivated by recent experiments on voltage-driven transport of MBP across nanopores exploring the influence of denaturation on translocation pathways. Our simplified approach allows a statistical mechanical interpretation of the process which may be convenient also to the experiments. Specifically, we identify and characterize short and long channel blockades, associated to the translocation of denaturated and folded MBP conformations, respectively.

Comparison of end-point continuum-solvation methods for the calculation of protein–ligand binding free energies

Samuel Genheden and Ulf Ryde [Lund University]

Proteins: Stru. Fun. & Bioinf. **80**, 1326–1342, 2012.

We have compared the predictions of ligand-binding affinities from several methods based on end-point molecular dynamics simulations and continuum solvation, that is, methods related to MM/PBSA (molecular mechanics combined with Poisson–Boltzmann and surface area solvation). Two continuum-solvation models were considered, viz., the Poisson–Boltzmann (PB) and generalised Born (GB) approaches. The nonelectrostatic energies were also obtained in two different ways, viz., either from the sum of the bonded, van der Waals, nonpolar solvation energies, and entropy terms (as in MM/PBSA), or from the scaled protein–ligand van der Waals interaction energy (as in the linear interaction energy approach, LIE).

3. JOURNAL REVIEWS

Journal of Computational Chemistry, 33(11), May, 2012.

- 1091–1100 **A TDDFT investigation of bay substituted perylenediimides: Absorption and intersystem crossing**, Angelo Domenico Quartarolo, Sandro Giuseppe Chiodo and Nino Russo [Università della Calabria]

The conformational structure and electronic spectra properties of a series of bay substituted perylenediimides (PDI) derivatives have been investigated by means of density functional theory (DFT) and time-dependent DFT. The B3LYP and PBE0 hybrid exchange-correlation functionals were applied in conjunction with the double- ζ quality SVP basis set.

- 1101–1110 **A density functional theory investigation on the mechanism and kinetics of dimethyl carbonate formation on Cu₂O catalyst**, Riguang Zhang, Luzhi Song, Baojun Wang [Taiyuan University of Technology] and Zhong Li

A theoretical analysis about the mechanism and kinetics of dimethyl carbonate (DMC) formation via oxidative carbonylation of methanol on Cu₂O catalyst is explored using periodic density functional calculations, both in gas phase and in solvent.

- 1111–1122 **Conjugated circuits currents in hexabenzocoronene and its derivatives formed by joining proximal carbons**, Milan Randić, Damir Vukičević, Alexandru T. Balaban [Texas A&M University at Galveston], Marjan Vračko and Dejan Plavšić

We report on calculated CC bond currents for a dozen derivatives of hexabenzocoronene in which one or more proximal carbon atoms at the molecular periphery have been bridged. The approach that we use is graph-theoretical in nature, following our outline of this method in 2003, which is based on finding all conjugated circuits in all Kekulé valence structures of these molecules.

- 1123–1130 **First-principles calculations on the four phases of BaTiO₃**, Robert A. Evarestov [St. Petersburg University] and Andrei V. Bandura

The calculations based on linear combination of atomic orbitals basis functions as implemented in CRYSTAL09 computer code have been performed for cubic, tetragonal, orthorhombic, and rhombohedral modifications of BaTiO₃ crystal.

- 1131–1141 **A theoretical investigation of the interaction between substituted carbonyl derivatives and water: Open or cyclic complexes?**, Asit K. Chandra [North Eastern Hill University] and Thérèse Zeegers-Huyskens

The structures and binding energies of complexes between substituted carbonyl bases and water are the B3LYP/6-311++G(d,p) computational level. The calculations also include the proton affinity (PA) of the O of the C=O group, the deprotonation enthalpies (DPE) of the CH bonds along a natural bond orbital analysis. The calculations reveal that stable open C=O $\cdots$ H_wO_w as well as cyclic CH $\cdots$ O_wH_w $\cdots$ O=C complexes are formed.

- 1142–1151 **Importance of electrostatic polarizability in calculating cysteine acidity constants and copper(I) binding energy of *Bacillus subtilis* CopZ**, Timothy H. Click, Sergei Y. Ponomarev and George A. Kaminski [Worcester Polytechnic Institute]

CopZ is a copper chaperone from *Bacillus subtilis*. It is an important part of Cu(I) trafficking. We have calculated pK_a values for the CXXC motif of this protein, which is responsible for the Cu(I) binding, and the Cu(I) binding constants.

- 1152–1164 **Formulation of a new and simple nonuniform size-modified poisson–boltzmann description**, Alexander H. Boschitsch and Pavel V. Danilov [Continuum Dynamics, Inc.]

The nonlinear Poisson–Boltzmann equation (PBE) governing biomolecular electrostatics neglects ion size and ion correlation effects, and recent research activity has focused on accounting for these effects to achieve better physical modeling realism. Here, attention is focused on the comparatively simpler challenge of addressing ion size effects within a continuum-based solvent modeling framework.

Journal of Computational Chemistry, 33(12), May, 2012.

- 1165–1178 **A complete set of self-consistent charge density-functional tight-binding parametrization of zinc chalcogenides (ZnX ; $X=O, S, Se, \text{ and } Te$)**, Supriya Saha, Sougata Pal, Pranab Sarkar [Visva-Bharati University], A. L. Rosa and Th. Frauenheim

We have developed a complete set of self-consistent charge density-functional tight-binding parameters for $Zn-X$ ($X = Zn, O, S, Se, Te, Cd, H, C, \text{ and } N$).

- 1179–1189 **A semiempirical approach to ligand-binding affinities: Dependence on the Hamiltonian and corrections**, Paulius Mikulskis, Samuel Genheden, Karin Wichmann and Ulf Ryde [Lund University]

See Applications / Ligand Binding.

- 1190–1196 **Simulated infrared spectra of triflic acid during proton dissociation**, Patrick Laflamme, Alexandre Beaudoin, Thomas Chapaton, Claude Spino and Armand Soldera [Université de Sherbrooke]

Vibrational analysis of triflic acid (TfOH) at different water uptakes was conducted. This molecule mimics the sulfonate end of the Nafion[®] side-chain. As the proton leaves the sulfonic acid group, structural changes within the Nafion[®] side-chain take place. They are revealed by signal shifts in the infrared spectrum.

- 1197–1206 **Curvature correction for microiterative optimizations with QM/MM electronic embedding**, Tibor András Rokob [Academy of Sciences of the Czech Republic] and Lubomír Rulíšek

One of the most common methods to treat the electrostatic effect of the environment in QM/MM calculations is to include the MM atoms as point charges in the QM Hamiltonian. In this case, a microiterative geometry optimization ignoring the QM contributions to the forces in the relaxation of the environment cannot yield exact stationary points. Here, we analyze the convergence properties of the gradient correction method and

point out that a smooth relaxation is not ensured if the curvature of the approximate, MM-based description of the potential energy surface of the environment is too small in comparison with the exact one.

Journal of Computational Chemistry, 33(13), May, 2012.

- 1225–1235 **Monomeric adenine decay dynamics influenced by the DNA environment**, You Lu, Zhenggang Lan and Walter Thiel [Max-Planck-Institut für Kohlenforschung]

See Applications / Nucleic Acids.

- 1236–1239 **A stepwise retro-imino-ene as a key step in the mechanism of allene formation via the Crabbé acetylene homologation**, Marta González, Roi Álvarez Rodríguez, Maria Magdalena Cid and Carlos Silva López [Universidade de Vigo]

The mechanism of the acetylene homologation procedure accidentally discovered and further developed by Crabbé and coworkers is unknown. Kinetic isotope effect (KIE) experiments, however, suggest that an intramolecular hydrogen shift is the key step of the transformation. In this work, we present a computational study of this mechanism.

- 1240–1251 **Chemical reactivity in the framework of pair density functional theories**, Nicolás Otero and Marcos Mandado [University of Vigo]

Chemical reactivity descriptors are derived within the framework of the pair density functional theory. These indices provide valuable information about bonding rearrangements and activating mechanisms upon electrophilic or nucleophilic reactions. In this work, we show how these nonlocal indices provide a quantum chemical basis to explain the success of qualitative resonance models in chemical reactivity predictions.

- 1252–1273 **Beta-decomposition for the volume and area of the union of three-dimensional balls and their offsets**, Deok-Soo Kim [Hanyang University], Joonghyun Ryu, Hayong Shin and Youngsong Cho

Given a set of spherical balls, called atoms, in three-dimensional space, its mass properties such as the volume and the boundary area of the union of the atoms are important for many disciplines, particularly for computational chemistry/biology and structural molecular biology. . In this article, we propose algorithms that compute the mass properties of both the union of atoms and their offsets both correctly and efficiently.

- 1274–1283 **Temperature dependence of vibrational modes of $\text{CH}_3\text{—C}\equiv\text{C}(\text{ads})$ and $\text{I}(\text{ads})$ coadsorbed on Ag(111): Ab initio molecular dynamics approach**, Jyh Shing Lin [Tamkang University], Shao-Yu Lu, Po-Jung Tseng and Wen-Chi Chou

Ab initio molecular dynamics simulations accompanied by a Fourier transform of the dipole moment (aligned perpendicular to the surface) autocorrelation function are implemented to investigate the temperature-dependent infrared (IR) active vibrational modes of $\text{CH}_3\text{—C}_{(\beta)}\equiv\text{C}_{(\alpha)}(\text{ads})$ and $\text{I}_{(\text{ads})}$ when coadsorbed on an Ag(111) surface at 200 and 400 K, respectively.

Journal of Computational Chemistry, 33(14), May, 2012.

- 1285–1303 **Diagnosis of the performance of the state-specific multireference coupled-cluster method with different truncation schemes**, Uttam Sinha Mahapatra [Maulana Azad College] and Sudip Chattopadhyay

We have tested the linked version of a iterative (partial) triples correction for the Jeziorski-Monkhorst ansatz based state-specific multireference coupled cluster (SS-MRCC) approach with singles and doubles (SD) excitations [abbreviated as SS-MRCCSDT-1a and SS-MRCCSDT-1a+d].

- 1304–1320 **Thermodynamics of chemical reactions with COSMO-RS: The extreme case of charge separation or recombination**, Peter Deglmann [BASF SE] and Stephan Schenk

Many technically relevant chemical processes in the condensed phase involve as elementary reactive steps the formation of ions from neutral species or, as the opposite, recombination of ions. In this work, for such types of reaction, a solvation treatment involving the COSMO-RS method is assessed, which leads to improved results, i.e., errors of only around 10 kJ/mol for both protic and aprotic solvents.

- 1321–1327 **Assessment of intermolecular interactions at three sites of the arylalkyne in phenylacetylene-containing lithium-bonded complexes: Ab initio and QTAIM studies**, Yanli Zeng, Min Zhu, Xiaoyan Li, Shijun Zheng and Lingpeng Meng [Hebei Normal University]

The intermolecular interactions existing at three different sites between phenylacetylene and LiX (X = OH, NH₂, F, Cl, Br, CN, NC) have been investigated by means of second-order Møller–Plesset perturbation theory (MP2) calculations and quantum theory of “atoms in molecules” (QTAIM) studies.

- 1328–1337 **Unexpectedly strong anion– π interactions on the graphene flakes**, Guosheng Shi, Yihong Ding and Haiping Fang [Jilin University]

Interactions of anions with simple aromatic compounds have received growing attention due to their relevancy in various fields. In this article, we report a type of particularly strong anion– π interactions by investigating the adsorptions of three halide anions, that is, F[–], Cl[–], and Br[–], on the hydrogenated-graphene flake using the density functional theory.

Journal of Molecular Modeling, 18(3), March, 2012.

- 835-842 **Computational characterization of the molecular structure and properties of Dye 7 for organic photovoltaics**, Jesús Baldenebro-López, José Castorena-González, Norma Flores-Holguin, Joel Calderón-Guillén and Daniel Glossman-Mitnik [Centro de Investigación en Materiales Avanzados]

Organic dyes have great potential for its use in solar cells. In this recent work, the molecular structure and properties of Dye 7 were obtained using density functional theory (DFT) and different levels of calculation.

- 843-849 **Problems with molecular mechanics implementations on the example of 4-benzoyl-1-(4-methylimidazol-5-yl)-carbonylthiosemicarbazide**, Agata Siwek [Medical University, Chodźki], Katarzyna Świderek and Stefan Jankowski

Results from force fields implemented in HyperChem, a program frequently used in studies of bioactive compounds, have been compared using the example of the conformational analysis of a 1-carbonylthiosemicarbazide that exhibits strong antibacterial activity.

- 851-858 **Density functional theory studies on the inclusion complexes of cyclic decapeptide with 1-phenyl-1-propanol enantiomers**, Hongge Zhao, Yanyan Zhu [Zhengzhou University], Mingqiong Tong, Juan He and Chunmei Liu, et al

See Methodology / QM and QM/MM.

- 859-870 **Ab initio simulation of the effect of the potential of water on the electronic structure of arginine**, Xingrong Wang and Haoping Zheng [Tongji University]

See Applications / Protein Dynamics.

- 871-879 **Influence of stereochemistry on proton transfer in protonated tripeptide models**, Namat Ali Soliman, Petr Kulhánek and Jaroslav Koča [Masaryk University]

Vectorial proton transfer among carbonyl oxygen atoms was studied in two models of tripeptide via quantum chemical calculations using the hybrid B3LYP functional and the 6-31++G** basis set.

- 881-889 **NMR and NQR parameters of the SiC-doped on the (4,4) armchair single-walled BPNT: a computational study**, Mohammad T. Baei, [Islamic Azad University], S. Zahra Sayyad-Alangi, Ali Varasteh Moradi and Parviz Torabi

The structural properties, NMR and NQR parameters in the pristine and silicon carbide (SiC) doped boron phosphide nanotubes (BPNTs) were calculated using DFT methods (BLYP, B3LYP/6-31G*) in order to evaluate the influence of SiC-doped on the (4,4) armchair BPNTs.

- 891-903 **Unique example of amyloid aggregates stabilized by main chain H-bond instead of the steric zipper: molecular dynamics study of the amyloidogenic segment of amylin wild-type and mutants**, Workalemahu Mikre Berhanu and Artëm E. Masunov [University of Central Florida]

See Applications / Protein Dynamics.

- 905-911 **Theoretical study on the structural, vibrational, and thermodynamic properties of the (Br₂GaN₃)_n (n = 1–4) clusters**, Qi-Ying Xia [Linyi University], Qing-Fu Lin and Wen-Wei Zhao

The molecular geometries, vibrational properties, and thermodynamic properties of the clusters (Br₂GaN₃)_n (n = 1–4) were studied at the B3LYP/6-311+G* level.

- 913-920 **Topological properties of some PhSeX compounds**, Nora Beatriz Okulik [Universidad Nacional del Chaco Austral], Alicia H. Jubert and Eduardo A. Castro

A theoretical study on the series of compounds "PhSeX", where Ph=phenyl, Se=selenium and X=Cl, Br, I, CN or SCN, is reported and compared with previously reported experimental data.

- 921-927 **The role of CS₂ in CS₂/NMP mixed solvent in weakening the hydrogen bond of OH–N in coal: a DFT investigation**, Baojun Wang [Taiyuan University of Technology], Liping Wang, Riguang Zhang and Lixia Ling

The interaction processes of trace amounts of N-methyl-2-pyrrolidinone (NMP), CS₂/NMP (1:1 by volume) and pure NMP solvent with the hydrogen bond of OH...N in coal were constructed and simulated by density functional theory methods.

- 929-936 **Ab initio DFT study of bisphosphonate derivatives as a drug for inhibition of cancer: NMR and NQR parameters**, Hussein Aghabozorg, Beheshteh Sohrabi [Iran University of Science and Technology], Sara Mashkouri and Hamid Reza Aghabozorg

See Methodology / QM and QM/MM.

- 937-945 **Time-dependent density functional theory study on the electronic excited-state hydrogen bonding of the chromophore coumarin 153 in a room-temperature ionic liquid**, Dandan Wang, Ce Hao [Dalian University of Technology], Se Wang, Hong Dong and Jieshan Qiu

In the present work, in order to investigate the electronic excited-state intermolecular hydrogen bonding between the chromophore coumarin 153 (C153) and the room-temperature ionic liquid N,N-dimethylethanolammonium formate (DAF), both the geometric structures and the infrared spectra of the hydrogen-bonded complex C153–DAF⁺ in the excited state were studied by a time-dependent density functional theory (TDDFT) method.

- 947-962 **Insights into the permeability of drugs and drug-likemolecules from MI-QSAR and HQSAR studies**, Ranajit N. Shinde, K. Srikanth and M. Elizabeth Sobhia [NIPER]

See Methodology / QSAR.

- 963-972 **Theoretical study of crown ethers with incorporated azobenzene moiety**, Yuan Miao, Xueye Wang [Xiangtan University] and Dan Ouyang

A series of crown ethers containing the azobenzene moiety incorporated into crowns of various sizes [Cr(O6), Cr(O7) and Cr(O8)] and their corresponding alkali metal cation (Li⁺, Na⁺, K⁺, Rb⁺) complexes have been studied theoretically.

- 973-990 **Molecular modeling studies on phosphonic acid-containing thiazole derivatives: design for fructose-1,6-bisphosphatase inhibitors**, Ping Lan, Zhi-Wei Wu, Wan-Na Chen, Ping-Hua Sun and Wei-Min Chen [Jinan University]

See Applications / Medicinal Chemistry and Drug Design.

- 991-1001 **Studies of H4R antagonists using 3D-QSAR, molecular docking and molecular dynamics**, Jing Liu, Yan Li [Dalian University of Technology], Hui-Xiao Zhang, Shu-Wei Zhang and Ling Yang

See Applications / Medicinal Chemistry and Drug Design.

- 1003-1008 **Ab initio study of MKr n₂⁺ (M = Cu, Ag, and Au, n = 1-6) clusters**, Xinying Li [Henan University]

Quantum chemical calculations of the structures and stabilities of the title series at the CCSD(T) theoretical level are performed. Laplacian, electron density deformation, electron localization function and reduced density gradient analysis are investigated to explore the nature of the interaction. The results show that a covalent contribution occurs in the Kr-M₂⁺ bonding.

- 1009-1013 **Interactions of uranyl ion with cytochrome b5 and its His39Ser variant as revealed by molecular simulation in combination with experimental methods**, Dun Wan, Li-Fu Liao [University of South China], Min-Min Zhao, Min-Long Wu and Yi-Mou Wu, et al.

See Applications / Protein Dynamics.

- 1015-1021 **The insertion reactions of the p-complex silylenoid H₂SiLiF with Si-X (X=F, Cl, Br, O, N) bonds**, Yuhua Qi [University of Jinan], Bing Geng and Zhonghe Chen

The insertion reactions of the silylenoid H₂SiLiF with SiH₃XHn-1 (X=F, Cl, Br, O, N; n=1, 1, 1, 2, 3) have been studied by DFT calculations. The results indicate that the insertions proceed in a concerted manner, forming H₃SiSiH₂XHn-1 and LiF.

- 1023-1036 **Predicting the potency of hERG K⁺ channel inhibition by combining 3D-QSAR pharmacophore and 2D-QSAR models**, Yayu Tan, Yadong Chen, Qidong You [China Pharmaceutical University], Haopeng Sun and Manhua Li

See Applications / Medicinal Chemistry and Drug Design.

- 1037-1048 **Molecular docking and structural analysis of cofactor-protein interaction between NAD⁺ and 11 β -hydroxysteroid dehydrogenase type 2**, Hideaki Yamaguchi [Meijo University], Tatsuo Akitaya, Tao Yu, Yumi Kidachi and Katsuyoshi Kamiie, et al.

See Methodology / Homology Modeling.

- 1049-1061 **Determination of best-fit potential parameters for a reactive force field using a genetic algorithm**, Poonam Pahari [Bhabha Atomic Research Centre, Visakhapatnam] and Shashank Chaturvedi

See Methodology / potentials and Parameters.

- 1063-1072 **Virtual screening for potential inhibitors of bacterial MurC and MurD ligases**, Tihomir Tomašić, Andreja Kovač, Gerhard Klebe, Lucija Peterlin Mašič [University of Ljubljana], Didier Blanot and Stanislav Gobec, et al.

See Applications / Enzyme Catalysis.

- 1073-1085 **Substrate binding and translocation of the serotonin transporter studied by docking and molecular dynamics simulations**, Mari Gabrielsen, Aina Westrheim Ravna, Kurt Kristiansen and Ingebrigt Sylte [University of Tromsø]

See Methodology / Homology Modeling.

- 1087-1095 **Replica exchange molecular dynamics simulation of structure variation from α /4 β -fold to 3 α -fold protein**, Raudah Lazim, Ye Mei and Dawei Zhang [Nanyang Technological University]

See Applications / Protein Folding.

- 1097-1106 **Improving the desolvation penalty in empirical protein pKa modeling**, Mats H. M. Olsson [University of Copenhagen]

Unlike atomistic and continuum models, empirical pKa predicting methods need to include desolvation contributions explicitly. This study describes a new empirical desolvation method based on the Born solvation model.

- 1107-1122 **Probing the structural requirements of A-type Aurora kinase inhibitors using 3D-QSAR and molecular docking analysis**, Hui-xiao Zhang, Yan Li, Xia Wang and Yong-hua Wang [Northwest A&F University]

See Applications / Medicinal Chemistry and Drug Design.

- 1123-1127 **Transformation of the θ -phase in Mg-Li-Al alloys: a density functional theory study**, Caili Zhang, Peide Han, Zhuxia Zhang, Minghui Dong, Bingshe Xu [Taiyuan University of Technology], and Lili Zhang, et al.

In Mg-Li-Al alloys, θ -phase MgAlLi₂ is a strengthening and metastable phase which is liable to be transformed to the equilibrium phase AlLi on overaging. While the structural details of the θ -phase MgAlLi₂ and the microscopic transformation are still unknown. In this paper, the structure of MgAlLi₂ unit cell was determined through X-ray powder diffraction simulation. Microscopic transformation process of θ -phase MgAlLi₂ was discussed in detail using first principles method.

- 1129-1142 **Controlling the aggregation and rate of release in order to improve insulin formulation: molecular dynamics study of full-length insulin amyloid oligomer models**, Workalemahu Mikre Berhanu and Artëm E. Masunov [University of Central Florida]

See Applications / Medicinal Chemistry and Drug Design.

- 1143-1151 **Analysis of surface cavity in serpin family reveals potential binding sites for chemical chaperone to reduce polymerization**, Poonam Singh, Mohammad Sazzad Khan, Asma Naseem and Mohamad Aman Jairajpuri [Jamia Millia Islamia University]

Serpin constitute about 10% of blood protein and are associated with mutations that results in aberrant intermolecular linkages which leads to polymer formation. Studies with short peptides have shown promise in depolymerization of serpins however a reactive center loop based peptide also makes the serpin inactive. We did an analysis of serpin cavity using CASTp and show that cavities are distributed throughout the molecule where the largest cavities are generally present in areas of major conformational change like shutter region, helix D and helix F.

- 1153-1166 **Insight into the binding interactions of CYP450 aromatase inhibitors with their target enzyme: a combined molecular docking and molecular dynamics study**, Roberta Galeazzi [Università Politecnica delle Marche] and Luca Massaccesi

See Applications / Enzyme Catalysis.

- 1167-1172 **Pressure-induced phase transition in wurtzite ZnTe: an ab initio study**, Sebahaddin Alptekin [Cankiri Karatekin University]

A constant pressure ab initio MD technique and density functional theory with a generalized gradient approximation (GGA) was used to study the pressure-induced phase transition in wurtzite ZnTe.

- 1173-1188 **Quantitative structure activity relationships of some pyridine derivatives as corrosion inhibitors of steel in acidic medium**, El Sayed H. El Ashry [Alexandria University], Ahmed El Nemr and Safaa Ragab

See Applications / QSAR.

- 1189-1205 **Homology modeling of the structure of acyl coA:isopenicillin N-acyltransferase (IAT) from *Penicillium chrysogenum*. IAT interaction studies with isopenicillin-N, combining molecular dynamics simulations and docking**, Liliana Moreno-Vargas, Jose Correa-Basurto, Rachid C. Maroun and Francisco J. Fernández [Universidad Autónoma Metropolitana-Iztapalapa]

See Applications / Enzyme Catalysis.

- 1207-1218 **Molecular docking and 3D-QSAR study on 4-(1H-indazol-4-yl) phenylamino and aminopyrazolopyridine urea derivatives as kinase insert domain receptor (KDR) inhibitors**, Xiaoyun Wu [Southern Medical University, Guangzhou], Shuguang Wu and Wen-Hua Chen

See Applications / Medicinal Chemistry and Drug Design.

- 1219-1227 **Homology modeling, molecular dynamics and QM/MM study of the regulatory protein PhoP from *Corynebacterium pseudotuberculosis***, Gleiciane Moraes, Vasco Azevedo, Marcília Costa, Jerônimo Lameira [Universidade Federal do Pará], Anderson Miyoshi and Artur Silva, et al.

See Applications / Homology Modeling.

- 1229-1239 **Mechanism of intermolecular hydroacylation of vinylsilanes catalyzed by a rhodium(I) olefin complex: a DFT study**, Qingxi Meng, Wei Shen and Ming Li [Southwest University]

Density functional theory (DFT) was used to investigate the Rh(I)-catalyzed intermolecular hydroacylation of vinylsilane with benzaldehyde.

- 1241-1254 **In silico screening of epidermal growth factor receptor (EGFR) in the tyrosine kinase domain through a medicinal plant compound database**, Orathai Sawatdichaikul, Supa Hannongbua, Chak Sangma, Peter Wolschann and Kiattawee Choowongkomon [Kasetsart University]

See Applications / Medicinal Chemistry and Drug Design.

4. ADDRESSES OF PRINCIPAL AUTHORS

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1. APPLICATIONS

1.1. Small Molecules

Water and Solvation

Molecular dynamics extended for fluctuating networks: Application to water

Jennifer M. Kashmirian [Monash University], Alfred Uhlherr, Alan Dorin and David G. Green

J. Comp. Chem. **33**, 1364–1373, 2012.

Molecular simulation models are increasingly important tools in efforts to understand the role that water plays in biochemical processes. However, existing models of water have limited capacity to deal with the characteristics of hydrogen bond networks. This article proposes a new fluctuating network (FN) algorithm as an extension of the standard molecular dynamics algorithm. The new algorithm allows for the simulation of a molecular system based on an underlying network, such as the hydrogen bond network in water. This algorithm distinguishes strong from weak network connections, applying a potential that best describes the specific connection behavior.

Benchmarking the thermodynamic analysis of water molecules around a model beta sheet

David J. Huggins [Cambridge Molecular Therapeutics]

J. Comp. Chem. **33**, 1383–1392, 2012.

Water molecules play a vital role in biological and engineered systems by controlling intermolecular interactions in the aqueous phase. Inhomogeneous fluid solvation theory provides a method to quantify solvent thermodynamics from molecular dynamics or Monte Carlo simulations and provides an insight into intermolecular interactions. In this study, simulations of TIP4P-2005 and TIP5P-Ewald water molecules around a model beta sheet are used to investigate the orientational correlations and predicted thermodynamic properties of water molecules at a protein surface.



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Water and Solvation (Cont'd)

Simulations of Solvation and Solvation Dynamics in an Idealized Ionic Liquid Model

Durba Roy and Mark Maroncelli [The Pennsylvania State University]

J. Phys. Chem. B., **116**, 5951–5970, 2012.

Equilibrium and nonequilibrium molecular dynamics simulations of solvation and solvation dynamics of a variety of solutes have been performed in the coarse-grained ionic liquid model ILM2 (Roy, D.; Maroncelli, M. J. *Phys. Chem. B* **2010**, 114, 12629). Some comparisons are made between ionic and dipolar solvation using parallel simulations in CH₃CN. Despite the fact that the multipolar character of electrostatic interactions and their spatial extent differ in the two solvents, solvation energies are equal to within about 10% in ILM2 and CH₃CN. This near equality also holds with reduced accuracy in the case of reorganization energies.

Medicinal Chemistry and Drug Design

Computer-assisted design for atenolol prodrugs for the use in aqueous formulations

Rafik Karaman [Al-Quds University], Khuloud Dajani and Hussein Hallak

J. Mol. Mod., **18**, 1523–1540, 2012

Based on stability studies on the drugs atenolol and propranolol and some of their derivatives it is believed that increasing the lipophilicity of the drug will lead to an increase in the stability of its aqueous solutions and will provide a prodrug system with the potential for releasing atenolol in a controlled manner. Using DFT theoretical calculations we have calculated an intramolecular acid catalyzed hydrolysis in nine maleamic (4-amino-4-oxo-2butenoic) acids (Kirby's N-alkylmaleamic acids), 1–9.

Protein Pharmacophore Selection Using Hydration-Site Analysis

Bingjie Hu and Markus A. Lill [Purdue University]

J. Chem. Infor. and Mod. **52**, 1046–1060, 2012.

Virtual screening using pharmacophore models is an efficient method to identify potential lead compounds for target proteins. However, in order to capture most potential interactions between all potentially binding ligands and the protein, the size of the pharmacophore model, i.e. number of pharmacophore elements, is typically quite large and therefore reduces the efficiency of pharmacophore based screening. We have developed a new method to select important pharmacophore elements using hydration-site information. We computed the free energy of water released from the binding site for each hydration site using thermodynamic analysis of molecular dynamics (MD) simulations.

Medicinal Chemistry and Drug Design (Cont'd)

The Structure, Thermodynamics, and Solubility of Organic Crystals from Simulation with a Polarizable Force Field

Michael J. Schnieders, Jonas Baltrusaitis, Yue Shi, Gaurav Chatterjee, Lianqing Zheng, Wei Yang, and Pengyu Ren [University of Texas at Austin]

J. Chem. Theor. and Comp., **8**, 1721–1736, 2012.

An important unsolved problem in materials science is prediction of the thermodynamic stability of organic crystals and their solubility from first principles. Solubility can be defined as the saturating concentration of a molecule within a liquid solvent, where the physical picture is of solvated molecules in equilibrium with their solid phase. Despite the importance of solubility in determining the oral bioavailability of pharmaceuticals, prediction tools are currently limited to quantitative structure–property relationships that are fit to experimental solubility measurements. For the first time, we describe a consistent procedure for the prediction of the structure, thermodynamic stability, and solubility of organic crystals from molecular dynamics simulations using the polarizable multipole AMOEBA force field.

Quantitative Structure-Activity Relations

Development of docking-based 3D-QSAR models for PPARGamma full agonists

Laura Guasch, Esther Sala, Cristina Valls, Miquel Mulero, Gerard Pujadas, Santiago Garcia-Vallvé [Universitat Rovira i Virgili]

J. Mol. Graph. and Mod., **36**, 1-9, 2012.

Peroxisome proliferator-activated receptor gamma (PPAR γ) has become an attractive molecular target for drugs that aim to treat diabetes mellitus type II, and its therapeutic potency against skin cancer and other skin diseases is also currently being explored. To study the relationship between the structure of several PPAR γ full agonists and the trans-activation activity of PPAR γ , we have performed a three-dimensional quantitative structure–activity relationship (3D-QSAR) study of tyrosine-based derivatives, based on the 3D alignment of conformations obtained by docking.

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Quantitative Structure-Activity Relations (Cont'd)

Docking-based 3D-QSAR analyses of pyrazole derivatives as HIV-1 non-nucleoside reverse transcriptase inhibitors

Elena Cichero [Università degli Studi di Genova] and Paola Fossa

J. Mol.Mod., **18**, 1573-1582, 2012

1,3,4,5-tetrasubstituted-pyrazoles (TPs) have been recently identified as a new class of potent non-nucleoside HIV-1 reverse transcriptase (RT) inhibitors. A computational strategy based on molecular docking studies, followed by docking-based comparative molecular fields analysis (CoMFA) and comparative molecular similarity indices analysis (CoMSIA), has been used to elucidate the atomic details of the RT/TP interactions and to identify the most important features impacting the TP antiretroviral activity.

Carbon Nanoparticles

OH-functionalized open-ended armchair single-wall carbon nanotubes (SWCNT) studied by density functional theory

Elzbieta Chelmecka, Karol Pasterny, Teobald Kupka [Medical University of Silesia] and Leszek Stobiński

J. Mol.Mod., **18**, 1463-1472, 2012

The structures of ideal armchair (5,5) single-wall carbon nanotubes (SWCNTs) of different lengths (3.7, 8.8, and 16.0 Å for C₄₀H₂₀, C₈₀H₂₀, and C₁₄₀H₂₀) and with 1–10 hydroxyl groups at the end of the nanotube were fully optimized at the B3LYP/3-21G level, and in some cases at the B3LYP/6-31G* level, and the energy associated with the attachment of the OH substituent was determined. The OH-group attachment energy was compared with the OH functionalization of phenanthrene and picene models and with previous results for zigzag (9,0) SWCNT systems.

Toward an Equation of State for Water inside Carbon Nanotubes

M. Sadeghi [Sharif University of Technology] and G. A. Parsafar

J. Phys. Chem. B., **116**, 4943–4951, 2012.

Water inside carbon nanotubes as an example of nanoconfined water has gained noticeable attention, in both theoretical and applied aspects. Molecular simulation has played a major role in the studies in this field. Yet, there is a need for systematic study of simulation results and compilation of scientifically reliable predictive relations. Here we present Monte Carlo simulations of water inside carbon nanotubes with different radii. An equation of state which was derived on the basis of the extended Lennard–Jones (12,6,3) as the effective pair potential is chosen for the system of water inside the carbon nanotubes.

1.2. Biopolymers

Bioinformatics and Cheminformatics

SMURFLite: combining simplified Markov random fields with simulated evolution improves remote homology detection for beta-structural proteins into the twilight zone

Noah M. Daniels, Raghavendra Hosur, Bonnie Berger, and Lenore J. Cowen [Tufts University]

Bioinformatics. **28**, 1216-1222, 2012.

One of the most successful methods to date for recognizing protein sequences that are evolutionarily related has been profile hidden Markov models (HMMs). However, these models do not capture pairwise statistical preferences of residues that are hydrogen bonded in beta sheets. These dependencies have been partially captured in the HMM setting by simulated evolution in the training phase and can be fully captured by Markov random fields (MRFs). However, the MRFs can be computationally prohibitive when beta strands are interleaved in complex topologies. We introduce SMURFLite, a method that combines both simplified MRFs and simulated evolution to substantially improve remote homology detection for beta structures.

MDWeb and MDMoby: an integrated web-based platform for molecular dynamics simulations

Adam Hospital, Pau Andrio, Carles Fenollosa, Damjan Cicin-Sain, Modesto Orozco, and Josep Lluís Gelpí [Barcelona Supercomputing Center]

Bioinformatics. **28**, 1278-1279, 2012.

MDWeb and MDMoby constitute a web-based platform to help access to molecular dynamics (MD) in the standard and high-throughput regime. The platform provides tools to prepare systems from PDB structures mimicking the procedures followed by human experts. It provides inputs and can send simulations for three of the most popular MD packages (Amber, NAMD and Gromacs). Tools for analysis of trajectories, either provided by the user or retrieved from our MoDEL database (<http://mmb.pcb.ub.es/MoDEL>) are also incorporated. The platform has two ways of access, a set of web-services based on the BioMoby framework (MDMoby), programmatically accessible and a web portal (MDWeb).

Application of information theory to feature selection in protein docking

Olaf G. Othersen, Arno G. Stefani, Johannes B. Huber and Heinrich Sticht [Friedrich-Alexander-Universität Erlangen-Nürnberg]

J. Mol.Mod., **18**, 1285-1297, 2012

In the era of structural genomics, the prediction of protein interactions using docking algorithms is an important goal. The success of this method critically relies on the identification of good docking solutions among a vast excess of false solutions. We have adapted the concept of mutual information (MI) from information theory to achieve a fast and quantitative screening of different structural features with respect to their ability to discriminate between physiological and nonphysiological protein interfaces. The strategy includes the discretization of each structural feature into distinct value ranges to optimize its mutual information.

Bioinformatics and Cheminformatics (Cont'd)

Routine Microsecond Molecular Dynamics Simulations with AMBER on GPUs. 1. Generalized Born

Andreas W. Götz, Mark J. Williamson, Dong Xu, Duncan Poole, Scott Le Grand, and Ross C. Walker [University of California San Diego]

J. Chem. Theor. and Comp., **8**, 1542–1555, 2012.

We present an implementation of generalized Born implicit solvent all-atom classical molecular dynamics (MD) within the AMBER program package that runs entirely on CUDA enabled NVIDIA graphics processing units (GPUs). We discuss the algorithms that are used to exploit the processing power of the GPUs and show the performance that can be achieved in comparison to simulations on conventional CPU clusters. The implementation supports three different precision models in which the contributions to the forces are calculated in single precision floating point arithmetic but accumulated in double precision (SPDP), or everything is computed in single precision (SPSP) or double precision (DPDP).

Comparative or Homology Modeling

Evaluation of natural and nitramine binding energies to 3-D models of the SIS2 domains in the N-methyl-D-aspartate receptor

Jason Ford-Green [Jackson State University], Olexandr Isayev, Leonid Gorb, Edward J. Perkins and Jerzy Leszczynski

J. Mol.Mod., **18**, 1273-1284, 2012

Overactivation of the N-methyl-D-aspartate receptor (NMDAR) in postsynaptic neurons leads to glutamate-related excitotoxicity in the central nervous system of mammals. We have built 3-D models of each domain for the universal screening of potential toxicants and their binding mechanisms. Our docking results show that the calculated pK_i values of glycine and L-glutamate significantly increase (>1) when the NR1 and NR2A SIS2 domains are closing, respectively. Inversely, D-cycloserine (DCS) and 5,7-dichlorokynurenic acid (5,7-DCKA) do not show such a dependence on domain closure.

Mechanism of isoproturon resistance in Phalaris minor: in silico design, synthesis and testing of some novel herbicides for regaining sensitivity

Durg Vijay Singh, Kuruba Adeppa and Krishna Misra [Center of Biomedical Magnetic Resonance SGPGIMS Campus]

J. Mol.Mod., **18**, 1431-1445, 2012

Isoproturon, 3-p-cumenyl-1 dimethylurea was the only herbicide controlling Phalaris minor, a major weed growing in wheat fields till the early 1980s. Since it has acquired resistance against isoproturon, like other substituted urea herbicides, where the identified target site for isoproturon is in the photosynthetic apparatus at D1 protein of Photosystem-II (PS-II). Nucleotide sequence of susceptible and resistant psbA gene of P. minor has been reported to have four point mutations. During the present work D1 protein of both susceptible and resistant biotypes of P Minor has been modeled. Transmembrane segments of amino acids were predicted by comparing with the nearest homolog of bacterial D1 protein.

Comparative or Homology Modeling (Cont'd)

De novo design of 7-aminocoumarin derivatives as novel falcipain-3 inhibitors

Anand S. Chintakrindi, Mushtaque S. Shaikh and Evans C. Coutinho [Bombay College of Pharmacy]

J. Mol.Mod., **18**, 1481-1493, 2012

The availability of the crystal structure of falcipain-3, knowledge of the peptides carrying the 7-aminocoumarin moiety as falcipain-3 ligands/substrates, and a need for new antimalarial agents stimulated us to look at the possibility of finding some novel falcipain-3 inhibitors. In this paper, we report the effect of substitution at the 7-amino position of the coumarin nucleus on the inhibition of falcipain-3, which is a well-validated antimalarial target. The de novo drug design was assisted by QSAR studies that shed light on the binding patterns of known and the newly designed inhibitors, thus taking this discovery process to the next level.

Molecular modeling of cytochrome b5 with a single cytochrome c-like thioether linkage

Ying-Wu Lin [University of South China], Yi-Mou Wu, Li-Fu Liao and Chang-Ming Nie

J. Mol.Mod., **18**, 1553-1560, 2012

Bovine liver cytochrome b 5 (cyt b 5), with heme bound noncovalently, has been converted into a cyt c-like protein (cyt b 5 N57C) by constructing a thioether linkage between the heme and the engineered cysteine residue. With no X-ray or NMR structure available, we herein performed a molecular modeling study of cyt b 5 N57C. On the other hand, using amino acid sequence information for a newly discovered member of the cyt b 5 family, domestic silkworm cyt b 5 (DS cyt b 5), we predicted the protein structure by homology modeling in combination with MD simulation.

Dynamics comparison of two myoglobins with a distinct heme active site

Ying-Wu Lin [University of South China], Yi-Mou Wu and Li-Fu Liao

J. Mol.Mod., **18**, 1591-1596, 2012

Sperm whale myoglobin (swMb) is a well-studied heme protein, both experimentally and theoretically. Comparatively, little attention has been paid to another member of Mb family, *Aplysia limacina* myoglobin (apMb). swMb and apMb have the same overall structure and perform the same biological function, i.e., O₂ carrier, while using a distinct heme active site. To provide insights into the structure-function relationship for these two Mbs, we herein made a comparison in terms of their dynamics properties using molecular dynamics simulation.

Ligand-based 3-D pharmacophore generation and molecular docking of mTOR kinase inhibitors

Karunakar Tanneeru and Lalitha Guruprasad [University of Hyderabad]

J. Mol.Mod., **18**, 1611-1624, 2012

The 3-D structure of the human mTOR kinase domain was modeled based on the crystal structure of PI3K γ using comparative modeling methods, and the ATP-binding site of mTOR was characterized. The mTOR kinase 3-D model structure is similar to the structure of the PI3K γ kinase domain, and exhibits great similarity to PI3K γ at the active site of the kinase. Pharmacophore generation, the docking of mTOR inhibitors, and molecular dynamics (MD) simulations of mTOR-inhibitor docked complexes were carried out in this work.

Comparative or Homology Modeling (Cont'd)

Analysis of Delta–Notch interaction by molecular modeling and molecular dynamic simulation studies

Riddhi Majumder, Sujata Roy & Ashoke Ranjan Thakur
[West Bengal State University]

J. Biomol. Stru. and Dyn., **30**, 13-29, 2012.

Notch is a single-pass transmembrane receptor protein. Delta (member of the DSL protein family), a Notch ligand, is also single-pass transmembrane protein that can interact with Notch to form the Delta–Notch complex. It has been demonstrated that of the 36 Epidermal Growth Factor (EGF) repeats of Notch, 11th and 12th are sufficient to mediate interactions with Delta. Crystal structure of mammalian Notch1 extracellular ligand binding domain shows the presence of 11th and 12th EGF-like repeats. Here a portion of the *Drosophila* Delta protein, known to interact with Notch extracellular domain, has been modeled using homology modeling.

Protein Conformational Analysis

Crucial Role of Protein Flexibility in Formation of a Stable Reaction Transition State in an α -Amylase Catalysis

Takahiro Kosugi and Shigehiko Hayashi [Kyoto University]

J. Am. Chem. Soc., **134**, 7045–7055, 2012.

Conformational flexibility of proteins provides enzymes with high catalytic activity. Although the conformational flexibility is known to be pivotal for the ligand binding and release, its role in the chemical reaction process of the reactive substrate remains unclear. We determined a transition state of an enzymatic reaction in a psychrophilic α -amylase by a hybrid molecular simulation that allows one to identify the optimal chemical state in an extensive conformational ensemble of protein.

Studies on the Interactions between β_2 Adrenergic Receptor and Gs Protein by Molecular Dynamics Simulations

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

J. Chem. Infor. and Mod. **52**, 1005–1014, 2012.

The β_2 adrenergic receptor (β_2 AR) plays a key role in the control of smooth muscle relaxation in airways, the therapy of asthma, and a series of other basic physiological functions. Recently, the crystal structure of the β_2 AR–Gs protein complex was reported, which facilitates study of the activation mechanism of the β_2 AR and G-protein-coupled receptors (GPCRs). In this work, we perform 20 ns molecular dynamics (MD) simulations of the β_2 AR–Gs protein complex with its agonist in an explicit lipid and water environment to investigate the activation mechanism of β_2 AR.

Sialyldisaccharide conformations: a molecular dynamics perspective

Jeyasigamani F. A. Selvin, Thanu R. K. Priyadarzini and Kasinadar Veluraja [Manonmaniam Sundaranar University]

J. Comp. Aided Mol. Des. **26**, 375-385, 2011.

Sialyldisaccharides are significant terminal components of glycoconjugates and their negative charge and conformation are extensively utilized in molecular recognition processes. The conformation and flexibility of four biologically important sialyldisaccharides [Neu5Ac α (2-3)Gal, Neu5Ac α (2-6)Gal, Neu5Ac α (2-8)Neu5Ac and Neu5Ac α (2-9)Neu5Ac] are studied using Molecular Dynamics simulations of 20 ns duration to deduce the conformational preferences of the sialyldisaccharides and the interactions which stabilize the conformations.

Protein Dynamics

Computer simulation studies of self-assembling macromolecules

Wataru Shinoda, Russell DeVane, Michael L Klein [Temple University]

Curr. Opin. Stru. Biol., **15**, 175-186, 2011.

Coarse-grained (CG) molecular models are now widely used to understand the structure and functionality of macromolecular self-assembling systems. In the last few years, significant efforts have been devoted to construct quantitative CG models based on data from molecular dynamics (MD) simulations with more detailed all-atom (AA) intermolecular force fields as well as experimental thermodynamic data. We review some of the recent progress pertaining to the MD simulation of self-assembling macromolecular systems.

Computer Simulation of Gas-Phase Neutralization of Electrospray-Generated Protein Macroions

Igor L. Kanev, Nikolay K. Balabaev, Anna V. Glyakina, and Victor N. Morozov [Russian Academy of Sciences, Pushchino]

J. Phys. Chem. B., **116**, 5872–5881, 2012.

The process of neutralizing hydrated multicharged gas-phase protein ions with small counterions was simulated using a molecular dynamics (MD) technique. Hen egg white lysozyme (HEWL) molecules with different numbers of positive charges, both dry and solvated by up to 1500 water molecules, were first equilibrated. Simulations revealed that the hydration layer over a highly charged protein surface adapted a spiny structure with water protrusions composed of oriented water dipoles.

Structural transitions and oligomerization along polyaniline fibril formation pathways from computer simulations

Erin M. Phelps and Carol K. Hall [North Carolina State University]

Proteins: Stru. Fun. & Bioinf. **80**, 1582–1597, 2012.

The results of a computer simulation study of the aggregation kinetics of a large system of model peptides with particular focus on the formation of intermediates are presented. Discontinuous molecular dynamic simulations were used in combination with our intermediate-resolution protein model, PRIME, to simulate the aggregation of a system of 192 polyaniline (KA₁₄K) peptides at a concentration of 5 mM and a reduced temperature of $T^* = 0.13$ starting from a random configuration and ending in the assembly of a fibrillar structure.

Multiscale modeling of cellular actin filaments: From atomistic molecular to coarse-grained dynamics

Marco A. Deriu [Politecnico di Torino], Ardita Shkurti, Giulia Paciello, Tamara C. Bidone, Umberto Morbiducci, Elisa Ficarra, Alberto Audenino and Andrea Acquaviva

Proteins: Stru. Fun. & Bioinf. **80**, 1598–1609, 2012.

In this article, we present a computational multiscale model for the characterization of subcellular proteins. The model is encoded inside a simulation tool that builds coarse-grained (CG) force fields from atomistic simulations. Equilibrium molecular dynamics simulations on an all-atom model of the actin filament are performed. Then, using the statistical distribution of the distances between pairs of selected groups of atoms at the output of the MD simulations, the force field is parameterized using the Boltzmann inversion approach. This CG force field is further used to characterize the dynamics of the protein via Brownian dynamics simulations.

Ligand Binding/Docking

Free energy calculations on the binding of novel thiolactomycin derivatives to E. coli fatty acid synthase I

Thomas Steinbrecher [Universität Karlsruhe], David A. Case, Andreas Labahn

Bioorg. and Med.Chem., **20**, 3446-3453, 2012.

In recent years, molecular dynamics based free energy calculations have emerged as a useful tool to accurately calculate receptor binding affinities of novel or modified ligands. Beta-ketoacyl [acyl carrier protein] synthase I, KAS I, facilitates a critical chain elongation step in the fatty acid synthesis pathway. Since the bacterial type II lipid synthesis system is fundamentally different from the mammalian type I multi-enzyme complex, this enzyme represents a promising target for the design of specific antibiotics. In this work, we study the binding of several recently synthesized derivatives of the natural KAS I inhibitor thiolactomycin in detail based on atomistic modeling.

Agonist Dynamics and Conformational Selection during Microsecond Simulations of the A_{2A} Adenosine Receptor

Ji Young Lee, Edward Lyman [University of Delaware]

Biophysical Journal. **102**, 2114-2120, 2012.

The G-protein-coupled receptors (GPCRs) are a ubiquitous family of signaling proteins of exceptional pharmacological importance. The recent publication of structures of several GPCRs cocrystallized with ligands of differing activity offers a unique opportunity to gain insight into their function. To that end, we performed microsecond-timescale simulations of the A_{2A} adenosine receptor bound to either of two agonists, adenosine or UK432097. Our data suggest that adenosine is highly dynamic when bound to A_{2A}, in stark contrast to the case with UK432097.

Identification of Small Molecule Inhibitors of the HIV-1 Nucleocapsid–Stem-Loop 3 RNA Complex

Douglas M. Warui and Anne M. Baranger [University of Illinois]

J.Med.Chem., **55**, 4132–4141, 2012.

Stem-loop 3 RNA (SL3) in ψ -RNA is a highly conserved motif in different strains of HIV-1 and serves as a principle determinant for viral packaging. Viral encapsulation is critical for viral replication, and disruption of the nucleocapsid- ψ -RNA complex interferes with viral replication. We have used SL3 RNA as a target for identification of small molecule inhibitors of the interactions of nucleocapsid protein (NCp7) and ψ -RNA. We report the use of computational and high-throughput screening approaches to identify 16 compounds that bind SL3 RNA with micromolar affinities.

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Ligand Binding / Docking (Cont'd)

The impact of *Trichoderma reesei* Cel7A carbohydrate binding domain mutations on its binding to a cellulose surface: a molecular dynamics free energy study

Tong Li, Shihai Yan and Lishan Yao [Chinese Academy of Sciences]

J. Mol.Mod., **18**, 1355-1364, 2012

A critical role of the Family 7 cellobiohydrolase (Cel7A) carbohydrate binding domain (CBD) is to bind to a cellulose surface and increase the enzyme concentration on the surface. Several residues of *Trichoderma reesei* Cel7A CBD, including Y5, N29, Y31, Y32 and Q34, contribute to cellulose binding, as revealed by early experimental studies. To investigate the interactions between these important residues and cellulose, we applied a thermodynamic integration method to calculate the cellulose–Cel7A CBD binding free energy changes caused by Y5A, N29A, Y31A, Y32A and Q34A mutations.

Conserved Functional Surface of Antimammalian Scorpion β -Toxins

Rong Chen [Australian National University] and Shin-Ho Chung

J. Phys. Chem. B., **116**, 4796–4800, 2012.

Scorpion β -toxins bind to the voltage-sensing domain of voltage-gated sodium (Na_v) channels and trap the voltage-sensing domain in the activated state. Two structurally similar β -toxins from scorpions, Csx4 and Cn2, selectively target different subtypes of mammalian Na_v channels. While the receptor site on the channels is known, the functional surface of the toxins remains to be understood. Here, we predict the binding modes of Csx4 and Cn2 to the voltage-sensing domains of $\text{Na}_v1.2$ and $\text{Na}_v1.6$, respectively, with a molecular docking method and molecular dynamics simulations.

Enzyme Catalysis

Molecular Mechanism of ATP Hydrolysis in F_1 -ATPase Revealed by Molecular Simulations and Single-Molecule Observations

Shigehiko Hayashi [Kyoto University], Hiroshi Ueno, Abdul Rajjak Shaikh, Myco Umemura, Motoshi Kamiya, Yuko Ito, Mitsunori Ikeguchi, Yoshihito Komoriya, Ryota Iino, and Hiroyuki Noji

J. Am. Chem. Soc., **134**, 8447–8454, 2012.

Enzymatic hydrolysis of nucleotide triphosphate (NTP) plays a pivotal role in protein functions. In spite of its biological significance, however, the chemistry of the hydrolysis catalysis remains obscure because of the complex nature of the reaction. Here we report a study of the molecular mechanism of hydrolysis of adenosine triphosphate (ATP) in F_1 -ATPase, an ATP-driven rotary motor protein. Molecular simulations predicted and single-molecule observation experiments verified that the rate-determining step (RDS) is proton transfer (PT) from the lytic water molecule, which is strongly activated by a metaphosphate generated by a preceding P_γ – O_β bond dissociation (POD).

Enzyme Catalysis (Cont'd)

Role of Environment for Catalysis of the DNA Repair Enzyme MutY

Elizabeth Brunk, J. Samuel Arey, and Ursula Rothlisberger
[Ecole Polytechnique Fédérale de Lausanne (EPFL)]

J. Am. Chem. Soc., **134**, 8608–8616, 2012.

Control of the N-glycosylase reaction by the DNA repair enzyme, MutY, entails the organization of solvent molecules. Classical molecular dynamics and QM/MM simulations were used to investigate the solvent and environment effects contributing to catalysis. Our findings suggest that the entire reaction is an energetically neutral process, in which the first step is rate determining, requiring protonation of adenine (N₇) to initiate cleavage, and the second step is strongly exothermic, involving hydrolysis of an oxacarbenium ion intermediate.

Trimethylaurintricarboxylic acid inhibits human DNA methyltransferase 1: insights from enzymatic and molecular modeling studies

Jakyung Yoo and José L. Medina-Franco [Torrey Pines Institute for Molecular Studies]

J. Mol. Mod., **18**, 1583-1589, 2012

DNA methyltransferase 1 (DNMT1) is an emerging target for the treatment of cancer, brain disorders, and other diseases. Currently, there are only a few DNMT1 inhibitors with potential application as therapeutic agents or research tools. 5,5-Methylenedisalicylic acid is a novel scaffold previously identified by virtual screening with detectable although weak inhibitory activity of DNMT1 in biochemical assays. We report enzyme inhibition of a structurally related compound, trimethylaurintricarboxylic acid (NSC97317) that showed a low micromolar inhibition of DNMT1 (IC₅₀ = 4.79 μM).

Structure-Based and Multiple Potential Three-Dimensional Quantitative Structure–Activity Relationship (SB-MP-3D-QSAR) for Inhibitor Design

Qi-Shi Du, Jing Gao, Yu-Tuo Wei, Li-Qin Du, Shu-Qing Wang [Tianjin Medical University], and Ri-Bo Huang

J. Chem. Infor. and Mod. **52**, 996–1004, 2012.

The inhibitions of enzymes (proteins) are determined by the binding interactions between ligands and targeting proteins. However, traditional QSAR (quantitative structure–activity relationship) is a one-side technique, only considering the structures and physicochemical properties of inhibitors. In this study, the structure-based and multiple potential three-dimensional quantitative structure–activity relationship (SB-MP-3D-QSAR) is presented, in which the structural information of host protein is involved in the QSAR calculations. The SB-MP-3D-QSAR actually is a combinational method of docking approach and QSAR technique.

On the active site of mononuclear B1 metallo β-lactamases: a computational study

Jacopo Sgrignani, Alessandra Magistrato, Matteo Dal Peraro, Alejandro J. Vila and Paolo Carloni, Roberta Pierattelli [University of Florence]

J. Comp. Aided Mol. Des. **26**, 425-435, 2011.

Metallo-β-lactamases (MβLs) are Zn(II)-based bacterial enzymes that hydrolyze β-lactam antibiotics, hampering their beneficial effects. In the most relevant subclass (B1), X-ray crystallography studies on the enzyme from *Bacillus Cereus* point to either two zinc ions in two metal sites (the so-called ‘3H’ and ‘DCH’ sites) or a single Zn(II) ion in the 3H site, where the ion is coordinated by Asp120, Cys221 and His263 residues. A structural model of this enzyme in its DCH mononuclear form, so far lacking, is therefore required for inhibitor design and mechanistic studies. By using force field based and mixed quantum–classical (QM/MM) molecular dynamics (MD) simulations of the protein in aqueous solution we constructed such structural model.

Enzyme Catalysis (Cont'd)

Elucidating the structural and conformational factors responsible for the activity and substrate specificity of alkanesulfonate monooxygenase

V. Ferrario, P. Braiuca, P. Tessaro, L. Knapic, C. Gruber, J. Pleiss, C. Ebert, E. Eichhorn & L. Gardossi [Università degli Studi di Trieste]

J. Biomol. Stru. and Dyn., **30**, 74-88, 2012.

The mechanism and substrate specificity of alkanesulfonate monooxygenase (SsuD) was investigated by combining molecular dynamics simulations, docking, and a comprehensive quantitative structure activity relationships (QSAR) analysis. The FMNH₂ dependent monooxygenase undergoes a dynamic conformational change of the active site, passing from a closed to an open state. As a consequence, substrates have access to the active site and the cofactor is then regenerated by the associated oxidoreductase FMN reductase SsuE..

Thermodynamic and Kinetic Stabilities of Active Site Protonation States of Class C β -Lactamase

Ravi Tripathi and Nisanth N. Nair [Indian Institute of Technology, Kanpur]

J. Phys. Chem. B., **116**, 4741–4753, 2012.

By employing computationally intensive MD simulations using hybrid quantum–mechanical/molecular–mechanical approach, we analyze here the kinetic and thermodynamic stabilities of various active site protonation states of a fully solvated class C β -lactamase. We report the detailed mechanism of proton transfer between catalytically important active site residues and the associated free energy barriers. In the apoenzyme, significant structural changes are associated with the proton transfer, and the orientations of active site residues are distinctly different for various protonation states.

Molecular Dynamics Investigation into Substrate Binding and Identity of the Catalytic Base in the Mechanism of Threonyl-tRNA Synthetase

Eric A. C. Bushnell, WenJuan Huang, Jorge Llano, and James W. Gauld [University of Windsor]

J. Phys. Chem. B., **116**, 5205–5212, 2012.

The structure and nature of the fully bound active site of Threonyl-tRNA Synthetase (ThrRS) for the second half-reaction has been investigated using molecular dynamics simulations. More specifically, we examined the ThrRS active site with both the substrate Threonyl-AMP and the cosubstrate cognate Threonyl-tRNA bound. Furthermore, we also considered the cases in which an active-site histidyl residue (His309) is either neutral or protonated. Moreover, we considered the role a water molecule may play in formation of a viable Michaelis complex.

Protein-Protein Interactions

Effect of interprotein polarization on protein–protein binding energy

Chang G. Ji and John Z. H. Zhang [East China Normal University]

J. Comp. Chem. **33**, 1416–1420, 2012.

Molecular dynamics simulation in explicit water for the binding of the benchmark barnase-barstar complex was carried out to investigate the effect polarization of interprotein hydrogen bonds on its binding free energy. Our study is based on the AMBER force field but with polarized atomic charges derived from fragment quantum mechanical calculation for the protein complex. The quantum-derived atomic charges include the effect of polarization of interprotein hydrogen bonds, which was absent in the standard force fields that were used in previous theoretical calculations of barnase-barstar binding energy.

Protein-Protein Interactions (Cont'd)

Mechanism of BAG1 repair on Parkinson's disease-linked DJ1 mutation

Calvin Yu-Chian Chen [China Medical University Beigang Hospital]

J. Biomol. Stru. and Dyn., **30**, 1-12, 2012.

Mutant oncogene DJ1 L166P has been linked to a familial form of early-onset Parkinson's disease (PD). The DJ1 mutant deformed C-terminal helices and prevented the formation of a functional DJ1 dimer. Intriguingly, chaperon modulator, BCL2-associated athanogene (BAG1), has been shown to repair DJ1 mutant and restore its functions. Molecular simulation techniques were employed to elucidate protein-protein interactions between BAG1 and DJ1. Interaction of BAG1 with DJ1 showed recovery of disrupted alpha helix structures and H-bonds stabilizing the functional site Cys106.

Membrane Proteins and Lipid Peptide Interactions

Effect of Calcium and Magnesium on Phosphatidylserine Membranes: Experiments and All-Atomic Simulations

Alberto Martín-Molina, César Rodríguez-Beas, Jordi Faraudo [Campus de la Universitat Autònoma de Barcelona]

Biophysical Journal. **102**, 2095-2103, 2012.

It is known that phosphatidylserine (PS⁻) lipids have a very similar affinity for Ca²⁺ and Mg²⁺ cations, as revealed by electrokinetic and stability experiments. However, despite this similar affinity, experimental evidence shows that the presence of Ca²⁺ or Mg²⁺ induces very different aggregation behavior for PS⁻ liposomes as characterized by their fractal dimensions. These puzzling results suggest that although these two cations have a similar affinity for PS⁻ lipids, they induce substantial structural differences in lipid bilayers containing each of these cations. In other words, these cations have strong ion-specific effects on the structure of PS⁻ membranes. This interpretation is supported by all-atomic molecular-dynamics simulations showing that Ca²⁺ and Mg²⁺ cations have different binding sites and induce different membrane hydration.

Protein-Ligand-Based Pharmacophores: Generation and Utility Assessment in Computational Ligand Profiling

Jamel Meslamani, Jiabo Li, Jon Sutter, Adrian Stevens, Hugues-Olivier Bertrand, and Didier Rognan [UMR7200 Université de Strasbourg/CNRS]

J.Chem. Infor. and Mod. **52**, 943-955, 2012.

Ligand profiling is an emerging computational method for predicting the most likely targets of a bioactive compound and therefore anticipating adverse reactions, side effects and drug repurposing. A few encouraging successes have already been reported using ligand 2-D similarity searches and protein-ligand docking. The current study describes the use of receptor-ligand-derived pharmacophore searches as a tool to link ligands to putative targets. A database of 68,056 pharmacophores was first derived from 8,166 high-resolution protein-ligand complexes.

Membrane Proteins and Lipid Peptide Interactions (Cont'd)

Modeling the Self-Assembly and Stability of DHPC Micelles Using Atomic Resolution and Coarse Grained MD Simulations

Johan F. Kraft, Mikkel Vestergaard, Birgit Schiøtt [Bioinformatics Research Centre, C.F. Møllers Alle 8], and Lea Thøgersen

J. Chem. Theor. and Comp., **8**, 1556–1569, 2012.

Membrane mimics such as micelles and bicelles are widely used in experiments involving membrane proteins. With the aim of being able to carry out molecular dynamics simulations in environments comparable to experimental conditions, we set out to test the ability of both coarse grained and atomistic resolution force fields to model the experimentally observed behavior of the lipid 1,2-dihexanoyl-sn-glycero-3-phosphocholine (DHPC), which is a widely used lipid for biophysical characterization of membrane proteins.

Insight into the Properties of Cardiolipin Containing Bilayers from Molecular Dynamics Simulations, Using a Hybrid All-Atom/United-Atom Force Field

Daniel Aguayo, Fernando D. González-Nilo, and Christophe Chipot [Université de Lorraine]

J. Chem. Theor. and Comp., **8**, 1765–1773, 2012.

Simulation of three models of cardiolipin (CL) containing membranes using a new set of parameters for tetramyristoyl and tetraoleoyl CLs has been developed in the framework of the united-atom CHARMM27-UA and the all-atom CHARMM36 force fields with the aim of performing molecular dynamics (MD) simulations of cardiolipin-containing mixed-lipid membranes. The new parameters use a hybrid representation of all-atom head groups in conjunction with implicit-hydrogen united-atom (UA) to describe the oleoyl and myristoyl chains of the CLs, in lieu of the fully atomistic description, thereby allowing longer simulations to be undertaken.

Interaction of Hematoporphyrin with Lipid Membranes

Michał Stepniewski, Mariusz Kepczynski, Dorota Jamróz, Maria Nowakowska, Sami Rissanen, Ilpo Vattulainen, and Tomasz Róg [Jagiellonian University]

J. Phys. Chem. B., **116**, 4889–4897, 2012.

Natural or synthetic porphyrins are being used as photosensitizers in photodiagnosis (PD) and photodynamic therapy (PDT) of malignancies and some other diseases. In this study, we consider the properties of hematoporphyrin (Hp), a well-known photosensitizer for PD and PDT, in the presence of a 1-palmitoyl-2-oleoyl-sn-glycero-3-phosphocholine (POPC) bilayer that we use as a model system for protein-free cell membranes. For this purpose, we employed 200 ns atomic-scale molecular dynamics (MD) simulations for five systems containing the neutral (Hp^0) or the dianionic form (Hp^{2-}) of Hp and the POPC bilayer.

Diffusion of 1,2-Dimethoxyethane and 1,2-Dimethoxypropane through Phosphatidycholine Bilayers: A Molecular Dynamics Study

Susruta Samanta, Samira Hezaveh, Giuseppe Milano, and Danilo Roccatano [Jacobs University Bremen]

J. Phys. Chem. B., **116**, 5141–5151, 2012.

In this paper, a theoretical study of 1,2-dimethoxyethane (DME) and 1,2-dimethoxypropane (DMP) at water/n-heptane and 1,2-dimyristoyl-sn-glycero-3-phosphatidycholine (DMPC) lipid bilayer/water interfaces using the umbrella sampling method is reported. Recently proposed GROMOS96/OPLS compatible models for DME and DMP have been used for the simulation studies. The percolation free energy barrier of one DME and DMP molecule from water to n-heptane phase calculated using the umbrella sampling method turned out to be equal to ~18.5 kJ/mol and ~6 kJ/mol, respectively.

Protein Folding

Atomistic molecular simulations of protein folding

Robert B Best [University of Cambridge]

Curr. Opin. Stru. Biol., **15**, 52-61, 2011.

Theory and experiment have provided answers to many of the fundamental questions of protein folding; a remaining challenge is an accurate, high-resolution picture of folding mechanism. Atomistic molecular simulations with explicit solvent are the most promising method for providing this information, by accounting more directly for the physical interactions that stabilize proteins. I review the recent progress in these areas, and highlight future challenges and questions that we may hope to address with these methods.

Appendant structure plays an important role in amyloidogenic cystatin dimerization prior to domain swapping

Yuanyuan Yu, Xin Liu, Jianwei He, Mengyuan Zhang, Hui Li, Dongqing Wei & Youtao Song [Liaoning University]

J. Biomol. Stru. and Dyn., **30**, 102-112, 2012.

It has been hypothesized that prior to protein domain swapping, unfolding occurs in regions important for the stability of the native monomeric structure, which probably increases the possibility of intermolecular interaction. In order to explore the detailed information of the important unfolding regions in cystatin prior to domain swapping, 20 ns molecular dynamic simulations were performed at atomic level with typical amyloidogenic chicken cystatin (cC) mutant I66Q monomer under conditions that enable forming amyloid fibrils in biological experiments.

Simulation of the Opening and Closing of Hsp70 Chaperones by Coarse-Grained Molecular Dynamics

Ewa Gołaś, Gia G. Maisuradze, Patrick Senet, Stanisław Oldziej, Cezary Czaplewski, Harold A. Scheraga, and Adam Liwo [University of Gdańsk]

J. Chem. Theor. and Comp., **8**, 1750–1764, 2012.

Heat-shock proteins 70 (Hsp70s) are key molecular chaperones, which assist in the folding and refolding/disaggregation of proteins. Hsp70s, which consist of a nucleotide-binding domain (NBD, consisting of NBD-I and NBD-II subdomains) and a substrate-binding domain [SBD, further split into the β -sheet (SBD- β) and α -helical (SBD- α) subdomains], occur in two major conformations having (a) a closed SBD, in which the SBD and NBD domains do not interact, and (b) an open SBD, in which SBD- α interacts with NBD-I and SBD- β interacts with the top parts of NBD-I and NBD-II. Here, we report canonical and multiplexed replica exchange simulations of the conformational dynamics of Hsp70s using a coarse-grained molecular dynamics approach with the UNRES force field.

Protein-Nucleic acid Interactions

Multistep Drug Intercalation: Molecular Dynamics and Free Energy Studies of the Binding of Daunomycin to DNA

Matthieu Wilhelm, Arnab Mukherjee, Benjamin Bouvier, Krystyna Zakrzewska, James T. Hynes, and Richard Lavery [Bases Moléculaires et Structurales des Systèmes Infectieux]

J. Am. Chem. Soc., **134**, 8588–8596, 2012.

Atomic-scale molecular dynamics and free energy calculations in explicit aqueous solvent are used to study the complex mechanism by which a molecule can intercalate between successive base pairs of the DNA double helix. We have analyzed the intercalation pathway for the anticancer drug daunomycin using two different methods: metadynamics and umbrella sampling. The resulting free energy pathways are found to be consistent with one another and point, within an equilibrium free energy context, to a three-step process. Daunomycin initially binds in the minor groove of DNA.

Insights on the acetylated NF- κ B transcription factor complex with DNA from molecular dynamics simulations

Cristina Fenollar-Ferrer [Max-Planck-Institut für Biophysik], Claudio Anselmi, Vincenzo Carnevale, Simone Raugei and Paolo Carloni

Proteins: Stru. Fun. & Bioinf. **80**, 1560–1568, 2012.

The nuclear factor- κ B (NF- κ B) is a DNA sequence-specific regulator of many important biological processes, whose activity is modulated by enzymatic acetylation. In one of the best functionally characterized NF- κ B complexes, the p50/p65 heterodimer, acetylation of K221 at p65 causes a decrease of DNA dissociation rate, whilst the acetylation of K122 and K123, also at p65, markedly decreases the binding affinity for DNA. By means of molecular dynamics simulations based on the X-ray structure of the p50/p65 complex with DNA, we provide insights on the structural determinants of the acetylated complexes in aqueous solution.

Surfaces, Catalysts, and Materials Subjects

Directed Assembly of DNA-Functionalized Gold Nanoparticles Using Pyrrole–Imidazole Polyamides

Željka Krpetić, Ishwar Singh, Wu Su, Luca Guerrini, Karen Faulds, Glenn A. Burley, and Duncan Graham [The University of Strathclyde]

J. Am. Chem. Soc., **134**, 8356–8359, 2012.

Traditional methods for the construction of nanoparticle arrays and lattices exploit Watson–Crick base pairing of single-stranded DNA sequences as a proxy for self-assembly. Although this approach has been utilized in a variety of applications in nanoassembly, diagnostics, and biomedicine, the diversity of this recognition lexicon could be considerably increased by developing strategies that recognize the base-pairing landscape of double-stranded DNA (dsDNA) sequences. Herein we describe the first report of programmed gold nanoparticle (GNP) aggregation directed by the recognition of dsDNA sequences using pyrrole–imidazole polyamide–GNP (PA–GNP) conjugates.

Surfaces, Catalysts and Material Subjects (Cont'd)

Molecular dynamics simulations of EMI-BF₄ in nanoporous carbon actuators

Endel Soolo, Daniel Brandell, Anti Liivat, Alvo Aabloo [University of Tartu], Heiki Kasemägi and Tarmo Tamm

J. Mol.Mod., **18**, 1541-1552, 2012

An artificial muscle composite material consisting of carbide derived carbon (CDC) and 1-ethyl-3-methylimidazolium tetrafluoroborate (EMI-BF₄) ionic liquid was modeled using molecular dynamics (MD) simulations, in order to determine the molecular structural rearrangements causing actuation. CDC was represented as separate curved graphene-like flakes with charges of +2, 0 or -2 on each flake, with 24–27 aromatic rings each. The charge distribution in the flakes was determined by PM6 semi-empirical optimization.

Effect of Hydrophilicity or Hydrophobicity of Polyelectrolyte on the Interaction between Polyelectrolyte and Surfactants: Molecular Dynamics Simulations

Zhenhai Liu, Yazhuo Shang [East China University of Science and Technology], Jian Feng, Changjun Peng, Honglai Liu, and Ying Hu

J. Phys. Chem. B., **116**, 5516–5526, 2012.

The effect of hydrophilicity or hydrophobicity of polyelectrolyte on the interaction between polyelectrolyte and oppositely charged surfactants was investigated by using coarse-grained molecular dynamics simulations. The aggregation of surfactants on the hydrophilic polyelectrolyte is significantly different from that on the hydrophobic polyelectrolyte. The complexes evolve from the “bottle brush”, through the “necklace”, then to the micelle. However, the rod-like micelle, in which polyelectrolyte wraps around the micelle surface, only appears in the hydrophilic polyelectrolyte system.

Probing Structure–Nanoaggregation Relations of Polyaromatic Surfactants: A Molecular Dynamics Simulation and Dynamic Light Scattering Study

Robel B. Teklebrhan, Lingling Ge, Subir Bhattacharjee, Zhenghe Xu [University of Alberta, Edmonton], and Johan Sjöblom

J. Phys. Chem. B., **116**, 5907–5918, 2012.

Four synthetic perylene bisimide-based polyaromatic (PA) surfactants with a structural or functional group difference in their attached hydrophilic/hydrophobic substituent side chains were used to probe structure–nanoaggregation relations in organic media by molecular dynamics simulations and dynamic light scattering. The results from the simulated radial distribution functions and light scattering experiments indicate that variation in the structure of side chains and polarity of functional groups leads to significant variations in molecular association, dynamics of molecular nanoaggregation and structure of nanoaggregates.

2. METHODOLOGY

Quantitative Structure-Activity Relations

Structure-based 3D-QSAR models and dynamics analysis of novel N-benzyl pyridinone as p38 α MAP kinase inhibitors for anticytokine activity

Zaheer Ul-Haq [University of Karachi], Waqasuddin Khan, Syeda Rehana Zia, Sadaf Iqbal

J. Mol.Graph. and Mod., **36**, 48-61, 2012.

A novel series of anticytokine N-benzyl pyridinone derivatives that targets p38 α MAP kinase has been analyzed by utilizing a combination of molecular modeling techniques. Statistically significant structure-based 3D-QSAR models were generated for both CoMFA and CoMSIA, and validated through acceptable predictive ability to support both internal and external set of compounds. Structural changes within the protein key backbone residues (Met109 and Gly110), DFG loop position, and side chain movements (Lys53 and Asn114) as resulted by different substituents on these inhibitors were also examined by molecular dynamics simulation.

Structure-based 3D-QSAR models and dynamics analysis of novel N-benzyl pyridinone as p38 α MAP kinase inhibitors for anticytokine activity

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Insights into ETA subtype selectivity of benzodiazepine endothelin receptor antagonists by 3D-QSAR approaches

Jun Xia, Jiabin Li and Hongbin Sun [China Pharmaceutical University]

J. Mol.Mod., **18**, 1299-1311, 2012

ETA subtype selective antagonists constitute a novel and potentially important class of agents for the treatment of pulmonary hypertension, heart failure, and other pathological conditions. In this paper, 60 benzodiazepine derivatives displaying potent activities against ETA and ETB subtypes of endothelin receptor were selected to establish the 3D-QSAR models using CoMFA and CoMSIA approaches. These models show excellent internal predictability and consistency, external validation using test-set 19 compounds yields a good predictive power for antagonistic potency.

Potentials and Parameters

Improving Internal Peptide Dynamics in the Coarse-Grained MARTINI Model: Toward Large-Scale Simulations of Amyloid- and Elastin-like Peptides

Mikyung Seo, Sarah Rauscher, Régis Pomès, and D. Peter Tieleman [University of Calgary]

J. Chem. Theor. and Comp. **8**, 1774–1785, 2012.

We present an extension of the coarse-grained MARTINI model for proteins and apply this extension to amyloid- and elastin-like peptides. Atomistic simulations of tetrapeptides, octapeptides, and longer peptides in solution are used as a reference to parametrize a set of pseudodihedral potentials that describe the internal flexibility of MARTINI peptides. We assess the performance of the resulting model in reproducing various structural properties computed from atomistic trajectories of peptides in water. The addition of new dihedral angle potentials improves agreement with the contact maps computed from atomistic simulations significantly.

Protein Loop Modeling with Optimized Backbone Potential Functions

Shide Liang [Osaka University], Chi Zhang, Jamaica Sarmiento, and Daron M. Standley

J. Chem. Theor. and Comp. **8**, 1820–1827, 2012.

We represented protein backbone potential as a Fourier series. The parameters of the backbone dihedral potential were initialized to random values and optimized by Monte Carlo simulations so that generated native-like loop decoys had a lower energy than non-native decoys. The low energy regions of the optimized backbone potential were consistent with observed Ramachandran plots derived from crystal structures. The backbone potential was then used for the prediction of loop conformations (OSCAR-loop) combining with the previously described OSCAR force field, which has been shown to be very accurate in side chain modeling.

Molecular Dynamics

The Molecular Mechanism by which PIP₂ Opens the Intracellular G-Loop Gate of a Kir3.1 Channel

Xuan-Yu Meng, Hong-Xing Zhang, Diomedes E. Logothetis, Meng Cui [Virginia Commonwealth University School of Medicine]

Biophysical Journal. **102**, 2049–2059, 2012.

Inwardly rectifying potassium (Kir) channels are characterized by a long pore comprised of continuous transmembrane and cytosolic portions. A high-resolution structure of a Kir3.1 chimera revealed the presence of the cytosolic (G-loop) gate captured in the closed or open conformations. Here, we conducted molecular-dynamics simulations of these two channel states in the presence and absence of phosphatidylinositol bisphosphate (PIP₂), a phospholipid that is known to gate Kir channels. Simulations of the closed state with PIP₂ revealed an intermediate state between the closed and open conformations involving direct transient interactions with PIP₂, as well as a network of transitional inter- and intrasubunit interactions.

Molecular Dynamics (Cont'd)

Signals of LOV1: a computer simulation study on the wildtype LOV1-domain of *Chlamydomonas reinhardtii* and its mutants

Emanuel Peter, Bernhard Dick and Stephan A. Baeurle
[University of Regensburg]

J. Mol.Mod., **18**, 1375-1388, 2012

Phototropins are photoreceptors regulating the blue-light response in plants and bacteria. They consist of two LOV (light oxygen voltage sensitive) domains each containing a non-covalently bound flavin-mononucleotide (FMN) chromophore, which are connected to a serine/threonine-kinase. Upon illumination, the LOV-domains undergo conformational changes, triggering a signal cascade in the organism through kinase activation. Here, we present results from molecular dynamics simulations in which we investigate the signal transduction pathway of the wildtype LOV1-domain of *Chlamydomonas reinhardtii* and a methyl-mercaptan (MM) adduct of its Cys57Gly-mutant at the molecular level.

The state of the guanosine nucleotide allosterically affects the interfaces of tubulin in protofilament

Joseph R. André, Marie-Jeanne Clément, Elisabeth Adjadj, Flavio Toma and Patrick A. Curmi, Philippe Manivet [Institut National de la Santé et de la Recherche Médicale (INSERM)]

J. Comp. Aided Mol. Des. **26**, 397-407, 2011.

The dynamics of microtubules is essential for many microtubule-dependent cellular functions such as the mitosis. It has been recognized for a long time that GTP hydrolysis in $\alpha\beta$ -tubulin polymers plays a critical role in this dynamics. However, the effects of the changes in the nature of the guanosine nucleotide at the E-site in β -tubulin on microtubule structure and stability are still not well understood. In the present work, we performed all-atom molecular dynamics simulations of a $\alpha\beta\alpha$ -tubulin heterotrimer harboring a guanosine nucleotide in three different states at the E-site: GTP, GDP-Pi and GDP.

Coarse-Grained Potential Model for Structural Prediction of Confined Water

S. Y. Mashayak and N. R. Aluru [University of Illinois at Urbana-Champaign]

J. Chem. Theor. and Comp., **8**, 1828–1840, 2012.

We propose a coarse-grained potential model to predict the concentration and potential profiles of confined water. In this model, we represent one water molecule with one coarse-grained bead, such that the interactions between the coarse-grained beads are given by isotropic two-body potentials. Due to the inherent inhomogeneity of the confined water microstructure, we find that a single spatially uniform coarse-grained water–water potential may not be sufficient to accurately predict the structure of water near the surface. To accurately capture surface effects on the water structure, we add a coarse-grained correction potential between wall atoms and water coarse-grained beads.

Computational Studies of Protonated β -d-Galactose and Its Hydrated Complex: Structures, Interactions, Proton Transfer Dynamics, and Spectroscopy

Hong-bin Xie [Dalian University of Technology], Lin Jin, Svemir Rudić, John P. Simons, and R. Benny Gerber

J. Phys. Chem. B., **116**, 4851–4859, 2012.

We present an exploration of proton transfer dynamics in a monosaccharide, based on ab initio molecular dynamic simulations, conducted “on-the-fly”, in β -d-galactose- H^+ (β Gal- H^+) and its hydrated complex, β Gal- H^+ - H_2O . Prior structural calculations identify O6 as the preferred protonation site for O-methyl α -d-galactopyranoside, but the β -anomeric configuration favors the inversion of the pyranose ring from the $^4C_1$ chair configuration, to $^1C_4$, and the formation of proton bridges to the (axial) O1 and O3 sites. In the hydrated complex, however, the proton bonds to the water molecule inserted between the O6 and Ow sites, and the ring retains its original $^4C_1$ conformation, supported by a circular network of co-operatively linked hydrogen bonds.

Molecular Dynamics (Cont'd)

Charybdotoxin and Margatoxin Acting on the Human Voltage-Gated Potassium Channel hK_v1.3 and Its H399N Mutant: An Experimental and Computational Comparison

Azadeh Nikouee, Morteza Khabiri, Stephan Grissmer, and Rüdiger Ettrich [University of South Bohemia in Ceske Budejovice]

J. Phys. Chem. B., **116**, 5132–5140, 2012.

The effect of the pore-blocking peptides charybdotoxin and margatoxin, both scorpion toxins, on currents through human voltage-gated hK_v1.3 wild-type and hK_v1.3_H399N mutant potassium channels was characterized by the whole-cell patch clamp technique. In the mutant channels, both toxins hardly blocked current through the channels, although they did prevent C-type inactivation by slowing down the current decay during depolarization. Molecular dynamics simulations suggested that the fast current decay in the mutant channel was a consequence of amino acid reorientations behind the selectivity filter and indicated that the rigidity–flexibility in that region played a key role in its interactions with scorpion toxins.

Interaction of Counterions with Subtilisin in Acetonitrile: Insights from Molecular Dynamics Simulations

Diana Lousa, Michele Cianci, John R. Helliwell, Peter J. Halling, António M. Baptista, and Cláudio M. Soares [Universidade Nova de Lisboa]

J. Phys. Chem. B., **116**, 5838–5848, 2012.

A recent X-ray structure has enabled the location of chloride and cesium ions on the surface of subtilisin Carlsberg in acetonitrile soaked crystals.(1) To complement the previous study and analyze the system in solution, molecular dynamics (MD) simulations, in acetonitrile, were performed using this structure. Additionally, Cl[−] and Cs⁺ ions were docked on the protein surface and this system was also simulated. Our results indicate that chloride ions tend to stay close to the protein, whereas cesium ions frequently migrate to the solvent.

Simulations of substrate transport in the multidrug transporter EmrD

Joseph Baker, Stephen H. Wright and Florence Tama [The University of Arizona]

Proteins: Stru. Fun. & Bioinf. **80**, 1620–1632, 2012.

EmrD is a multidrug resistance (MDR) transporter from *Escherichia coli*, which is involved in the efflux of amphipathic compounds from the cytoplasm, and the first MDR member of the major facilitator superfamily to be crystallized. Molecular dynamics simulation of EmrD in a phospholipid bilayer was used to characterize the conformational dynamics of the protein. Motions that support a previously proposed lateral diffusion pathway for substrate from the cytoplasmic membrane leaflet into the EmrD central cavity were observed. In addition, the translocation pathway of meta-chloro carbonylcyanide phenylhydrazone (CCCP) was probed using both standard and steered molecular dynamics simulation.

Computational investigation of the HIV-1 Rev multimerization using molecular dynamics simulations and binding free energy calculations

Tom Venken, Dirk Daelemans, Marc De Maeyer [Celestijnenlaan 200G] and Arnout Voet

Proteins: Stru. Fun. & Bioinf. **80**, 1633–1646, 2012.

The HIV Rev protein mediates the nuclear export of viral mRNA, and is thereby essential for the production of late viral proteins in the replication cycle. Rev forms a large organized multimeric protein-protein complex for proper functioning. Recently, the three-dimensional structures of a Rev dimer and tetramer have been resolved and provide the basis for a thorough structural analysis of the binding interaction. Here, molecular dynamics (MD) and binding free energy calculations were performed to elucidate the forces thriving dimerization and higher order multimerization of the Rev protein.

QM and QM/MM

QM/MM Study on the Catalytic Mechanism of Heme-Containing Aliphatic Aldoxime Dehydratase

Xiao-Liang Pan, Feng-Chao Cui, Wei Liu, and Jing-Yao Liu [Jilin University]

J. Phys. Chem. B., **116**, 5689–5693, 2012.

Aliphatic aldoxime dehydratase (Oxd) catalyzes the dehydration of aliphatic aldoximes ($R-CH=N-OH$) to the corresponding nitriles ($R-C\equiv N$). Quantum mechanics/molecular mechanics (QM/MM) calculations are performed to elucidate the catalytic mechanism of the enzyme on the basis of the X-ray crystal structure of the Michaelis complex. On the basis of the calculations, we propose a complete catalytic cycle of Oxd in which the distal histidine (His320) acts as a general acid/base. In the Michaelis complex, the elimination of the hydroxyl group of aldoxime is facilitated by His320 donating a proton to the hydroxyl group in a concerted way, which is the rate-limiting step.

Comparative or Homology Modeling

Accelerating Membrane Insertion of Peripheral Proteins with a Novel Membrane Mimetic Model

Y. Zenmei Ohkubo, Taras V. Pogorelov, Mark J. Arcario, Geoff A. Christensen, Emad Tajkhorshid [University of Illinois at Urbana-Champaign]

Biophysical Journal. **102**, 2130-2139, 2012.

Characterizing atomic details of membrane binding of peripheral membrane proteins by molecular dynamics (MD) has been significantly hindered by the slow dynamics of membrane reorganization associated with the phenomena. To expedite lateral diffusion of lipid molecules without sacrificing the atomic details of such interactions, we have developed a novel membrane representation, to our knowledge, termed the highly mobile membrane-mimetic (HMMM) model to study binding and insertion of various molecular species into the membrane. The HMMM model takes advantage of an organic solvent layer to represent the hydrophobic core of the membrane and short-tailed phospholipids for the headgroup region.

Conformation analysis of a surface loop that controls active site access in the GH11 xylanase A from *Bacillus subtilis*

Davi Serradella Vieira [Letras de Ribeirão Preto - Universidade de São Paulo] and Richard John Ward

J. Mol.Mod., **18**, 1473-1479, 2012

Xylanases (EC 3.2.1.8 endo-1,4-glycosyl hydrolase) catalyze the hydrolysis of xylan, an abundant hemicellulose of plant cell walls. Access to the catalytic site of GH11 xylanases is regulated by movement of a short β -hairpin, the so-called thumb region, which can adopt open or closed conformations. A crystallographic study has shown that the D11F/R122D mutant of the GH11 xylanase A from *Bacillus subtilis* (BsXA) displays a stable “open” conformation, and here we report a molecular dynamics simulation study comparing this mutant with the native enzyme over a range of temperatures.

Comparative or Homology Modeling (Cont'd)

Affinity and Selectivity of ShK Toxin for the Kv1 Potassium Channels from Free Energy Simulations

M. Harunur Rashid and Serdar Kuyucak [University of Sydney]

J. Phys. Chem. B., **116**, 4812–4822, 2012.

The voltage-gated potassium channel Kv1.3 is an attractive target for treatment of autoimmune diseases. ShK toxin from sea anemone is one of the most potent blockers of Kv1.3, and therefore ShK and its analogues have been proposed as therapeutic leads for such diseases. Increasing the selectivity of the proposed leads for Kv1.3 over other Kv1 channels is a major issue in this endeavor. Here we study binding of ShK toxin to Kv1 channels using free energy simulation methods. Homology models for Kv1.1 and Kv1.3 channels are constructed using the crystal structure of Kv1.2. The initial poses for the Kv1.x–ShK complexes are obtained using HADDOCK, which are then refined via molecular dynamics simulations.

Ligand Docking

Deciphering the binding mode of Zolpidem to GABAA $\alpha 1$ receptor – insights from molecular dynamics simulation

R. S. K. Vijayan, Dhananjay Bhattacharyya and Nanda Ghoshal [Indian Institute of Chemical Biology]

J. Mol.Mod., **18**, 1345-1354, 2012

To investigate the binding mode of Zolpidem to GABAA and to delineate the conformational changes induced upon agonist binding, we carried out atomistic molecular dynamics simulation using the ligand binding domain of GABAA $\alpha 1$ receptor. Comparative molecular dynamics simulation of the apo and the holo form of GABAA receptor revealed that $\gamma 2/\alpha 1$ interface housing the benzodiazepine binding site undergoes distinct conformational changes upon Zolpidem binding.

The molecular basis of IGF-II/IGF2R recognition: a combined molecular dynamics simulation, free-energy calculation and computational alanine scanning study

Jingjing Guo, Xiaoting Wang, Huijun Sun, Huanxiang Liu and Xiaojun Yao [Lanzhou]

J. Mol.Mod., **18**, 1421-1430, 2012

Insulin-like growth factor-II (IGF-II) is a key regulator of cell growth, survival, migration and differentiation, and is thus pivotal in many cancers. In this study, in order to investigate the interaction of the IGF-II/IGF2R complex and to characterize the binding hot spots of this interaction, a 10 ns molecular dynamics simulation combined with MM-PBSA/MM-GBSA computations and computational alanine scanning was performed on the IGF-II/IGF2R complex. From the results of the free-energy decomposition and the computational alanine scanning calculation, we identified the key residues in the IGF-II/IGF-2R interaction.

Ligand Docking (Cont'd)

Interpreting the structural mechanism of action for MT7 and human muscarinic acetylcholine receptor 1 complex by modeling protein–protein interaction

Jianrong Xu, Jun Xu & Hongzhuan Chen [Shanghai Jiao Tong University School of Medicine]

J. Biomol. Stru. and Dyn., **30**, 30-44, 2012.

MT7 is a selective human muscarinic acetylcholine receptor 1 (hM1) allosteric binder with subnanomolar affinity. Understanding the binding mode of hM1–MT7 will give insights to discover small molecular ligand for hM1. MT7 is a peptide, and hM1 is a G-protein-coupled membrane receptor. Therefore, we have employed homology modeling, protein–protein docking, explicit membrane molecular dynamics (MD) simulations, and molecular mechanic/Poisson-Boltzmann surface area energy decomposition analysis approaches to reveal the hM1–MT7 binding mode.

How Does Darunavir Prevent HIV-1 Protease Dimerization?

Danzhi Huang and Amedeo Caflisch [University of Zürich]

J. Chem. Theor. and Comp., **8**, 1786–1794, 2012.

The drug Darunavir (DRV) is a potent inhibitor of HIV-1 protease (PR), a homodimeric essential enzyme of the AIDS virus. Recent experimental data suggest that DRV is able to prevent dimerization of HIV-1 PR, which, together with its high affinity for the mature enzyme, has been linked to the high genetic barrier to the development of viral resistance. The mechanism of dimerization inhibition and the binding mode(s) of DRV to monomeric HIV-1 PR are unknown. Here, multiple molecular dynamics simulations with explicit solvent (for a total of 11 μ s with the CHARMM force field and 1 μ s with the Amber force field) show that the monomer of HIV-1 PR is structurally stable and reveal a major binding mode of DRV.

3. JOURNAL REVIEWS

Journal of Computational Chemistry, 33(15), June, 2012.

- 1347–1352 **Assessment of ab initio MP2 and density functionals for characterizing the potential energy profiles of the SN2 reactions at N center**, Feng Yu [Xi'an Technological University]

The potential energy profiles of five selected bimolecular nucleophilic substitution (S_N2) reactions at nitrogen (N) center have been reinvestigated with the CCSD(T), G3[MP2,CCSD(T)], MP2, and some density functional methods.

- 1353–1363 **Design of donors with broad absorption regions and suitable frontier molecular orbitals to match typical acceptors via substitution on oligo(thienylenevinylene) toward solar cells**, Shanshan Tang and Jingping Zhang [Northeast Normal University]

A series of oligo(thienylenevinylene) derivatives with or without thieno[3,2-b]thiophene analogs as cores and three types substituent has been investigated at the PBE0/6-31G(d) and the TD-PBE0/6-31+G(d,p) levels to design materials with high performance such as suitable frontier molecular orbital (FMO) energies to match those of [6,6]-phenyl- C_{61} -butyric acid methyl ester (PCBM) and its derivatives, broad absorption spectra, higher and balance transfer property, and better stability.

- 1364–1373 **Molecular dynamics extended for fluctuating networks: Application to water**, Jennifer M. Kashmirian [Monash University], Alfred Uhlherr, Alan Dorin and David G. Green

See Applications / Water and Solvation.

- 1374–1382 **Electrostatic polarization is critical for the strong binding in streptavidin-biotin system**, Ye Mei, Yong L. Li, Juan Zeng and John Z. H. Zhang [East China Normal University]

The origin of strong affinity of biotin and its analogs binding to (strept)avidin is still the subject of an ongoing controversy. In this work, thermodynamic integration is carried out to study of the difference of binding free energies between biotin and iminobiotin to streptavidin.

- 1383–1392 **Benchmarking the thermodynamic analysis of water molecules around a model beta sheet**, David J. Huggins [Cambridge Molecular Therapeutics]

See Applications / Water and Solvation.

Journal of Computational Chemistry, 33(16), June, 2012.

- 1407–1415 **The role of macrocyclic ligands in the peroxo/superoxo nature of Ni–O₂ biomimetic complexes**, Jhon Zapata-Rivera, Rosa Caballol [Universitat Rovira i Virgili] and Carmen J. Calzado

The impact of the macrocyclic ligand on the electronic structure of two LNi—O₂ biomimetic adducts, [Ni(12-TMC)O₂]⁺ (12-TMC = 1,4,7,10-tetramethyl-1,4,7,10-tetraazacyclododecane) and [Ni(14-TMC)O₂]⁺ (14-TMC = 1,4,8,11-tetramethyl-1,4,8,11-tetraazacyclotetradecane), has been inspected by means of difference-dedicated configuration interaction calculations and a valence bond reading of the wavefunction.

- 1416–1420 **Effect of interprotein polarization on protein–protein binding energy**, Chang G. Ji and John Z. H. Zhang [East China Normal University]

See Applications / Protein–Protein Interactions.

- 1421–1432 **DCMB that combines divide-and-conquer and mixed-basis set methods for accurate geometry optimizations, total energies, and vibrational frequencies of large molecules**, Anan Wu and Xin Xu [Xiamen University]

We present a method, named DCMB, for the calculations of large molecules. It is a combination of a parallel divide-and-conquer (DC) method and a mixed-basis (MB) set scheme. In this approach, atomic forces, total energy and vibrational frequencies are obtained from a series of MB calculations, which are derived from the target system utilizing the DC concept.

- 1433–1439 **Insulator–metal transition driven by pressure and B-site disorder in double perovskite La₂CoMnO₆**, Shuhui Lv, Xiaojuan Liu, Hongping Li, Lin Han, Zhongchang Wang and Jian Meng [Chinese Academy of Sciences]

The ground state of double perovskite oxide La₂CoMnO₆ (LCMO) and how it is influenced by external pressure and antisite disorder are investigated systematically by first-principles calculations.

- 1440–1447 **The statistical significance of selected sense–antisense peptide interactions**, Christopher J. R. Illingworth, Sree V. Chintipalli, Stefano A. Serapian, Andrew D. Miller, Vaclav Veverka, Mark D. Carr and Christopher A. Reynolds [University of Essex]

Sense and antisense peptides, encoded by sense and corresponding antisense DNA strands, are capable of specific interactions that could be a driving force to mediate protein–protein or protein–peptide binding associations. We examined the potential of the hypothesis for general identification of protein–protein interaction sites, and the possible role of the hypothesis in determining folding in a broad set of protein structures.

- 1448–1457 **Comparison of the FeO₂⁺ and FeS₂⁺ complexes in the cyanide and isocyanide ligand environment for methane hydroxylation**, Hao Tang, Zhuo Li, Yu-Hong Yang, Ying Zhao, Su-Qin Wan, Hui-Ling Liu [Jilin University] and Xu-Ri Huang

A general comparison of fundamental distinctions between the FeO₂⁺ and FeS₂⁺ complexes in an identical cyanide or isocyanide ligand environment for methane hydroxylation has been probed computationally in this work in a series of hypothetical [Fe^{IV}(X)(CN)₅]^{3–}, [Fe^{IV}(X)(NC)₅]^{3–}, (X = O, S) complexes. We have detailed an analysis of the geometric and electronic structures using density functional theory calculations.

- 1458–1466 **Simulation of multiphase systems utilizing independent force fields to control intraphase and interphase behavior**, Pradip K. Biswas, Nadeem A. Vellore, Jeremy A. Yancey, Tugba G. Kucukkal, Galen Collier, Bernard R. Brooks, Steven J. Stuart and Robert A. Latour [Clemson University]

Fixed-charge empirical force fields have been developed and widely used over the past three decades for all-atom molecular simulations. Most simulation programs providing these methods enable only one set of force field parameters to be used for the entire system. Whereas this is generally suitable for single-phase systems, the molecular environment at the interface between two phases may be sufficiently different from the individual phases to require a different set of parameters to be used to accurately represent the system. We have developed a dual-force-field approach (Dual-FF) to address this problem and implemented it in the CHARMM simulation package.

Journal of Computational Chemistry, 33(17), June, 2012.

- 1467–1477 **Calculation of the relative free energy of oxidation of azurin at pH 5 and pH 9**, Denise Steiner, Chris Oostenbrink and Wilfred F. van Gunsteren [Swiss Federal Institute of Technology Zürich]

Free energy calculations are described for the small copper-containing redox protein Azurin from *Pseudomonas aeruginosa*. A thermodynamic cycle connecting the reduced and oxidized states at pH 5 and pH 9 is considered, allowing for an assessment of convergence in terms of hysteresis and cycle closure.

- 1478–1494 **Efficient treatment of solvation shells in 3D molecular theory of solvation**, Sergey Gusarov, Bhalchandra S. Pujari and Andriy Kovalenko [National Institute for Nanotechnology, 11421 Saskatchewan Drive]

We developed a technique to decrease memory requirements when solving the integral equations of three-dimensional (3D) molecular theory of solvation, a.k.a. 3D reference interaction site model (3D-RISM), using the modified direct inversion in the iterative subspace (MDIIS) numerical method of generalized minimal residual type.

- 1495–1510 **Localization of molecular orbitals on fragments**, Alexander F. Sax [University of Graz]

A non-iterative algorithm for the localization of molecular orbitals (MOs) from complete active space self consistent field (CASSCF) and for single-determinantal wave functions on predefined moieties is given.

- 1511–1516 **Interaction between alkyl radicals and single wall carbon nanotubes**, Pablo A. Denis [DETEMA, Facultad de Química]

The addition of primary, secondary, and tertiary alkyl radicals to single wall carbon nanotubes (SWCNTs) was studied by means of dispersion corrected density functional theory.

- 1517–1523 **The effect of conjugated spacer on novel carbazole derivatives for dye-sensitized solar cells: Density functional theory/time-dependent density functional theory study**, Siriporn Jungsuttiwong [Ubon Ratchathani University], Thanisorn Yakhantip, Yaowarat Surakhot, Janeeya Khunchalee, Taweesak Sudyoasuk, Vinich Promarak, Nawe Kungwan and Supawadee Namuangruk

The ground-state structure and frontier molecular orbital of D- π -A organic dyes, CFT1A, CFT2A, and CFT1PA were theoretically investigated using density functional theory (DFT) on B3LYP functional with 6-31G(d,p) basis set.

Journal of Molecular Modeling, 18(4), April, 2012.

- 1255-1262 **Density functional theory analysis of carbonyl sulfide hydrolysis: effect of solvation and nucleophile variation**, Ri-Guang Zhang, Li-Xia Ling and Bao-Jun Wang [Taiyuan University of Technology]

The detailed mechanisms of the hydrolysis of carbonyl sulfide (OCS) by nucleophilic water and hydroxide ion in both the gas phase and bulk water solvent have been investigated using density functional theory.

- 1263-1271 **A combined experimental and computational study on the material properties of shape memory polyurethane**, Cuili Zhang, Jinlian Hu [The Hong Kong Polytechnic University], Fenglong Ji, Ying Fan and Yan Liu

A type of shape memory polyurethane with 60 wt% hard segments (SMPU60) was prepared. Its material properties were tested by dynamic mechanical analysis (DMA) and Instron, and simulated using fully atomistic molecular dynamics (MD).

- 1273-1284 **Evaluation of natural and nitramine binding energies to 3-D models of the S1S2 domains in the N-methyl-D-aspartate receptor**, Jason Ford-Green [Jackson State University], Olexandr Isayev, Leonid Gorb, Edward J. Perkins and Jerzy Leszczynski

See Applications / Homology Modeling.

- 1285-1297 **Application of information theory to feature selection in protein docking**, Olaf G. Othersen, Arno G. Stefani, Johannes B. Huber and Heinrich Sticht [Friedrich-Alexander-Universität Erlangen-Nürnberg]

See Applications / Bioinformatics.

- 1299-1311 **Insights into ETA subtype selectivity of benzodiazepine endothelin receptor antagonists by 3D-QSAR approaches**, Jun Xia, Jiabin Li and Hongbin Sun [China Pharmaceutical University]

See Methodology / QSAR.

- 1313-1324 **Proton transfer from H₂O to p-substituted anilide anion: can the size of water cluster influence the N $\cdots$ H-OH $\rightarrow$ N-H $\cdots$ OH $^-$ switching**, Hossein Roohi [University of Guilan] and Behnaz Moghadam

The effects of the H₂O cluster size and the substituent (X=H, Me, OMe, CHO, NO and NO₂) in the para position of anilide ion on the HN $\cdots$ H-OH $\rightarrow$ HN-H $\cdots$ OH $^-$ switching were investigated by means of B3LYP and MP2 methods.

- 1325-1331 **Molecular design of new nitramine explosives: 1,3,5,7-tetranitro-8-(nitromethyl)-4-imidazolino[4,5-b]4-imidazolino-[4,5-e] pyridine and its N-oxide**, Hui Liu, Hongchen Du, Guixiang Wang, Yan Liu and Xuedong Gong [Nanjing University of Science and Technology]

Two new nitramine compounds containing pyridine, 1,3,5,7-tetranitro-8-(nitromethyl)-4-imidazolino[4,5-b]4-imidazolino-[4,5-e]pyridine and its N-oxide 1,3,5,7-tetranitro-8-(nitromethyl)-4-imidazolino[4,5-b]4-imidazolino-[4,5-e]pyridine-4-ol were proposed.

- 1333-1343 **A systematic search for the structures, stabilities, and electronic properties of bimetallic Ca₂-doped gold clusters: comparison with pure gold clusters**, Ya-Ru Zhao, Xiao-Yu Kuang [Sichuan University], Peng Shao, Cheng-Gang Li and Su-Juan Wang, et al.

The local meta-GGA exchange correlation density functional (TPSS) with a relativistic effective core potential was employed to systematically investigate the geometric structures, stabilities, and electronic properties of bimetallic Ca₂Au_n ($n = 1-9$) and pure gold Au_n ($n \leq 11$) clusters.

- 1345-1354 **Deciphering the binding mode of Zolpidem to GABAA α 1 receptor – insights from molecular dynamics simulation**, R. S. K. Vijayan, Dhananjay Bhattacharyya and Nanda Ghoshal [Indian Institute of Chemical Biology]

See Methodology / Ligand Docking.

- 1355-1364 **The impact of Trichoderma reesei Cel7A carbohydrate binding domain mutations on its binding to a cellulose surface: a molecular dynamics free energy study**, Tong Li, Shihai Yan and Lishan Yao [Chinese Academy of Sciences]

See Applications / Ligand Binding.

- 1365-1374 **A quantum-chemical study of the binding ability of β XaaHisGlyHis towards copper(II) ion**, Żaneta Czyżnikowska [Wrocław Medical University] and Justyna Brasuń

The present study analyzed binding of Cu²⁺ to tetrapeptides in water solution at several levels of theoretical approximation. The methods used to study the energetic and structural properties of the complexes in question include semiempirical hamiltonians, density functional theory as well as ab initio approaches including electron correlation effects.

- 1375-1388 **Signals of LOV1: a computer simulation study on the wildtype LOV1-domain of Chlamydomonas reinhardtii and its mutants**, Emanuel Peter, Bernhard Dick and Stephan A. Baeurle [University of Regensburg]

See Methodology / Molecular Dynamics.

- 1389-1399 **Effects of the position and manner of hydration on the stability of solvated N-methylacetamides and the strength of binding between N-methylacetamide and water clusters: a computational study**, Xiuchan Xiao, Ying Tan, Lijuan Zhu, Xuemei Pu [Sichuan University], Yanzhi Guo and Zhining Wen, et al.

This work mainly studies the effects of the position (there are two possible hydrated sites) and the manner (i.e., whether water acts as a proton donor or acceptor) of hydration by various numbers of water molecules on

the stability of 14 solvated N-methylacetamide structures, NMA-(H₂O)_n ($n = 1-3$), as well as the binding strength between the NMA and the water cluster, using molecular dynamics (MD) and B3LYP methods.

- 1401-1408 **Theoretical investigation of the radical scavenging activity of shikonin and acylshikonin derivatives**, Ruifa Jin [Chifeng University] and Yin Bai

The radical scavenging activity of shikonin and acylshikonin derivatives was studied by using density functional theory.

- 1409-1420 **Computational synthesis of C60 cyano- and azopolyderivatives**, Elena F. Sheka [Peoples' Friendship University of Russia]

The cyanation of C₆₀ to C₆₀(CN)₁₈ and the aziridination of C₆₀ to C₆₀(NH)₉ were studied by an unrestricted broken spin symmetry Hartree–Fock approach implemented in semiempirical codes based on the AM1 technique.

- 1421-1430 **The molecular basis of IGF-II/IGF2R recognition: a combined molecular dynamics simulation, free-energy calculation and computational alanine scanning study**, Jingjing Guo, Xiaoting Wang, Huijun Sun, Huanxiang Liu and Xiaojun Yao [Lanzhou University]

See Methodology / Ligand Docking.

- 1431-1445 **Mechanism of isoproturon resistance in Phalaris minor: in silico design, synthesis and testing of some novel herbicides for regaining sensitivity**, Durg Vijay Singh, Kuruba Adeppa and Krishna Misra [Center of Biomedical Magnetic Resonance SGPGIMS Campus]

See Applications / Homology Modeling.

- 1447-1454 **First principles investigation of oxygen adsorptions on hydrogen-terminated ZnO graphene-like nanosheets**, Benjawan Kaewruksa and Vithaya Ruangpornvisuti [Chulalongkorn University]

The structures of ZnO graphene-like nanosheets (ZnOGLNS), i.e., ZnO aromatic-like (AL-ZnONS), naphthalene-like (NLL-ZnONS), pyrene-like (PRL-ZnONS), coronene-like (CNL-ZnONS) and circumcoronene-like (CCL-ZnONS) and their oxygen adsorptions were obtained using the B3LYP/LanL2DZ method.

- 1455-1462 **UV-spectroscopy, electronic structure and ozonolytic reactivity of sesquiterpenes: a theoretical study**, Shu-Xian Hu, Jian-Guo Yu and Eddy Yongping Zeng [Chinese Academy of Sciences]

Sesquiterpenes, one of the most important classes of biogenic volatile organic compounds, are potentially significant precursors to secondary organic aerosols (SOAs) in nature. The electronic structure of sesquiterpenes and their reactivity in the ozonolysis reaction were investigated by density functional theory.

- 1463-1472 **OH-functionalized open-ended armchair single-wall carbon nanotubes (SWCNT) studied by density functional theory**, Elzbieta Chelmecka, Karol Pasterny, Teobald Kupka [Medical University of Silesia] and Leszek Stobiński

See Applications / Carbon Nanoparticles.

- 1473-1479 **Conformation analysis of a surface loop that controls active site access in the GH11 xylanase A from *Bacillus subtilis***, Davi Serradella Vieira [Letras de Ribeirão Preto - Universidade de São Paulo] and Richard John Ward

See Applications / Homology Modeling.

- 1481-1493 **De novo design of 7-aminocoumarin derivatives as novel falcipain-3 inhibitors**, Anand S. Chintakrindi, Mushtaque S. Shaikh and Evans C. Coutinho [Bombay College of Pharmacy]

See Applications / Homology Modeling.

- 1495-1502 **Atomistic modeling of water diffusion in hydrolytic biomaterials**, Alfonso Gautieri, Andrea Mezzanzanica, Alberto Motta, Alberto Redealli and Simone Vesentini [Politecnico di Milano]

One of the most promising applications of hydrolytically degrading biomaterials is their use as drug release carriers. We present here an atomistic-based approach to investigate the diffusion of water (through which hydrolytic degradation occurs) in degrading bulk models of poly(lactic acid) or PLA.

- 1503-1512 **Understanding the desensitizing mechanism of olefin in explosives: shear slide of mixed HMX-olefin systems**, Chaoyang Zhang [China Academy of Engineering Physics (CAEP)], Xia Cao and Bin Xiang

We simulated the shear slide behavior of typical mixed HMX-olefin systems and the effect of thickness of olefin layers (4–22 Å) on the behavior at a molecular level by considering two cases: bulk shear and interfacial shear.

- 1513-1521 **Structure and electronic absorption spectra of nematogenic alkoxy cinnamic acids – a comparative study based on semiempirical and DFT methods**, Pogula Lakshmi Praveen and Durga Prasad Ojha [Andhra Loyola College]

Structure of nematogenic p-n-Alkoxy cinnamic acids (nOCAC) with various alkyl chain carbon atoms ($n = 2, 4, 6, 8$) has been optimized using density functional B3LYP with 6-31+G (d) basis set using crystallographic geometry as input.

- 1523-1540 **Computer-assisted design for atenolol prodrugs for the use in aqueous formulations**, Rafik Karaman [Al-Quds University], Khuloud Dajani and Hussein Hallak

See Applications / Medicinal Chemistry and Drug Design.

- 1541-1552 **Molecular dynamics simulations of EMI-BF₄ in nanoporous carbon actuators**, Endel Soolo, Daniel Brandell, Anti Liivat, Alvo Aabloo [University of Tartu], Heiki Kasemägi and Tarmo Tamm

See Applications / Surfaces, Catalysts and Material Substances.

- 1553-1560 **Molecular modeling of cytochrome b₅ with a single cytochrome c-like thioether linkage**, Ying-Wu Lin [University of South China], Yi-Mou Wu, Li-Fu Liao and Chang-Ming Nie

See Applications / Homology Modeling.

- 1561-1572 **Theoretical studies on 2-diazo-4,6-dinitrophenol derivatives aimed at finding superior propellants**, Yan Liu, Lianjun Wang, Guixiang Wang, Hongchen Du and Xuedong Gong [Nanjing University of Science and Technology]

In an attempt to find superior propellants, 2-diazo-4,6-dinitrophenol (DDNP) and its –NO₂, –NH₂, –CN, –NC, –ONO₂, and –NF₂ derivatives were studied at the B3LYP/6-311++G** level of density functional theory (DFT).

- 1573-1582 **Docking-based 3D-QSAR analyses of pyrazole derivatives as HIV-1 non-nucleoside reverse transcriptase inhibitors**, Elena Cichero [Università degli Studi di Genova] and Paola Fossa

See Applications / QSAR.

- 1583-1589 **Trimethylaurintricarboxylic acid inhibits human DNA methyltransferase 1: insights from enzymatic and molecular modeling studies**, Jakyung Yoo and José L. Medina-Franco [Torrey Pines Institute for Molecular Studies]

See Applications / Enzyme Catalysis.

- 1591-1596 **Dynamics comparison of two myoglobins with a distinct heme active site**, Ying-Wu Lin [University of South China], Yi-Mou Wu and Li-Fu Liao

See Applications / Homology Modeling.

- 1597-1610 **A novel, customizable and optimizable parameter method using spherical harmonics for molecular shape similarity comparisons**, Chaoqian Cai, Jiayu Gong, Xiaofeng Liu, Hualiang Jiang and Daqi Gao [East China University of Science and Technology], et al.

A novel molecular shape similarity comparison method, namely SHeMS, derived from spherical harmonic (SH) expansion, is presented in this study.

- 1611-1624 **Ligand-based 3-D pharmacophore generation and molecular docking of mTOR kinase inhibitors**, Karunakar Tanneeru and Lalitha Guruprasad [University of Hyderabad]

See Applications / Homology Modeling.

- 1625-1632 **A theoretical study on the hydrolysis mechanism of carbon disulfide**, Lixia Ling, Riguang Zhang, Peide Han and Baojun Wang [Taiyuan University of Technology]

The hydrolysis mechanism of CS₂ was studied using density functional theory.

- 1633-1644 **Proton transfer reaction and intermolecular interactions in associates of 2,5-dihydroxy-1,8-naphthyridine**, Borys Ośmiałowski [University of Technology and Life Sciences]

Tautomerism in monomers/dimers and association of 2,5-dihydroxy-1,8-naphthyridine was studied at the DFT level recently recommended for studies of non-covalent interactions.

- Theoretical studies on models of lysine-arginine cross-links derived from α -oxoaldehydes: a new mechanism for glucosepane formation,** Rasoul Nasiri, Mansour Zahedi [Shahid Beheshti University], H  l  ne Jamet and Ali Akbar Moosavi-Movahedi

Availability and high reactivity of α -oxoaldehydes have been approved by experimental techniques not only in vivo systems but also in foodstuffs. In this article we re-examine the mechanism of glucosepane formation by using computational model chemistry.

- 1661-1666 **BON-BONS: cyclic molecules with a boron-oxygen-nitrogen backbone. Computational studies of their thermodynamic properties,** Aloysius K. Lawong and David W. Ball [Cleveland State University]

Here we report on the calculated structures and properties, including thermodynamics, of several so-called “BON-BON” molecules.

- 1667-1676 **Structural and electronic properties of Z isomers of (4 α →6'',2 α →O→1'')-phenylflavans substituted with R=H, OH and OCH3 calculated in aqueous solution with PCM solvation model,**
Rosana Maria Lobayan [Universidad de la Cuenca del Plata], Erika N. Bentz, Alicia H. Jubert and Alicia B. Pomilio

In the search for new antioxidants, flavan structures called our attention, as substructures of many important natural compounds, including catechins (flavan-3-ols), simple and dimeric proanthocyanidins, and condensed tannins. In this work the conformational space of the Z-isomers of (4 α →6'', 2 α →O→1'')-phenylflavans substituted with R□=□H, OH and OCH3 was scanned in aqueous solution, simulating the solvent by the polarizable continuum model (PCM).

* * * * *

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1. APPLICATIONS

1.1. Small Molecules

Water and Solvation

Toward Temperature-Dependent Coarse-Grained Potentials of Side-Chain Interactions for Protein Folding Simulations. II. Molecular Dynamics Study of Pairs of Different Types of Interactions in Water at Various Temperatures

Emil Sobolewski, Stanisław Oldziej, Marta Wiśniewska, Adam Liwo, and Mariusz Makowski [University of Gdańsk]

J. Phys. Chem. B., **116**, 6844–6853, 2012.

By means of molecular dynamics simulations of 15 pairs of molecules selected to model the interactions of nonpolar, nonpolar and polar, nonpolar and charged, polar, and polar and charged side chains in water, we determined the potentials of mean force (PMFs) of pairs of interacting molecules in water as functions of distance between the interacting particles or their distance and orientations at three temperatures: 283, 323, and 373 K, respectively. For each pair of PMFs, entropic and energetic contributions have been discussed.

Medicinal Chemistry and Drug Design

Synthesis, biological evaluation and 3D-QSAR studies of novel 4,5-dihydro-1H-pyrazole niacinamide derivatives as BRAF inhibitors

Cui-Yun Li, Qing-Shan Li, Li Yan, Xiao-Guang Sun, Ran Wei, Hai-Bin Gong, Hai-Liang Zhu [Nanjing University]

Bioorg. and Med.Chem., **20**, 3746-3755, 2012.

A series of novel 4,5-dihydropyrazole derivatives containing niacinamide moiety as potential V600E mutant BRAF kinase (BRAF^{V600E}) inhibitors were designed and synthesized. Results of the bioassays against BRAF^{V600E} and WM266.4 human melanoma cell line showed several compounds to be endowed potent activities with IC₅₀ and GI₅₀ value in low micromolar range, among which compound **27e**, (5-(4-Chlorophenyl)-3-(4-methoxyphenyl)-4,5-dihydro-1H-pyrazol-1-yl)6-methylpyridin-3-yl methanone (IC₅₀ = 0.20 μM, GI₅₀ = 0.89 μM) was bearing the best bioactivity comparable with the positive control Sorafenib.



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Medicinal Chemistry and Drug Design (Cont'd)

Novel Substituted Benzothiophene and Thienothiophene Carboxanilides and Quinolones: Synthesis, Photochemical Synthesis, DNA-Binding Properties, Antitumor Evaluation and 3D-Derived QSAR Analysis

Maja Aleksić, Branimir Bertoša, Raja Nhili, Lidija Uzelac, Ivana Jarak, Sabine Depauw, Marie-Hélène David-Cordonnier, Marijeta Kralj, Sanja Tomić, and Grace Karminski-Zamola [University of Zagreb]

J. Med. Chem., **55**, 5044–5060, 2012.

A series of new N,N-dimethylaminopropyl- and 2-imidazolyl-substituted derivatives of benzo[b]thienyl- and thieno[2,3-b]thienylcarboxanilides and benzo[b]thieno[2,3-c]- and thieno[3',2':4,5]thieno[2,3-c]quinolones were prepared. Quinolones were prepared by the reaction of photochemical dehydrohalogenation of corresponding anilides. Carboxanilides and quinolones were tested for the antiproliferative activity. 2-Imidazolyl-substituted derivatives showed very prominent activity. By use of the experimentally obtained antitumor measurements, 3D-derived QSAR analysis was performed for the set of compounds.

Discovery of Selective LRRK2 Inhibitors Guided by Computational Analysis and Molecular Modeling

Huifen Chen [Genentech, Inc.], Bryan K. Chan, Jason Drummond, Anthony A. Estrada, Janet Gunzner-Toste, Xingrong Liu, Yichin Liu, John Moffat, Daniel Shore, Zachary K. Sweeney, Thuy Tran, Shumei Wang, Guiling Zhao, Haitao Zhu, and Daniel J. Burdick

J. Med. Chem., **55**, 5536–5545, 2012.

Mutations in the genetic sequence of leucine-rich repeat kinase 2 (LRRK2) have been linked to increased LRRK2 activity and risk for the development of Parkinson's disease (PD). Potent and selective small molecules capable of inhibiting the kinase activity of LRRK2 will be important tools for establishing a link between the kinase activity of LRRK2 and PD. In the absence of LRRK2 kinase domain crystal structures, a LRRK2 homology model was developed that provided robust guidance in the hit-to-lead optimization of small molecule LRRK2 inhibitors. Through a combination of molecular modeling, sequence analysis, and matched molecular pair (MMP) activity cliff analysis, a potent and selective lead inhibitor was discovered.

Extensive ligand-based modeling and in silico screening reveal nanomolar inducible nitric oxide synthase (iNOS) inhibitors

Ghadeer A.R.Y. Suaifan, Mayyada Shehadehh, Hebah Al-Ijel, Mutasem O. Taha [University of Jordan]

J. Mol. Graph. and Mod., **37**, 1-26, 2012.

Inducible nitric oxide synthase (iNOS) has been implicated in a variety of diseases prompting several attempts to discover and optimize new iNOS inhibitors. Accordingly, we explored the pharmacophoric space of 143 iNOS inhibitors. Subsequently, genetic algorithm and multiple linear regression analysis were employed to select an optimal combination of pharmacophoric models and 2D physicochemical descriptors to produce self-consistent quantitative structure–activity relationship (QSAR) of optimal predictive potential (correlation coefficient $r_{115} = 0.83$, $F = 23.92$, $r_{\text{Loo}}^2 = 0.61$, r_{PRESS}^2 against 28 external test inhibitors = 0.51).

Medicinal Chemistry and Drug Design (Cont'd)

Pharmacophore identification, docking and “in silico” screening for novel CDK1 inhibitors

Xiaowu Dong, Jingying Yan, Lilin Du, Peng Wu, Shufang Huang, Tao Liu, Yongzhou Hu [Zhejiang University]

J. Mol.Graph. and Mod., **37**, 77-86, 2012.

Pharmacophore models of cyclin-dependent kinase-1 (CDK1) inhibitors were established by using the Catalyst/HypoGen. The best pharmacophore model, Hypo1, consists of one hydrogen bond acceptor (HBA), one hydrogen bond donor (HBD), one hydrophobic (HY) and one ring aromatic (RA) feature. The validation results of Hypo1 through cost analysis, test set prediction, Fisher's cross method and receiver operating characteristic (ROC) study indicated that the Hypo1 was statistically valuable and reliable in identifying structural diverse CDK1 inhibitors. It is further supported by the consistent results from molecular docking studies.

Structural determinants of imidacloprid-based nicotinic acetylcholine receptor inhibitors identified using 3D-QSAR, docking and molecular dynamics

Qinfan Li, Xiangya Kong, Zhengtao Xiao, Yonghua Wang [Northwest A & F University], Lihui Zhang and Fangfang Wang, et al.

J. Mol.Mod., **18**, 2279-2289, 2012

Nicotinic acetylcholine receptor (nAChR) is a target for insect-selective neonicotinoid insecticides (NNs), exemplified by imidacloprid (IMI). In the present study, 78 IMI derivatives reported as inhibitors of *Drosophila melanogaster* nAChR (Dm-nAChR) and *Musca domestica* nAChR (Md-nAChR) were used for three-dimensional quantitative structure–activity relationship (3D-QSAR) studies. Two optimal models with good predictive power were obtained: $Q^2 = 0.64$, $R^2_{pred} = 0.72$ for Dm-nAChR, and $Q^2 = 0.63$, $R^2_{pred} = 0.62$ for Md-nAChR.

Pharmacophore modeling, molecular docking, QSAR, and in silico ADMET studies of gallic acid derivatives for immunomodulatory activity

Dharmendra Kumar Yadav, Feroz Khan [Central Institute of Medicinal and Aromatic Plants, Lucknow] and Arvind Singh Negi

J. Mol.Mod., **18**, 2513-2525, 2012

Immunomodulation refers to an alteration in the immune response due to the intrusion of foreign molecules into the body. In the present communication, QSAR and docking studies of gallic acid derivatives were performed in relation to their immunomodulatory activities. Screening through the use of a QSAR model suggested that the compounds G-4, G-7, G-9, G-10, G-12, and G-13 possess immunomodulatory activity. Activity was predicted using a statistical model developed by the forward stepwise multiple linear regression method.

Predicting functional residues of the *Solanum lycopersicum* aspartic protease inhibitor (SLAPI) by combining sequence and structural analysis with molecular docking

Yasel Guerra [Universidad de La Habana], Pedro A. Valiente, Colin Berry and Tirso Pons

J. Mol.Mod., **18**, 2673-2687, 2012

The *Solanum lycopersicum* aspartic protease inhibitor (SLAPI), which belongs to the STI-Kunitz family, is an effective inhibitor of the aspartic proteases human cathepsin D and *Saccharomyces* proteinase A. However, in contrast with the large number of studies on the inhibition mechanism of the serine proteases by the STI-Kunitz inhibitors, the structural aspects of the inhibition mechanism of aspartic proteases from this family of inhibitors are poorly understood. In the present study, we have combined sequence and structural analysis methods with protein-protein docking to gain a better understanding of the SLAPI inhibition mechanism of the proteinase A.

Medicinal Chemistry and Drug Design (Cont'd)

A specific pharmacophore model of sodium-dependent glucose co-transporter 2 (SGLT2) inhibitors

Chunlei Tang, Xiaoyun Zhu, Dandan Huang, Hai Qian [China Pharmaceutical University], Xin Zan and Baowei Yang, et al.

J. Mol.Mod., **18**, 2795-2804, 2012

Sodium-dependent glucose co-transporter 2 (SGLT2) plays a pivotal role in maintaining glucose equilibrium in the human body, emerging as one of the most promising targets for the treatment of diabetes mellitus type 2. Pharmacophore models of SGLT2 inhibitors have been generated with a training set of 25 SGLT2 inhibitors using Discovery Studio V2.1. The best hypothesis (Hypo1SGLT2) contains one hydrogen bond donor, five excluded volumes, one ring aromatic and three hydrophobic features, and has a correlation coefficient of 0.955, cost difference of 68.76, RMSD of 0.85.

Quantitative Structure-Activity Relations

A QSAR study of radical scavenging antioxidant activity of a series of flavonoids using DFT based quantum chemical descriptors – the importance of group frontier electron density

Ananda Sarkar, Tapas Ranjan Middy and Atish Dipnagar Jana [Behala College, Parnasree, Kolakata]

J. Mol.Mod., **18**, 2621-2631, 2012

In a pursuit of electronic level understanding of the antioxidant activity of a series of flavonoids, quantitative structure-activity relationship (QSAR) studies have been carried out using density functional theory (DFT) based quantum chemical descriptors. The best QSAR model have been selected for which the computed square correlation coefficient $r^2 = 0.937$ and cross-validated squared correlation coefficient $q^2 = 0.916$. The QSAR model indicates that hardness (η), group electrophilic frontier electron density (FAE) and group philicity (B^+) of individual molecules are responsible for in vitro biological activity.

Host-Guest Systems

How to simulate affinities for host–guest systems lacking binding mode information: application to the liquid chromatographic separation of hexabromocyclododecane stereoisomers

Vedat Durmaz [ZIB Zuse-Institut Berlin], Marcus Weber and Roland Becker

J. Mol.Mod., **18**, 2399-2408, 2012

A novel approach for the simulation of host–guest systems by systematically scanning the host molecule's orientations within the guest cavity is presented along with a thermodynamic strategy for determining preferential binding modes and corresponding optimal interaction energies between host and guest molecules. By way of example, the elution order of hexabromocyclododecane stereoisomers from high performance liquid chromatography separation on a permethylated β -cyclodextrin stationary phase has been computed using classical molecular dynamics simulations with the explicit solvents water and acetonitrile.

Host-Guest Systems (Cont'd)

Calculation of Host–Guest Binding Affinities Using a Quantum-Mechanical Energy Model

Hari S. Muddana and Michael K. Gilson [University of California San Diego]

J. Chem. Theor. and Comp., **8**, 2023–2033, 2012.

The prediction of protein–ligand binding affinities is of central interest in computer-aided drug discovery, but it is still difficult to achieve a high degree of accuracy. Recent studies suggesting that available force fields may be a key source of error motivate the present study, which reports the first mining minima (M2) binding affinity calculations based on a quantum mechanical energy model, rather than an empirical force field. We apply a semiempirical quantum-mechanical energy function, PM6-DH+, coupled with the COSMO solvation model, to 29 host–guest systems with a wide range of measured binding affinities.

Zeolites

Molecular simulation of water removal from simple gases with zeolite NaA

Éva Csányi, Zoltán Ható and Tamás Kristóf [University of Pannonia]

J. Mol.Mod., **18**, 2349-2356, 2012

Water vapor removal from some simple gases using zeolite NaA was studied by molecular simulation. The equilibrium adsorption properties of H₂O, CO, H₂, CH₄ and their mixtures in dehydrated zeolite NaA were computed by grand canonical Monte Carlo simulations. The simulations employed Lennard-Jones + Coulomb type effective pair potential models, which are suitable for the reproduction of thermodynamic properties of pure substances. Based on the comparison of the simulation results with experimental data for single-component adsorption at different temperatures and pressures, a modified interaction potential model for the zeolite is proposed.

Carbon Nanoparticles

Mutual Exclusivity in the Synthesis of High Crystallinity and High Yield Single-Walled Carbon Nanotubes

Hiroe Kimura, Don N. Futaba, Motoo Yumura, and Kenji Hata [Technology Research Association for Single Wall Carbon Nanotubes (TASC)]

J. Am. Chem. Soc., **134**, 9219–9224, 2012.

We report the mutually exclusive relationship between carbon nanotube (CNT) yield and crystallinity. Growth conditions were optimized for CNT growth yield and crystallinity through sequential tuning of three input variables: growth enhancer level, growth temperature, and carbon feedstock level. This optimization revealed that, regardless of the variety of carbon feedstock and growth enhancer, the optimum conditions for yield and crystallinity differed significantly with yield/crystallinity, preferring lower/higher growth temperatures and higher/lower carbon feedstock levels.

Carbon Nanoparticles (Cont'd)

Bulk Purification and Deposition Methods for Selective Enrichment in High Aspect Ratio Single-Walled Carbon Nanotubes

Nidhi P. Bhatt, Pornnipa Vichchulada, and Marcus D. Lay
[University of Georgia]

J. Am. Chem. Soc., **134**, 9352–9361, 2012.

Aqueous batch processing methods for the concurrent purification of single-walled carbon nanotube (SWNT) soot and enrichment in high aspect ratio nanotubes are essential to their use in a wide variety of electronic, structural, and mechanical applications. This manuscript presents a new route to the bulk purification and enrichment of unbundled SWNTs having average lengths in excess of 2 μm . Iterative centrifugation cycles at low centripetal force not only removed amorphous C and catalyst nanoparticles but also allowed the enhanced buoyancy of surfactant encapsulated, unbundled, high aspect ratio SWNTs to be used to isolate them in the supernatant.

1.2. Biopolymers

Bioinformatics and Cheminformatics

Expanding molecular modeling and design tools to non-natural sidechains

David Gfeller, Olivier Michielin [Swiss Institute of Bioinformatics (SIB)] and Vincent Zoete

J. Comp. Chem. **33**, 1525–1535, 2012.

Protein–protein interactions encode the wiring diagram of cellular signaling pathways and their deregulations underlie a variety of diseases, such as cancer. Inhibiting protein–protein interactions with peptide derivatives is a promising way to develop new biological and therapeutic tools. Here, we develop a general framework to computationally handle hundreds of non-natural amino acid sidechains and predict the effect of inserting them into peptides or proteins. We first generate all structural files (pdb and mol2), as well as parameters and topologies for standard molecular mechanics software (CHARMM and Gromacs).

Placevent: An algorithm for prediction of explicit solvent atom distribution—Application to HIV-1 protease and F-ATP synthase

Daniel J. Sindhikara, Norio Yoshida and Fumio Hirata
[Institute for Molecular Science, Okazaki]

J. Comp. Chem. **33**, 1536–1543, 2012.

We have created a simple algorithm for automatically predicting the explicit solvent atom distribution of biomolecules. The explicit distribution is coerced from the three-dimensional (3D) continuous distribution resulting from a 3D reference interaction site model (3D-RISM) calculation. This procedure predicts optimal location of solvent molecules and ions given a rigid biomolecular structure and the solvent composition. We show examples of predicting water molecules near the KNI-272 bound form of HIV-1 protease and predicting both sodium ions and water molecules near the rotor ring of F-adenosine triphosphate (ATP) synthase.

Bioinformatics and Cheminformatics (Cont'd)

Structural informatics, modeling, and design with an open-source Molecular Software Library (MSL)

Daniel W. Kulp, Sabareesh Subramaniam, Jason E. Donald, Brett T. Hannigan, Benjamin K. Mueller, Gevorg Grigoryan and Alessandro Senes [University of Wisconsin, Madison]

J. Comp. Chem. **33**, 1645–1661, 2012.

We present the Molecular Software Library (MSL), a C++ library for molecular modeling. MSL is a set of tools that supports a large variety of algorithms for the design, modeling, and analysis of macromolecules. Among the main features supported by the library are methods for applying geometric transformations and alignments, the implementation of a rich set of energy functions, side chain optimization, backbone manipulation, calculation of solvent accessible surface area, and other tools. MSL has a number of unique features, such as the ability of storing alternative atomic coordinates (for modeling) and multiple amino acid identities at the same backbone position (for design).

Molecular Docking Using the Molecular Lipophilicity Potential as Hydrophobic Descriptor: Impact on GOLD Docking Performance

Alessandra Nurisso, Juan Bravo, Pierre-Alain Carrupt [University of Geneva], and Antoine Daina

J. Chem. Infor. and Mod. **52**, 1319–1327, 2012.

GOLD is a molecular docking software widely used in drug design. In the initial steps of docking, it creates a list of hydrophobic fitting points inside protein cavities that steer the positioning of ligand hydrophobic moieties. These points are generated based on the Lennard-Jones potential between a carbon probe and each atom of the residues delimitating the binding site. To thoroughly describe hydrophobic regions in protein pockets and properly guide ligand hydrophobic moieties toward favorable areas, an in-house tool, the MLP filter, was developed and herein applied.

Protein Secondary Structure

Experiments and Comprehensive Simulations of the Formation of a Helical Turn

Gouri S. Jas, Wendy A. Hegefeld, Peter Májek, Krzysztof Kuczera, and Ron Elber [University of Texas at Austin]

J. Phys. Chem. B., **116**, 6598–6610, 2012.

We investigate the kinetics and thermodynamics of a helical turn formation in the peptide Ac-WAAAH-NH₂. NMR measurements indicate that this peptide has significant tendency to form a structure of a helical turn, while temperature dependent CD establishes the helix fraction at different temperatures. Molecular dynamics and milestoning simulations agree with experimental observables and suggest an atomically detailed picture for the turn formation.

Protein Structure Prediction

Ab initio protein structure assembly using continuous structure fragments and optimized knowledge-based force field

Dong Xu and Yang Zhang [University of Michigan]

Proteins: Stru. Fun. & Bioinf., **80**, 1715–1735, 2012.

Ab initio protein folding is one of the major unsolved problems in computational biology owing to the difficulties in force field design and conformational search. We developed a novel program, QUARK, for template-free protein structure prediction. Query sequences are first broken into fragments of 1–20 residues where multiple fragment structures are retrieved at each position from unrelated experimental structures. Full-length structure models are then assembled from fragments using replica-exchange Monte Carlo simulations, which are guided by a composite knowledge-based force field.

Comparative or Homology Modeling

Comparative homology modeling of pyruvate dehydrogenase kinase isozymes from *Xenopus tropicalis* reveals structural basis for their subfunctionalization

Alexander A. Tokmakov [Kobe University]

J. Mol.Mod., **18**, 2567-2576, 2012

Structural–functional divergence is responsible for the preservation of highly homologous genes. Protein functions affected by mutagenesis in divergent sequences require investigation on an individual basis. In the present study, comparative homology modeling and predictive bioinformatics analysis were used to reveal for the first time the subfunctionalization of two pyruvate dehydrogenase kinase (PDK) isozymes in the western clawed frog *Xenopus tropicalis*. Three-dimensional structures of the two proteins were built by homology modeling based on the crystal structures of mammalian PDKs.

The *Caenorhabditis elegans* DAF-12 nuclear receptor: Structure, dynamics, and interaction with ligands

Lautaro D. Alvarez, Pau Arroyo Mañez, Darío A. Estrin and Gerardo Burton [Ciudad Universitaria]

Proteins: Stru. Fun. & Bioinf., **80**, 1798–1809, 2012.

A structure for the ligand binding domain (LBD) of the DAF-12 receptor from *Caenorhabditis elegans* was obtained from the X-ray crystal structure of the receptor LBD from *Strongyloides stercoralis* bound to (25R)- Δ^7 -dafachronic acid (DA) (pdb:3GYU). The model was constructed in the presence of the ligand using a combination of Modeller, Autodock, and molecular dynamics (MD) programs, and then its dynamical behavior was studied by MD. A strong ligand binding mode (LBM) was found, with the three arginines in the ligand binding pocket (LBP) contacting the C-26 carboxylate group of the DA.

Protein Conformational Analysis

Spinor product computations for protein conformations

Pieter Chys and Pablo Chacón [Consejo Superior de Investigaciones Científicas]

J. Comp. Chem. **33**, 1717–1729, 2012.

Spinor operators in geometric algebra (GA) can efficiently describe conformational changes of proteins by ordered products that act on individual bonds and represent their net rotations. Backward propagation through the protein backbone yields all rotational spinor axes in advance allowing the efficient computation of atomic coordinates from internal coordinates. The introduced mathematical framework enables to efficiently manipulate and generate protein conformations to any arbitrary degree. Moreover, several new formulations in the context of rigid body motions are added.

Exploration of conformational transition in the aryl-binding site of human FXa using molecular dynamics simulations

Jing-Fang Wang [Shanghai Jiaotong University], Pei Hao, Yi-Xue Li, Jian-Liang Dai and Xuan Li

J. Mol.Mod., **18**, 2717-2725, 2012

Human coagulation Factor X (FX), a member of the vitamin K-dependent serine protease family, is a crucial component of the human coagulation cascade. Activated FX (FXa) participates in forming the prothrombinase complex on activated platelets to convert prothrombin to thrombin in coagulation reactions. In the current study, 30-ns MD simulations were performed on both the open and closed states of human FXa. Root mean squares (RMS) fluctuations showed that structural fluctuations concentrated on the loop regions of FXa, and the presence of a ligand in the closed system resulted in larger fluctuations of the gating residues.

Insights on P-Glycoprotein's Efflux Mechanism Obtained by Molecular Dynamics Simulations

Ricardo J. Ferreira, Maria-José U. Ferreira, and Daniel J. V. A. dos Santos [University of Lisbon]

J. Chem. Theor. and Comp., **8**, 1853–1864, 2012.

P-Glycoprotein (P-gp) is often involved in multidrug resistance (MDR) to the pharmacological action of a wide number of anticancer agents. In this article, a series of molecular dynamics simulations of murine's P-gp were developed, elucidating the importance of the lipid membrane and linker sequence in the protein structure stability. The behavior of several molecules inside the drug-binding pocket revealed a striking difference between substrates or modulators, and motion patterns were identified that could be correlated with conformational alterations due to substrate binding, corresponding to the initial step in the efflux mechanism.

Exploring Protein Flexibility: Incorporating Structural Ensembles From Crystal Structures and Simulation into Virtual Screening Protocols

David J. Osguthorpe, Woody Sherman, and Arnold T. Hagler [Shifa Biomedical]

J. Phys. Chem. B., **116**, 6952–6959, 2012.

The capacity of proteins to adapt their structure in response to various perturbations including covalent modifications, and interactions with ligands and other proteins plays a key role in biological processes. Here, we explore the ability of molecular dynamics (MD), replica exchange molecular dynamics (REMD), and a library of structures of crystal-ligand complexes, to sample the protein conformational landscape and especially the accessible ligand binding site geometry. The extent of conformational space sampled is measured by the diversity of the shapes of the ligand binding sites.

Protein Dynamics

Temperature-Enhanced Association of Proteins Due to Electrostatic Interaction: A Coarse-Grained Simulation of Actin–Myosin Binding

Kei-ichi Okazaki, Takato Sato, and Mitsunori Takano
[Waseda University]

J. Am. Chem. Soc., **134**, 8918–8925, 2012.

Despite the fundamental importance, the thermodynamic aspect of protein–protein binding, particularly the issues relating to the entropy change upon binding, remains elusive. The binding of actin and myosin, which are vital proteins in motility, is a typical example, in which two different binding mechanisms have been argued: the binding affinity increases with increasing temperature and with decreasing salt-concentration, indicating the entropy-driven binding and the enthalpy-driven binding, respectively. We conducted an in silico titration of the actin–myosin system by molecular dynamics simulation using a residue-level coarse-grained model, with particular focus on the role of the electrostatic interaction.

Conformational and stereoelectronic investigation of tryptamine. An AIM/NBO study

Rosana M. Lobayan [Universidad de la Cuenca del Plata],
María C. Pérez Schmit, Alicia H. Jubert and Arturo Vitale

J. Mol. Mod., **18**, 2577–2588, 2012

Due to the free radical scavenger properties of Tryptamine (TRA), as well as of others indole derivatives, it is in our interest to explore deeply the stereoelectronic aspects that would be relevant in their stabilization and antioxidant activity. In this work the conformational space of TRA was scanned using molecular dynamics complemented with functional density calculations at B3LYP/6-31++G** level. Twenty one conformers of lowest energy were obtained, their electronic distributions were analyzed at a higher calculation level, thus improving the basis set (B3LYP/6-311++G**).

Modeling the Interface between Islet Amyloid Polypeptide and Insulin-Based Aggregation Inhibitors: Correlation to Aggregation Kinetics and Membrane Damage

Hector Figueroa, Durgaprasad Peddi, Joshua M. Osborne, Brenan M. Wilson, Ranadheer Reddy Pesaru, Balakrishna Kurva, Swathi Ramaraju, Maria C. Milletti, and Deborah L. Heyl [Eastern Michigan University]

J. Chem. Infor. and Mod. **52**, 1298–1307, 2012.

Human islet amyloid polypeptide (hIAPP) forms cytotoxic fibrils in type-2 diabetes and insulin is known to inhibit formation of these aggregates. In this study, a series of insulin-based inhibitors were synthesized and assessed for their ability to slow aggregation and impact hIAPP-induced membrane damage. Computational studies were employed to examine the underlying mechanism of inhibition. Overall, all compounds were able to slow aggregation at sufficiently high concentrations (10× molar excess); however, only two peptides showed any inhibitory capability at the 1:1 molar ratio (EALYLV and VEALYLV).

Protein Dynamics (Cont'd)

Modeling Structural Flexibility of Proteins with Go-Models

Ping Jiang [University of Oklahoma] and Ulrich H. E. Hansmann

J. Chem. Theor. and Comp., **8**, 2127–2133, 2012.

Structure-based models are an efficient tool for folding studies of proteins since by construction their energy landscape is only minimally frustrated. However, their intrinsic drawback is a lack of structural flexibility as usually only one target structure is employed to construct the potentials. Hence, a Go-model may not capture differences in mutation-induced protein dynamics, if—as in the case of the disease-related A629P mutant of the Menkes protein ATP7A—the structural differences between mutant and wild type are small. We introduced three implementations of Go-models that take into account the flexibility of proteins in the NMR ensemble.

Initiation of the Reaction of Deamidation in Triosephosphate Isomerase: Investigations by Means of Molecular Dynamics Simulations

Ilke Ugur, Viktorya Aviyente, and Gerald Monard [Boğaziçi University]

J. Phys. Chem. B., **116**, 6288–6301, 2012.

Deamidation of asparagine is the spontaneous degradation of this residue into aspartic acid. The kinetics of this slow reaction is mainly dependent on the nature of the adjacent amino acid that follows asparagine in a peptide or protein primary sequence. In the homodimer triosephosphate isomerase (TPI), there are two main deamidation sites per subunit: Asn15–Gly16 and Asn71–Gly72 for which deamidation dynamics are known to be interrelated. We investigate the initiation of the deamidation reaction in TPI by means of MD. Simulations based on classical AMBER force field are performed in a 60 to 90 ns time scale.

Assembly of the Five-Way Junction in the Ribosomal Small Subunit Using Hybrid MD-Go Simulations

Ke Chen, John Eargle, Jonathan Lai, Hajin Kim, Sanjaya Abeyasirigunawardena, Megan Mayerle, Sarah Woodson, Taekjip Ha, and Zaida Luthey-Schulten [University of Illinois at Urbana–Champaign]

J. Phys. Chem. B., **116**, 6819–6831, 2012.

Assembly of the bacterial ribosomal small subunit (SSU) begins with the folding of the five-way junction upon interaction with the primary binding protein S4. This complex contains the largest contiguous molecular signature, which is a conserved feature in all bacterial 16S rRNAs. In a previous study, we used all-atom MD simulations to demonstrate that the co-evolving signature in the N-terminus of S4 is intrinsically disordered and capable of accelerating the binding process through a fly casting mechanism. In this paper, comparisons between the all-atom MD simulations and FRET experiments identify multiple metastable conformations of the naked five-way junction without the presence of S4.

Structural and Electrostatic Asymmetry at the Active Site in Typical and Atypical Peroxiredoxin Dimers

Freddie R. Salsbury, Jr., Ye Yuan, Michael H. Knaggs, Leslie B. Poole, and Jacquelyn S. Fetrow [Wake Forest University]

J. Phys. Chem. B., **116**, 6832–6843, 2012.

The peroxiredoxins (Prx) are ubiquitous peroxidases involved in important biological processes; however, details of their enzymatic mechanism remain elusive. To probe potential dynamics–function relationships, MD simulations and electrostatic calculations were performed on the atypical 2-cysteine thiol peroxidase (Tpx) from *Streptococcus pneumoniae* and results compared to a previous study of a typical 2-cysteine Prx from *Trypanosoma cruzi*. The analyses indicate a commonality between both typical and atypical Prx: dynamic asymmetry.

Protein Dynamics (Cont'd)

Improved Atomistic Monte Carlo Simulations Demonstrate That Poly-l-Proline Adopts Heterogeneous Ensembles of Conformations of Semi-Rigid Segments Interrupted by Kinks

Aditya Radhakrishnan, Andreas Vitalis, Albert H. Mao, Adam T. Steffen, and Rohit V. Pappu [Washington University in St. Louis]

J. Phys. Chem. B., **116**, 6862–6871, 2012.

Poly-l-proline (PLP) polymers are useful mimics of biologically relevant proline-rich sequences. Biophysical and computational studies of PLP polymers in aqueous solutions are challenging because of the diversity of length scales and the slow time scales for conformational conversions. We describe an atomistic simulation approach that combines an improved ABSINTH implicit solvation model, with conformational sampling based on standard and novel Metropolis Monte Carlo moves. Refinements to forcefield parameters were guided by published experimental data for proline-rich systems.

Homodimerization of the PAS-B Domains of Hypoxia-Inducible Factors

Jing Zhu, Maria Martinez-Yamout, Rosa Cardoso, Jiangli Yan, Robert A. Love, Neil Grodsky, Alexei Brooun, and H. Jane Dyson [The Scripps Research Institute]

J. Phys. Chem. B., **116**, 6960–6965, 2012.

The Per-Arnt-Sim (PAS) domains of hypoxia-inducible transcription factors (HIF) mediate heterodimer formation between the HIF- α forms that are induced in the event of cellular hypoxia and the constitutive HIF- β variants. Previous efforts toward structural characterization of the HIF-1 α PAS domains were limited by protein stability. Using homology modeling based on the published crystal structure of the PAS-B domain of the homologous protein HIF-2 α in complex with the partner HIF- β (also known as ARNT), we have identified a variant of HIF-1 α with improved solubility, monodispersity, and stability.

From Coarse-Grained to Atomic-Level Characterization of Protein Dynamics: Transition State for the Folding of B Domain of Protein A

Sebastian Kmiecik, Dominik Gront, Maksim Kouza, and Andrzej Kolinski [University of Warsaw]

J. Phys. Chem. B., **116**, 7026–7032, 2012.

Atomic-level molecular dynamics simulations are widely used for the characterization of the structural dynamics of proteins; however, they are limited to shorter time scales than the duration of most of the relevant biological processes. Properly designed coarse-grained models that trade atomic resolution for efficient sampling allow access to much longer time-scales. In-depth understanding of the structural dynamics, however, must involve atomic details. In this study, we tested a method for the rapid reconstruction of all-atom models from α carbon atom positions in the application to convert a coarse-grained folding trajectory of a well described model system: the B domain of protein A.

Exploring the essential collective dynamics of interacting proteins: Application to prion protein dimers

Bilkiss B. Issack, Mark Berjanskii, David S. Wishart and Maria Stepanova [National Institute for Nanotechnology, Edmonton AB]

Proteins: Stru. Fun. & Bioinf., **80**, 1847–1865, 2012.

Essential collective dynamics is a promising and robust approach for analysing the slow motions of macromolecules from short molecular dynamics trajectories. In this study, an extension of the method to treat a collection of interacting protein molecules is presented. The extension is applied to investigate the effects of dimerization on the collective dynamics of ovine prion protein molecules in two different arrangements. Examination of the structural plasticity shows that aggregation has a restricting effect on the local mobility of the prion protein molecules in the interfacial regions.

Ligand Binding/Docking

Dual inhibition of chaperoning process by taxifolin: Molecular dynamics simulation study

Sharad Verma, Amit Singh, Abha Mishra [Banaras Hindu University]

J. Mol.Graph. and Mod., **37**, 27-38, 2012.

Hsp90 (heat shock protein 90), a molecular chaperone, stabilizes more than 200 mutated and over expressed oncogenic proteins in cancer development. Cdc37 (cell division cycle protein 37), a co-chaperone of Hsp90, has been found to facilitate the maturation of protein kinases by acting as an adaptor and load these kinases onto the Hsp90 complex. Taxifolin (a natural phytochemical) was found to bind at ATP-binding site of Hsp90 and stabilized the inactive “open” or “lid-up” conformation as evidenced by molecular dynamic simulation.

Molecular basis of the initial platelet adhesion in arterial thrombosis: Molecular dynamics simulations

Jian Li, Lin Zhang, Yan Sun [Tianjin University]

J. Mol.Graph. and Mod., **37**, 49-58, 2012.

Molecular interactions between the von Willebrand factor (VWF) A1 domain and glycoprotein Iba (GPIba) promote the initial adhesion of platelets and subsequent arterial thrombus formation. However, little is understood about the interactions at a molecular level. Therefore, the binding dynamics and involved molecular interactions between VWF A1 domain and GPIba in both water and physiological saline are investigated using molecular dynamics simulations and all-atom models. Faster binding is observed in water than that in physiological saline, and patches of opposite charges are observed at the binding interface.

Exploration of the valproic acid binding site on histone deacetylase 8 using docking and molecular dynamic simulations

Jorge Antonio Bermúdez-Lugo, Oscar Perez-Gonzalez, Martha Cecilia Rosales-Hernández, Ian Ilizaliturri-Flores and José Trujillo-Ferrara, Jose Correa-Basurto [Instituto Politécnico Nacional].

J. Mol.Mod., **18**, 2301-2310, 2012

Epigenetic therapy is an important focus of research for drug development in the treatment of cancer. Valproic acid (VPA) is an HDAC inhibitor that has been evaluated in clinical studies. Despite its success in treating cancer, the mechanism of inhibition of VPA in HDAC is unknown. To this end, we have used docking and molecular dynamic simulations to investigate VPA binding to HDAC, employing both native and rebuilt 3-D structures. The results showed that VPA, via its carboxyl group, coordinates the Zn atom and other local residues (H141-142 and Y360) located at the catalytic site (CS) of HDAC.

Mapping multiple potential ATP binding sites on the matrix side of the bovine ADP/ATP carrier by the combined use of MD simulation and docking

Daniele Di Marino, Francesco Oteri, Blasco Morozzo della Rocca, Ilda D'Annessa and Mattia Falconi [Via della Ricerca Scientifica]

J. Mol.Mod., **18**, 2377-2386, 2012

The mitochondrial adenosine diphosphate/adenosine triphosphate (ADP/ATP) carrier—AAC—was crystallized in complex with its specific inhibitor carboxyatractyloside (CATR). The protein consists of a six-transmembrane helix bundle that defines the nucleotide translocation pathway, which is closed towards the matrix side due to sharp kinks in the odd-numbered helices. In this paper, we describe the interaction between the matrix side of the AAC transporter and the ATP4⁻ molecule using carrier structures obtained through classical molecular dynamics simulation (MD) and a protein–ligand docking procedure.

Ligand Binding / Docking (Cont'd)

Molecular dynamics simulation studies of betulinic acid with human serum albumin

Chandramouli Malleda, Navjeet Ahalawat, Mahesh Gokara and Rajagopal Subramanyam [University of Hyderabad]

J. Mol.Mod., **18**, 2589-2597, 2012

Betulinic acid (BA) is a naturally occurring pentacyclic triterpenoid possessing anti-retroviral, anti-cancer, and anti-inflammatory properties. Here, we studied the interaction of BA with human serum albumin (HSA) by using molecular docking, and molecular dynamic simulation methods. Molecular docking studies revealed that BA can bind in the large hydrophobic cavity of drug binding site I of sub-domain IIA and IIB, mainly by the hydrophobic interactions and also by hydrogen bond interactions.

Exploration of the binding of curcumin analogues to human P450 2C9 based on docking and molecular dynamics simulation

Rongwei Shi, Yin Wang, Xiaolei Zhu [Nanjing University of Technology] and Xiaohua Lu

J. Mol.Mod., **18**, 2599-2611, 2012

Molecular docking and molecular dynamics (MD) simulations are used to investigate the interactions of curcumin analogues (CAs) with human cytochrome P450 2 C9 (CYP2C9 or 2 C9) and the conformations of their binding sites. In order to examine conformations of CAs/2 C9 and interaction characteristics of their binding sites, RMSDs, RMSFs, and B-factors are computed, and electrostatic and hydrophobic interactions between CAs and 2 C9 are analyzed and discussed. Results demonstrate that the most CAs studied lie 4~15 Å above the heme of CYP2C9.

Aminoglycoside induced nephrotoxicity: molecular modeling studies of calreticulin-gentamicin complex

Gururao Hariprasad, Manoj Kumar, Komal Rani, Punit Kaur and Alagiri Srinivasan [All India Institute of Medical Sciences]

J. Mol.Mod., **18**, 2645-2652, 2012

Gentamicin is a member of aminoglycoside group of broad spectrum antibiotics. It impairs protein synthesis by binding to A site of the 30S subunit of bacterial ribosomes. One of the main side effects of this drug is nephrotoxicity. The drug is known to bind to calreticulin, a chaperone essential for the folding of glycosylated proteins. We provide a detailed structural insight of the calreticulin-gentamicin complex by molecular modeling and the binding of the drug in the presence of explicit solvent was analyzed by molecular dynamics simulation.

Elements of Nucleotide Specificity in the Trypanosoma brucei Mitochondrial RNA Editing Enzyme RET2

Özlem Demir and Rommie E. Amaro [University of California, San Diego]

J.Chem. Infor. and Mod. **52**, 1308–1318, 2012.

The causative agent of African sleeping sickness, *Trypanosoma brucei*, undergoes an unusual mitochondrial RNA editing process that is essential for its survival. RNA editing terminal uridylyl transferase 2 of *T. brucei* (TbRET2) is an indispensable component of the editosome machinery that performs this editing. Neither the exclusive requirement of uridine 5'-triphosphate (UTP) for catalysis, nor the RNA primer preference of TbRET2 is well-understood. Using all-atom explicitly solvated molecular dynamics (MD) simulations, we investigated the effect of UTP binding on TbRET2 structure and dynamics, as well as the determinants governing TbRET2's exclusive UTP preference.

Ligand Binding / Docking (Cont'd)

Validation of the AmpC β -Lactamase Binding Site and Identification of Inhibitors with Novel Scaffolds

Fung-Yi Chan, Marco A. C. Neves, Ning Sun, Man-Wah Tsang, Yun-Chung Leung, Tak-Hang Chan, Ruben Abagyan, and Kwok-Yin Wong [The Hong Kong Polytechnic University]

J.Chem. Infor. and Mod. **52**, 1367–1375, 2012.

AmpC β -lactamase confers resistance to β -lactam antibiotics in multiple Gram-negative bacteria. Therefore, identification of non- β -lactam compounds that inhibit the enzyme is considered crucial to the development of novel antibacterial therapies. Given the highly solvent-exposed active site, it is important to study the induced-fit movements and water-mediated interactions to improve docking accuracy and virtual screening enrichments in structure-based design of new AmpC inhibitors. Here, we tested multiple models of the AmpC binding site to investigate the importance of conserved water molecules and binding site plasticity on molecular docking.

Recognition of Cello-Oligosaccharides by CBM17 from *Clostridium cellulovorans*: Molecular Dynamics Simulation

Ruyin Cao, Yongdong Jin, and Dingguo Xu [Sichuan University]

J. Phys. Chem. B., **116**, 6087–6096, 2012.

The basic function of carbohydrate binding module (CBM) is believed to enhance local concentration of glycosidases on the carbohydrate molecule, and thus facilitates the subsequent degradation of carbohydrate. Full understanding of the recognition mechanism of carbohydrates by CBM can be helpful to enhance the enzyme activity. In this work, the detailed recognition specificity of two soluble cello-oligosaccharide substrates, cellotetraose and cellohexaose, by a family 17 CBM from *Clostridium cellulovorans* was investigated by molecular dynamics simulation.

Delineation of the Unbinding Pathway of α -Conotoxin ImI from the $\alpha 7$ Nicotinic Acetylcholine Receptor

Rilei Yu, Quentin Kaas, and David J. Craik [The University of Queensland, Brisbane]

J. Phys. Chem. B., **116**, 6097–6105, 2012.

α -Conotoxins potently and specifically inhibit isoforms of nicotinic acetylcholine receptors (nAChRs) and are used as molecular probes and as drugs or drug leads. Interactions occurring during binding and unbinding events are linked to binding kinetics, and knowledge of these interactions could help in the development of α -conotoxins as drugs. Here, the unbinding process for the prototypical α -conotoxin ImI/ $\alpha 7$ -nAChR system was investigated theoretically, and three exit routes were identified using random accelerated molecular dynamics simulations.

Enzyme Catalysis

Stereoselection in the diels–alderase ribozyme: A molecular dynamics study

Tomasz Bereźniak, Andres Jäschke, Jeremy C. Smith and Petra Imhof [University of Heidelberg]

J. Comp. Chem. **33**, 1603–1614, 2012.

The Diels-Alderase ribozyme is an in vitro-evolved ribonucleic acid enzyme that catalyzes a [4 + 2] cycloaddition reaction between an anthracene diene and a maleimide dienophile. The ribozyme can in principle be used to selectively synthesize only one product enantiomer, depending on which of the two entrances to the catalytic pocket, “front” or “back”, the substrate is permitted to use. Here, we investigate stereoselection and substrate recognition in the ribozyme by means of multiple molecular dynamics simulations, performed on each of the two substrates individually in the pocket, on the reactant state, and on the product state.

Enzyme Catalysis (Cont'd)

QM/MM study of catalytic mechanism of Xylanase Cex from *Cellulomonas fimi*

Jingli Liu, Chunchun Zhang, Dingguo Xu [Sichuan University]

J. Mol. Graph. and Mod., **37**, 67-76, 2012.

Xylanase Cex from *Cellulomonas fimi* is a bifunctional enzyme that catalyzes the degradation of both cellulose and xylan. As a result, it might find valuable applications in production of biofuels. In this work, we presented a detailed theoretical investigation of hydrolysis of the xylopentaose molecule catalyzed by Cex, using a hybrid quantum mechanical and molecular mechanical approach. Our results support the experimental observation that the hydrolysis proceeds via the net retention mechanism.

Conserved water-mediated H-bonding dynamics of catalytic His159 and Asp158: insight into a possible acid–base coupled mechanism in plant thiol protease

Tapas K. Nandi, Hridoy R. Bairagya, Bishnu P. Mukhopadhyay [National Institute of Technology, Durgapur], Payel Mallik and Dipankar Sukul, et al.

J. Mol. Mod., **18**, 2633-2644, 2012

Cysteine protease is ubiquitous in nature. Excess activity of this enzyme causes intercellular proteolysis, muscle tissue degradation, etc. The role of water-mediated interactions in the stabilization of catalytically significant Asp158 and His159 was investigated by performing molecular dynamics simulation studies of 16 three-dimensional structures of plant thiol proteases. In the simulated structures, the hydrophilic W1, W2 and WD1 centers form hydrogen bonds with the OD1 atom of Asp158 and the ND1 atom of His159.

Global and local molecular dynamics of a bacterial carboxylesterase provide insight into its catalytic mechanism

Xiaozhen Yu, Sara C. Sigler, Delwar Hossain, Randy M. Wadkins [University of Mississippi], Monika Wierdl and Steven R. Gwaltney, et al.

J. Mol. Mod., **18**, 2869-2883, 2012

Carboxylesterases (CEs) are ubiquitous enzymes responsible for the detoxification of xenobiotics. In humans, substrates for these enzymes are far-ranging, and include the street drug heroin and the anticancer agent irinotecan. Hence, their ability to bind and metabolize substrates is of broad interest to biomedical science. In this study, we focused our attention on dynamic motions of a CE from *B. subtilis* (pnbCE), with emphasis on the question of what individual domains of the enzyme might contribute to its catalytic activity. We used a 10 ns all-atom molecular dynamics simulation, normal mode calculations, and enzyme kinetics to understand catalytic consequences of structural changes within this enzyme.

Molecular modeling of formate dehydrogenase: the formation of the Michaelis complex

Dmitry K. Nilov, Ivan G. Shabalin, Vladimir O. Popov & Vytas K. Švedas [Lomonosov Moscow State University]

J. Biomol. Stru. and Dyn., **30**, 170-179, 2012.

The formation of the reactive enzyme–substrate complex of formate dehydrogenase has been investigated by molecular dynamics techniques accounting for different conformational states of the enzyme. Simulations revealed that the transport of substrate to the active site through the substrate channel proceeds in the open conformation of enzyme due to the crucial role of the Arg284 residue acting as a vehicle. However, formate binding in the active site of the open conformation leads to the formation of a nonproductive enzyme–substrate complex.

Enzyme Catalysis (Cont'd)

Protonation States of the Catalytic Dyad of β -Secretase (BACE1) in the Presence of Chemically Diverse Inhibitors: A Molecular Docking Study

Arghya Barman and Rajeev Prabhakar [University of Miami]

J.Chem. Infor. and Mod. **52**, 1275–1287, 2012.

In this molecular docking study, the protonation states of the catalytic Asp dyad of the beta-secretase (BACE1) enzyme in the presence of eight chemically diverse inhibitors have been predicted. BACE1 catalyzes the rate-determining step in the generation of Alzheimer amyloid beta peptides and is widely considered as a promising therapeutic target. All the inhibitors were redocked into their corresponding X-ray structures using a combination of eight different protonation states of the Asp dyad for each inhibitor.

Catalytic Mechanism of 4-Oxalocrotonate Tautomerase: Significances of Protein–Protein Interactions on Proton Transfer Pathways

Pan Wu, G. Andrés Cisneros, Hao Hu, Robin Chaudret, Xiangqian Hu, and Weitao Yang [Duke University]

J. Phys. Chem. B., **116**, 6889–6897, 2012.

4-Oxalocrotonate tautomerase (4-OT), a member of tautomerase superfamily, is an essential enzyme in the degradative metabolism pathway occurring in the Krebs cycle. The proton transfer process catalyzed by 4-OT has been explored previously using both experimental and theoretical methods; however, the elaborate catalytic mechanism of 4-OT still remains unsettled. By combining classical molecular mechanics with quantum mechanics, our results demonstrate that the native hexameric 4-OT enzyme, including six protein monomers, must be employed to simulate the proton transfer process in 4-OT due to protein–protein steric and electrostatic interactions.

Substrate and Enzyme Functional Groups Contribute to Translational Quality Control by Bacterial Prolyl-tRNA Synthetase

Sandeep Kumar, Mom Das, Christopher M. Hadad, and Karin Musier-Forsyth [The Ohio State University]

J. Phys. Chem. B., **116**, 6991–6999, 2012.

Aminoacyl-tRNA synthetases activate specific amino acid substrates and attach them via an ester linkage to cognate tRNA molecules. In addition to cognate proline, prolyl-tRNA synthetase (ProRS) can activate cysteine and alanine and misacylate tRNA^{Pro}. An editing domain (INS) appended to bacterial ProRS selectively hydrolyzes Ala-tRNA^{Pro}, whereas Cys-tRNA^{Pro} is cleared by a freestanding editing domain, YbaK, through a unique mechanism involving substrate sulfhydryl chemistry. The detailed mechanism of catalysis by INS is currently unknown. To understand the alanine specificity and mechanism of catalysis by INS, we have explored several possible mechanisms of Ala-tRNA^{Pro} deacylation via hybrid QM/MM calculations.

Membrane Proteins and Lipid Peptide Interactions

The Influenza Fusion Peptide Adopts a Flexible Flat V Conformation in Membranes

Sébastien Légaré, Patrick Lagüe [Université Laval]

Biophysical Journal. **102**, 2270–2278, 2012.

Knowledge about the influenza fusion peptide (FP) membrane insertion mode is crucial for understanding its fusogenic mechanism. NMR and electron paramagnetic resonance experiments showed that in micelles, the FP inserted as a fixed-angle inverted V. In membranes, however, it was shown to insert as a straight α -helix (by molecular-dynamics simulations) and to adopt multiple kinked conformations (by solid-state NMR). In this work we performed explicit-solvent molecular-dynamics simulations of the influenza FP, and its F9A and W14A mutants, in POPC membranes.

Hydrophobic Mismatch and Lipid Sorting Near OmpA in Mixed Bilayers: Atomistic and Coarse-Grained Simulations

Fuchang Yin, James T. Kindt [Emory University]

Biophysical Journal. **102**, 2279–2287, 2012.

To understand the effects of lipid composition on membrane protein function in a mixture as complex as a biomembrane, one must know whether the lipid composition local to the protein differs from the mean lipid composition. In this study, we simulated the transmembrane domain of a β -barrel protein, OmpA, in mixtures of lipids of different tail lengths under conditions of negative hydrophobic mismatch, i.e., local bilayer thinning. We modeled the influence of OmpA on the local lipid composition both at a coarse-grained (CG) resolution using conventional molecular dynamics.

Comparison of Molecular Dynamics with Classical Density Functional and Poisson–Boltzmann Theories of the Electric Double Layer in Nanochannels

Jonathan W. Lee, Robert H. Nilson, Jeremy A. Templeton [Sandia National Laboratories], Stewart K. Griffiths, Andy Kung, and Bryan M. Wong

J. Chem. Theor. and Comp, **8**, 2012–2022, 2012.

Comparisons are made among Molecular Dynamics (MD), Classical Density Functional Theory (c-DFT), and Poisson–Boltzmann (PB) modeling of the electric double layer (EDL) for the nonprimitive three component model (3CM) in which the two ion species and solvent molecules are all of finite size. Unlike previous comparisons between c-DFT and Monte Carlo (MC), the present 3CM incorporates Lennard-Jones interactions rather than hard-sphere and hard-wall repulsions. c-DFT and MD results are compared over normalized surface charges ranging from 0.2 to 1.75 and bulk ion concentrations from 10 mM to 1 M.

Protein–Ligand Binding Free Energies from Exhaustive Docking

Enrico O. Purisima [National Research Council of Canada] and Hervé Hogues

J. Phys. Chem. B., **116**, 6872–6879, 2012.

We explore the use of exhaustive docking as an alternative to Monte Carlo and molecular dynamics sampling for the direct integration of the partition function for protein–ligand binding. We enumerate feasible poses for the ligand and calculate the Boltzmann factor contribution of each pose to the partition function. From the partition function, the free energy, enthalpy, and entropy can be derived. All our calculations are done with a continuum solvation model that includes solving the Poisson equation.

Protein Folding

The Folding Transition State of Protein L Is Extensive with Nonnative Interactions (and Not Small and Polarized)

Tae Yeon Yoo, Aashish Adhikari, Zhen Xia, Tien Huynh, Karl F. Freed, Ruhong Zhou, Tobin R. Sosnick [University of Chicago, Chicago]

J. Molec. Bio. **420**, 220-234, 2012.

Progress in understanding protein folding relies heavily upon an interplay between experiment and theory. In particular, readily interpretable experimental data that can be meaningfully compared to simulations are required. According to standard mutational ϕ analysis, the transition state for Protein L contains only a single hairpin. However, we demonstrate here using ψ analysis with engineered metal ion binding sites that the transition state is extensive, containing the entire four-stranded β sheet.

Effects of Mutation, Truncation, and Temperature on the Folding Kinetics of a WW Domain

Gia G. Maisuradze, Rui Zhou, Adam Liwo, Yi Xiao, Harold A. Scheraga [Cornell University, Ithaca]

J. Molec. Bio. **420**, 350-365, 2012.

The purpose of this work is to show how mutation, truncation, and change of temperature can influence the folding kinetics of a protein. This is accomplished by principal component analysis of molecular-dynamics-generated folding trajectories of the triple β -strand WW domain from formin binding protein 28 (FBP28) (Protein Data Bank ID: 1E0L) and its full-size, and singly- and doubly-truncated mutants at temperatures below and very close to the melting point. The reasons for biphasic folding kinetics [i.e., coexistence of slow (three-state) and fast (two-state) phases], including the involvement of a solvent-exposed hydrophobic cluster and another delocalized hydrophobic core in the folding kinetics, are discussed.

Effect of the thermostat in the molecular dynamics simulation on the folding of the model protein chignolin

Carlos A. Fuzo [Universidade de São Paulo] and Léo Degreè

J. Mol.Mod., **18**, 2785-2794, 2012

Molecular dynamics simulations of the model protein chignolin with explicit solvent were carried out, in order to analyze the influence of the Berendsen thermostat on the evolution and folding of the peptide. The dependence of the peptide behavior on temperature was tested with the commonly employed thermostat scheme consisting of one thermostat for the protein and another for the solvent. The thermostat coupling time of the protein was increased to infinity, when the protein is not in direct contact with the thermal bath, a situation known as minimally invasive thermostat.

Computational investigation of the effect of thermal perturbation on the mechanical unfolding of titin I27

Navneet Bung and U. Deva Priyakumar [International Institute of Information Technology, Hyderabad]

J. Mol.Mod., **18**, 2823-2829, 2012

The emergence of single-molecule force measurement experiments has facilitated a better understanding of protein folding pathways and the thermodynamics involved. Computational methods such as steered molecular dynamics (SMD) simulations are helpful in providing atomistic level information on the unfolding pathways. In this study, we report results from extensive computations (a total of about 60 SMD simulations with a total length of about 0.4 μ s) that address the effect of thermal perturbation on the mechanical stability of the I27 domain of the protein titin.

Protein Folding (Cont'd)

Dynamics of Metastable β -Hairpin Structures in the Folding Nucleus of Amyloid β -Protein

L. Cruz [Drexel University], J. Srinivasa Rao, D. B. Teplow, and B. Urbanc

J. Phys. Chem. B., **116**, 6311–6325, 2012.

The amyloid β -protein ($A\beta$), which is present predominately as a 40- or 42-residue peptide, is postulated to play a seminal role in the pathogenesis of Alzheimer's disease (AD). Folding of the $A\beta_{21-30}$ decapeptide region is a critical step in the aggregation of $A\beta$. We report results of constant temperature all-atom molecular dynamics simulations in explicit water of the dynamics of monomeric $A\beta_{21-30}$ and its Dutch [Glu22Gln], Arctic [Glu22Gly], and Iowa [Asp23Asn] isoforms that are associated with familial forms of cerebral amyloid angiopathy and AD.

Folding Simulations of the A and B Domains of Protein G

Maksim Kouza and Ulrich H. E. Hansmann [Michigan Technological University]

J. Phys. Chem. B., **116**, 6645–6653, 2012.

We study wild type and mutants of the A and B domain of protein G using all-atom Go-models. Our data substantiate the usefulness of such simulation for probing the folding mechanism of proteins and demonstrate that multifunnel versions of such models also allow probing of more complicated funnel landscapes. In our case, such models reproduce the experimentally observed distributions of the GA98 and GB98 mutants which differ only by one residue but fold into different structures. They also reveal details on the folding mechanism in these two proteins.

A Simple Model Predicts Experimental Folding Rates and a Hub-Like Topology

Thomas J. Lane and Vijay S. Pande [Stanford University]

J. Phys. Chem. B., **116**, 6764–6774, 2012.

A simple model is presented that describes general features of protein folding, in good agreement with experimental results and detailed all-atom simulations. Starting from microscopic physics, and with no free parameters, this model predicts that protein folding occurs remarkably quickly because native-like states are kinetic hubs. A hub-like network arises naturally out of microscopic physical concerns, specifically the kinetic longevity of native contacts during a search of globular conformations.

Mirror Images as Naturally Competing Conformations in Protein Folding

Jeffrey K. Noel, Alexander Schug, Abhinav Verma, Wolfgang Wenzel, Angel E. Garcia, and José N. Onuchic [Rice University]

J. Phys. Chem. B., **116**, 6880–6888, 2012.

Evolution has selected a protein's sequence to be consistent with the native state geometry, as this configuration must be both thermodynamically stable and kinetically accessible to prevent misfolding and loss of function. In simple protein geometries, such as coiled-coil helical bundles, symmetry produces a competing, globally different, near mirror image with identical secondary structure and similar native contact interactions. Here, we want to clarify whether the native fold and mirror image are energetically competitive by investigating the free energy landscape of three-helix bundles.

Protein Folding (Cont'd)

Folding Models of Mini-Protein FSD-1

In-Ho Lee, Seung-Yeon Kim, and Jooyoung Lee [Korea Institute for Advanced Study]

J. Phys. Chem. B., **116**, 6916–6922, 2012.

We have carried out all-atom action-derived molecular dynamics (ADMD) folding simulations of the full-size FSD-1. FSD-1 is a designed mini-protein of 28 residues containing both α and β secondary structure elements. Multiple folding pathways are found for FSD-1, which is consistent with existing computational studies. Hydrophobic collapse is observed first, and then subsequent folding events proceeds by forming either α -helix or β -hairpin. Concurrent formation of the full tertiary structure and the secondary structure elements of α -helix and β -hairpin is observed.

Protein-Nucleic acid Interactions

Calculating the Na⁺ translocating V-ATPase catalytic site affinity for substrate binding by homology modeled NtpA monomer using molecular dynamics/free energy calculation

Zahed Muhammed, Satoshi Arai, Shinya Saijo, Ichiro Yamato, Takeshi Murata, Atsushi Suenaga [Tokyo University of Science]

J. Mol. Graph. and Mod., **37**, 59-66, 2012.

Vacuolar ATPase (V-ATPase) of *Enterococcus hirae* is composed of a soluble catalytic domain (V₁; NtpA₃-B₃-D-G) and an integral membrane domain (V₀; NtpI-K₁₀) connected by a central and two peripheral stalks (NtpC, NtpD-G and NtpE-F). Recently nucleotide binding of catalytic NtpA monomer has been reported (Arai et al. [19]). In the present study, we calculated the nucleotide binding affinity of NtpA by molecular dynamics (MD) simulation/free energy calculation using MM-GBSA approach based on homology modeled structure of NtpA monomer docked with ATP analogue, adenosine 5'-[β , γ -imido] triphosphate (AMP-PNP).

A protein-RNA docking benchmark (II): Extended set from experimental and homology modeling data

Laura Pérez-Cano, Brian Jiménez-García and Juan Fernández-Recio [Barcelona Supercomputing Center (BSC)]

Proteins: Stru. Fun. & Bioinf., **80**, 1872–1882, 2012.

We present here an extended protein–RNA docking benchmark composed of 71 test cases in which the coordinates of the interacting protein and RNA molecules are available from experimental structures, plus an additional set of 35 cases in which at least one of the interacting subunits is modeled by homology. All cases in the experimental set have available unbound protein structure, and include five cases with available unbound RNA structure, four cases with a pseudo-unbound RNA structure, and 62 cases with the bound RNA form. The additional set of modeling cases comprises five unbound-model, eight model-unbound, 19 model-bound, and three model-model protein–RNA cases.

Nucleic Acids

Nucleosome Dynamics between Tension-Induced States

Laleh Mollazadeh-Beidokhti [Institute for Advanced Studies in Basic Sciences, Zanjan], Farshid Mohammad-Rafiee, Helmut Schiess

Biophysical Journal. **102**, 2235–2240, 2012.

We studied the dynamical behavior of a mononucleosome under tension using a theoretical model that takes into account the nucleosomal geometry, DNA elasticity, nonspecific DNA-protein binding, and effective repulsion between the two DNA turns. Using a dynamical Monte-Carlo simulation algorithm, we demonstrate that this model shows a behavior that for an appropriate set of parameters is in quantitative agreement with data from micromanipulation experiments on individual nucleosomes.

DNA–Water Interactions Distinguish Messenger RNA Genes from Transfer RNA Genes

Garima Khandelwal and B. Jayaram [Indian Institute of Technology Delhi]

J. Am. Chem. Soc., **134**, 8814–8816, 2012.

Physicochemical properties of DNA sequences as a guide to developing insights into genome organization has received little attention. Here, we utilize the energetics of DNA to further advance the knowledge on its language at a molecular level. Specifically, we ask the question whether physicochemical properties of different functional units on genomes differ. We extract intramolecular and solvation energies of different DNA base pair steps from a comprehensive set of molecular dynamics simulations. We then investigate the solvation behavior of DNA sequences coding for mRNAs and tRNAs.

Molecular Dynamics Studies of the STAT3 Homodimer:DNA Complex: Relationships between STAT3 Mutations and Protein–DNA Recognition

Jarmila Husby, Alan K. Todd, Shozeb M. Haider, Giovanna Zinzalla, David E. Thurston, and Stephen Neidle [University College London]

J. Chem. Infor. and Mod. **52**, 1179–1192, 2012.

Signal Transducers and Activators of Transcription (STAT) proteins are a group of latent cytoplasmic transcription factors involved in cytokine signaling. Understanding the dynamics of the STAT3 dimer interface, accounting for both protein–DNA and protein–protein interactions, with respect to the dynamics of the latent unphosphorylated STAT3 monomer, is important for designing potential small-molecule inhibitors of the activated dimer. Molecular dynamics (MD) simulations have been used to study the activated STAT3 homodimer:DNA complex and the latent unphosphorylated STAT3 monomer in an explicit water environment.

Predicting Ion–Nucleic Acid Interactions by Energy Landscape-Guided Sampling

Zhaojian He and Shi-Jie Chen [University of Missouri, Columbia]

J. Chem. Theor. and Comp. **8**, 2095–2102, 2012.

The recently developed Tightly Bound Ion (TBI) model offers improved predictions for ion effect in nucleic acid systems by accounting for ion correlation and fluctuation effects. However, further application of the model to larger systems is limited by the low computational efficiency of the model. Here, we develop a new computationally efficient TBI model using free energy landscape-guided sampling method. The method leads to drastic reduction in the computer time by a factor of 50 for RNAs of 50–100 nucleotides long. The improvement in the computational efficiency would be more significant for larger structures.

Nucleic Acids (Cont'd)

DNA Bending through Large Angles Is Aided by Ionic Screening

Justin Spiriti, Hiqmet Kamberaj, Adam M. R. de Graff, M. F. Thorpe, and Arjan van der Vaart [University of South Florida]

J. Chem. Theor. and Comp., **8**, 2145–2156, 2012.

We used adaptive umbrella sampling on a modified version of the roll angle to simulate the bending of DNA dodecamers. Simulations were carried out with the AMBER and CHARMM force fields for 10 sequences in which the central base pair step was varied. On long length scales, the DNA behavior was found to be consistent with the worm-like chain model. Persistence lengths calculated directly from the simulated structures and indirectly through the use of sequence-independent coarse-grained models based on simulation data were similar to literature values.

Nitroxide Sensing of a DNA Microenvironment: Mechanistic Insights from EPR Spectroscopy and Molecular Dynamics Simulations

Anna M. Popova, Ma'mon M. Hatmal, Maria P. Frushicheva, Eric A. Price, Peter Z. Qin [University of Southern California], and Ian S. Haworth

J. Phys. Chem. B., **116**, 6387–6396, 2012.

The behavior of the nitroxide spin labels 1-oxy-4-bromo-2,2,5,5-tetramethylpyrroline (R5a) and 1-oxy-2,2,5,5-tetramethylpyrroline (R5) attached at a phosphorothioate-substituted site in a DNA duplex is modulated by the DNA in a site- and stereospecific manner. A better understanding of the mechanisms of R5a/R5 sensing of the DNA microenvironment will enhance our capability to relate information from nitroxide spectra to sequence-dependent properties of DNA. Toward this goal, electron paramagnetic resonance (EPR) spectroscopy and molecular dynamics (MD) simulations were used to investigate R5 and R5a attached as R_p and S_p diastereomers at phosphorothioate _{ps}C₇ of d(CTACTG_{ps}C₇Y₈TTAG). d(CTAAAGCAGTAG) (Y = T or U).

Surfaces, Catalysts, and Materials Subjects

A- to B-Form Transition in DNA Between Gold Surfaces

One-Sun Lee, Vince Y. Cho, and George C. Schatz [Northwestern University]

J. Phys. Chem. B., **116**, 7000–7005, 2012.

Molecular dynamics simulations have been performed to characterize the conformation of DNA that is present when DNA links gold nanoparticles to form nanoparticle superlattice crystals. To model the DNA-linked gold nanoparticles, four strands of DNA are used to connect two gold surfaces, with a small interstrand separation and high added salt to match experiment. A-form DNA was assumed for the initial conformation, as this form of DNA has a length per base-pair that matches lengths that have been inferred from X-ray measurements.

2. METHODOLOGY

Quantitative Structure-Activity Relations

Toward the Identification of a Reliable 3D QSAR Pharmacophore Model for the CCK2 Receptor Antagonism

Amit K. Gupta, Kanika Varshney, and Anil K. Saxena
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J. Chem. Infor. and Mod. **52**, 1376–1390, 2012.

The present study describes application of computational approaches to identify a validated and reliable 3D QSAR pharmacophore model for the CCK-2R antagonism through integrated ligand and structure based studies using anthranilic sulfonamide and 1,3,4-benzotriazepine based CCK-2R antagonists. The best hypothesis consisted five features viz. two aliphatic hydrophobic, one aromatic hydrophobic, one H-bond acceptor, and one ring aromatic feature with an excellent correlation for 34 training set ($r^2_{\text{training}} = 0.83$) and 58 test set compounds ($r^2_{\text{test}} = 0.74$).

Potentials and Parameters

Force-Field Development and Molecular Dynamics of [NiFe] Hydrogenase

Dayle M. A. Smith [Pacific Northwest National Laboratory],
Yijia Xiong, T. P. Straatsma, Kevin M. Rosso, and Thomas C.
Squier

J. Chem. Theor. and Comp. **8**, 2103–2114, 2012.

Classical molecular force-field parameters describing the structure and motion of metal clusters in [NiFe] hydrogenase enzymes can be used to compare the dynamics and thermodynamics of [NiFe] under different oxidation, protonation, and ligation circumstances. Using density functional theory (DFT) calculations of small model clusters representative of the active site and the proximal, medial, and distal Fe/S metal centers and their attached protein side chains, we have calculated classical force-field parameters for [NiFe] in reduced and oxidized states, including internal coordinates, force constants, and atom-centered charges.

Molecular Dynamics

Theory of the Molecular Transfer Model for Proteins with Applications to the Folding of the src-SH3 Domain

Zhenxing Liu, Govardhan Reddy [University of Maryland],
and D. Thirumalai

J. Phys. Chem. B. **116**, 6707–6716, 2012.

A theoretical basis for the molecular transfer model (MTM), which takes into account the effects of denaturants by combining experimental data and molecular models for proteins, is provided. We show that the MTM is a mean field-like model that implicitly takes into account denaturant-induced many body interactions. The MTM in conjunction with the coarse-grained self organized polymer model with side chains (SOP-SC) for polypeptide chains is used to simulate the folding of the src-SH3 domain as a function of temperature (T) and guanidine hydrochloride (GdmCl) concentration [C].

Monte Carlo

Structure of Immune Stimulating Complex Matrices and Immune Stimulating Complexes in Suspension Determined by Small-Angle X-Ray Scattering

Jan Skov Pedersen [Aarhus University], Cristiano L.P. Oliveira, Henriette Baun Hübschmann, Lise Arleth, Søren Manniche, Nicolai Kirkby, Hanne Mørck Nielsen

Biophysical Journal. **102**, 2372-2380, 2012.

Immune stimulating complex (ISCOM) particles consisting of a mixture of Quil-A, cholesterol, and phospholipids were structurally characterized by small-angle x-ray scattering (SAXS). The ISCOM particles are perforated vesicles of very well-defined structures. We developed and implemented a novel (to our knowledge) modeling method based on Monte Carlo simulation integrations to describe the SAXS data. This approach is similar to the traditional modeling of SAXS data, in which a structure is assumed, the scattering intensity is calculated, and structural parameters are optimized by weighted least-squares methods when the model scattering intensity is fitted to the experimental data.

Establishing Uniform Acceptance in Force Biased Monte Carlo Simulations

E. C. Neyts [Universiteitsplein 1], B. J. Thijsse, M. J. Mees, K. M. Bal, and G. Pourtois

J. Chem. Theor. and Comp, **8**, 1865–1869, 2012.

Uniform acceptance force biased Monte Carlo (UFMC) simulations have previously been shown to be a powerful tool to simulate atomic scale processes, enabling one to follow the dynamical path during the simulation. In this contribution, we present a simple proof to demonstrate that this uniform acceptance still complies with the condition of detailed balance, on the condition that the characteristic parameter $\lambda = 1/2$ and that the maximum allowed step size is chosen to be sufficiently small.

QM and QM/MM

Substituent effects on geometric and electronic properties of iron tetraphenylporphyrin: a DFT investigation

Lu Wei, Yuanbin She [Beijing University of Technology], Yanmin Yu, Xiaoqian Yao and Suojian Zhang

J. Mol.Mod., **18**, 2483-2491, 2012

To investigate the effects of the substituents, substituent positions and axial chloride ligand on the geometric and electronic properties of the iron tetraphenylporphyrin (FeTPP), a series of the substituted iron tetraphenylporphyrins and their chlorides, FeT(o/p-R)PP and FeT(o/p-R)PPCl (R = -H, -Cl, -NO₂, -OH, -OCH₃), were systematically calculated without any symmetry constraint by using DFT method. For geometric structure, the substituent position and axial Cl ligand change the configuration of the iron porphyrin obviously.

Quantum mechanical studies of lincosamides

Katarzyna Kulczycka-Mierzejewska, Joanna Trylska and Joanna Sadlej [University of Warsaw]

J. Mol.Mod., **18**, 2727-2740, 2012

Lincosamides are a class of antibiotics used both in clinical and veterinary practice for a wide range of pathogens. This group of drugs inhibits the activity of the bacterial ribosome by binding to the 23S RNA of the large ribosomal subunit and blocking protein synthesis. Currently, three X-ray structures of the ribosome in complex with clindamycin are available in the Protein Data Bank, which reveal that there are two distinct conformations of the pyrrolidiny propyl group of the bound clindamycin. We used quantum mechanical methods to investigate the probable conformations of clindamycin in order to explain the two binding modes in the ribosomal 23S RNA.

QM and QM/MM (Cont'd)

Structural and electronic properties of 4H-cyclopenta[2,1-b,3;4-b']dithiophene S-oxide (BTO) derivatives with an S, S=O, O, SiH₂, or BH₂ bridge: semi-empirical and DFT study

Semire Banjo [Ladoke Akintola University of Technology],
Odunola Olusegun Ayobami and Adejoro Isaiah Ajibade

J. Mol.Mod., **18**, 2755-2760, 2012

In this paper, we theoretically studied the geometries, stabilities, and the electronic and thermodynamic properties of 4H-cyclopenta[2,1-b,3;4-b']dithiophene S-oxide derivatives (BTO-X, with X = BH₂, SiH₂, S, S=O, or O) using semi-empirical methods, ab initio methods, and density functional theory. The geometries and thermodynamic parameters calculated by PM3 were in good agreement with those calculated with B3LYP/6-31 G*. The band gap calculated using B3LYP/6-31 G* ranged from 3.94 eV (BTO-O) to 3.16 eV (BTO-B). The absorption λ max calculated using B3LYP/6-31 G* was shifted to longer wavelengths when X = BH₂, SiH₂, or S=O (due to their electron-withdrawing effects) and to shorter wavelengths for BTO-S and BTO-O as compared to the λ max for the thiophene S-oxide (2TO) dimer.

Comparative or Homology Modeling

Homology modeling and docking analyses of M. leprae Mur ligases reveals the common binding residues for structure based drug designing to eradicate leprosy

Anusuya Shanmugam and Jeyakumar Natarajan [Bharathiar University]

J. Mol.Mod., **18**, 2659-2672, 2012

Multi drug resistance capacity for Mycobacterium leprae (MDR-Mle) demands the profound need for developing new anti-leprosy drugs. Since most of the drugs target a single enzyme, mutation in the active site renders the antibiotic ineffective. Peptidoglycan is an important component of the cell wall of M. leprae. Biosynthesis of peptidoglycan is a multi-step process that involves four key Mur ligase enzymes: MurC (EC:6.3.2.8), MurD (EC:6.3.2.9), MurE (EC:6.3.2.13) and MurF (EC:6.3.2.10). Hence in our work, we modeled the three-dimensional structure of the above Mur ligases using homology modeling method and analyzed its common binding features.

Molecular docking of 2-(benzimidazol-2-ylthio)-N-phenylacetamide-derived small-molecule agonists of human formyl peptide receptor 1

Andrei I. Khlebnikov, Igor A. Schepetkin, Liliya N. Kirpotina, Mark T. Quinn [Montana State University], Lars Brive and Claes Dahlgren, et al.

J. Mol.Mod., **18**, 2831-2843, 2012

Human N-formyl peptide receptor 1 (FPR1) is a G protein-coupled receptor (GPCR) involved in host defense and sensing cellular damage. Since structure-based ligand design for many GPCRs, including FPR1, is restricted by the lack of experimental three dimensional structures, homology modeling has been widely used to study GPCR-ligand binding. Indeed, receptor-ligand binding mode predictions can be derived from homology modeling with supporting ligand information. In the present work, we report comparative docking studies of 2-(benzimidazol-2-ylthio)-N-phenylacetamide derived FPR1 agonists, identified here and previously, with several known FPR1 peptide agonists in a FPR1 homology model that is based on the crystal structure of bovine rhodopsin.

Comparative or Homology Modeling (Cont'd)

On the Value of Homology Models for Virtual Screening: Discovering hCXCR3 Antagonists by Pharmacophore-Based and Structure-Based Approaches

Dane Huang, Qiong Gu, Hu, Ge, Jiming Ye, Noeris K. Salam, Arnie Hagler, Hongzhuan Chen, and Jun Xu [Sun Yat-sen University]

J.Chem. Infor. and Mod. **52**, 1356–1366, 2012.

Human chemokine receptor CXCR3 (hCXCR3) antagonists have potential therapeutic applications as antiviral, antitumor, and anti-inflammatory agents. A novel virtual screening protocol, which combines pharmacophore-based and structure-based approaches, was proposed. A three-dimensional QSAR pharmacophore model and a structure-based docking model were built to virtually screen for hCXCR3 antagonists. The hCXCR3 antagonist binding site was constructed by homology modeling and molecular dynamics (MD) simulation. By combining the structure-based and ligand-based screenings results, 95% of the compounds satisfied either pharmacophore or docking score criteria and would be chosen as hits if the union of the two searches was taken.

Multi-LZerD: Multiple protein docking for asymmetric complexes

Juan Esquivel-Rodríguez, Yifeng David Yang and Daisuke Kihara [Purdue University]

Proteins: Stru. Fun. & Bioinf., **80**, 1818–1833, 2012.

The tertiary structures of protein complexes provide a crucial insight about the molecular mechanisms that regulate their functions and assembly. However, solving protein complex structures by experimental methods is often more difficult than single protein structures. Here, we have developed a novel computational multiple protein docking algorithm, Multi-LZerD, that builds models of multimeric complexes by effectively reusing pairwise docking predictions of component proteins.

Mimicking the action of folding chaperones by Hamiltonian replica-exchange molecular dynamics simulations: Application in the refinement of de novo models

Hao Fan, Xavier Periole and Alan E. Mark [University of Queensland]

Proteins: Stru. Fun. & Bioinf., **80**, 1744–1754, 2012.

The efficiency of using a variant of Hamiltonian replica-exchange molecular dynamics (Chaperone H-replica-exchange molecular dynamics [CH-REMD]) for the refinement of protein structural models generated de novo is investigated. In CH-REMD, the interaction between the protein and its environment, specifically, the electrostatic interaction between the protein and the solvating water, is varied leading to cycles of partial unfolding and refolding mimicking some aspects of folding chaperones. In 10 of the 15 cases examined, the CH-REMD approach sampled structures in which the root-mean-square deviation (RMSD) of secondary structure elements (SSE-RMSD) with respect to the experimental structure was more than 1.0 Å lower than the initial de novo model.

Ligand Docking

The importance of secondary structure in determining CO₂-protein binding patterns

Michael L. Drummond [University of North Texas], Angela K. Wilson and Thomas R. Cundari

J. Mol.Mod., **18**, 2527-2541, 2012

One potential means to decrease the level of atmospheric carbon dioxide is through the utilization of protein-CO₂ interactions. A recent bioinformatics analysis [Cundari TR et al. (2009) *J Chem Inf Model* 49:2111–2115] of these interactions revealed a marked disparity in CO₂ affinity between α -helices and β -sheets. In order to understand this difference, a series of molecular dynamics simulations was performed on polypeptide model systems. Numerous factors that may influence CO₂ affinity were systematically investigated.

Accurate prediction of the binding free energy and analysis of the mechanism of the interaction of replication protein A (RPA) with ssDNA

Claudio Carra [2101 NASA Parkway, Houston] and Francis A. Cucinotta

J. Mol.Mod., **18**, 2761-2783, 2012

The eukaryotic replication protein A (RPA) has several pivotal functions in the cell metabolism, such as chromosomal replication, prevention of hairpin formation, DNA repair and recombination, and signaling after DNA damage. Moreover, RPA seems to have a crucial role in organizing the sequential assembly of DNA processing proteins along single stranded DNA (ssDNA). In view of these results we performed a study based on molecular dynamics aimed to reproduce the absolute binding free energy of RPA70AB with the dC5 and dC8 oligonucleotides.

3. JOURNAL REVIEWS

Journal of Molecular Graphics and Modelling, 37, July, 2012.

- 1-26 **Extensive ligand-based modeling and in silico screening reveal nanomolar inducible nitric oxide synthase (iNOS) inhibitors**, Ghadeer A.R.Y. Suaifan, Mayyada Shehadehh, Hebah Al-Ijel, Mutasem O. Taha [University of Jordan]

See Applications / Medicinal Chemistry and Drug Design.

- 27-38 **Dual inhibition of chaperoning process by taxifolin: Molecular dynamics simulation study**, Sharad Verma, Amit Singh, Abha Mishra [Banaras Hindu University]

See Applications / Ligand Binding.

- 39-48 **Identification of a mechanism of transformation of clathrate hydrate structures I to II or H**, Shuzo Yoshioki [Yatsushiro National College of Technology]

Binary mixed-gas hydrates including methane and other guest gases demonstrate a structural transition between the sI and sII phases. Recently, molecular dynamics simulations of methane hydrates suggest there may exist uncommon 15-hedral cages ($5^{12}6^3$), linking the sI and sII cages. In addition, xenon hydrate involving 15-hedral cages has been synthesized and named an hsI hydrate. Based on the hsI cages, we propose a mechanism for the transition of sI to sII or sH at atomic level resolution.

- 49-58 **Molecular basis of the initial platelet adhesion in arterial thrombosis: Molecular dynamics simulations**, Jian Li, Lin Zhang, Yan Sun [Tianjin University]

See Applications / Ligand Binding.

- 59-66 **Calculating the Na^+ translocating V-ATPase catalytic site affinity for substrate binding by homology modeled NtpA monomer using molecular dynamics/free energy calculation**, Zahed Muhammed, Satoshi Arai, Shinya Saijo, Ichiro Yamato, Takeshi Murata, Atsushi Suenaga [Tokyo University of Science]

See Applications / Protein-Nucleic Acid interactions.

- 67-76 **QM/MM study of catalytic mechanism of Xylanase Cex from *Cellulomonas fimi***, Jingli Liu, Chunchun Zhang, Dingguo Xu [Sichuan University]

See Applications / Enzyme Catalysis.

- 77-86 **Pharmacophore identification, docking and “in silico” screening for novel CDK1 inhibitors**, Xiaowu Dong, Jingying Yan, Lilin Du, Peng Wu, Shufang Huang, Tao Liu, Yongzhou Hu [Zhejiang University]

See Applications / Medicinal Chemistry and Drug Design.

Journal of Computational Chemistry, 33(18), July, 2012.

- 1525–1535 **Expanding molecular modeling and design tools to non-natural sidechains**, David Gfeller, Olivier Michielin [Swiss Institute of Bioinformatics (SIB)] and Vincent Zoete

See Applications / Bioinformatics.

- 1536–1543 **Placevent: An algorithm for prediction of explicit solvent atom distribution—Application to HIV-1 protease and F-ATP synthase**, Daniel J. Sindhikara, Norio Yoshida and Fumio Hirata [Institute for Molecular Science, Okazaki]

See Applications / Bioinformatics.

- 1544–1553 **Comparison of the electronic structure of different perylene-based dye-aggregates**, Volker Settels, Wenlan Liu, Jens Pflaum, Reinhold F. Fink and Bernd Engels [Universität Würzburg]

Aggregates of functionalized polycyclic aromatic molecules like perylene derivatives differ in important optoelectronic properties such as absorption and emission spectra or exciton diffusion lengths. As this knowledge is of interest for the development of materials with optimized functionalities, we investigate this question by comparing the electronic structures of dimer systems of representative perylene-based chromophores.

- 1554–1563 **First-principles calculations on thermodynamic properties of BaTiO₃ rhombohedral phase**, Andrei V. Bandura and Robert A. Evarestov [St. Petersburg State University]

The calculations based on the linear combination of atomic orbitals have been performed for the low-temperature phase of BaTiO₃ crystal. Structural and electronic properties, as well as phonon frequencies were obtained using hybrid PBE0 exchange–correlation functional.

- 1564–1571 **GPU accelerated numerical simulations of viscoelastic phase separation model**, Keda Yang, Jiaye Su and Hongxia Guo [Chinese Academy of Sciences]

We introduce a complete implementation of viscoelastic model for numerical simulations of the phase separation kinetics in dynamic asymmetry systems such as polymer blends and polymer solutions on a graphics processing unit (GPU) by CUDA language and discuss algorithms and optimizations in details.

Journal of Computational Chemistry, 33(19), July, 2012.

- 1587–1593 **The electronic spectra and the H-bonding pattern of the sulfur and selenium substituted guanines**, Jing Wang, Jiande Gu [Jackson State University] and Jerzy Leszczynski

The density functional theory (DFT) with B3LYP, M05-2x, and M06-2x functionals, along with the 6-311+G(d, p) basis set, were used in the study of the UV absorption spectra and the H-bonding pairing patterns of the sulfur and selenium substituted guanines.

- 1594–1602 **Ab initio study of the positronation of the CaO and SrO molecules including calculation of annihilation rates**, Robert J. Buenker [Bergische Universität Wuppertal] and Heinz-Peter Liebermann

Ab initio multireference single- and double-excitation configuration interaction calculations have been performed to compute potential curves for ground and excited states of the CaO and SrO molecules and their positronic complexes, e^+CaO , and e^+SrO .

- 1603–1614 **Stereoselection in the diels–alderase ribozyme: A molecular dynamics study**, Tomasz Bereźniak, Andres Jäschke, Jeremy C. Smith and Petra Imhof [University of Heidelberg]

See Applications / Enzyme Catalysis.

- 1615–1622 **Empirical van der Waals corrections to solid-state density functional theory: Iodine and phosphorous containing molecular crystals**, John Kendrick [University of Bradford], Frank J. J. Leusen and Marcus A. Neumann

Parameters are derived for a molecular mechanics type dispersive correction to solid-state density functional theory calculations on molecular crystals containing iodine and phosphorous. The molecular C_6 coefficients are derived from photoabsorption differential oscillator strength spectra determined from accurate (e,e) dipole spectra.

- 1623–1631 **Adsorption of metadiiodobenzene on Cu(110): A theoretical study**, Chiara Panosetti [University of Liverpool] and Werner A. Hofer

In this work, we have computationally modeled the adsorption of 1,3-diiodobenzene (meta-diiodobenzene or m-DIB) on Cu(1 1 0) by means of density functional theory including van der Waals interaction using Grimme's method.

Journal of Computational Chemistry, 33(20), July, 2012.

- 1645–1661 **Structural informatics, modeling, and design with an open-source Molecular Software Library (MSL)**, Daniel W. Kulp, Sabareesh Subramaniam, Jason E. Donald, Brett T. Hannigan, Benjamin K. Mueller, Gevorg Grigoryan and Alessandro Senes [University of Wisconsin, Madison]

See Applications / Bioinformatics.

- 1662–1672 **Molecule-specific determination of atomic polarizabilities with the polarizable atomic multipole model**, Hyun Woo Kim and Young Min Rhee [Pohang University of Science and Technology]

Recently, many polarizable force fields have been devised to describe induction effects between molecules. In popular polarizable models based on induced dipole moments, atomic polarizabilities are the essential parameters and should be derived carefully. Here, we present a parameterization scheme for atomic polarizabilities using a minimization target function containing both molecular and atomic information.

- 1673–1688 **Atomic multipoles: Electrostatic potential fit, local reference axis systems, and conformational dependence**, Christian Kramer [University of Basel], Peter Gedeck and Markus Meuwly

Currently, all standard force fields for biomolecular simulations use point charges to model intermolecular electrostatic interactions. This is a fast and simple approach but has deficiencies when the electrostatic potential (ESP) is compared to that from ab initio methods. Here, we show how atomic multipoles can be rigorously implemented into common biomolecular force fields.

- 1689–1700 **DFT study of the mechanism of hydroamination of ethylene with ammonia catalyzed by diplatinum(II) complexes: Inner- or outer-sphere?**, Christos E. Kefalidis and Constantinos A. Tsipis [Aristotle University of Thessaloniki]

A detailed analysis of the reaction profiles of the hydroamination reaction between ethylene and ammonia catalyzed by the diplatinum(II) [$\{\text{Pt}(\text{NH}_2)(\mu\text{-H})(\text{PPh}_3)\}_2$] complex is presented herein using density functional theory computational techniques.

- 1701–1708 **Theoretical study of the excited-state double proton transfer in the (3-methyl-7-azaindole)-(7-azaindole) heterodimer**, Xue-Fang Yu, Shohei Yamazaki and Tetsuya Taketsugu [Hokkaido University]

Excited-state double proton transfer (ESDPT) in the (3-methyl-7-azaindole)-(7-azaindole) heterodimer is theoretically investigated by the long-range corrected time-dependent density functional theory method and the complete-active-space second-order perturbation theory method.

- 1709–1715 **The dynamics of the calcium-induced chain–chain association in the polyuronate systems**, Wojciech Plazinski [Polish Academy of Sciences] and Mateusz Drach

The calcium-induced formation of strong, hydrophilic gels is the important feature of polyuronates, connected with most of their practical applications. The insight into the molecular details of gelling process dynamics is hardly feasible for both experimental and theoretical methods. Here, the application of the transition path sampling method for studying this problem is reported; the focus was on the poly(α -L-gulonate) systems, treated as the representative for all polyuronate-containing systems.

Journal of Computational Chemistry, 33(21), August, 2012.

- 1717–1729 **Spinor product computations for protein conformations**, Pieter Chys and Pablo Chacón [Consejo Superior de Investigaciones Científicas]

See Applications / Protein Confirmation Analysis.

- 1730–1739 **Fully ab initio protein-ligand interaction energies with dispersion corrected density functional theory**, Jens Antony and Stefan Grimme [Universität Bonn]

Dispersion corrected density functional theory (DFT-D3) is used for fully ab initio protein-ligand (PL) interaction energy calculation via molecular fractionation with conjugated caps (MFCC) and applied to PL complexes from the PDB comprising 3680, 1798, and 1060 atoms.

- 1740–1747 **Metabolic-intermediate complex formation with cytochrome P450: Theoretical studies in elucidating the reaction pathway for the generation of reactive nitroso intermediate**, Nikhil Taxak, Prashant V. Desai, Bhargav Patel, Michael Mohutsky, Valentine J. Klimkowski, Vijay Gombar and Prasad V. Bharatam [NIPER, Mohali]

Mechanism-based inhibition (MBI) of cytochrome P450 (CYP) can lead to drug–drug interactions and often to toxicity. Some aliphatic and aromatic amines can undergo biotransformation reactions to form reactive metabolites such as nitrosoalkanes, leading to MBI of CYPs. It has been proposed that the nitrosoalkanes coordinate with the heme iron, forming metabolic-intermediate complex (MIC), resulting in the quasi-irreversible inhibition of CYPs. A quantum chemical analysis was performed to elucidate potential reaction pathways for the generation of nitroso intermediate and the formation of MIC.

- 1748–1761 **Rationalization of the behavior of $M_2(\text{CH}_3\text{CS}_2)_4\text{I}$ ($M = \text{Ni}, \text{Pt}$) chains at room temperature from periodic density functional theory and ab initio cluster calculations**, Zahra Tabookht, Xavier López [Universitat Rovira i Virgili], Coen de Graaf, Nathalie Guihéry, Nicolas Suaud and Nadia Benamor

The electrical conductivities and plausible charge-ordering states in the room temperature (r.t.) phase for MMX chains $[\text{Ni}_2(\text{dta})_4\text{I}]_\infty$ and $[\text{Pt}_2(\text{dta})_4\text{I}]_\infty$ ($\text{dta} = \text{CH}_3\text{CS}_2^-$) have been analyzed with periodic density functional theory (DFT) and correlated ab initio calculations combined with the effective Hamiltonian theory.

- 1762–1772 **Computational investigations on covalent dimerization/oligomerization of polyacenes: Is it relevant to soot formation?**, D. Koley [Indian Institute of Science, Bangalore], E. Arunan and S. Ramakrishnan

We have postulated a novel pathway that could assist in the nucleation of soot particles through covalent dimerization and oligomerizations of a variety of PAHs.

- 1773–1780 **Multi-zinc-expanded graphene patches: Tetraradical versus diradical character**, Hongfang Yang, Qisheng Song, Xinyu Song [Shandong University] and Yuxiang Bu

Three classes of multi-Zn-expanded graphene patches in different shapes are computationally designed through introducing a Zn chain into the corresponding middle benzenoid chain.

Journal of Molecular Modeling, 18(6), June, 2012.

- 2279–2289 **Structural determinants of imidacloprid-based nicotinic acetylcholine receptor inhibitors identified using 3D-QSAR, docking and molecular dynamics**, Qinfan Li, Xiangya Kong, Zhengtao Xiao, Yonghua Wang [Northwest A & F University], Lihui Zhang and Fangfang Wang, et al.

See Applications / Medicinal Chemistry and Drug Design.

- 2291–2299 **Computational investigation of a new ion-pair receptor for calix[4]pyrrole**, Yong Xia, Xueye Wang [Xiangtan University], Yu Zhang, Benhua Luo and Yi Liu

Theoretical studies of a new ion-pair receptor, meso-octamethylcalix[4]pyrrole (OMCP), and its interactions with the halide anions F⁻, Cl⁻, and Br⁻ and the cesium halides CsF, CsCl, and CsBr have been performed.

- 2301-2310 **Exploration of the valproic acid binding site on histone deacetylase 8 using docking and molecular dynamic simulations**, Jorge Antonio Bermúdez-Lugo, Oscar Perez-Gonzalez, Martha Cecilia Rosales-Hernández, Ian Ilizaliturri-Flores and José Trujillo-Ferrara, Jose Correa-Basurto [Instituto Politécnico Nacional].

See Applications / Ligand Binding.

- 2311-2319 **The structure, properties, and nature of unconventional π halogen bond in the complexes of Al₄₂- and halo hydrocarbons**, Ran Li, Qingzhong Li [Yantai University], Jianbo Cheng and Wenzuo Li

Quantum chemical calculations have been performed to study the all-metal π halogen bonding in Al₄₂-••halo hydrocarbon complexes. The result shows the existence of the all-metal π halogen bond in the complexes.

- 2321-2331 **Size and chain length effects on structural behaviors of biphenylcyclohexane-based liquid crystal nanoclusters by a coarse-grained model**, Ming-Liang Liao, Shin-Pon Ju [National Sun-Yat-Sen University], Chun-Yi Chang and Wei-Lin Huang

Size and chain length effects on structural behaviors of liquid crystal nanoclusters were examined by a coarse-grained model and the configurational-bias Monte Carlo (CBMC) simulation.

- 2333-2341 **Molecular modeling of temperature dependence of solubility parameters for amorphous polymers**, Xianping Chen [Delft University of Technology], Cadmus Yuan, Cell K. Y. Wong and Guoqi Zhang

A molecular modeling strategy is proposed to describe the temperature (T) dependence of solubility parameter (δ) for the amorphous polymers which exhibit glass-rubber transition behavior. The commercial forcefield "COMPASS" is used to support the atomistic simulations of the polymer.

- 2343-2348 **The H₂ dissociation on the BN, AlN, BP and AlP nanotubes: a comparative study**, Javad Beheshtian, Hamed Soleymanabadi, Mohammad Kamfiroozi and Ali Ahmadi [Islamic Azad University]

The thermodynamic and kinetic feasibility of H₂ dissociation on the BN, AlN, BP and AlP zigzag nanotubes has been investigated theoretically by calculating the dissociation and activation energies.

- 2349-2356 **Molecular simulation of water removal from simple gases with zeolite NaA**, Éva Csányi, Zoltán Ható and Tamás Kristóf [University of Pannonia]

See Applications / Zeolites.

- 2357-2367 **Theoretical investigation of the two-photon absorption properties of 3,6-bis(4-vinylpyridinium) carbazole derivatives—new biological fluorescent probes**, Ying Sun, Yang Zhao, Xiao-Ting Liu, Ai-Min Ren [Jilin University] and Ji-Kang Feng, et al.

The present study focuses on a series of carbazole derivatives, which are being investigated as potential two-photon fluorescent probes (TFP) for DNA detection and two-photon bioimaging.

- 2369-2376 **Crystal structure, detonation performance, and thermal stability of a new polynitro cage compound: 2, 4, 6, 8, 10, 12, 13, 14, 15-nonanitro-2, 4, 6, 8, 10, 12, 13, 14, 15-nonaazaheptacyclo [5.5.1.1.13, 11. 15, 9] pentadecane**, Jian-ying Zhang, Hong-chen Du, Fang Wang, Xue-dong Gong [Nanjing University of Science and Technology] and San-jiu Ying

A new polynitro cage compound 2, 4, 6, 8, 10, 12, 13, 14, 15-nonanitro-2, 4, 6, 8, 10, 12, 13, 14, 15-nonaazaheptacyclo [5.5.1.1.13,11. 15,9] pentadecane (NNNAHP) was designed in the present work. Its molecular structure was optimized at the B3LYP/6-31 G(d,p) level of density functional theory (DFT) and crystal structure was predicted using the Compass and Dreiding force fields and refined by DFT GGA-RPBE method.

- 2377-2386 **Mapping multiple potential ATP binding sites on the matrix side of the bovine ADP/ATP carrier by the combined use of MD simulation and docking**, Daniele Di Marino, Francesco Oteri, Blasco Morozzo della Rocca, Ilda D'Annessa and Mattia Falconi [Via della Ricerca Scientifica]

See Applications / Ligand Binding.

- 2387-2398 **Are formal oxidation states above one viable in cyclopentadienylcopper cyanides?**, Congzhi Wang, Xiuhui Zhang [Beijing Institute of Technology], Qian-shu Li, Yaoming Xie and R. Bruce King, et al.

Recent experiments have led to the discovery of the thermally unstable organocopper compounds $(\eta^3\text{-C}_3\text{H}_5)\text{CuMe}_2$, $[(\eta^3\text{-C}_3\text{H}_5)\text{CuMe}_3]^-$, and CuMe_4^- in which the copper atom is in the +3 formal oxidation state. In a quest for more stable organocopper compounds with copper in formal oxidation states above one, the binuclear cyclopentadienylcopper cyanides $\text{Cp}_2\text{Cu}_2(\text{CN})_n$ ($\text{Cp} = \eta^5\text{-C}_5\text{H}_5$; $n = 1, 2, 3$) have been studied using density functional theory (DFT).

- 2399-2408 **How to simulate affinities for host–guest systems lacking binding mode information: application to the liquid chromatographic separation of hexabromocyclododecane stereoisomers**, Vedat Durmaz [ZIB Zuse-Institut Berlin], Marcus Weber and Roland Becker

See Applications / Host-Guest Systems.

- 2409-2422 **DFT modeling, UV-Vis and IR spectroscopic study of acetylacetone-modified zirconia sol-gel materials**, Ivelina Georgieva [Bulgarian Academy of Sciences], Nina Danchova, Stoyan Gutzov and Natasha Trendafilova

Theoretical and spectroscopic studies of a series of monomeric and dimeric complexes formed through the modification of a zirconium butoxide precursor with acetylacetone and subsequent hydrolysis and/or condensation have been performed by applying DFT/B3LYP/6-31++G(d) and highly accurate RI-ADC(2) methods as well as IR and UV-Vis transmittance and diffuse reflectance spectroscopies.

- 2423-2431 **Hydrogen storage in C3Ti complex using quantum chemical methods and molecular dynamics simulations**, Vijayanand Kalamse, Nitin Wadnerkar and Ajay Chaudhari [Swami Ramanand Teerth Marathwada University]

The hydrogen storage capacity of C3Ti and C3Ti+ complex was studied using second order Møller-Plesset (MP2) and density functional theory (DFT) methods with different exchange and correlation functionals.

- 2433-2442 **First-principles molecular dynamics simulations of the H₂O / Cu(111) interface**, Roger Nadler [University of Seville] and Javier Fernandez Sanz

A first-principles theoretical study of the water-Cu(111) interface based on density functional calculations is reported.

- 2443-2451 **Theoretical studies on the structures and detonation properties of nitramine explosives containing benzene ring**, GuoZheng Zhao and Ming Lu [Nanjing University of Science & Technology]

The nitramine compounds containing benzene ring were optimized to obtain their molecular geometries and electronic structures at DFT-B3LYP/6-31+G(d) level.

- 2453-2460 **Aromatic character of heptafulvene and its complexes with halogen atoms**, Tadeusz M. Krygowski, Wojciech P. Oziminski [National Medicines Institute, Chelmska] and Michał K. Cyrański

Geometry optimization of heptafulvene-halogen complexes (halogens: F, Cl, Br, I, and At) carried out at the B3LYP/6-311+G(d,p) level of theory allowed us to estimate the geometry-based aromaticity index HOMA, the magnetism-based indices NICS, NICS(1), and NICS(1)ZZ, as well as the energy of complex formation.

- 2461-2469 **Polarization-induced σ -holes and hydrogen bonding**, Matthias Hennemann, Jane S. Murray, Peter Politzer, Kevin E. Riley and Timothy Clark [Friedrich-Alexander-Universität Erlangen-Nürnberg]

The strong collinear polarizability of the A-H bond in A-H...B hydrogen bonds is shown to lead to an enhanced σ -hole on the donor hydrogen atom and hence to stronger hydrogen bonding. This effect helps to explain the directionality of hydrogen bonds, the well known cooperative effect in hydrogen bonding, and the occurrence of blue-shifting.

- 2471-2478 **Estimating the carbonyl anharmonic vibrational frequency from affordable harmonic frequency calculations**, Aneta Buczek, Teobald Kupka [University of Opole], Stephan P. A. Sauer and Małgorzata A. Broda

A linear correlation between harmonic and anharmonic frequencies of water calculated at B3LYP level of theory was observed with a number of basis sets. Similar relationships were found in both the gas phase and solution for several small molecules.

- 2479-2482 **Molecular mechanics modeling of azobenzene-based photoswitches**, Patrick Duchstein, Christian Neiss, Andreas Görling and Dirk Zahn [Friedrich-Alexander Universität Erlangen-Nürnberg]

We present an extension of the generalized amber force field to allow the modeling of azobenzenes by means of classical molecular mechanics. TD-DFT calculations were employed to derive different interaction models for 4-hydroxy-4'-methyl-azobenzene, including the ground (S₀) and S₁ excited state.

- 2483-2491 **Substituent effects on geometric and electronic properties of iron tetraphenylporphyrin: a DFT investigation**, Lu Wei, Yuanbin She [Beijing University of Technology], Yanmin Yu, Xiaoqian Yao and Suojiang Zhang

See Methodology / QM and QM/MM.

- 2493-2500 **Role of cationic size in the optical properties of the LiCl crystal surface: theoretical study**, Wael Salah Abdel Halim, Noha Abdullah, Safaa Abdel-Aal and A. S. Shalabi [Benha University]

The size of the cations (either Ca²⁺, Sr²⁺, Ga⁺, or Au⁺) at the FA1-type color centers on the (100) surface of LiCl crystal plays an important role in the optical properties of this surface. In this work, double-well potentials at this surface were investigated using ab initio quantum mechanical methods.

- 2501-2512 **Metastable region of phase diagram: optimum parameter range for processing ultrahigh molecular weight polyethylene blends**, Jing-Gang Gai [Polymer Research Institute of Sichuan University] and Yuan Zuo

Numerous studies suggest that two-phase morphology and thick interface are separately beneficial to the viscosity reduction and mechanical property maintenance of the matrix when normal molecular weight polymer (NMWP) is used for modification of ultrahigh molecular weight polyethylene (UHMWPE). In this work, dissipative particle dynamics simulations and Flory-Huggins theory are applied in predicting the optimum NMWP and the corresponding conditions, wherein the melt flowability of UHMWPE can be improved while its mechanical properties can also be retained.

- 2513-2525 **Pharmacophore modeling, molecular docking, QSAR, and in silico ADMET studies of gallic acid derivatives for immunomodulatory activity**, Dharmendra Kumar Yadav, Feroz Khan [Central Institute of Medicinal and Aromatic Plants, Lucknow] and Arvind Singh Negi

See Applications / Medicinal Chemistry and Drug Design.

- 2527-2541 **The importance of secondary structure in determining CO₂-protein binding patterns**, Michael L. Drummond [University of North Texas], Angela K. Wilson and Thomas R. Cundari

See Methodology / Ligand Docking.

- 2543-2551 **Ab initio and DFT study of luminescent cyclometalated N-heterocyclic carbene organogold(III) complexes**, Baozhu Yang, Qi Zhang, Jing Zhong [Changzhou University], Shuang Huang and Hong-Xing Zhang

The structures of versatile N-heterocyclic carbene-containing Au(III) complexes in the ground and low-lying excited states have been optimized at the B3LYP functional and the single-excitation configuration interaction (CIS) method, respectively.

- 2553-2566 **Hit clustering can improve virtual fragment screening: CDK2 and PARP1 case studies**, Alexey A. Zeifman, Victor S. Stroylov, Fedor N. Novikov, Ghermes G. Chilov [N. D. Zelinsky Institute Of Organic Chemistry], Oleg V. Stroganov and Alexandra L. Zakharenko, et al.

Virtual fragment screening could be a promising alternative to existing experimental screening techniques. However, reliable methods of in silico fragment screening are yet to be established and validated. In order to develop such an approach we first checked how successful the existing molecular docking methods can be in predicting fragment binding affinities and poses. Using our Lead Finder docking software the RMSD of the binding energy prediction was observed to be 1.35 kcal/mol-1 on a set of 26 experimentally characterized fragment inhibitors, and the RMSD of the predicted binding pose from the experimental one was <1.5 Å.

- 2567-2576 **Comparative homology modeling of pyruvate dehydrogenase kinase isozymes from *Xenopus tropicalis* reveals structural basis for their subfunctionalization**, Alexander A. Tokmakov [Kobe University]

See Applications / Homology Modeling.

- 2577-2588 **Conformational and stereoelectronic investigation of tryptamine. An AIM/NBO study**, Rosana M. Lobayan [Universidad de la Cuenca del Plata], María C. Pérez Schmit, Alicia H. Jubert and Arturo Vitale

See Applications / Protein Dynamics.

- 2589-2597 **Molecular dynamics simulation studies of betulinic acid with human serum albumin**, Chandramouli Malleda, Navjeet Ahalawat, Mahesh Gokara and Rajagopal Subramanyam [University of Hyderabad]

See Applications / Ligand Binding

- 2599-2611 **Exploration of the binding of curcumin analogues to human P450 2C9 based on docking and molecular dynamics simulation**, Rongwei Shi, Yin Wang, Xiaolei Zhu [Nanjing University of Technology] and Xiaohua Lu

See Applications / Ligand Binding

- 2613-2620 **An ONIOM investigation on anion recognition of alkali-metal complexes with diurea calix[4]arene receptor**, Pornpan Chanapiwat and Vithaya Ruangpornvisuti [Chulalongkorn University]

The ONIOM(B3LYP/6–31G(d):AM1) optimized structures of complexes of diurea calix[4]arene receptor (L) with alkali metals Li⁺, Na⁺ and K⁺ and their complexes with halide ions F[–], Cl[–], Br[–], oxygen-containing anions HCO₃[–], HSO₄[–] and CH₃COO[–] ions were obtained.

- 2621-2631 **A QSAR study of radical scavenging antioxidant activity of a series of flavonoids using DFT based quantum chemical descriptors – the importance of group frontier electron density**, Ananda Sarkar, Tapas Ranjan Middy and Atish Dipnagar Jana [Behala College, Parnasree, Kolakata]

See Applications / QSAR.

- 2633-2644 **Conserved water-mediated H-bonding dynamics of catalytic His159 and Asp158: insight into a possible acid–base coupled mechanism in plant thiol protease**, Tapas K. Nandi, Hridoy R. Bairagya, Bishnu P. Mukhopadhyay [National Institute of Technology, Durgapur], Payel Mallik and Dipankar Sukul, et al.

See Applications / Enzyme Catalysis.

- 2645-2652 **Aminoglycoside induced nephrotoxicity: molecular modeling studies of calreticulin-gentamicin complex**, Gururao Hariprasad, Manoj Kumar, Komal Rani, Punit Kaur and Alagiri Srinivasan [All India Institute of Medical Sciences]

See Applications / Ligand Binding

- 2653-2658 **A comparative study on the B12N12, Al12N12, B12P12 and Al12P12 fullerene-like cages**, Javad Beheshtian, Zargham Bagheri, Mohammad Kamfiroozi and Ali Ahmadi [Islamic Azad University]

The stability, geometry and electronic structure of the title nanoclusters were compared by using density functional theory (DFT) calculations.

- 2659-2672 **Homology modeling and docking analyses of M. leprae Mur ligases reveals the common binding residues for structure based drug designing to eradicate leprosy**, Anusuya Shanmugam and Jeyakumar Natarajan [Bharathiar University]

See Methodology / Homology Modeling.

- 2673-2687 **Predicting functional residues of the Solanum lycopersicum aspartic protease inhibitor (SLAPI) by combining sequence and structural analysis with molecular docking**, Yasel Guerra [Universidad de La Habana], Pedro A. Valiente, Colin Berry and Tirso Pons

See Applications / Medicinal Chemistry and Drug Design.

- 2689-2698 **Structure and stability of kaolinite/TiO₂ nanocomposite: DFT and MM computations**, Jonáš Tokarský [VŠB-Technical University of Ostrava], Pavla Čapková and Jaroslav V. Burda

The adhesion of TiO₂ (anatase structure) nanoparticles to kaolinite substrate was investigated using molecular modeling. Universal force field computation, density function theory computation, and a combination of both two approaches were used.

- 2699-2708 **Methane storage in homogeneous armchair open-ended single-walled boron nitride nanotube triangular arrays: a grand canonical Monte Carlo simulation study**, Sayyed Jalil Mahdizadeh [Ferdowsi University of Mashhad] and Sayyed Faramarz Tayyari

The physisorption of methane in homogeneous armchair open-ended SWBNNT triangular arrays was evaluated using grand canonical ensemble Monte Carlo simulation for tubes 11.08, 13.85, 16.62, and 19.41 Å [(8,8), (10,10), (12,12), and (14,14), respectively] in diameter, at temperatures of 273, 298, 323, and 373 K, and at fugacities of 0.5–9.0 Mpa.

- 2709-2716 **Quantum chemical modeling study of adsorption of benzoic acid on anatase TiO₂ nanoparticles**, Hilal S. Wahab [Al-Nahrain University]

The semi-empirical MSINDO method has been used to investigate the mode of adsorption of benzoic acid on the nano anatase TiO₂ (100) surface. The (100) surface is modeled with a Ti₃₆O₉₀H₃₆ cluster. Molecular dynamics simulations for the adsorption behavior of benzoic acid indicate it is linked to the TiO₂ surface through interactions from the oxygen atoms of the carboxylic acid moiety with surface titanium atoms.

- 2717-2725 **Exploration of conformational transition in the aryl-binding site of human FXa using molecular dynamics simulations**, Jing-Fang Wang [Shanghai Jiaotong University], Pei Hao, Yi-Xue Li, Jian-Liang Dai and Xuan Li

See Applications / Protein Conformational Analysis.

- 2727-2740 **Quantum mechanical studies of lincosamides**, Katarzyna Kulczycka-Mierzejewska, Joanna Trylska and Joanna Sadlej [University of Warsaw]

See Methodology / QM and QM/MM.

- 2741-2754 **Dimensionality reduction in computational demarcation of protein tertiary structures**, Rajani R. Joshi [Indian Institute of Technology Bombay], Priyabrata R. Panigrahi and Reshma N. Patil

Predictive classification of major structural families and fold types of proteins is investigated deploying logistic regression.

- 2755-2760 **Structural and electronic properties of 4H-cyclopenta[2,1-b,3;4-b']dithiophene S-oxide (BTO) derivatives with an S, S=O, O, SiH₂, or BH₂ bridge: semi-empirical and DFT study**, Semire Banjo [Ladoke Akintola University of Technology], Odunola Olusegun Ayobami and Adejoro Isaiah Ajibade

See Methodology / QM and QM/MM.

- 2761-2783 **Accurate prediction of the binding free energy and analysis of the mechanism of the interaction of replication protein A (RPA) with ssDNA**, Claudio Carra [2101 NASA Parkway, Houston] and Francis A. Cucinotta

See Methodology / Ligand Docking.

- 2785-2794 **Effect of the thermostat in the molecular dynamics simulation on the folding of the model protein chignolin**, Carlos A. Fuzo [Universidade de São Paulo] and Léo Degrevè

See Applications / Protein Folding.

- 2795-2804 **A specific pharmacophore model of sodium-dependent glucose co-transporter 2 (SGLT2) inhibitors**, Chunlei Tang, Xiaoyun Zhu, Dandan Huang, Hai Qian [China Pharmaceutical University], Xin Zan and Baowei Yang, et al.

See Applications / Medicinal Chemistry and Drug Design.

- 2805-2811 **Harmonic force field for nitro compounds**, Edson P. Bellido and Jorge M. Seminario [Texas A&M University]

Molecular simulations leading to sensors for the detection of explosive compounds require force field parameters that can reproduce the mechanical and vibrational properties of energetic materials. We developed precise harmonic force fields for alanine polypeptides and glycine oligopeptides using the FUERZA procedure that uses the Hessian tensor (obtained from ab initio calculations) to calculate precise parameters.

- 2813-2821 **Oxygenation of the phenylhalocarbenes. Are they spin-allowed or spin-forbidden reactions?**, Al Mokhtar Lamsabhi [Universidad Autónoma de Madrid], Inés Corral, Patricia Pérez, Orlando Tapia and Manuel Yáñez

Oxygenation mechanisms of phenylhalocarbenes in vacuum are investigated through the use of density functional theory and CASSCF-PT2 approaches.

- 2823-2829 **Computational investigation of the effect of thermal perturbation on the mechanical unfolding of titin I27**, Navneet Bung and U. Deva Priyakumar [International Institute of Information Technology, Hyderabad]

See Applications / Protein Folding.

- 2831-2843 **Molecular docking of 2-(benzimidazol-2-ylthio)-N-phenylacetamide-derived small-molecule agonists of human formyl peptide receptor 1**, Andrei I. Khlebnikov, Igor A. Schepetkin, Liliya N. Kirpotina, Mark T. Quinn [Montana State University], Lars Brive and Claes Dahlgren, et al.

See Methodology / Homology Modeling..

- 2845-2854 **Theoretical aspects of binary and ternary complexes of aziridine...ammonia ruled by hydrogen bond strength**, Boaz G. Oliveira [Universidade Federal da Bahia] and Regiane C. M. U. Araújo

B3LYP calculations, ChelpG atomic charges, and quantum theory of atoms in molecules (QTAIM) integrations were used to investigate the binary (1:1) and ternary (1:2) hydrogen-bonded complexes formed by aziridine (1) and ammonia (2).

- 2855-2860 **First-principles study of energetic complexes (II): (5-cyanotetrazolato-N2) pentaammine cobalt (III) perchlorate (CP) and Ni, Fe and Zn analogues**, Jing Shang, Jian-Guo Zhang [Beijing Institute of Technology], Tong-Lai Zhang, Hui-Sheng Huang and Shao-Wen Zhang, et al.

First-principles methods using the TPSS density functional level of theory with the basis set 6-31G** were applied to study (5-cyanotetrazolato-N2) pentaammine cobalt (III) perchlorate (CP) and Ni, Fe and Zn analogues in the gas phase.

- 2861-2868 **Chemical functionalization of graphene via aryne cycloaddition: a theoretical study**, Jing-xiang Zhao [Harbin Normal University], Hong-xia Wang, Bo Gao, Xiao-guang Wang and Qing-hai Cai, et al.

Chemical functionalization of graphene provides a promising route to improve its solubility in water and organic solvents as well as modify its electronic properties, thus significantly expanding its potential applications. In this article, by using density functional theory (DFT) methods, we have studied the effects of the chemical functionalization of graphenes via aryne cycloaddition on its properties.

- 2869-2883 **Global and local molecular dynamics of a bacterial carboxylesterase provide insight into its catalytic mechanism**, Xiaozhen Yu, Sara C. Sigler, Delwar Hossain, Randy M. Wadkins [University of Mississippi], Monika Wierdl and Steven R. Gwaltney, et al.

See Applications / Enzyme Catalysis.

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1. APPLICATIONS

1.1. Small Molecules

Water and Solvation

Dynamical Coupling of Intrinsically Disordered Proteins and Their Hydration Water: Comparison with Folded Soluble and Membrane Proteins

F.-X. Gallat, A. Laganowsky, K. Wood, F. Gabel, L. van Eijck, J. Wuttke, M. Moulin, M. Härtlein, D. Eisenberg, J.-P. Colletier, G. Zaccai, M. Weik [Institut de Biologie Structurale, Grenoble]

Biophysical Journal. **103**, 129-136, 2012.

Hydration water is vital for various macromolecular biological activities, such as specific ligand recognition, enzyme activity, response to receptor binding, and energy transduction. Without hydration water, proteins would not fold correctly and would lack the conformational flexibility that animates their three-dimensional structures. Here, we provide insight into the coupling between hydration-water dynamics and atomic motions in intrinsically disordered proteins (IDP), a largely unexplored class of proteins that, in contrast to folded proteins, lack a well-defined three-dimensional structure.

Medicinal Chemistry and Drug Design

Synthesis, biological evaluation and molecular docking studies of 3-(1,3-diphenyl-1H-pyrazol-4-yl)-N-phenylacrylamide derivatives as inhibitors of HDAC activity

Xi Li, Jia-Lin Liu, Xian-Hui Yang, Xiang Lu, Ting-Ting Zhao, Hai-Bin Gong, Hai-Liang Zhu [Nanjing University]

Bioorg. and Med.Chem., **20**, 4430-4436, 2012.

In present study, a series of 3-(1,3-diphenyl-1H-pyrazol-4-yl)-N-phenylacrylamide derivatives (**5a-8d**) were designed, synthesized, and evaluated for HDAC inhibition and tumor cell antiproliferation. All of these compounds are reported for the first time, the chemical structures of these compounds were confirmed by means of ¹H NMR, ESI-MS and elemental analyzes. Docking simulation was performed to position compound **8c** into the HDAC active site to determine the probable binding model.



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Medicinal Chemistry and Drug Design (Cont'd)

Mechanistic insights into the dual inhibition strategy for checking Leishmaniasis

Abhinav Grover, Shashank Prakash Katiyar, Jeyaraman Jeyakanthan, Vikash Kumar Dubey & Durai Sundar [Indian Institute of Technology (IIT) Delhi]

J. Biomol. Stru. and Dyn., **30**, 474-487, 2012.

Leishmaniasis is an endemic disease mainly caused by the protozoan *Leishmania donovani* (Ld). Polyamines have been identified as essential organic compounds for the growth and survival of Ld. These are synthesized in Ld by polyamine synthesis pathway comprising of many enzymes such as ornithine decarboxylase (ODC), spermidine synthase (SS), and S-adenosylmethionine decarboxylase. Inhibition of these enzymes in Ld offers a viable prospect to check its growth and development. In the present work, we used computational approaches to search natural inhibitors against ODC and SS enzymes.

Large-scale virtual screening for the identification of new *Helicobacter pylori* urease inhibitor scaffolds

Homa Azizian, Farzaneh Nabati, Amirhossein Sharifi, Farideh Siavoshi and Mohammad Mahdavi, Massoud Amanlou [Tehran University of Medical Sciences].

J. Mol.Mod., **18**, 2917-2927, 2012.

Here, we report a structure-based virtual screening of the ZINC database (containing about five million compounds) by computational docking and the analysis of docking energy calculations followed by in vitro screening against *H. pylori* urease enzyme. One of the compounds selected showed urease inhibition in the low micromolar range. Barbituric acid and compounds 1a, 1d, 1e, 1f, 1g, 1h were found to be more potent urease inhibitors than the standard inhibitor hydroxyurea, yielding IC₅₀ values of 41.6, 83.3, 66.6, 50, 58.8, and 60 μ M, respectively (IC₅₀ of hydroxyurea = 100 μ M).

Pharmacophore modeling and virtual screening studies to identify new c-Met inhibitors

Wenting Tai, Tao Lu, Haoliang Yuan, Fengxiao Wang, Yadong Chen [China Pharmaceutical University] and Haichun Liu, et al.

J. Mol.Mod., **18**, 3087-3100, 2012.

Mesenchymal epithelial transition factor (c-Met) is an attractive target for cancer therapy. Three-dimensional pharmacophore hypotheses were built based on a set of known structurally diverse c-Met inhibitors. The best pharmacophore model, which identified inhibitors with an associated correlation coefficient of 0.983 between their experimental and estimated IC₅₀ values, consisted of two hydrogen-bond acceptors, one hydrophobic, and one ring aromatic feature. The highly predictive power of the model was rigorously validated by test set prediction and Fischer's randomization method.

In-silico modeling of a novel OXA-51 from β -lactam-resistant *Acinetobacter baumannii* and its interaction with various antibiotics

Vishvanath Tiwari, Isha Nagpal, Naidu Subbarao and Rajeswari R. Moganty [All India Institute of Medical Sciences, New Delhi]

J. Mol.Mod., **18**, 3351-3361, 2012.

Acinetobacter baumannii causes nosocomial infections such as pneumonia, urinary tract infection, meningitis, etc. β -lactam-based antibiotics like penicillin are used conventionally to treat infections of *A. baumannii*; however, they are becoming progressively less effective as the bacterium produces diverse types of β -lactamases to inactivate the antibiotics. We have recently identified a novel β -lactamase, OXA-51 from clinical strains of *A. baumannii* from our hospital. In the present study, we generated the structure of OXA-51 using MODELLER9v7 and studied the interaction of OXA-51 with a number of β -lactams (penicillin, oxacillin, ceftazidime, aztreonam and imipenem) using two independent programs: GLIDE and GOLD.

Medicinal Chemistry and Drug Design (Cont'd)

Application of Drug-Perturbed Essential Dynamics/Molecular Dynamics (ED/MD) to Virtual Screening and Rational Drug Design

Rima Chaudhuri, Oliver Carrillo, Charles Anthony Laughton, and Modesto Orozco [Institute for Research in Biomedicine, Barcelona]

J. Chem. Theor. and Comp., **8**, 2204–2214, 2012.

We present here the first application of a new algorithm, essential dynamics/molecular dynamics (ED/MD), to the field of small molecule docking. The method uses a previously existing molecular dynamics (MD) ensemble of a protein or protein–drug complex to generate, with a very small computational cost, perturbed ensembles which represent ligand-induced binding site flexibility in a more accurate way than the original trajectory. The use of these perturbed ensembles in a standard docking program leads to superior performance than the same docking procedure using the crystal structure or ensembles obtained from conventional MD simulations as templates. The simplicity and accuracy of the method opens up the possibility of introducing protein flexibility in high-throughput docking experiments.

Quantitative Structure-Activity Relations

Pharmacophore, QSAR, and ADME based semisynthesis and in vitro evaluation of ursolic acid analogs for anticancer activity

Komal Kalani, Dharmendra Kumar Yadav, Feroz Khan, Santosh K. Srivastava [Central Institute of Medicinal and Aromatic Plants, Lucknow] and Nitasha Suri

J. Mol. Mod., **18**, 3389–3413, 2012.

In the present work, QSAR models for predicting the activities of ursolic acid analogs against human lung (A-549) and CNS (SF-295) cancer cell lines were developed by a forward stepwise multiple linear regression method using a leave-one-out approach. The regression coefficient (r^2) and the cross-validation regression coefficient (r_{CV}^2) of the QSAR model for cytotoxic activity against the human lung cancer cell line (A-549) were 0.85 and 0.80, respectively. The QSAR study indicated that the LUMO energy, ring count, and solvent-accessible surface area were strongly correlated with anticancer activity.

Chirality Measures of α -Amino Acids

Michał H. Jamróz, Joanna E. Rode, Sławomir Ostrowski, Piotr F. J. Lipiński, and Jan Cz. Dobrowolski [Industrial Chemistry Research Institute, 01-793 Warsaw]

J. Chem. Infor. and Mod. **52**, 1462–1479, 2012.

To measure molecular chirality, the molecule is treated as a finite set of points in the Euclidean R^3 space supplemented by k properties, $p_1^{(i)}, p_2^{(i)}, \dots, p_k^{(i)}$ assigned to the i th atom, which constitute a point in the Property P^k space. Chirality measures are described as the distance between a molecule and its mirror image minimized over all its arbitrary orientation-preserving isometries in the $R^3 \times P^k$ Cartesian product space. An exemplary quantitative structure–activity relationship (QSAR) application of the chirality measures was presented by an introductory model for the benchmark Cramer data set of steroidal ligands of the sex-hormone binding globulin.

Carbon Nanoparticles

Probing the linear and nonlinear optical properties of nitrogen-substituted carbon nanotube

Shi-Ling Sun, Yang-Yang Hu, Hong-Liang Xu [Northeast Normal University], Zhong-Min Su and Li-Zhu Hao

J. Mol.Mod., **18**, 3219-3225, 2012.

In view of their intriguing structural and electrical properties, the linear and nonlinear optical (NLO) responses of six carbon nanotube (CNT) molecules substituted by nitrogen atoms at one end have been explored by using the CAM-B3LYP method. Molecules 1, 2 and 3 were obtained by increasing the lengths of the CNTs, and 1-Li, 2-Li and 3-Li were constructed by doping one Li atom into the N-substituted end of 1, 2 and 3 (mentioned above), respectively. Two effective approaches have been proposed to increase nonlinear optical properties(NLO): increasing the length of the CNT as well as doping one Li atom into the N-substituted end.

The solvation study of carbon, silicon and their mixed nanotubes in water solution

Haleh Hashemi Haeri [Islamic Azad University], Sepideh Ketabi and Seyed Majid Hashemianzadeh

J. Mol.Mod., **18**, 3379-3388, 2012.

Nanotubes are believed to open the road toward different modern fields, either technological or biological. However, the applications of nanotubes have been badly impeded for the poor solubility in water which is especially essential for studies in the presence of living cells. Therefore, water soluble samples are in demand. Herein, the outcomes of Monte Carlo simulations of different sets of multiwall nanotubes immersed in water are reported. A number of multi wall nanotube samples, comprised of pure carbon, pure silicon and several mixtures of carbon and silicon are the subjects of study.

Can trans-polyacetylene be formed on single-walled carbon-doped boron nitride nanotubes?

Ying Chen, Hong-xia Wang, Jing-xiang Zhao [Harbin Normal University], Qing-hai Cai and Xiao-guang Wang, et al.

J. Mol.Mod., **18**, 3415-3425, 2012.

Recently, the grafting of polymer chains onto nanotubes has attracted increasing attention as it can potentially be used to enhance the solubility of nanotubes and in the development of novel nanotube-based devices. In this article, based on density functional theory (DFT) calculations, we report the formation of trans-polyacetylene on single-walled carbon-doped boron nitride nanotubes (BNNTs) through their adsorption of a series of C₂H₂ molecules. The results show that, rather than through [2+2] cycloaddition, an individual molecule would preferentially attach to a carbon-doped BNNT via "carbon attack".

1.2. Biopolymers

Bioinformatics and Cheminformatics

DoGSiteScorer: a web server for automatic binding site prediction, analysis and druggability assessment

Andrea Volkamer, Daniel Kuhn, Friedrich Rippmann, and Matthias Rarey [University of Hamburg]

Bioinformatics. **28**, 2074-2075, 2012.

Many drug discovery projects fail because the underlying target is finally found to be undruggable. Progress in structure elucidation of proteins now opens up a route to automatic structure-based target assessment. DoGSiteScorer is a newly developed automatic tool combining pocket prediction, characterization and druggability estimation and is now available through a web server. The DoGSiteScorer web server is freely available for academic use at <http://dogsite.zbh.uni-hamburg.de>

Balancing target flexibility and target denaturation in computational fragment-based inhibitor discovery

Theresa J. Foster, Alexander D. MacKerell Jr. and Olgun Guvench [University of New England College of Pharmacy]

J. Comp. Chem. **33**, 1880–1891, 2012.

Accounting for target flexibility and selecting “hot spots” most likely to be able to bind an inhibitor continue to be challenges in the field of structure-based drug design, especially in the case of protein–protein interactions. Computational fragment-based approaches using MD simulations are a promising emerging technology having the potential to address both of these challenges. Using one such technology (Site Identification by Ligand Competitive Saturation, SILCS), conditions were identified to either prevent denaturation or identify and exclude trajectories in which subtle but important denaturation was occurring.

SWIFT MODELLER v2.0: a platform-independent GUI for homology modeling

Abhinav Mathur, Shankaracharya and Ambarish S. Vidyarthi [Birla Institute of Technology, Mesra]

J. Mol.Mod., **18**, 3021-3023, 2012.

SWIFT MODELLER v2.0 is a platform-independent Java-based graphical user interface to MODELLER. It provides an interactive homology modeling solution by automating the formatting, scripting, and data extraction processes, meaning that the user only needs to paste in the protein target sequence as input. SWIFT MODELLER v2.0 takes a step-by-step approach where the flow of the software screens depicts steps in the homology modeling protocol.

PROLIX: Rapid Mining of Protein–Ligand Interactions in Large Crystal Structure Databases

Martin Weisel [Hoffmann-La Roche, Inc.], Hans-Marcus Bitter, François Diederich, W. Venus So, and Rama Kondru

J.Chem. Infor. and Mod. **52**, 1450–1461, 2012.

A central problem in structure-based drug design is understanding protein–ligand interactions quantitatively and qualitatively. Several recent studies have highlighted from a qualitative perspective the nature of these interactions and their utility in drug discovery. we introduce PROLIX (Protein Ligand Interaction Explorer), a tool that uses sophisticated fingerprint representations of protein–ligand interaction patterns for rapid data mining in large crystal structure databases. Our implementation strategy pursues a branch-and-bound technique that enables mining against thousands of complexes within a few seconds.

Bioinformatics and Cheminformatics (Cont'd)

2D SMARTCyp Reactivity-Based Site of Metabolism Prediction for Major Drug-Metabolizing Cytochrome P450 Enzymes

Ruifeng Liu [U.S. Army Medical Research and Material Command], Jin Liu, Greg Tawa, and Anders Wallqvist

J.Chem. Infor. and Mod. **52**, 1698–1712, 2012.

Cytochrome P450 (CYP) 3A4, 2D6, 2C9, 2C19, and 1A2 are the most important drug-metabolizing enzymes in the human liver. Knowledge of which parts of a drug molecule are subject to metabolic reactions catalyzed by these enzymes is crucial for rational drug design to mitigate ADME/toxicity issues. SMARTCyp, a recently developed 2D ligand structure-based method, is able to predict site-specific metabolic reactivity of CYP3A4 and CYP2D6 substrates with an accuracy that rivals the best and more computationally demanding 3D structure-based methods. In this article, the SMARTCyp approach was extended to predict the metabolic hotspots for CYP2C9, CYP2C19, and CYP1A2 substrates.

Contribution of 2D and 3D Structural Features of Drug Molecules in the Prediction of Drug Profile Matching

Ágnes Peragovics, Zoltán Simon, Ildikó Brandhuber, Balázs Jelinek, Péter Hári, Csaba Hetényi, Pál Czobor, and András Málnási-Csizmadia [Eötvös Loránd University]

J.Chem. Infor. and Mod. **52**, 1733–1744, 2012.

Drug Profile Matching (DPM), a novel virtual affinity fingerprinting method capable of predicting the medical effect profiles of small molecules, was introduced by our group recently. The method exploits the information content of interaction patterns generated by flexible docking to a series of rigidly kept nontarget protein active sites. We presented the ability of DPM to classify molecules excellently, and the question arose, what the contribution of 2D and 3D structural features of the small molecules is to the intriguingly high prediction power of DPM. The present study compared the prediction powers for effect profiles of 1163 FDA-approved drug compounds determined by DPM and ChemAxon 2D and 3D similarity fingerprinting approaches.

Protein Secondary Structure

Comparison of Secondary Structure Formation Using 10 Different Force Fields in Microsecond Molecular Dynamics Simulations

Elio A. Cino, Wing-Yiu Choy [The University of Western Ontario, and Mikko Karttunen

J. Chem. Theor. and Comp. **8**, 2725–2740, 2012.

We have compared molecular dynamics (MD) simulations of a β -hairpin forming peptide derived from the protein Nrf2 with 10 biomolecular force fields using trajectories of at least 1 μ s. The total simulation time was 37.2 μ s. Previous studies have shown that different force fields, water models, simulation methods, and parameters can affect simulation outcomes. The MD simulations were done in explicit solvent with a 16-mer Nrf2 β -hairpin forming peptide using Amber ff99SB-ILDN, Amber ff99SB*-ILDN, Amber ff99SB, Amber ff99SB*, Amber ff03, Amber ff03*, GROMOS96 43a1p, GROMOS96 53a6, CHARMM27, and OPLS-AA/L force fields.

Protein Structure Prediction

Structure prediction and binding sites analysis of curcin protein of *Jatropha curcas* using computational approaches

Mugdha Srivastava [National Botanical Research Institute (CSIR), Lucknow], Shishir K. Gupta, P. C. Abhilash and Nandita Singh

J. Mol.Mod., **18**, 2971-2979, 2012.

Ribosome inactivating proteins (RIPs) are defense proteins in a number of higher-plant species that are directly targeted toward herbivores. *Jatropha curcas* is one of the biodiesel plants having RIPs. The *Jatropha* seed meal, after extraction of oil, is rich in curcin, a highly toxic RIP similar to ricin, which makes it unsuitable for animal feed. Although the toxicity of curcin is well documented in the literature, the detailed toxic properties and the 3D structure of curcin has not been determined. In this pursuit, the structure of curcin was modeled by a composite approach of 3D structure prediction using threading and ab initio modeling.

Full-length structural model of RET3 and SEC21 in COPI: identification of binding sites on the appendage for accessory protein recruitment motifs

Laleh Alisaraie and Isabelle Rouiller [McGill University]

J. Mol.Mod., **18**, 3199-3212, 2012.

COPI, a 600 kD heptameric complex (consisting of subunits α , β , γ , δ , ϵ , ζ , and β') "coatomer," assembles non-clathrin-coated vesicles and is responsible for intra-Golgi and Golgi-to-ER protein trafficking. Here, we report the three-dimensional structures of the entire sequences of yeast Sec21 (γ -COPI mammalian ortholog), yeast Ret3 (ζ -COPI mammalian ortholog), and the results of successive molecular dynamics investigations of the subunits and assembly based on a protein-protein docking experiment.

Dynamic and Thermodynamic Signatures of Native and Non-Native Protein States with Application to the Improvement of Protein Structures

Da-Wei Li and Rafael Brüschweiler [Florida State University]

J. Chem. Theor. and Comp., **8**, 2531–2539, 2012.

Accurate knowledge of the 3D structural ensemble of proteins is important for understanding of their biological function. We report here the application of microsecond all-atom molecular dynamics (MD) simulations in explicit solvent for the improvement of the quality of low-resolution structures obtained by protein structure prediction (decoys). Seventy MD simulations of $\sim 1 \mu\text{s}$ average duration were performed on 13 different protein systems starting from X-ray crystal structures and decoys.

Structures of A β 17–42 Trimers in Isolation and with Five Small-Molecule Drugs Using a Hierarchical Computational Procedure

Yasmine Chebaro, Ping Jiang, Tong Zang, and Yuguang Mu, Phuong H. Nguyen, Normand Mousseau, Philippe Derreumaux [Université Paris Diderot]

J. Phys. Chem. B., **116**, 8412–8422, 2012.

The amyloid- β protein (A β) oligomers are believed to be the main culprits in the cytotoxicity of Alzheimer's disease (AD) and p3 peptides (A β 17–42 fragments) are present in AD amyloid plaques. Many small-molecule or peptide-based inhibitors are known to slow down A β aggregation and reduce the toxicity in vitro, but their exact modes of action remain to be determined since there has been no atomic level of A β (p3)–drug oligomers. In this study, we have determined the structure of A β 17–42 trimers both in aqueous solution and in the presence of five small-molecule inhibitors using a multiscale computational study.

Protein Structure Prediction (Cont'd)

AWSEM-MD: Protein Structure Prediction Using Coarse-Grained Physical Potentials and Bioinformatically Based Local Structure Biasing

Aram Davtyan, Nicholas P. Schafer, Weihua Zheng, Cecilia Clementi, Peter G. Wolynes, and Garegin A. Papoian [University of Maryland, College Park]

J. Phys. Chem. B., **116**, 8494–8503, 2012.

The associative memory, water mediated, structure and energy model (AWSEM) is a coarse-grained protein force field. AWSEM contains physically motivated terms, such as hydrogen bonding, as well as a bioinformatically based local structure biasing term, which efficiently takes into account many-body effects that are modulated by the local sequence. When combined with appropriate local or global alignments to choose memories, AWSEM can be used to perform de novo protein structure prediction. Herein we present structure prediction results for a particular choice of local sequence alignment method based on short residue sequences called fragments.

The Coarse-Grained OPEP Force Field for Non-Amyloid and Amyloid Proteins

Yasmine Chebaro, Samuela Pasquali, and Philippe Derreumaux [Université Paris Diderot]

J. Phys. Chem. B., **116**, 8741–8752, 2012.

Coarse-grained protein models with various levels of granularity and degrees of freedom offer the possibility to explore many phenomena including folding, assembly, and recognition in terms of dynamics and thermodynamics that are inaccessible to all-atom representations in explicit aqueous solution. Here, we present a refined version of the coarse-grained optimized potential for efficient protein structure prediction (OPEP) based on a six-bead representation. The OPEP version 4.0 parameter set, which uses a new analytical formulation for the nonbonded interactions and adds specific side-chain–side-chain interactions for α -helix, is subjected to three tests.

GSAFold: A new application of GSA to protein structure prediction

Marcelo C. R. Melo, Rafael C. Bernardi [Qualidade e Tecnologia], Tácio V. A. Fernandes and Pedro G. Pascutti

Proteins: Stru. Fun. & Bioinf., **80**, 2305–2310, 2012.

The folding process defines three-dimensional protein structures from their amino acid chains. A protein's structure determines its activity and properties; thus knowing such conformation on an atomic level is essential for both basic and applied studies of protein function and dynamics. However, the acquisition of such structures by experimental methods is slow and expensive, and current computational methods mostly depend on previously known structures to determine new ones. Here we present a new software called GSAFold that applies the generalized simulated annealing (GSA) algorithm on ab initio protein structure prediction.

Comparative or Homology Modeling

Structural analysis of secretory phospholipase A2 from *Clonorchis sinensis*: therapeutic implications for hepatic fibrosis

Gururao Hariprasad [All India Institute of Medical Sciences, New Delhi], Punit Kaur, Alagiri Srinivasan, Tej Pal Singh and Manoj Kumar

J. Mol.Mod., **18**, 3139-3145, 2012.

Hepatic fibrosis is a common complication of the infection by the parasite, *Clonorchis sinensis*. There is a high incidence of this disease in the Asian countries with an increased risk of conversion to cancer. A secretory phospholipase A2 (PLA2) enzyme from the parasite is implicated in the pathology. This is an attractive drug target in the light of extensive structural characterization of this class of enzyme. In this study, the structure of the enzyme was modeled based on its sequence homology to the group III bee venom PLA2. On analysis, the overall structure essentially is comprised of three helices, two sets of β -wings and an elongated C-terminal extension.

Structural requirements of pyrimidine, thienopyridine and ureido thiophene carboxamide-based inhibitors of the checkpoint kinase 1: QSAR, docking, molecular dynamics analysis

Fangfang Wang, Zhi Ma, Yan Li, Jinan Wang and Yonghua Wang [Northwest A&F University]

J. Mol.Mod., **18**, 3227-3242, 2012.

Our focus of current research is directed toward clarification of novel inhibitors (pyrazolo[1,5-a] pyrimidine (PP), thienopyridines (TP) and 2-ureido thiophene carboxamide (UTC) derivatives) targeting Checkpoint kinase 1 (CHK1), which is an oncology target of significant current interest. Our computational approaches include: (i) QSAR analysis was carried out on the computed steric/electrostatic/hydrophobic/hydrogen bond donor/hydrogen bond acceptor interactions with the pseudoreceptor surface, which yielded predictive models capable of explaining much of the variance of inhibitors.

Pharmacophore modeling, molecular docking, and molecular dynamics simulation approaches for identifying new lead compounds for inhibiting aldose reductase 2

Sugunadevi Sakkiyah, Sundarapandian Thangapandian and Keun Woo Lee [Gyeongsang National University]

J. Mol.Mod., **18**, 3267-3282, 2012.

Aldose reductase 2 (ALR2), which catalyzes the reduction of glucose to sorbitol using NADP as a cofactor, has been implicated in the etiology of secondary complications of diabetes. A pharmacophore model, Hypo1, was built based on 26 compounds with known ALR2-inhibiting activity values. Hypo1 contains important chemical features required for an ALR2 inhibitor, and demonstrates good predictive ability by having a high correlation coefficient (0.95) as well as the highest cost difference (128.44) and the lowest RMS deviation (1.02) among the ten pharmacophore models examined.

Protein Conformational Analysis

LeuT Conformational Sampling Utilizing Accelerated Molecular Dynamics and Principal Component Analysis

James R. Thomas, Patrick C. Gedeon, Barry J. Grant, Jeffrey D. Madura [Duquesne University]

Biophysical Journal. **103**, L1-L3, 2012.

Monoamine transporters (MATs) function by coupling ion gradients to the transport of dopamine, norepinephrine, or serotonin. Despite their importance in regulating neurotransmission, the exact conformational mechanism by which MATs function remains elusive. To this end, we have performed seven 250 ns accelerated molecular dynamics simulations of the leucine transporter, a model for neurotransmitter MATs. By varying the presence of binding-pocket leucine substrate and sodium ions, we have sampled plausible conformational states representative of the substrate transport cycle.

Predicting the Effect of Ions on the Conformation of the H-NS Dimerization Domain

Jocelyne Vreede [University of Amsterdam], Remus Th. Dame

Biophysical Journal. **103**, 89-98, 2012.

The histone-like nucleoid structuring protein (H-NS) is a DNA-organizing protein in bacteria. It contains a DNA-binding domain and a dimerization domain, connected by a flexible linker region. Dimerization occurs through the formation of a helical bundle, including a coiled-coil interaction motif. Two conformations have been resolved, for different sequences of *Escherichia coli* H-NS, resulting in an antiparallel coiled-coil for the shorter wild-type sequence, and a parallel coiled-coil for the longer C21S mutant.

Molecular and Thermodynamic Insights into the Conformational Transitions of Hsp90

Mijo Simunovic, Gregory A. Voth [University of Chicago, Chicago]

Biophysical Journal. **103**, 284-292, 2012.

Hsp90, the most abundant cellular protein, has been implicated in numerous physiological and pathological processes. It controls protein folding and prevents aggregation, but it also plays a role in cancer and neurological disorders, making it an attractive drug target. Experimental efforts have demonstrated its remarkable structural flexibility and conformational complexity, which enable it to accommodate a variety of clients, but have not been able to provide a detailed molecular description of the conformational transitions. In our molecular dynamics simulations, Hsp90 underwent dramatic structural rearrangements into energetically favorable stretched and compact states.

Role of β -Hairpin Formation in Aggregation: The Self-Assembly of the Amyloid- β (25–35) Peptide

Luca Larini, Joan-Emma Shea [University of California, Santa Barbara]

Biophysical Journal. **103**, 576-586, 2012.

The amyloid- β (25–35) peptide plays a key role in the etiology of Alzheimer's disease due to its extreme toxicity even in the absence of aging. Because of its high tendency to aggregate and its low solubility in water, the structure of this peptide is still unknown. In this work, we sought to understand the early stages of aggregation of the amyloid- β (25–35) peptide by conducting simulations of oligomers ranging from monomers to tetramers.

Protein Conformational Analysis (Cont'd)

Molecular modeling study for conformational changes of Sirtuin 2 due to substrate and inhibitor binding

Sugunadevi Sakthiah, Meganathan Chandrasekaran, Yuno Lee, Songmi Kim & Keun Woo Lee [Gyeongsang National University]

J. Biomol. Stru. and Dyn., **30**, 235-254, 2012.

Sirtuin is a member of NAD⁺-dependent deacetylase family. The structural details of Sirtuin 2 (SIRT2) complex will be very useful to discover the drug which might have beneficial effects on various diseases like cancer, diabetes, etc. Unfortunately, SIRT2 complex structure is not available yet, hence molecular docking was carried out to dock the substrate (NAD⁺ and acetylated lysine) and inhibitor (sirtinol) in the NAD⁺ binding site. The suitable binding orientation of substrate and inhibitor in the SIRT2 active site was selected and subjected to 500 ns MD simulations to adjust the binding orientation of inhibitor and substrate as well as to identify the conformational changes in the active site.

Conformational analysis of GT1B ganglioside and its interaction with botulinum neurotoxin type B: a study by molecular modeling and molecular dynamics

Sureshkumar Venkateshwari & Kasinadar Veluraja [Manonmaniam Sundaranar University]

J. Biomol. Stru. and Dyn., **30**, 255-268, 2012.

The conformational property of oligosaccharide GT1B in aqueous environment was studied by molecular dynamics (MD) simulation using all-atom model. Based on the trajectory analysis, three prominent conformational models were proposed for GT1B. Direct and water-mediated hydrogen bonding interactions stabilize these structures. The molecular modeling and 1500 ns MD simulation of the Botulinum Neuro Toxin/B (BoNT/B) – GT1B complex revealed that BoNT/B can accommodate the GT1B in the single binding mode. Least mobility was seen for oligo-GT1B in the binding pocket.

The Large Scale Conformational Change of the Human DPP III–Substrate Prefers the “Closed” Form

Antonija Tomić, Miguel González, and Sanja Tomić [Universitat de Barcelona]

J.Chem. Infor. and Mod. **52**, 1583–1594, 2012.

Human dipeptidyl peptidase III (DPP III) is a two domain metallo-peptidase from the M49 family. The wide interdomain cleft and broad substrate specificity suggest that this enzyme could experience significant conformational change. Long (>100 ns) molecular dynamics (MD) simulations of DPP III revealed large range conformational changes of the protein, suggesting the pre-existing equilibrium model for a substrate binding. The binding free energy calculations revealed tighter binding of the preferred synthetic substrate Arg–Arg–2–naphthylamide to the “closed” than to the “open” DPP III conformation.

Multiscale Simulation on a Light-Harvesting Molecular Triad

Guoxiong Su, Arkadiusz Czader, Dirar Homouz, Gabriela Bernardes, Sana Mateen, and Margaret S. Cheung [University of Houston, Houston]

J. Phys. Chem. B., **116**, 8460–8473, 2012.

We have investigated the effect of solvation and confinement on an artificial photosynthetic material, carotenoid-porphyrin-C₆₀ molecular triad, by a multiscale approach and an enhanced sampling technique. We have developed a combined approach of quantum chemistry, statistical physics, and all-atomistic molecular dynamics simulation to determine the partial atomic charges of the ground-state triad. To fully explore the free energy landscape of triad, the replica exchange method was applied to enhance the sampling efficiency of the simulations.

Protein Conformational Analysis (Cont'd)

Effect of Bisecting GlcNAc and Core Fucosylation on Conformational Properties of Biantennary Complex-Type N-Glycans in Solution

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

J. Phys. Chem. B., **116**, 8504–8512, 2012.

The introduction of bisecting GlcNAc and core fucosylation in N-glycans is essential for fine functional regulation of glycoproteins. The effect of these modifications on the conformational properties of N-glycans is examined at the atomic level by performing replica-exchange MD (REMD) simulations. We simulate four biantennary complex-type N-glycans, namely, unmodified, two single-substituted with either bisecting GlcNAc or core fucose, and disubstituted forms. By using REMD as an enhanced sampling technique, five distinct conformers in solution, each of which is characterized by its local orientation of the Man α 1-6Man glycosidic linkage, are observed for all four N-glycans.

Analysis and Elimination of a Bias in Targeted Molecular Dynamics Simulations of Conformational Transitions: Application to Calmodulin

Victor Ovchinnikov and Martin Karplus [Harvard University, Cambridge]

J. Phys. Chem. B., **116**, 8584–8603, 2012.

The popular targeted molecular dynamics (TMD) method for generating transition paths in complex biomolecular systems is revisited. In a typical TMD transition path, the large-scale changes occur early and the small-scale changes tend to occur later. As a result, the order of events in the computed paths depends on the direction in which the simulations are performed. To identify the origin of this bias, and to propose a method in which the bias is absent, variants of TMD in the restraint formulation are introduced and applied to the complex open $\leftrightarrow$ closed transition in the protein calmodulin.

Protein Dynamics

Normal-Mode-Analysis-Guided Investigation of Crucial Intersubunit Contacts in the cAMP-Dependent Gating in HCN Channels

Farzana Marni, Shengjun Wu, Gaurav M. Shah, Xin-ping Xu, Amber R. Hackett, Changan Xie, Sabisha Shrestha, Lin Liu, Qinglian Liu, Lei Zhou [Virginia Commonwealth University]

Biophysical Journal. **103**, 19-28, 2012.

Protein structures define a complex network of atomic interactions in three dimensions. Direct visualization of the structure and analysis of the interaction potential energy are not straightforward approaches to pinpoint the atomic contacts that are crucial for protein function. We used the tetrameric hyperpolarization-activated cAMP-regulated (HCN) channel as a model system to study the intersubunit contacts in cAMP-dependent gating. To obtain a systematic survey of the contacts between each pair of residues, we used normal-mode analysis, a computational approach for studying protein dynamics, and constructed the covariance matrix for C- α atoms.

The Dynamic Structure of Thrombin in Solution

Brian Fuglestad, Paul M. Gasper, Marco Tonelli, J. Andrew McCammon, Phineus R.L. Markwick, Elizabeth A. Komives [University of California at San Diego]

Biophysical Journal. **103**, 79-88, 2012.

The backbone dynamics of human α -thrombin inhibited at the active site serine were analyzed using R₁, R₂, and heteronuclear NOE experiments, variable temperature TROSY 2D [¹H-¹⁵N] correlation spectra, and R_{ex} measurements. The N-terminus of the heavy chain, which is formed upon zymogen activation and inserts into the protein core, is highly ordered, as is of the double beta-barrel core. MD simulations yielded a molecular ensemble consistent with measured dipolar couplings that revealed dynamic motions up to milliseconds.

Protein Dynamics (Cont'd)

The extracellular subunit interface of the 5-HT₃ receptors: a computational alanine scanning mutagenesis study

Francesca De Rienzo, Arménio J. Moura Barbosa, Marta A.S. Perez, Pedro A. Fernandes, Maria J. Ramos & Maria Cristina Menziani [University of Modena and Reggio Emilia]

J. Biomol. Stru. and Dyn., **30**, 280-298, 2012.

The functional serotonin 5-HT type-3 (5-HT₃) receptor, the target of many neuroactive drugs, is known to be a pseudo-symmetric pentamer made either of five identical subunits A (homomeric 5-HT_{3A}-R) or of subunits A and B (heteromeric 5-HT_{3A/B}-R) in a still debated arrangement. The serotonin binding site is located in the extracellular region, at the interface between two monomers, called the principal and the complementary subunits. The results of MD simulations and computational alanine scanning mutagenesis studies applied here to the homomeric human 5-HT_{3A}-R disclose an aromatic "hot" cluster in the centre of the interface formed by residues W178 (principal subunit), Y68, Y83, W85 and Y148 (complementary subunit).

Molecular modelling of the mass density of single proteins

Meike Hutt, Tobias Kulschewski & Jürgen Pleiss [Universität Stuttgart]

J. Biomol. Stru. and Dyn., **30**, 318-327, 2012.

Using molecular dynamics (MD) simulations, the density of single proteins and its temperature dependence was modelled starting from the experimentally determined protein structure and a generic, transferable force field, without the need of prior parameterization. Although all proteins consist of the same 20 amino acids, their density in aqueous solution varies up to 10% and the thermal expansion coefficient up to twofold. To model the protein density, systematic MD simulations were carried out for 10 proteins with a broad range of densities (1.32–1.43 g/cm³) and molecular weights (7–97 kDa).

Multiscale Simulations of the Antimicrobial Peptide Maculatin 1.1: Water Permeation through Disordered Aggregates

Daniel L. Parton, Elena V. Akhmatskaya, and Mark S. P. Sansom [University of Oxford, South Parks Road]

J. Phys. Chem. B., **116**, 8485–8493, 2012.

The antimicrobial peptide maculatin 1.1 (M1.1) is an amphipathic α -helix that permeabilizes lipid bilayers. In coarse-grained molecular dynamics (CG MD) simulations, M1.1 has previously been shown to form membrane-spanning aggregates in DPPC bilayers. In this study, a simple multiscale methodology has been applied to allow sampling of important regions of the free energy surface at higher resolution. Thus, by back-converting the CG configurations to atomistic representations, it is shown that water is able to permeate through the M1.1 aggregates.

Conformational Sampling of Peptides in the Presence of Protein Crowders from AA/CG-Multiscale Simulations

Alexander V. Predeus, Seref Gul, Srinivasa M. Gopal, and Michael Feig [Michigan State University, East Lansing]

J. Phys. Chem. B., **116**, 8610–8620, 2012.

Macromolecular crowding is recognized as an important factor influencing folding and conformational dynamics of proteins and nucleic acids. Previous views of crowding have focused on the mostly entropic volume exclusion effect of crowding, but recent studies are indicating the importance of enthalpic effects, in particular, changes in electrostatic interactions due to crowding. Here, temperature replica exchange molecular dynamics simulations of trp-cage and melittin in the presence of explicit protein crowders are presented to further examine the effect of protein crowders on peptide dynamics.

Protein Dynamics (Cont'd)

A Comparison of Multiscale Methods for the Analysis of Molecular Dynamics Simulations

Noah C. Benson [University of Washington] and Valerie Daggett

J. Phys. Chem. B., **116**, 8722–8731, 2012.

Molecular dynamics (MD) is the only technique available for obtaining dynamic protein data at atomic spatial resolution and picosecond or finer temporal resolution. In recent years, the cost of computational resources has decreased exponentially while the number of known protein structures, many of which are not characterized biochemically, has increased rapidly. Here, we address the multiscale nature of the problem by comparing several MD analysis methods to show their strengths and weaknesses at various scales using the wild-type and R282W mutant forms of the DNA-binding domain of protein p53.

pH-Replica Exchange Molecular Dynamics in Proteins Using a Discrete Protonation Method

Danial Sabri Dashti, Yilin Meng, and Adrian E. Roitberg [University of Florida, Gainesville]

J. Phys. Chem. B., **116**, 8805–8811, 2012.

Protonation equilibria in biological molecules modulates structure, dynamics, and function. A pH-replica exchange molecular dynamics (pH-REMD) method is described here to improve the coupling between conformational and protonation sampling. Under a Hamiltonian replica exchange setup, conformations are swapped between two neighboring replicas, which themselves are at different pHs. The method has been validated on a series of biological systems.

Coherent Microscopic Picture for Urea-Induced Denaturation of Proteins

Zaixing Yang, Peng Xiu, Biyun Shi, Lan Hua, and Ruhong Zhou [Zhejiang University]

J. Phys. Chem. B., **116**, 8856–8862, 2012.

In a previous study, we explored the mechanism of urea-induced denaturation of proteins by performing molecular dynamics (MD) simulations of hen lysozyme in 8 M urea and supported the “direct interaction mechanism” whereby urea denatures protein via dispersion interaction (Hua, L.; Zhou, R. H.; Thirumalai, D.; Berne, B. J. *Proc. Natl. Acad. Sci. U.S.A.* **2008**, 105, 16928). Here we perform large scale MD simulations of five representative protein/peptide systems in aqueous urea to investigate if the above mechanism is common to other proteins.

Characterization of the impact of alternative splicing on protein dynamics: The cases of glutathione S-transferase and ectodysplasins-A isoforms

Montserrat Barbany, Jordi Morata, Tim Meyer, Sergi Lois, Modesto Orozco and Xavier de la Cruz [IBMB-CSIC, 08028 Barcelona]

Proteins: Stru. Fun. & Bioinf., **80**, 2235–2249, 2012.

Recent studies have shown how alternative splicing (AS), the process by which eukaryotic genes express more than one product, affects protein sequence and structure. However, little information is available on the impact of AS on protein dynamics, a property fundamental for protein function. In this work, we have addressed this issue using molecular dynamics simulations of the isoforms of two model proteins: glutathione S-transferase and ectodysplasins-A. We have found that AS does not have a noticeable impact on global or local structure fluctuations.

Free Energy Calculations

Insights from Free-Energy Calculations: Protein Conformational Equilibrium, Driving Forces, and Ligand-Binding Modes

Yu-ming M. Huang, Wei Chen, Michael J. Potter, Chia-en A. Chang [University of California, Riverside]

Biophysical Journal. **103**, 342-351, 2012.

Accurate free-energy calculations provide mechanistic insights into molecular recognition and conformational equilibrium. In this work, we performed free-energy calculations to study the thermodynamic properties of different states of molecular systems in their equilibrium basin, and obtained accurate absolute binding free-energy calculations for protein-ligand binding using a newly developed M2 algorithm. We used a range of Asp-Phe-Gly (DFG)-in/out p38 α mitogen-activated protein kinase inhibitors as our test cases. We also focused on the flexible DFG motif, which is closely connected to kinase activation and inhibitor binding.

Discovering Free Energy Basins for Macromolecular Systems via Guided Multiscale Simulation

Yuriy V. Sereda, Abhishek B. Singharoy, Martin F. Jarrold, and Peter J. Ortoleva [Indiana University]

J. Phys. Chem. B., **116**, 8534–8544, 2012.

An approach for the automated discovery of low free energy states of macromolecular systems is presented. The method does not involve delineating the entire free energy landscape but proceeds in a sequential free energy minimizing state discovery; i.e., it first discovers one low free energy state and then automatically seeks a distinct neighboring one. These states and the associated ensembles of atomistic configurations are characterized by coarse-grained variables capturing the large-scale structure of the system.

Ligand Binding/Docking

Binding of Congo Red to Amyloid Protofibrils of the Alzheimer A β_{9-40} Peptide Probed by Molecular Dynamics Simulations

Chun Wu, Justin Scott, Joan-Emma Shea [University of California, Santa Barbara]

Biophysical Journal. **103**, 550-557, 2012.

Congo red (CR) is a commonly used histological amyloid dye and a weak amyloid inhibitor. There is currently no experimentally available structure of CR bound to an amyloid fibril and the binding modes, and the mechanisms governing its inhibitory and optical properties are poorly understood. We present the first, to our knowledge, atomistically detailed picture of CR binding to protofibrils of the Alzheimer A β_{9-40} peptide. We identify three major binding modes, with the primary mode residing in the grooves formed by the β -sheets, and observe a restriction of the torsional rotation of the CR molecule upon binding.

The effect of fucoidan on tyrosinase: computational molecular dynamics integrating inhibition kinetics

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

J. Biomol. Stru. and Dyn., **30**, 460-473, 2012.

Fucoidan is a complex sulfated polysaccharide extracted from brown seaweed and has a wide variety of biological activities. We investigated the inhibitory effect of fucoidan on tyrosinase via a combination of inhibition kinetics and computational simulations. Time-interval kinetics showed that the inhibition was processed as first order with biphasic processes. For further insight, we simulated dockings with various sizes of molecular models (monomer to decamer) of fucoidan and showed that the best binding energy change results were obtained from the pentamer (−1.89 kcal/mol) and the hexamer (−1.97 kcal/mol) models of AutoDock Vina.

Ligand Binding / Docking (Cont'd)

Computational study of ligand binding in lipid transfer proteins: Structures, interfaces, and free energies of protein-lipid complexes

Luis F. Pacios [Universidad Politécnica de Madrid], Cristina Gómez-Casado, Leticia Tordesillas, Arantxa Palacín, Rosa Sánchez-Monge and Araceli Díaz-Perales

J. Comp. Chem. **33**, 1831–1844, 2012.

Plant nonspecific lipid transfer proteins (nsLTPs) bind a wide variety of lipids, which allows them to perform disparate functions. Recent reports on their multifunctionality in plant growth processes have posed new questions on the versatile binding abilities of these proteins. The lack of binding specificity has been customarily explained in qualitative terms on the basis of a supposed structural flexibility and nonspecificity of hydrophobic protein-ligand interactions. We present here a computational study of protein-ligand complexes formed between five nsLTPs and seven lipids bound in two different ways in every receptor protein.

Computational Studies of Darunavir into HIV-1 Protease and DMPC Bilayer: Necessary Conditions for Effective Binding and the Role of the Flaps

Georgios Leonis [National Hellenic Research Foundation, Athens], Żaneta Czyżnikowska, Grigorios Megariotis, Heribert Reis, and Manthos G. Papadopoulos

J. Chem. Infor. and Mod. **52**, 1542–1558, 2012.

Human immunodeficiency virus type 1 protease (HIV-1 PR) is one of the main targets toward AIDS therapy. We have selected the potent drug darunavir and a weak inhibitor (fullerene analog) as HIV-1 PR substrates to compare protease's conformational features upon binding. Molecular dynamics (MD), molecular mechanics Poisson–Boltzmann surface area (MM–PBSA), and quantum-mechanical (QM) calculations indicated the importance of the stability of HIV-1 PR flaps toward effective binding: a weak inhibitor may induce flexibility to the flaps, which convert between closed and semiopen states.

Molecular Modeling to Provide Insight into the Substrate Binding and Catalytic Mechanism of Human Biliverdin-IX α Reductase

Gang Fu, Haining Liu, and Robert J. Doerksen [University of Mississippi]

J. Phys. Chem. B., **116**, 9580–9594, 2012.

Human biliverdin-IX α reductase (hBVR-A) catalyzes the conversion of biliverdin-IX α to bilirubin-IX α in the last step of heme degradation and is a key enzyme in regulating a wide range of cellular responses. Though the X-ray structure of hBVR-A is available including cofactor, a crystal structure with a bound substrate would be even more useful as a starting point for protein-structure-based inhibitor design, but none have been reported. The present study employed induced fit docking (IFD) to study the substrate binding modes to hBVR-A of biliverdin-IX α and four analogues.

Enzyme Catalysis

The Catalytic Mechanism of HIV-1 Integrase for DNA 3'-End Processing Established by QM/MM Calculations

António J. M. Ribeiro, Maria J. Ramos, and Pedro A. Fernandes [Universidade do Porto]

J. Am. Chem. Soc., **134**, 13436–13447, 2012.

The development of HIV-1 integrase (INT) inhibitors has been hampered by incomplete structural and mechanistic information. In this work, we have used all experimental information available for INT and similar enzymes, to build a model of the holo-integrase:DNA complex that includes an entire central core domain, a ssDNA GCAGT substrate, and two magnesium ions. Subsequently, we used a large array of computational techniques, which included molecular dynamics, thermodynamic integration, and high-level quantum mechanics/molecular mechanics (QM/MM) calculations to study the possible pathways for the mechanism of 3' end processing catalyzed by INT.

The role of residue S139 of mandelate racemase: synergistic effect of S139 and E317 on transition state stabilization

Jiali Gu & Hongwei Yu [Zhejiang University]

J. Biomol. Stru. and Dyn., **30**, 585-593, 2012.

Mandelate racemase (MR) from *Pseudomonas putida* catalyzes the specific carbon–hydrogen bond cleavage of carbon acids with high pK_a values. To further explore the catalytic mechanism of MR, “hot spots” contributing to transition state (TS) stabilization were identified by molecular dynamics (MD) simulations. MD simulations of MR with mandelic acid interpreted S139 in the active site cavity formed a hydrogen bond (HB) with one carboxyl oxygen of mandelate which also interacts with E317 through HB.

Theoretical investigation of the enzymatic phosphoryl transfer of β -phosphoglucomutase: revisiting both steps of the catalytic cycle

Brigitta Elsässer [University of Paderborn, Warburgerstr. 100], Silvia Dohmeier-Fischer and Gregor Fels

J. Mol.Mod., **18**, 3169-3179, 2012.

Mutases transfer a phosphoryl group while nucleases cleave the phosphodiester linkages between two nucleotides. The subject of our present study is the *Lactococcus lactis* β -phosphoglucomutase (β -PGM), which effectively catalyzes the interconversion of β -D-glucose-1-phosphate (β -G1P) to β -D-glucose-6-phosphate (β -G6P) and vice versa via stable intermediate β -D-glucose-1,6-(bis)phosphate (β -G1,6diP) in the presence of Mg^{2+} . In this paper we revisited the reaction mechanism of the phosphoryl transfer starting from the bisphosphate β -G1,6diP in both directions (toward β -G1P and β -G6P) combining docking techniques and QM/MM theoretical method at the DFT/PBE0 level of theory.

An Active Site Water Broadens Substrate Specificity in S-Ribosylhomocysteinase (LuxS): A Docking, MD, and QM/MM Study

WenJuan Huang, Rami Gherib, and James W. Gauld [University of Windsor, Windsor]

J. Phys. Chem. B., **116**, 8916–8929, 2012.

Type-2 quorum sensing (QS-2) is a cell–cell signaling process known to be used by a number of pathogenic bacteria and to play important roles in their population growth and virulence. S-ribosyl homocysteinase (LuxS) is a key enzyme in the formation of the signaling molecule of QS-2, autoinducer II (AI-2). In this study, substrate (S-ribosylhomocysteine: SRH) binding and possible initial reaction steps of its catalytic mechanism leading to formation of a putative 2-keto-SRH intermediate have been examined.

Enzyme Catalysis (Cont'd)

Multifaceted Substrate Capture Scheme of a Rhomboid Protease

Tyler Reddy and Jan K. Rainey [Dalhousie University]

J. Phys. Chem. B., **116**, 8942–8954, 2012.

Rhomboid proteases are integral membrane serine proteases that catalyze peptide bond hydrolysis in biological membranes. Little is currently known about the interaction of enzyme and substrate. Coarse-grained molecular dynamics simulations in hydrated lipid bilayers are employed herein to study the interaction of the *E. coli* rhomboid protease GlpG (ecGlpG) with the transmembrane domain (TMD) of the substrate Spitz. Spitz does not associate with ecGlpG exclusively at the putative substrate gate near TMD 5.

Simulation reveals two major docking pathways between the hexapeptide GDYMN and the catalytic domain of the insulin receptor protein kinase

Zunnan Huang and Chung F. Wong [University of Missouri-Saint Louis]

Proteins: Stru. Fun. & Bioinf., **80**, 2275–2286, 2012.

Extending a previous mining-minima approach to identifying the docking pathways between the hexapeptide GDYMN and the catalytic domain of the insulin receptor tyrosine kinase (IRK), we found two major docking pathways connecting the binding pocket and the surface of the protein. One pathway was more likely to lead to phosphate transfer from ATP to the peptide as the distance between the γ -phosphate of ATP and the hydroxyl oxygen of the target tyrosine approached one that could facilitate reaction.

Protein-Protein Interactions

Inhibition of protein–protein interaction of HER2–EGFR and HER2–HER3 by a rationally designed peptidomimetic

Sashikanth Banappagari, Miriam Corti, Seth Pincus & Seetharama Satyanarayanajois [University of Louisiana at Monroe]

J. Biomol. Stru. and Dyn., **30**, 594–606, 2012.

Protein–protein interactions (PPI) play a crucial role in many biological processes and modulation of PPI using small molecules to target hot spots has therapeutic value. As a model system we will use PPI of human epidermal growth factor receptors (EGFRs). Among the four EGFRs, EGFR–HER2 and HER2–HER3 are well known in cancer. We have designed a small molecule that is targeted to modulate HER2-mediated signaling. Our approach is novel because the small molecule designed disrupts dimerization not only of EGFR–HER2, but also of HER2–HER3.

Membrane Proteins and Lipid Peptide Interactions

Supramolecular Structure of Membrane-Associated Polypeptides by Combining Solid-State NMR and Molecular Dynamics Simulations

Markus Weingarth, Christian Ader, Adrien J.S. Melquiond, Deepak Nand, Olaf Pongs, Stefan Becker, Alexandre M.J.J. Bonvin, Marc Baldus [Utrecht University]

Biophysical Journal. **103**, 29-37, 2012.

Elemental biological functions such as molecular signal transduction are determined by the dynamic interplay between polypeptides and the membrane environment. Determining such supramolecular arrangements poses a significant challenge for classical structural biology methods. We introduce an iterative approach that combines magic-angle spinning solid-state NMR spectroscopy and atomistic molecular dynamics simulations for the determination of the structure and topology of membrane-bound systems with a resolution and level of accuracy difficult to obtain by either method alone.

Structural Determinants of the Supramolecular Organization of G Protein-Coupled Receptors in Bilayers

Xavier Periole [University of Groningen], Adam M. Knepp, Thomas P. Sakmar, Siewert J. Marrink, and Thomas Huber

J. Am. Chem. Soc., **134**, 10959–10965, 2012.

The G protein-coupled receptor (GPCR) rhodopsin self-assembles into supramolecular structures in native bilayers, but the structural determinants of receptor oligomerization are not known. We carried out multiple self-assembly coarse-grained molecular dynamics (CGMD) simulations of model membranes containing up to 64 molecules of the visual receptor rhodopsin over time scales reaching 100 μ s. The simulations show strong preferential interaction modes between receptors.

Influence of the Membrane Lipophilic Environment on the Structure and on the Substrate Access/Egress Routes of the Human Aromatase Enzyme. A Computational Study

Jacopo Sgrignani and Alessandra Magistrato [CNR-IOM-Democritos National Simulation Center]

J.Chem. Infor. and Mod. **52**, 1595–1606, 2012.

Human aromatase (HA), an enzyme located on the membrane of the endoplasmatic reticulum, is of crucial biological importance in the biosynthesis of estrogens. High levels of estrogens are related with important pathologies, conferring to HA a key role as a pharmacological target. In this study we provide, for the first time, an atomistic model of HA embedded on a membrane model to understand the influence of the membrane lipophilic environment on the structural and dynamical properties of HA and on the access/egress pathways of the substrate (androstenedione, ASD) and of the oxygen molecule (involved in the enzymatic process) into/from the HA active site.

The Transmembrane Helix Tilt May Be Determined by the Balance between Precession Entropy and Lipid Perturbation

Yana Gofman, Turkan Haliloglu, and Nir Ben-Tal [Tel-Aviv University]

J. Chem. Theor. and Comp., **8**, 2896–2904, 2012.

Hydrophobic helical peptides interact with lipid bilayers in various modes, determined by the match between the length of the helix's hydrophobic core and the thickness of the hydrocarbon region of the bilayer. For example, long helices may tilt with respect to the membrane normal to bury their hydrophobic cores in the membrane, and the lipid bilayer may stretch to match the helix length. The tilt is driven by a gain in the helix precession entropy, which compensates for the free energy penalty resulting from membrane deformation. Using this free energy balance, we derived theoretically an equation of state, describing the dependence of the tilt on the helix length and membrane thickness.

Membrane Proteins and Lipid Peptide Interactions (Cont'd)

A Novel Approach to the Investigation of Passive Molecular Permeation through Lipid Bilayers from Atomistic Simulations

Zhaleh Ghaemi, Manuela Minozzi, Paolo Carloni, and Alessandro Laio [SISSA- Scuola Internazionale Superiore di Studi Avanzati]

J. Phys. Chem. B., **116**, 8714–8721, 2012.

Predicting the permeability coefficient (P) of drugs permeating through the cell membrane is of paramount importance in drug discovery. We here propose an approach for calculating P based on bias-exchange metadynamics. The approach allows constructing from atomistic simulations a model of permeation taking explicitly into account not only the “trivial” reaction coordinate, the position of the drug along the direction normal to the lipid membrane plane, but also other degrees of freedom, for example, the torsional angles of the permeating molecule, or variables describing its solvation/desolvation.

Diffusive Nature of Xenon Anesthetic Changes Properties of a Lipid Bilayer: Molecular Dynamics Simulations

Eiji Yamamoto, Takuma Akimoto, Hiroyuki Shimizu, Yoshinori Hirano, Masato Yasui, and Kenji Yasuoka [Keio University]

J. Phys. Chem. B., **116**, 8989–8995, 2012.

Effects of general anesthesia can be controllable by the ambient pressure. We perform molecular dynamics simulations for a 1-palmitoyl-2-oleoyl phosphatidylethanolamine lipid bilayer with or without xenon molecules by changing the pressure to elucidate the mechanism of the pressure reversal of general anesthesia. According to the diffusive nature of xenon molecules in the lipid bilayer, a decrease in the orientational order of the lipid tails, an increase in the area and volume per lipid molecule, and an increase in the diffusivity of lipid molecules are observed.

Mechanisms of Budding of Nanoscale Particles through Lipid Bilayers

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

J. Phys. Chem. B., **116**, 9595–9603, 2012.

We examine the budding of a nanoscale particle through a lipid bilayer using molecular dynamics simulations, free energy calculations, and an elastic theory, with the aim of determining the extent to which equilibrium elasticity theory can describe the factors that control the mechanism and efficiency of budding. The particle is a smooth sphere which experiences attractive interactions to the lipid head groups. Depending on the parameters, we observe four classes of dynamical trajectories: particle adhesion to the membrane, stalled partially wrapped states, budding followed by scission, and membrane rupture.

Coarse grain lipid–protein molecular interactions and diffusion with MsbA flippase

Andrew B. Ward, Olgun Guvench and Ronald D. Hills Jr [University of New England]

Proteins: Stru. Fun. & Bioinf., **80**, 2178–2190, 2012.

Coarse-grained (CG) modeling has proven effective for simulating lipid bilayer dynamics on scales of biological interest. Modeling the dynamics of flexible membrane proteins within the bilayer, on the other hand, poses a considerable challenge due to the complexity of the folding or conformational landscape. In the present work, the multiscale coarse-graining method is applied to atomistic peptide-lipid “soup” simulations to develop a general set of CG protein–lipid interaction potentials.

Protein Folding

Smoothing of the GB1 Hairpin Folding Landscape by Interfacial Confinement

Apratim Bhattacharya, Robert B. Best, Jeetain Mittal [, Lehigh University, Bethlehem]

Biophysical Journal. **103**, 596-600, 2012.

We study the effects of confinement between planar walls on the folding thermodynamics of a β -hairpin, using large-scale replica-exchange molecular-dynamics simulations with an all-atom model and explicit solvent. We find that the folding free-energy landscape of this peptide observed in bulk is significantly modified when the peptide is confined between the walls. Most notably, the propensity of the peptide to form a misfolded state observed in the bulk solution becomes negligible under confinement.

Slow Unfolded-State Structuring in Acyl-CoA Binding Protein Folding Revealed by Simulation and Experiment

Vincent A. Voelz, Marcus Jäger, Shuhuai Yao, Yujie Chen, Li Zhu, Steven A. Waldauer, Gregory R. Bowman, Mark Friedrichs, Olgica Bakajin, Lisa J. Lapidus, Shimon Weiss, and Vijay S. Pande [Stanford University, Stanford]

J. Am. Chem. Soc., **134**, 12565–12577, 2012.

Protein folding is a fundamental process in biology, key to understanding many human diseases. Experimentally, proteins often appear to fold via simple two- or three-state mechanisms involving mainly native-state interactions, yet recent network models built from atomistic simulations of small proteins suggest the existence of many possible metastable states and folding pathways. We reconcile these two pictures in a combined experimental and simulation study of acyl-coenzyme A binding protein (ACBP), a two-state folder (folding time ~ 10 ms) exhibiting residual unfolded-state structure, and a putative early folding intermediate.

Folding Dynamics of Cytochrome c Using Pulse Radiolysis

Jungkweon Choi, Mamoru Fujitsuka, Sachiko Tojo, and Tetsuro Majima [Osaka University]

J. Am. Chem. Soc., **134**, 13430–13435, 2012.

Pulse radiolysis is a powerful method to realize real-time observation of various redox processes, which induces various structural and functional changes occurring in biological systems. In this study, we report that in the presence of the high concentration of the denaturant, guanidine HCl (GdHCl), the selective reduction of the oxidized cytochrome c (Cyt c) takes place in time scales of a few microseconds by the electron transfer from the guanidine radical that is formed by the fast reaction of e_{aq}^- with GdHCl, consequently leading to folding kinetics of Cyt c.

Discrete Molecular Dynamics: An Efficient And Versatile Simulation Method For Fine Protein Characterization

David Shirvanyants, Feng Ding, Douglas Tsao, Srinivas Ramachandran, and Nikolay V. Dokholyan [University of North Carolina]

J. Phys. Chem. B., **116**, 8375–8382, 2012.

Until now it has been impractical to observe protein folding in silico for proteins larger than 50 residues. Limitations of both force field accuracy and computational efficiency make the folding problem very challenging. Here we employ discrete molecular dynamics (DMD) simulations with an all-atom force field to fold fast-folding proteins. We extend the DMD force field by introducing long-range electrostatic interactions to model salt-bridges and a sequence-dependent semiempirical potential accounting for natural tendencies of certain amino acid sequences to form specific secondary structures.

Protein Folding (Cont'd)

Reversibility of Prion Misfolding: Insights from Constant-pH Molecular Dynamics Simulations

Diogo Vila-Viçosa, Sara R. R. Campos, António M. Baptista, and Miguel Machuqueiro [Universidade de Lisboa]

J. Phys. Chem. B., **116**, 8812–8821, 2012.

The prion protein (PrP) is the cause of a group of diseases known as transmissible spongiform encephalopathies (TSEs). Creutzfeldt–Jakob disease and bovine spongiform encephalopathy are examples of TSEs. Although the normal form of PrP (PrP^C) is monomeric and soluble, it can misfold into a pathogenic form (PrP^{Sc}) that has a high content of β -structure and can aggregate forming amyloid fibrils. The mechanism of conversion of PrP^C into PrP^{Sc} is not known but different triggers have been proposed. The goal of the present work was to study the effects of a change in pH to 7 in several transient conformations of this simulation, in order to draw some conclusions about the reversibility of PrP misfolding.

Protein-Nucleic acid Interactions

Theoretical prediction of the binding free energy for mutants of replication protein A

Claudio Carra [Universities Space Research Association, Columbia], Janapriya Saha and Francis A. Cucinotta

J. Mol.Mod., **18**, 3035-3049, 2012.

The replication protein A (RPA) is a heterotrimeric (70, 32, and 14 kDa subunits), single stranded DNA (ssDNA) binding protein required for pivotal functions in the cell metabolism, such as chromosomal replication, prevention of hairpin formation, DNA repair and recombination, and signaling after DNA damage. We performed a study based on molecular dynamics simulation aimed to reproduce the experimental change in binding free energy, $\Delta\Delta G$, of RPA70 mutants to further elucidate the nature of the protein-ssDNA interaction.

BROMOC-D: Brownian Dynamics/Monte-Carlo Program Suite to Study Ion and DNA Permeation in Nanopores

Pablo M. De Biase, Carlos J. F. Solano, Suren Markosyan, Luke Czapla, and Sergei Yu. Noskov [University of Calgary]

J. Chem. Theor. and Comp., **8**, 2540–2551, 2012.

A theoretical framework is presented to model ion and DNA translocation across a nanopore confinement under an applied electric field. A combined Grand Canonical Monte Carlo Brownian Dynamics (GCMC/BD) algorithm offers a general approach to study ion permeation through wide molecular pores with a direct account of ion–ion and ion–DNA correlations. This work extends previously developed theory by incorporating the recently developed coarse-grain polymer model of DNA by de Pablo and colleagues [Knotts, T. A.; Rathore, N.; Schwartz, D. C.; de Pablo, J. J. *J. Chem. Phys.* **2007**, 126] with explicit ions for simulations of polymer dynamics.

Nucleic Acids

Competition between Supercoils and Toroids in Single Molecule DNA Condensation

David Argudo, Prashant K. Purohit [University of Pennsylvania]

Biophysical Journal. **103**, 118-128, 2012.

The condensation of free DNA into toroidal structures in the presence of multivalent ions and polypeptides is well known. Recent single molecule experiments have shown that condensation into toroids occurs even when the DNA molecule is subjected to tensile forces. Here we show that the combined tension and torsion of DNA in the presence of condensing agents dramatically modifies this picture by introducing supercoiled DNA as a competing structure in addition to toroids. We combine a fluctuating elastic rod model of DNA with phenomenological models for DNA interaction in the presence of condensing agents to compute the minimum energy configuration for given tension and end-rotations.

Probing the Elasticity of DNA on Short Length Scales by Modeling Supercoiling under Tension

Robert Schöpflin, Hergen Brutzer, Oliver Müller, Ralf Seidel, Gero Wedemann [University of Applied Sciences Stralsund]

Biophysical Journal. **103**, 323-330, 2012.

The wormlike-chain (WLC) model is widely used to describe the energetics of DNA bending. Motivated by recent experiments, alternative, so-called subelastic chain models were proposed that predict a lower elastic energy of highly bent DNA conformations. Until now, no unambiguous verification of these models has been obtained because probing the elasticity of DNA on short length scales remains challenging. Here we investigate the limits of the WLC model using coarse-grained Monte Carlo simulations to model the supercoiling of linear DNA molecules under tension.

Crowding Effects on the Formation and Maintenance of Nuclear Bodies: Insights from Molecular-Dynamics Simulations of Simple Spherical Model Particles

Eun Jin Cho, Jun Soo Kim [Ewha Womans University]

Biophysical Journal. **103**, 424-433, 2012.

The physics of structure formation and maintenance of nuclear bodies (NBs), such as nucleoli, Cajal bodies, promyelocytic leukemia bodies, and speckles, in a crowded nuclear environment remains largely unknown. We investigate the role of macromolecular crowding in the formation and maintenance of NBs using computer simulations of a simple spherical model, called Lennard-Jones (LJ) particles. LJ particles form a one-phase, dilute fluid when the intermolecular interaction is weaker than a critical value, above which they phase separate and form a condensed domain.

Magnesium Fluctuations Modulate RNA Dynamics in the SAM-I Riboswitch

Ryan L. Hayes, Jeffrey K. Noel, Udayan Mohanty, Paul C. Whitford, Scott P. Hennelly, José N. Onuchic, and Karissa Y. Sanbonmatsu [Los Alamos National Laboratories]

J. Am. Chem. Soc., **134**, 12043–12053, 2012.

Experiments demonstrate that Mg^{2+} is crucial for structure and function of RNA systems, yet the detailed molecular mechanism of Mg^{2+} action on RNA is not well understood. We investigate the interplay between RNA and Mg^{2+} at atomic resolution through ten 2- μ s explicit solvent molecular dynamics simulations of the SAM-I riboswitch with varying ion concentrations. The structure, including three stemloops, is very stable on this time scale. Simulations reveal that outer-sphere coordinated Mg^{2+} ions fluctuate on the same time scale as the RNA, and that their dynamics couple.

Nucleic Acids (Cont'd)

Kinetic Mechanism of Conformational Switch between Bistable RNA Hairpins

Xiaojun Xu and Shi-Jie Chen [University of Missouri, Columbia]

J. Am. Chem. Soc., **134**, 12499–12507, 2012.

Transitions between the different conformational states play a critical role in many RNA catalytic and regulatory functions. In this study, we use the Kinetic Monte Carlo method to investigate the kinetic mechanism for the conformational switches between bistable RNA hairpins. We find three types of conformational switch pathways for RNA hairpins: refolding after complete unfolding, folding through basepair-exchange pathways and through pseudoknot-assisted pathways, respectively.

Self-assembly of DNA on a gapped carbon nanotube

Alfredo D. Bobadilla and Jorge M. Seminario [Texas A&M University College Station]

J. Mol. Mod., **18**, 3291–3300, 2012.

We perform molecular dynamics simulations to analyze the wrapping process of a single-stranded (ss) DNA around a gapped CNT immersed in a bath of water. We observe the formation of a stable molecular junction with the ssDNA adopting a helical or circular conformation around one CNT electrode and a linear conformation around the opposite electrode. We find that DNA undergoes several conformational changes during equilibration of the self-assembled molecular junction.

Screening for the Location of RNA using the Chloride Ion Distribution in Simulations of Virus Capsids

Daniel S. D. Larsson and David van der Spoel [Uppsala University]

J. Chem. Theor. and Comp., **8**, 2474–2483, 2012.

The complete structure of the genomic material inside a virus capsid remains elusive, although a limited amount of symmetric nucleic acid can be resolved in the crystal structure of 17 icosahedral viruses. The negatively charged sugar–phosphate backbone of RNA and DNA as well as the large positive charge of the interior surface of the virus capsids suggest that electrostatic complementarity is an important factor in the packaging of the genomes in these viruses. To test how much packing information is encoded by the electrostatic and steric envelope of the capsid interior, we performed extensive all-atom molecular dynamics (MD) simulations of virus capsids with explicit water molecules and solvent ions.

Reference Simulations of Noncanonical Nucleic Acids with Different χ Variants of the AMBER Force Field: Quadruplex DNA, Quadruplex RNA, and Z-DNA

Miroslav Krepl, Marie Zgarbová, Petr Stadlbauer, Michal Otyepka, Pavel Banáš, Jaroslav Koča, Thomas E. Cheatham, III, Petr Jurečka, and Jiří Šponer [Academy of Sciences of the Czech Republic]

J. Chem. Theor. and Comp., **8**, 2506–2520, 2012.

Refinement of empirical force fields for nucleic acids requires their extensive testing using as wide range of systems as possible. However, finding unambiguous reference data is not easy. In this paper, we analyze four systems that we suggest should be included in standard portfolio of molecules to test nucleic acids force fields, namely, parallel and antiparallel stranded DNA guanine quadruplex stems, RNA quadruplex stem, and Z-DNA. We highlight parameters that should be monitored to assess the force field performance. The work is primarily based on 8.4 μ s of 100–250 ns trajectories analyzed in detail followed by 9.6 μ s of additional selected backup trajectories that were monitored to verify that the results of the initial analyses are correct.

Nucleic Acids (Cont'd)

Multiscale Modeling of Double-Helical DNA and RNA: A Unification through Lie Groups

Kevin C. Wolfe, Whitney A. Hastings, Samrat Dutta, Andrew Long, Bruce A. Shapiro, Thomas B. Woolf, Martin Guthold, and Gregory S. Chirikjian [Johns Hopkins University, Baltimore]

J. Phys. Chem. B., **116**, 8556–8572, 2012.

Several different mechanical models of double-helical nucleic-acid structures that have been presented in the literature are reviewed here together with a new analysis method that provides a reconciliation between these disparate models. In all cases, terminology and basic results from the theory of Lie groups are used to describe rigid-body motions in a coordinate-free way, and when necessary, coordinates are introduced in a way in which simple equations result. We consider double-helical DNAs and RNAs which, in their unstressed referential state, have backbones that are either straight, slightly precurved, or bent by the action of a protein or other bound molecule.

2. METHODOLOGY

Quantitative Structure-Activity Relations

Molecular simulation of a series of benzothiazole PI3K α inhibitors: probing the relationship between structural features, anti-tumor potency and selectivity

Jinan Wang, Fangfang Wang, Zhengtao Xiao, Guowen Sheng and Yan Li, Yonghua Wang [Northwest A & F University].

J. Mol. Mod., **18**, 2943-2958, 2012.

The phosphatidylinositol 3-kinase α (PI3K α) was genetically validated as a promising therapeutic target for developing novel anticancer drugs. In order to explore the structure-activity correlation of benzothiazole series as inhibitors of PI3K α , comparative molecular field analysis (CoMFA), comparative molecular similarity indices analysis (CoMSIA) were performed on 61 promising molecules to build 3D-QSAR models based on both the ligand- and receptor-based methods. The best CoMFA and CoMSIA models had a cross-validated coefficient r_{cv}^2 of 0.618 and 0.621, predicted correlation coefficient r_{pred}^2 of 0.812 and 0.83, respectively, proving their high correlative and predictive abilities on both the training and test sets.

3-D QSAutogrid/R: An Alternative Procedure To Build 3-D QSAR Models. Methodologies and Applications

Flavio Ballante and Rino Ragno [Sapienza Università di Roma]

J. Chem. Infor. and Mod. **52**, 1674–1685, 2012.

Since it first appeared in 1988 3-D QSAR has proved its potential in the field of drug design and activity prediction. Although thousands of citations now exist in 3-D QSAR, its development was rather slow with the majority of new 3-D QSAR applications just extensions of CoMFA. An alternative way to build 3-D QSAR models, based on an evolution of software, has been named 3-D QSAutogrid/R and has been developed to use only software freely available to academics. 3-D QSAutogrid/R covers all the main features of CoMFA and GRID/GOLPE with implementation by multiprobe/multiregion variable selection (MPGRS) that improves the simplification of interpretation of the 3-D QSAR map.

Quantitative Structure-Activity Relations (Cont'd)

Four-Dimensional Structure–Activity Relationship Model to Predict HIV-1 Integrase Strand Transfer Inhibition using LQTA-QSAR Methodology

Eduardo B. de Melo and Márcia M. C. Ferreira [University of Campinas–UNICAMP]

J.Chem. Infor. and Mod. **52**, 1722–1732, 2012.

Despite highly active antiretroviral therapy (HAART) implementation, there is a continuous need to search for new anti-HIV agents. HIV-1 integrase (HIV-1 IN) is a recently validated biological target for AIDS therapy. In this work, a four-dimensional quantitative structure–activity relationship (4D-QSAR) study using the new methodology named LQTA-QSAR approach with a training set of 85 HIV-1 IN strand transfer inhibitors (INSTI), containing the β -diketo acid (DKA) substructure, was carried out.

QM/MM Prediction of the Stark Shift in the Active Site of a Protein

Daniel J. Sandberg, Aleksandra N. Rudnitskaya, and José A. Gascón [University of Connecticut]

J. Chem. Theor. and Comp. **8**, 2817–2823, 2012.

Recent developments in the biophysical characterization of proteins have provided a means of directly measuring electrostatic fields by introducing a probe molecule to the system of interest and interpreting photon absorption in the context of the Stark effect. To fully account for this effect, the development of accurate atomistic models is of paramount importance. However, suitable computational protocols for evaluating Stark shifts in proteins are yet to be established. In this work, we present a comprehensive computational method to predict the change in absorption frequency of a probe functional group as a direct result of a perturbation in its surrounding electrostatic field created by a protein environment, i.e., the Stark shift.

Application of Adaptive QM/MM Methods to Molecular Dynamics Simulations of Aqueous Systems

Kyoyeon Park, Andreas W. Götz, Ross C. Walker, and Francesco Paesani [University of California, San Diego]

J. Chem. Theor. and Comp. **8**, 2868–2877, 2012.

The difference-based adaptive solvation quantum mechanics/molecular mechanics (adQM/MM) method (*J. Chem. Theory Comput.* **2009**, 5, 2212) as implemented in the Amber software was applied to the study of several chemical processes in solution. The adQM/MM method is based on an efficient selection scheme that enables quantum-mechanical treatment of the active region of a molecular system in solution taking explicitly into account diffusion of solvent molecules between the QM and the MM regions. Specifically, adQM/MM MD simulations are carried out to characterize (1) the free energy profiles of halide exchange S_N2 reactions in water, (2) the hydration structure of the Cl^- ion, and (3) the solvation structure of the zwitterionic form of glycine in water.

Solvation Energy

Implicit Solvation Parameters Derived from Explicit Water Forces in Large-Scale Molecular Dynamics Simulations

Jens Kleinjung, Walter R. P. Scott, Jane R. Allison, Wilfred F. van Gunsteren, and Franca Fraternali [King's College London]

J. Chem. Theor. and Comp. **8**, 2391–2403, 2012.

Implicit solvation is a mean force approach to model solvent forces acting on a solute molecule. It is frequently used in molecular simulations to reduce the computational cost of solvent treatment. In the first instance, the free energy of solvation and the associated solvent–solute forces can be approximated by a function of the solvent-accessible surface area (SASA) of the solute and differentiated by an atom-specific solvation parameter σ_i^{SASA} . A procedure for the determination of values for the σ_i^{SASA} parameters through matching of explicit and implicit solvation forces is proposed.

Potentials and Parameters

The Effect of Newly Developed OPLS-AA Alanine Radical Parameters on Peptide Secondary Structure

Michael C. Owen, László Tóth, Balázs Jojárt, István Komáromi, Imre G. Csizmadia, and Bela Viskolcz [University of Szeged]

J. Chem. Theor. and Comp. **8**, 2569–2580, 2012.

Recent studies using ab initio calculations have shown that C $_{\alpha}$ -centered radical formation by H-abstraction from the backbone of peptide residues has dramatic effects on peptide structure and have suggested that this reaction may contribute to the protein misfolding observed in Alzheimer's and Parkinson's diseases. To enable the effects of C $_{\alpha}$ -centered radicals to be studied in longer peptides and proteins over longer time intervals, force-field parameters for the C $_{\alpha}$ -centered Ala radical were developed for use with the OPLS force field by minimizing the sum of squares deviation between the quantum chemical and OPLS-AA energy hypersurfaces.

Molecular Dynamics

Population Shift between the Open and Closed States Changes the Water Permeability of an Aquaporin Z Mutant

Lin Xin, Claus Hélix-Nielsen, Haibin Su, Jaume Torres, Chuyang Tang, Rong Wang, Anthony Gordon Fane, Yuguang Mu [Nanyang Technological University]

Biophysical Journal. **103**, 212–218, 2012.

Aquaporins are tetrameric transmembrane channels permeable to water and other small solutes. Wild-type (WT) and mutant Aquaporin Z (AqpZ) have been widely studied and multiple factors have been found to affect their water permeability. In this study, molecular dynamics simulations have been performed for the tetrameric AqpZ F43W/H174G/T183F mutant. It displayed ~10% average water permeability compared to WT AqpZ, which had been attributed to the increased channel lumen hydrophobicity.

Molecular Dynamics (Cont'd)

Carbon monoxide binding to the heme group at the dimeric interface modulates structure and copper accessibility in the Cu,Zn superoxide dismutase from *Haemophilus ducreyi*: in silico and in vitro evidences

Giovanni Chillemi [CASPUR], Serena De Santis, Mattia Falconi, Giordano Mancini, Valentina Migliorati, Andrea Battistoni, Francesca Pacello, Alessandro Desideri & Paola D'Angelo

J. Biomol. Stru. and Dyn., **30**, 269-279, 2012.

X-ray absorption near-edge structure (XANES) spectroscopy and MD simulations have been jointly applied to the study of the Cu,Zn superoxide dismutase from *Haemophilus ducreyi* (HdSOD) in interaction with the carbon monoxide molecule. The configurational flexibility of the Fe(II)-heme group, intercalated between the two subunits, has been sampled by MD simulations and included in the XANES data analysis without optimization in the structural parameter space. Our results provide an interpretation of the observed discrepancy in the Fe-heme distances as detected by extended X-ray absorption fine structure (EXAFS) spectroscopy and the classical XANES analysis, in which the structural parameters are optimized in a unique structure.

Protein kinase C mediated pHi-regulation of ROMK1 channels via a phosphatidylinositol-4,5-bisphosphate-dependent mechanism

Po-Tsang Huang, Chien-Hsing Lee, Horng-Huei Liou and Kuo-Long Lou [National Taiwan University]

J. Mol.Mod., **18**, 2929-2941, 2012.

The protein kinase C (PKC) pathway is important for the regulation of K⁺ transport. The renal outer medullar K⁺ (ROMK1) channels show an exquisite sensitivity to intracellular protons (pH_i) and play a key role in K⁺ homeostasis during metabolic acidosis. Our MD simulation results suggest that PKC-mediated phosphorylation on Thr-193 may disrupt the PIP₂-channel interaction via a charge-charge interaction between Thr-193 and Arg-188. We investigated the role of PKC and pH_i in regulation of ROMK1 channel activity using a giant patch clamp with *Xenopus* oocytes expressing wild-type and mutant ROMK1 channels.

Inter- versus intra-molecular cyclization of tripeptides containing tetrahydrofuran amino acids: a density functional theory study on kinetic control

N. V. Suresh Kumar, U. Deva Priyakumar, Harjinder Singh [International Institute of Information Technology, Hyderabad], Saumya Roy and Tushar Kanti Chakraborty

J. Mol.Mod., **18**, 3181-3197, 2012.

Density functional B3LYP method was used to investigate the preference of intra- and inter-molecular cyclizations of linear tripeptides containing tetrahydrofuran amino acids. Two distinct model pathways were conceived for the cyclization reaction, and all possible transition states and intermediates were located. Analysis of the energetics indicate intermolecular cyclization being favored by both thermodynamic and kinetic control.

Equipartition Principle for Internal Coordinate Molecular Dynamics

Abhinandan Jain [California Institute of Technology], In-Hee Park, and Nagarajan Vaidehi

J. Chem. Theor. and Comp., **8**, 2581-2587, 2012.

The principle of equipartition of (kinetic) energy for all-atom Cartesian molecular dynamics states that each momentum phase space coordinate on the average has $kT/2$ of kinetic energy in a canonical ensemble. This principle is used in MD simulations to initialize velocities, and to calculate statistical properties such as entropy. Internal coordinate molecular dynamics (ICMD) models differ from Cartesian models in that the overall kinetic energy depends on the generalized coordinates and includes cross-terms. We introduce noncanonical modal coordinates to recover some of the structural simplicity of Cartesian models and develop a new equipartition principle for ICMD models.

Molecular Dynamics (Cont'd)

Assessment of Common Simulation Protocols for Simulations of Nanopores, Membrane Proteins, and Channels

Jirasak Wong-ekkabut and Mikko Karttunen [University of Waterloo]

J. Chem. Theor. and Comp., **8**, 2905–2911, 2012.

Molecular dynamics (MD) simulation has become a common technique to study biological systems. Transport of small molecules through carbon nanotubes and membrane proteins has been an intensely studied topic, and MD simulations have been able to provide valuable predictions, many of which have later been experimentally proven. Simulations of such systems pose challenges, and unexpected problems in commonly used protocols and methods have been found in the past few years. We assessed the reliability of the most common simulations protocols by MD and stochastic dynamics (SD) or Langevin dynamics, simulations of an alpha hemolysin nanochannel embedded in a palmitoylcholine (POPC) lipid bilayer.

Dynamics and Calcium Association to the N-Terminal Regulatory Domain of Human Cardiac Troponin C: A Multiscale Computational Study

Steffen Lindert [University of California San Diego], Peter M. Keken-Huskey, Gary Huber, Levi Pierce, and J. Andrew McCammon

J. Phys. Chem. B., **116**, 8449–8459, 2012.

Troponin C (TnC) is an important regulatory molecule in cardiomyocytes. Calcium binding to site II in TnC initiates a series of molecular events that result in muscle contraction. The most direct change upon Ca^{2+} binding is an opening motion of the molecule that exposes a hydrophobic patch on the surface allowing for Troponin I to bind. Molecular dynamics simulations were used to elucidate the dynamics of this crucial protein in three different states: apo, Ca^{2+} -bound, and Ca^{2+} -TnI-bound. Dynamics between the states are compared, and the Ca^{2+} -bound system is investigated for opening motions.

Monte Carlo

Efficient Monte Carlo Simulations of Gas Molecules Inside Porous Materials

Jihan Kim [Lawrence Berkeley National Laboratory, Berkeley] and Berend Smit

J. Chem. Theor. and Comp., **8**, 2336–2343, 2012.

Monte Carlo (MC) simulations are commonly used to obtain adsorption properties of gas molecules inside porous materials. In this work, we discuss various optimization strategies that lead to faster MC simulations with CO_2 gas molecules inside host zeolite structures used as a test system. The reciprocal space contribution of the gas–gas Ewald summation and both the direct and the reciprocal gas–host potential energy interactions are stored inside energy grids to reduce the wall time in the MC simulations.

Tunable, Mixed-Resolution Modeling Using Library-Based Monte Carlo and Graphics Processing Units

Artem B. Mamonov, Steven Lettieri, Ying Ding, Jessica L. Sarver, Rohith Palli, Timothy F. Cunningham, Sunil Saxena, and Daniel M. Zuckerman [University of Pittsburgh]

J. Chem. Theor. and Comp., **8**, 2921–2929, 2012.

Building on our recently introduced library-based Monte Carlo (LBMC) approach, we describe a flexible protocol for mixed coarse-grained (CG)/all-atom (AA) simulation of proteins and ligands. In the present implementation of LBMC, protein side chain configurations are precalculated and stored in libraries, while bonded interactions along the backbone are treated explicitly. Because the AA side chain coordinates are maintained at minimal run-time cost, arbitrary sites and interaction terms can be turned on to create mixed-resolution models.

QM and QM/MM

The Role of Magnesium for Geometry and Charge in GTP Hydrolysis, Revealed by Quantum Mechanics/Molecular Mechanics Simulations

Till Rudack, Fei Xia, Jürgen Schlitter, Carsten Kötting, Klaus Gerwert [Ruhr-University Bochum]

Biophysical Journal. **103**, 293-302, 2012.

The coordination of the magnesium ion in proteins by triphosphates plays an important role in catalytic hydrolysis of GTP or ATP, either in signal transduction or energy conversion. For example, in Ras the magnesium ion contributes to the catalysis of GTP hydrolysis. The cleavage of GTP to GDP and P_i in Ras switches off cellular signaling. We analyzed GTP hydrolysis in water, Ras, and Ras-Ras-GTPase-activating protein using quantum mechanics/molecular mechanics simulations. By comparison of the theoretical IR-difference spectra for magnesium ion coordinated triphosphate to experimental ones, the simulations are validated.

Quantum-chemical investigation of the structure and the antioxidant properties of α -lipoic acid and its metabolites

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

J. Mol.Mod., **18**, 2907-2916, 2012.

Quantum-chemical computations were used to investigate the structure-antioxidant parameter relationships of α -lipoic acid and its natural metabolites bisnorlipoic acid and tetranorlipoic acid in their oxidized and reduced forms. The enantiomers of lipoic and dihydrolipoic acid were optimized using the B3LYP/6-311+G(3df,2p), B3LYP/aug-cc-pVDZ and MP2(full)/6-31+G(d,p) levels of theory as isolated molecules and in the presence of water. The results obtained reveal similarities between these structures: a pentatomic, nonaromatic ring is present in the oxidized forms, while an unbranched aliphatic chain (as found in saturated fatty acids) is present in both the oxidized and the reduced forms.

Quantum-mechanical computations on the electronic structure of trans-resveratrol and trans-piceatannol: a theoretical study of the stacking interactions in trans-resveratrol dimers

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

J. Mol.Mod., **18**, 3255-3266, 2012.

Accurate quantum-chemical calculations based on the second-order Møller-Plesset perturbation method (MP2) and density functional theory (DFT) were performed for the first time to investigate the electronic structures of trans-resveratrol and trans-piceatannol, as well as to study the stacking interaction between trans-resveratrol molecules. Ab initio MP2 calculations performed with using standard split-valence Pople basis sets led us to conclude that these compounds have structures that deviate strongly from planarity, whereas the DFT computations for the same basis sets revealed that the equilibrium geometries of these bioactive polyphenols are planar.

Intrinsic Energy Landscapes of Amino Acid Side-Chains

Xiao Zhu, Pedro E.M. Lopes, Jihyun Shim, and Alexander D. MacKerell, Jr. [University of Maryland]

J.Chem. Infor. and Mod. **52**, 1559–1572, 2012.

Amino acid side-chain conformational properties influence the overall structural and dynamic properties of proteins and, therefore, their biological functions. In this study, quantum mechanical (QM) potential energy surfaces for the rotation of side-chain χ_1 and χ_2 torsions in dipeptides in the alphaR, beta, and alphaL backbone conformations were calculated. The QM energy surfaces provide a broad view of the intrinsic conformational properties of each amino acid side-chain.

QM and QM/MM (Cont'd)

Hybrid QM/MM Molecular Dynamics Study of Benzocaine in a Membrane Environment: How Does a Quantum Mechanical Treatment of Both Anesthetic and Lipids Affect Their Interaction

Rafael C. Bernardi [Qualidade e Tecnologia (INMETRO)] and Pedro G. Pascutti

J. Chem. Theor. and Comp., **8**, 2197–2203, 2012.

Biomolecular dynamics studies using a QM/MM approach have been largely used especially to study enzymatic reactions. However, to the best of our knowledge, the very same approach has not been used to study the water/membrane interface using a quantum mechanical treatment for the lipids. Since a plethora of biochemical processes take place in this region, we believe that it is of primary importance to understand, at the level of molecular orbitals, the behavior of a drug in such an odd environment. In this work, we take advantage of an integration of the CPMD and the GROMACS code, using the Car–Parrinello method, to treat the benzocaine local anesthetic as well as two of the membrane lipids and the GROMOS force field to treat the remaining lipids and the water molecules.

Quantum and Classical Dynamics Simulations of ATP Hydrolysis in Solution

Christopher B. Harrison and Klaus Schulten [University of Illinois at Urbana–Champaign]

J. Chem. Theor. and Comp., **8**, 2328–2335, 2012.

ATP hydrolysis is a key reaction in living cells that drives many cellular processes. The reaction, which involves gamma phosphate cleavage from ATP, converting it to ADP, has been suggested to occur via an associative or dissociative mechanism dependent upon the surrounding environment. Prior quantum chemical studies suffered from short simulation time scales failing to capture free energy contributions due to relaxation of the surrounding aqueous environment. We have developed a highly parallelized QM/MM implementation in the NAMD and OpenAtom simulation packages, using the dual grid, dual length scale method for combined plane-wave and Euler exponential spline-based QM/MM simulations.

Collective Reaction Coordinate for Hybrid Quantum and Molecular Mechanics Simulations: A Case Study of the Hydride Transfer in Dihydrofolate Reductase

Dvir Doron, Amnon Kohen, and Dan Thomas Major [Bar-Ilan University]

J. Chem. Theor. and Comp., **8**, 2484–2496, 2012.

The optimal description of the reaction coordinate in chemical systems is of great importance in simulating condensed phase reactions. In the current work, we present a collective reaction coordinate which is composed of several geometric coordinates which represent structural progress during the course of a hydride transfer reaction: the antisymmetric reactive stretch coordinate, the donor–acceptor distance (DAD) coordinate, and an orbital rehybridization coordinate. In this approach, the former coordinate serves as a distinguished reaction coordinate, while the latter two serve as environmental, Marcus-type inner-sphere reorganization coordinates.

Comparative or Homology Modeling

A simplified homology-model builder toward highly protein-like structures: An inspection of restraining potentials

Tae-Rae Kim, Sangho Oh, Joshua SungWoo Yang, Sanghyuk Lee, Seokmin Shin [Seoul National University] and Jinhyuk Lee

J. Comp. Chem. **33**, 1927–1935, 2012.

A homology model builder using simple restraining potentials based on spline-interpolated quadratic functions is developed and interfaced with CHARMM package. The continuity and stability of the potential function were validated, and the parameters were optimized using the CASP7 targets. The performance of the model builder was benchmarked to the Modeller program using the template-based modeling targets in CASP9. The benchmark results show that, while our builder yields the structures with slightly lower packing, backbone, and template modeling scores, our models show much better protein-like scores in terms of normalized discrete optimized protein energy, dipolar distance-scaled finite-ideal gas reference, Molprobit clash, Ramachandran appearance Z-score, and rotamer Z-score.

Receptor-guided 3D-QSAR approach for the discovery of c-kit tyrosine kinase inhibitors

Anna Maria Almerico [Università di Palermo], Marco Tutone and Antonino Lauria

J. Mol.Mod., **18**, 2885-2895, 2012.

Studies of the the three-dimensional quantitative structure–activity relationships for ninety-five c-kit tyrosine kinase inhibitors were performed. Based on a co-crystallized compound (1 T46), known inhibitors were aligned with c-kit by induced-fit docking, and multiple training/test set splitting was performed to validate the selected pharmacophore model. The best pharmacophore model consisted of five features: one hydrogen-bond donor and four aromatic rings. Reliable statistics were obtained ($R^2=0.95$, $R_{pred}^2=0.75$), and the model was validated by using it to select c-kit inhibitors from a database; 82.1% of the hits it retrieved were active.

New Model of Cystic Fibrosis Transmembrane Conductance Regulator Proposes Active Channel-like Conformation

James Dalton, Ori Kalid, Maya Schushan, Nir Ben-Tal, and Jordi Villà-Freixa [IMIM Hospital del Mar and Universitat Pompeu Fabra]

J.Chem. Infor. and Mod. **52**, 1842–1853, 2012.

The cystic fibrosis transmembrane conductance regulator (CFTR) is an unusual ABC transporter, functioning as a chloride channel critical for fluid homeostasis in multiple organs. Disruption of CFTR function is associated with cystic fibrosis making it an attractive therapeutic target. In addition, CFTR blockers are being developed as potential antidiarrheals. CFTR drug discovery is hampered by the lack of high resolution structural data, and considerable efforts have been invested in modeling the channel structure. Here, we make available a model of CFTR in such a “channel-like” conformation, derived by a unique modeling approach combining restrained homology modeling and ROSETTA refinement.

Ligand Docking

Binding of β -Amyloid (1–42) Peptide to Negatively Charged Phospholipid Membranes in the Liquid-Ordered State: Modeling and Experimental Studies

Hasna Ahyayauch, Michal Raab, Jon V. Busto, Nagore Andracka, José-Luis R. Arrondo, Massimo Masserini, Igor Tvaroska, Félix M. Goñi [Universidad del País Vasco]

Biophysical Journal. **103**, 453-463, 2012.

To explore the initial stages of amyloid β peptide (A β 42) deposition on membranes, we have studied the interaction of A β 42 in the monomeric form with lipid monolayers and with bilayers in either the liquid-disordered or the liquid-ordered (L_o) state, containing negatively charged phospholipids. Molecular dynamics (MD) simulations of the system have been performed, as well as experimental measurements. For bilayers in the L_o state, in the absence of the negatively charged lipids, interaction is weak and it cannot be detected by isothermal calorimetry.

Thumbs Down for HIV: Domain Level Rearrangements Do Occur in the NNRTI-Bound HIV-1 Reverse Transcriptase

David W. Wright, S. Kashif Sadiq, Gianni De Fabritiis, and Peter V. Coveney [University College London]

J. Am. Chem. Soc., **134**, 12885–12888, 2012.

One of the principal targets in human immunodeficiency virus type 1 (HIV-1) therapy is the reverse transcriptase (RT) enzyme. Non-nucleoside RT inhibitors (NNRTIs) are a class of highly specific drugs which bind to a pocket approximately 10 Å from the polymerase active site, inhibiting the enzyme allosterically. It is widely believed that NNRTIs function as “molecular wedges”, disrupting the region between thumb and palm subdomains of the p66 subunit and locking the thumb in a wide-open conformation. Using ensemble MD simulations (aggregate sampling ~600 ns), we have captured RT bound to the NNRTI efavirenz in a closed conformation similar to that of the apo enzyme, suggesting the constraint of thumb motion is not as complete as previously believed.

Dynamical probing of allosteric control in nuclear receptors

Mark A. Cunningham [University of Texas-Pan American]

J. Mol. Mod., **18**, 3147-3152, 2012.

The dynamical behavior of the nuclear receptor LXR/RXR heterodimer was investigated with molecular dynamics simulations. The simulations reveal correlated motion between residues across the dimer interface that depends significantly on occupation of the ligand binding sites of the monomers. These results are broadly consistent with the observed experimental behavior of the dimers, where structural perturbation is thought to be a key element in signal transduction. Our results provide dynamical support for this model of allosteric control.

Cytochrome P450 3A4 Inhibition by Ketoconazole: Tackling the Problem of Ligand Cooperativity Using Molecular Dynamics Simulations and Free-Energy Calculations

Urban Bren and Chris Oostenbrink [University of Natural Resources and Life Sciences]

J. Chem. Infor. and Mod. **52**, 1573–1582, 2012.

Cytochrome P450 3A4 (CYP3A4) metabolizes more than 50% of clinically used drugs and is often involved in adverse drug–drug interactions. It displays atypical binding and kinetic behavior toward a number of ligands characterized by a sigmoidal shape of the corresponding titration curves, which is indicative of a positive homotropic cooperativity. This requires a participation of at least two ligand molecules, whereby the binding of the first ligand molecule increases the affinity of CYP3A4 for the binding of the second ligand. In the current study, a combination of MD simulations and free-energy calculations was applied to elucidate the physicochemical

origin of the observed positive homotropic cooperativity in ketoconazole binding to CYP3A4.

Ligand Docking (Cont'd)

Application of Binding Free Energy Calculations to Prediction of Binding Modes and Affinities of MDM2 and MDMX Inhibitors

Hui Sun Lee, Sunhwan Jo, Hyun-Suk Lim, and Wonpil Im
[The University of Kansas]

J.Chem. Infor. and Mod. **52**, 1821–1832, 2012.

Molecular docking is widely used to obtain binding modes and binding affinities of a molecule to a given target protein. Despite considerable efforts, however, prediction of both properties by docking remains challenging mainly due to protein's structural flexibility and inaccuracy of scoring functions. Here, an integrated approach has been developed to improve the accuracy of binding mode and affinity prediction and tested for small molecule MDM2 and MDMX antagonists. In this approach, initial candidate models selected from docking are subjected to equilibration MD simulations to further filter the models.

3. JOURNAL REVIEWS

Journal of Computational Chemistry, 33(22), August, 2012.

- 1781–1789 **Prediction of the properties and thermodynamics of formation for energetic nitrogen-rich salts composed of triaminoguanidinium cation and 5-nitroiminotetrazolate-based anions**, Weihua Zhu, Qingli Yan, Jinshan Li, Bibo Cheng, Yuling Shao, Xuelan Xia and Heming Xiao [Nanjing University of Science and Technology]

Density functional theory and volume-based thermodynamics calculations were performed to study the effects of different substituents and linkages on the densities, heats of formation (HOFs), energetic properties, and thermodynamics of formation for a series of energetic nitrogen-rich salts composed of triaminoguanidinium cation and 5-nitroiminotetrazolate anions.

- 1790–1796 **Theoretical investigations on structure, density, detonation properties, and sensitivity of the derivatives of PYX**, Hui Liu, Fang Wang, Gui-Xiang Wang and Xue-Dong Gong [Nanjing University of Science and Technology]

The —NH_2 , —NO_2 , —N_3 , —NHNO_2 , and —ONO_2 substitution derivatives of PYX (2,6-bis(picrylamino)-3,5-dinitropyridine) were studied at the B3LYP/6-31G** level of density functional theory. The sublimation enthalpies and heats of formation (HOFs) in gas phase and solid state of these compounds were calculated.

- 1797–1805 **Computational design of improved two-photon active caging compounds based on nitrodibenzofuran**, Andreas Dreuw [Ruprecht-Karls-University], Matthias A. Polkehn, Robert Binder, Alexander Heckel and Stefan Knippenberg

Nitrodibenzofuran (NDBF) has recently been established as photolabile protecting group and efficiently used as two-photon active cage. In this work, a computational approach is exploited to rationally design improved two-photon active caging groups based on this NDBF chromophore.

- 1806–1819 **A full dimensional grid empowered simulation of the $\text{CO}_2 + \text{CO}_2$ processes**, Massimiliano Bartolomei, Fernando Pirani, Antonio Laganà and Andrea Lombardi [Università di Perugia]

A recently introduced bond–bond formulation of the intermolecular interaction has been extended to six-atom systems to the end of assembling a new potential energy surface (PES) and has been incorporated into a grid empowered simulator able to handle the modeling of the $\text{CO}_2 + \text{CO}_2$ processes.

- 1820–1830 **Density functional theory study of high-pressure effect on crystalline 4,4',6,6'-tetra(azido)hydrazo-1,3,5-triazine**, Fang Wang, Hong-Chen Du, Hui Liu and Xue-Dong Gong [Nanjing University of Science and Technology]

Periodic density functional theory calculations are performed to study the hydrostatic compression effects on the structure, electronic, and thermodynamic properties of the energetic polyazide 4,4',6,6'-tetra(azido)hydrazo-1,3,5-triazine (TAHT) in the range of 0–100 GPa.

- 1831–1844 **Computational study of ligand binding in lipid transfer proteins: Structures, interfaces, and free energies of protein-lipid complexes**, Luis F. Pacios [Universidad Politécnica de Madrid], Cristina Gómez-Casado, Leticia Tordesillas, Arantxa Palacín, Rosa Sánchez-Monge and Araceli Díaz-Perales

See Applications / Ligand Binding.

Journal of Computational Chemistry, 33(23), September, 2012.

- 1845–1853 **Nuclear magnetic resonance J coupling constant polarizabilities of hydrogen peroxide: A basis set and correlation study**, Hanna Kjær, Monia R. Nielsen, Gabriel I. Pagola, Marta B. Ferraro, Paolo Lazzeretti and Stephan P. A. Sauer [University of Copenhagen]

In this article, we present the so far most extended investigation of the calculation of the coupling constant polarizability of a molecule. The components of the coupling constant polarizability are derivatives of the nuclear magnetic resonance (NMR) indirect nuclear spin–spin coupling constant with respect to an external electric field and play an important role for both chiral discrimination and solvation effects on NMR coupling constants.

- 1854–1861 **Comparative DFT study of N₂ and no adsorption on vanadium clusters V_n (n = 2–13)**, Guangfen Wu, Mingli Yang, Xingyu Guo and Jinlan Wang [Southeast University]

Using gradient-corrected density functional theory, we have comparatively studied the adsorption properties of diatomic molecules N₂ and NO on vanadium clusters up to 13 atoms.

- 1862–1869 **Quantum chemical insights into the aggregation induced emission phenomena: A QM/MM study for pyrazine derivatives**, Qunyan Wu, Chunmei Deng, Qian Peng, Yingli Niu and Zhigang Shuai [Tsinghua University]

There have been intensive studies on the newly discovered phenomena called aggregation induced emission (AIE), in contrast to the conventional aggregation quenching. Through combined quantum mechanics and molecular mechanics computations, we have investigated the aggregation effects on the excited state decays, both via radiative and nonradiative routes, for pyrazine derivatives 2,3-dicyano-5,6-diphenylpyrazine (**DCDPP**) and 2,3-dicyanopyrazino phenanthrene (**DCPP**) in condensed phase.

- 1870–1879 **Kinetics for the hydrogen-abstraction of CH₄ with NO₂**, Yulei Guan and Bolun Yang [Xi'an Jiaotong University]

The detailed mechanism of the NO₂+CH₄ reaction has been computationally investigated at the M06-2X/MG3S, B3LYP/6-311G(2d,d,p), and MP2/6-311+G(2df,p) levels.

- 1880–1891 **Balancing target flexibility and target denaturation in computational fragment-based inhibitor discovery**, Theresa J. Foster, Alexander D. MacKerell Jr. and Olgun Guvench [University of New England College of Pharmacy]

See Applications / Bioinformatics.

- 1892–1901 **Quantum chemical comparison of vertical, adiabatic, and 0-0 excitation energies: The PYP and GFP chromophores**, Malin Uppsten and Bo Durbeej [Linköping University]

A number of benchmark studies investigating the performance of quantum chemical methods for calculating vertical excitation energies are today available in the literature. To this end, such excitation energies are here calculated for the bright S_1 states of the anionic chromophores of the photoactive yellow protein (PYP) and the green fluorescent protein (GFP) in the gas phase using configuration interaction singles, complete active space self-consistent field, coupled-cluster singles and doubles, and time-dependent density functional theory methods.

Journal of Computational Chemistry, 33(24), September, 2012.

- 1907–1917 **Reoptimized interaction parameters for the peptide-backbone model compound N-methylacetamide in the GROMOS force field: Influence on the folding properties of two beta-peptides in methanol**, Bruno A. C. Horta [Swiss Federal Institute of Technology], Zhixiong Lin, Wei Huang, Sereina Riniker, Wilfred F. van Gunsteren and Philippe H. Hünenberger

Considering N-methylacetamide (NMA) as a model compound, new interaction parameters are developed for the amide function in the GROMOS force field that are compatible with the recently derived 53A6_{OXY} parameter set for oxygen-containing chemical functions.

- 1918–1926 **Gas-phase reactions of SiH_n^+ ($n = 1,2$) with NF_3 : A computational investigation on the detailed mechanistic aspects**, Paola Antoniotti [Università di Torino], Elena Bottizzo, Stefano Borocci, Maria Giordani and Felice Grandinetti

The mechanism of the gas-phase reactions of SiH_n^+ ($n = 1,2$) with NF_3 were investigated by ab initio calculations at the MP2 and CAS-MCSCF level of theory.

- 1927–1935 **A simplified homology-model builder toward highly protein-like structures: An inspection of restraining potentials**, Tae-Rae Kim, Sangho Oh, Joshua SungWoo Yang, Sanghyuk Lee, Seokmin Shin [Seoul National University] and Jinhyuk Lee

See Methodology / Homology Modeling.

- 1936–1947 **A quantum chemical calculation on $\text{Fe}(\text{CO})_5$ revealing the operation of the Dewar–Chatt–Duncanson model**, Vinzenz Bachler [Max-Planck-Institut für Bioanorganische Chemie]

A nonstandard computational scheme has been applied to calculate $\text{Fe}(\text{CO})_5$ with the aim to illustrate the operation of the Dewar–Chatt–Duncanson model by computation.

- 1948–1959 **Computational study on hydrolysis of cefotaxime in gas phase and in aqueous solution**, Conchín Meliá, Silvia Ferrer, Vicent Moliner [Universitat Jaume I], Iñaki Tuñón and Juan Bertrán

We are presenting a theoretical study of the hydrolysis of a β -lactam antibiotic in gas phase and in aqueous solution by means of hybrid quantum mechanics/molecular mechanics potentials.

Journal of Molecular Modeling, 18(7), July, 2012.

- 2885–2895 **Receptor-guided 3D-QSAR approach for the discovery of c-kit tyrosine kinase inhibitors**, Anna Maria Almerico [Università di Palermo], Marco Tutone and Antonino Lauria

See Methodology / QSAR.

- 2897–2905 **Theoretical studies on vibrational spectra, thermodynamic properties, detonation properties and pyrolysis mechanism for 1,2-bis(2,4,6-trinitrophenyl) hydrazine**, Li Xiao-Hong [Henan University of Science and Technology], Zhang Rui-Zhou and Zhang Xian-Zhou

The thermal stability and pyrolysis mechanism of 1,2-bis(2,4,6-trinitrophenyl) hydrazine were investigated based on fully optimized molecular geometric structures. The results demonstrate the existence of intramolecular hydrogen bond interactions 1,2-bis(2,4,6-trinitrophenyl) hydrazine.

- 2907–2916 **Quantum-chemical investigation of the structure and the antioxidant properties of α -lipoic acid and its metabolites**, Małgorzata Szeląg [A. Mickiewicz University], Damian Mikulski and Marcin Molski

See Methodology / QM and QM/MM.

- 2917–2927 **Large-scale virtual screening for the identification of new *Helicobacter pylori* urease inhibitor scaffolds**, Homa Azizian, Farzaneh Nabati, Amirhossein Sharifi, Farideh Siavoshi and Mohammad Mahdavi, Massoud Amanlou [Tehran University of Medical Sciences].

See Applications / Medicinal Chemistry and Drug Design.

- 2929–2941 **Protein kinase C mediated pHi-regulation of ROMK1 channels via a phosphatidylinositol-4,5-bisphosphate-dependent mechanism**, Po-Tsang Huang, Chien-Hsing Lee, Horng-Huei Liou and Kuo-Long Lou [National Taiwan University]

See Methodology / Molecular Dynamics.

- 2943–2958 **Molecular simulation of a series of benzothiazole PI3K α inhibitors: probing the relationship between structural features, anti-tumor potency and selectivity**, Jinan Wang, Fangfang Wang, Zhengtao Xiao, Guowen Sheng and Yan Li, Yonghua Wang [Northwest A & F University].

See Methodology / QSAR.

- 2959-2969 **A (U)MP2(full) and (U)CCSD(T) theoretical investigation into the substituent effects on the intermolecular T-shaped F–H... π interactions between HF and LBBL (L = –H, :CO, :NN, –Cl, –CN and –NC),** Zhao-ming Yang, Lin Zhang, Li-zhen Chen, Fu-de Ren [North University of China] and Shan Du, et al.

The substituent effects on the intermolecular T-shaped F–H... π interactions are investigated between HF and LBBL (L = –H, :CO, :NN, –Cl, –CN and –NC) using the (U)MP2(full) and (U)CCSD(T) methods with the 6-311++G(2 d,p) basis set.

- 2971-2979 **Structure prediction and binding sites analysis of curcun protein of *Jatropha curcas* using computational approaches,** Mugdha Srivastava [National Botanical Research Institute (CSIR), Lucknow], Shishir K. Gupta, P. C. Abhilash and Nandita Singh

See Applications / Protein Structure Prediction.

- 2981-2991 **Hydrogen adsorption capacities of multi-walled boron nitride nanotubes and nanotube arrays: a grand canonical Monte Carlo study,** Zohreh Ahadi [Islamic Azad University], Muhammad Shadman, Saeed Yeganegi and Farid Asgari

Hydrogen adsorption in multi-walled boron nitride nanotubes and their arrays was studied using grand canonical Monte Carlo simulation. The results show that hydrogen storage increases with tube diameter and the distance between the tubes in multi-walled boron nitride nanotube arrays.

- 2993-3001 **Structural, electronic and magnetic effects of Al-doped niobium clusters: a density functional theory study,** Huai-Qian Wang [Huaqiao University], Hui-Fang Li, Jia-Xian Wang and Xiao-Yu Kuang

The application of the ab initio stochastic search procedure with Saunders “kick” method has been carried out for the elucidation of global minimum structures of a series of Al-doped clusters, NbnAl ($1 \leq n \leq 10$).

- 3003-3012 **High-pressure phase transition and thermoelastic properties of europium chalcogenides,** Dinesh C. Gupta [Jiwaji University] and Kailash C. Singh

The pressure-induced crystal properties of Eu chalcogenides were investigated using two different models: a modified charge-transfer potential model consisting of Coulomb screening due to the delocalization of the f electron of the rare earth atom, and modified by covalency and zero-point energy effects along with attractive and repulsive interactions; and a charge-transfer model that excluded the covalency and zero-point energy effects in the previous model.

- 3013-3020 **Molecular design of aminopolynitroazole-based high-energy materials,** Vikas D. Ghule [University of Hyderabad], Dharavath Srinivas, Radhakrishnan Sarangapani, Pandurang M. Jadhav and Surya P. Tewari

The density functional theory (DFT) was employed to calculate the energetic properties of several aminopolynitroazoles. The calculations were performed to study the effect of amino and nitro substituents on the heats of formation, densities, detonation performances, thermal stabilities, and sensitivity characteristics of azoles.

- 3021-3023 **SWIFT MODELLER v2.0: a platform-independent GUI for homology modeling,** Abhinav Mathur, Shankaracharya and Ambarish S. Vidyarthi [Birla Institute of Technology, Mesra]

See Applications / Bioinformatics.

- 3025-3033 **Computational study of the Sonogashira cross-coupling reaction in the gas phase and in dichloromethane solution**, Lauri Sikk [University of Tartu], Jaana Tammiku-Taul, Peeter Burk and András Kotschy

The Sonogashira cross-coupling reaction, consisting of oxidative addition, cis-trans isomerization, transmetalation, and reductive elimination, was computationally modeled using the DFT B3LYP/cc-pVDZ method for reaction between bromobenzene and phenylacetylene.

- 3035-3049 **Theoretical prediction of the binding free energy for mutants of replication protein A**, Claudio Carra [Universities Space Research Association, Columbia], Janapriya Saha and Francis A. Cucinotta

See Applications / Nucleic acid-Protein interactions.

- 3051-3060 **A comparative theoretical study for the methanol dehydrogenation to CO over Pt₃ and PtAu₂ clusters**, Wenhui Zhong, Yuxia Liu and Dongju Zhang [Shandong University]

The density functional theory (DFT) calculations are carried out to study the mechanism details and the ensemble effect of methanol dehydrogenation over Pt₃ and PtAu₂ clusters, which present the smallest models of pure Pt clusters and bimetallic PtAu clusters.

- 3061-3072 **Density functional study on size-dependent structures, stabilities, electronic and magnetic properties of Au_nM (M = Al and Si, n = 1–9) clusters: comparison with pure gold clusters**, Yan-Fang Li, Ai-Jie Mao, Yang Li and Xiao-Yu Kuang [Sichuan University]

The density functional theory (DFT) method has been employed to systematically investigate the geometrical structures, relative stabilities, and electronic and magnetic properties of Au_nM (M = Al and Si, n = 1–9) clusters for clarifying the effect of Al (Si) modulation on the gold nanostructures.

- 3073-3086 **On the potential application of DFT methods in predicting the interaction-induced electric properties of molecular complexes. Molecular H-bonded chains as a case of study**, Agnieszka Zawada [University of Technology], Anna Kaczmarek-Kędziera and Wojciech Bartkowiak

A detailed analysis of the selected DFT functionals for the calculations of interaction-induced dipole moment, polarizability and first-order hyperpolarizability has been carried out.

- 3087-3100 **Pharmacophore modeling and virtual screening studies to identify new c-Met inhibitors**, Wenting Tai, Tao Lu, Haoliang Yuan, Fengxiao Wang, Yadong Chen [China Pharmaceutical University] and Haichun Liu, et al.

See Applications / Medicinal Chemistry and Drug Design.

- 3101-3112 **Structural, electronic, and elastic properties of K-As compounds: a first principles study**, Havva Bogaz Ozisik [Gazi University], Kemal Colakoglu, Engin Deligoz and Haci Ozisik

First-principle calculations are performed to investigate the structural, elastic and electronic properties of K-As compounds (KAs in NaP, LiAs and AuCu-type structures, KAs₂ in MgCu₂-type structure, K₃As in Na₃As, Cu₃P and Li₃Bi-type structures, and K₅As₄ in A₅B₄-type structure).

- 3113-3123 **Hydrogen-bonding interactions in adrenaline–water complexes: DFT and QTAIM studies of structures, properties, and topologies**, Hongke Wang, Zhengguo Huang [Tianjin Normal University], Tingting Shen and Lingfei Guo

ω B97XD/6-311++G(d,p) calculations were carried out to investigate the hydrogen-bonding interactions between adrenaline (Ad) and water. Six Ad–H₂O complexes possessing various types of hydrogen bonds (H-bonds) were characterized in terms of their geometries, energies, vibrational frequencies, and electron-density topology.

- 3125-3138 **Design and selection of nitrogen-rich bridged di-1,3,5-triazine derivatives with high energy and reduced sensitivity**, Yong Pan, Weihua Zhu [Nanjing University of Science and Technology] and Heming Xiao

The heats of formation (HOFs), electronic structures, energetic properties, and thermal stabilities of a series of energetic bridged di-1,3,5-triazine derivatives with different substituents and linkages were studied using density functional theory.

- 3139-3145 **Structural analysis of secretory phospholipase A2 from *Clonorchis sinensis*: therapeutic implications for hepatic fibrosis**, Gururao Hariprasad [All India Institute of Medical Sciences, New Delhi], Punit Kaur, Alagiri Srinivasan, Tej Pal Singh and Manoj Kumar

See Applications / Homology Modeling.

- 3147-3152 **Dynamical probing of allosteric control in nuclear receptors**, Mark A. Cunningham [University of Texas-Pan American]

See Methodology / Ligand Docking.

- 3153-3160 **Experimental and theoretical study of dilute polyacrylamide solutions: effect of salt concentration**, Panke Chen, Lin Yao, Yanyan Liu, Jianhui Luo and Ge Zhou, Bo Jiang [Sichuan University].

The structure and intrinsic viscosity of the partially hydrolyzed polyacrylamide (HAPM) and polyacrylamide (PAM) in aqueous solution were investigated by comparative studies of molecular dynamics simulation over a wide range of the NaCl concentration.

- 3161-3167 **Planar π -aromatic C_{3h} B₆H³⁺ and π -antiaromatic C_{2h} B₈H₂: boron hydride analogues of D_{3h} C₃H³⁺ and D_{2h} C₄H₄**, Da-Zhi Li, Hai-Gang Lu and Si-Dian Li [Shanxi University]

Based upon extensive density functional theory and wave function theory calculations performed in this work, we predict the existence of the perfectly planar triangle C_{3h} B₆H³⁺ (1, 1A') and the double-chain stripe C_{2h} B₈H₂ (9, 1Ag) which are the ground states of the systems and the inorganic analogues of cyclopropene cation D_{3h} C₃H³⁺ and cyclobutadiene D_{2h} C₄H₄, respectively.

- 3169-3179 **Theoretical investigation of the enzymatic phosphoryl transfer of β -phosphoglucomutase: revisiting both steps of the catalytic cycle**, Brigitta Elsässer [University of Paderborn, Warburgerstr. 100], Silvia Dohmeier-Fischer and Gregor Fels

See Applications / Enzyme Catalysis.

- 3181-3197 **Inter- versus intra-molecular cyclization of tripeptides containing tetrahydrofuran amino acids: a density functional theory study on kinetic control**, N. V. Suresh Kumar, U. Deva Priyakumar, Harjinder Singh [International Institute of Information Technology, Hyderabad], Saumya Roy and Tushar Kanti Chakraborty

See Methodology / Molecular Dynamics.

- 3199-3212 **Full-length structural model of RET3 and SEC21 in COPI: identification of binding sites on the appendage for accessory protein recruitment motifs**, Laleh Alisaraie and Isabelle Rouiller [McGill University]

See Applications / Protein Structure Prediction.

- 3213-3217 **Density functional studies on the endohedral complex of fullerene C70 with tetrahedrane (C4H4): C4H4@C70**, Xiao-Yuan Ren [Zhejiang Sci-Tech University] and Cai-Ying Jiang

B3LYP/6-31G(d) hybrid HF/DFT calculations were carried out to determine the structural and electronic properties of the endohedral complex of a C70 cage with tetrahedrane (C4H4).

- 3219-3225 **Probing the linear and nonlinear optical properties of nitrogen-substituted carbon nanotube**, Shi-Ling Sun, Yang-Yang Hu, Hong-Liang Xu [Northeast Normal University], Zhong-Min Su and Li-Zhu Hao

See Applications / Carbon Nanoparticles.

- 3227-3242 **Structural requirements of pyrimidine, thienopyridine and ureido thiophene carboxamide-based inhibitors of the checkpoint kinase 1: QSAR, docking, molecular dynamics analysis**, Fangfang Wang, Zhi Ma, Yan Li, Jinan Wang and Yonghua Wang [Northwest A&F University]

See Applications / Homology Modeling.

- 3243-3253 **First- and second-row transition metal oxa-aza macrocyclic complexes: a DFT study of an octahedral conformation**, Francisco C. A. Lima, Rommel B. Viana, Thais T. da Silva, Solange M. S. V. Wardell and Armando P. Nascimento do Filho, Albérico B. F. da Silva [Universidade de São Paulo].

A theoretical study of structures of the 1,7,1 1,17-tetraoxa-2,6,12,16-tetraaza-cycloeicosane ligand ([20]AneN4O4) coordinated to Fe²⁺, Co²⁺, Ni²⁺, Ru²⁺, Rh²⁺, and Pd²⁺ transition metals ions was carried out with the DFT/B3LYP method.

- 3255-3266 **Quantum-mechanical computations on the electronic structure of trans-resveratrol and trans-piceatannol: a theoretical study of the stacking interactions in trans-resveratrol dimmers**, Damian Mikulski [A. Mickiewicz University ul] and Marcin Molski

See Methodology / QM and QM/MM.

- 3267-3282 **Pharmacophore modeling, molecular docking, and molecular dynamics simulation approaches for identifying new lead compounds for inhibiting aldose reductase 2**, Sugunadevi Sakkiah, Sundarapandian Thangapandian and Keun Woo Lee [Gyeongsang National University]

See Applications / Homology Modeling.

- 3283-3289 **Vector correlations in the $F + HO \rightarrow HF + O$ reaction and its isotopic variant**, Dan Zhao, TianShu Chu [Chinese Academy of Sciences] and Ce Hao

The $F + H(D)O \rightarrow HF(DF) + O$ reactions have been studied using quasi-classical trajectory (QCT) calculation method, based on the three different potential energy surfaces (PESs) of Gomez-Carrasco et al. (J Chem Phys 2004, 121:4605; J Chem Phys 2005, 123:114310; Chem Phys Lett 2007, 435:188).

- 3291-3300 **Self-assembly of DNA on a gapped carbon nanotube**, Alfredo D. Bobadilla and Jorge M. Seminario [Texas A&M University College Station]

See Applications / Nucleic Acids.

- 3301-3310 **Tetraethylorthosilicate as molecular precursor to the formation of amorphous silica networks. A DFT-SCRF study of the base catalyzed hydrolysis**, Lorenzo Fernandez [Universitat de Valencia], Iñaki Tuñón, Julio Latorre, Carmen Guillem and Aurelio Beltrán, et al.

Quantum chemical calculations using density functional theory have been carried out to investigate two chemical pathways for the last step of the hydrolysis of tetraethylorthosilicate (TEOS) in basic catalyzed environment.

- 3311-3320 **Anion recognition based on halogen bonding: a case study of macrocyclic imidazoliophane receptors**, Yunxiang Lu [East China University of Science and Technology], Haiying Li, Xiang Zhu, Honglai Liu and Weiliang Zhu

The structures and properties of noncovalent interactions involving three imidazoliophane receptors 1–3 and halide anions have been investigated by means of density functional theory calculations.

- 3321-3328 **Large gallanes and the PSEPT theory: a theoretical study of Ga_nH_{n+2} clusters ($n = 7-9$)**, Mohamed Maatallah, Driss Cherqaoui, Abdellah Jarid [Université Cadi Ayyad] and Joel F. Liebman

Do alanes Al_nH_{n+2} and gallanes Ga_nH_{n+2} satisfy the polyhedral skeletal electron pair theory (PSEPT)? Taking into account previous work on this question, this paper provides a convincing answer and proposes the reformulation of the $(n + 1)$ electron pairs rule of Wade and Mingos (W–M) for such systems.

- 3329-3339 **Acetylene hydrogenation on anatase $TiO_2(101)$ supported Pd4 cluster: oxygen deficiency effect**, Jie Yang, Li-Xin Cao and Gui-Chang Wang [Nankai University]

Acetylene hydrogenation on both the perfect and oxygen defective anatase $TiO_2(101)$ surfaces supported Pd4 cluster has been studied using density functional theory calculations with a Hubbard U correction (DFT + U).

- 3341-3350 **Study of semiconducting nanomaterials under pressure**, Dinesh C. Gupta [Jiwaji University] and P. Rana

The pressure induced structural and mechanical properties of nanocrystalline ZnO, ZnS, ZnSe, GaN, CoO, CdSe, CeO₂, SnO₂, SiC, c-BC₂N, and β -Ga₂O₃ with different grain sizes have been analyzed under high pressures.

- 3351-3361 **In-silico modeling of a novel OXA-51 from β -lactam-resistant *Acinetobacter baumannii* and its interaction with various antibiotics**, Vishvanath Tiwari, Isha Nagpal, Naidu Subbarao and Rajeswari R. Moganty [All India Institute of Medical Sciences, New Delhi]

See Applications / Medicinal Chemistry and Drug Design.

- 3363-3378 **Molecular simulations of adsorption of RDX and TATP on IRMOF-1(Be)**, Andrea Michalkova Scott [U.S. Army Engineer Research and Development Center], Tetyana Petrova, Khorgolkhuu Odbadrakh, Donald M. Nicholson and Miguel Fuentes-Cabrera, et al.

The influence of different sorption sites of isorecticular metal-organic frameworks (IRMOFs) on interactions with explosive molecules is investigated. Different connector effects are taken into account by choosing IRMOF-1(Be) (IRMOF-1 with Zn replaced by Be), and two high explosive molecules: 1,3,5-trinitro-s-triazine (RDX) and triacetone triperoxide (TATP).

- 3379-3388 **The solvation study of carbon, silicon and their mixed nanotubes in water solution**, Haleh Hashemi Haeri [Islamic Azad University], Sepideh Ketabi and Seyed Majid Hashemianzadeh

See Applications / Carbon Nanoparticles.

- 3389-3413 **Pharmacophore, QSAR, and ADME based semisynthesis and in vitro evaluation of ursolic acid analogs for anticancer activity**, Komal Kalani, Dharmendra Kumar Yadav, Feroz Khan, Santosh K. Srivastava [Central Institute of Medicinal and Aromatic Plants, Lucknow] and Nitasha Suri

See Applications / QSAR.

- 3415-3425 **Can trans-polyacetylene be formed on single-walled carbon-doped boron nitride nanotubes?**, Ying Chen, Hong-xia Wang, Jing-xiang Zhao [Harbin Normal University], Qing-hai Cai and Xiao-guang Wang, et al.

See Applications / Carbon Nanoparticles.

- 3427-3438 **Does Al₄H₁₄— cluster anion exist? High-level ab initio study**, Jerzy Moc [Wroclaw University]

A comprehensive ab initio investigation using coupled cluster theory with the aug-cc-pVnZ, n = 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20, 21, 22, 23, 24, 25, 26, 27, 28, 29, 30, 31, 32, 33, 34, 35, 36, 37, 38, 39, 40, 41, 42, 43, 44, 45, 46, 47, 48, 49, 50, 51, 52, 53, 54, 55, 56, 57, 58, 59, 60, 61, 62, 63, 64, 65, 66, 67, 68, 69, 70, 71, 72, 73, 74, 75, 76, 77, 78, 79, 80, 81, 82, 83, 84, 85, 86, 87, 88, 89, 90, 91, 92, 93, 94, 95, 96, 97, 98, 99, 100 basis sets is carried out to identify distinct structures of the Al₄H₁₄— cluster anion and to evaluate its fragmentation stability.

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1. APPLICATIONS

1.1. Small Molecules

Medicinal Chemistry and Drug Design

Mechanisms and kinetics of thiotepa and tepa hydrolysis: DFT study

Hedieh Torabifard and Alireza Fattahi [Sharif University of Technology]

J. Mol.Mod., **18**, 3563-3576, 2012.

N,N',N''-triethylenethiophosphoramidate (Thiotepa) and its oxo analogue (Tepa) as the major metabolite are trifunctional alkylating agents with a broad spectrum of antitumor activity. In this study, we calculated the activation free energy and kinetic rate constant for hydrolysis of these agents and explored interaction of aziridine with Guanine to predict the most probable mechanism by applying density functional theory (DFT) using B3LYP method.

A novel halogen bond and a better-known hydrogen bond cooperation of neonicotinoid and insect nicotinic acetylcholine receptor recognition

Hongxia Duan [China Agricultural University], Weiwei Zhang, Jin Zhao, Desheng Liang and Xinling Yang, et al.

J. Mol.Mod., **18**, 3867-3875, 2012.

Neonicotinoid insecticides target the insect nicotinic acetylcholine receptor (nAChR) and are highly effective against the piercing-sucking pests. To explore the molecular interaction mechanism between the neonicotinoids and the insect nAChR, some key neonicotinoid compounds were docked into *Aplysia californica* acetylcholine binding protein (Ac-AChBP), which serves as a suitable structural surrogate of the insect nAChR. The binding mode study showed that the hydrogen bond force between the electronegative pharmacophore of the neonicotinoids and Cys190NH of the target binding pocket is crucial to the high efficiency of the neonicotinoids.



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Medicinal Chemistry and Drug Design (Cont'd)

Chemical reactivity analysis of deoxyribonucleosides and deoxyribonucleoside analogues (NRTIs): a first-principles density functional approach

Vipin Kumar [J. V. College, Baraut], Shyam Kishor and Lavanya M. Ramaniah

J. Mol.Mod., **18**, 3969-3980, 2012.

The structures, energetics, as well as several important chemical parameters, of antiretroviral drugs - nucleoside reverse transcriptase inhibitors (NRTIs) - and natural deoxyribonucleosides in both neutral, and positively and negatively charged states, are investigated. These studies are carried out within the frame work of first-principles density-functional theory (DFT), using the Becke-Lee-Yang-Parr (BLYP) generalized gradient corrections to the local spin density approximation exchange and correlation energy, norm-conserving pseudopotentials and a plane-wave expansion of Kohn-Sham orbitals. Conceptual DFT is used to determine global and local chemical reactivity parameters.

Quantitative Structure-Activity Relations

Combined QM/MM (ONIOM) and QSAR Approach to the Study of Complex Formation of Matrix Metalloproteinase-9 with a Series of Biphenylsulfonamides–LERE-QSAR Analysis (V)

Tatsusada Yoshida, Seiji Hitaoka, Akira Mashima, Takuya Sugimoto, Hiroshi Matoba [The University of Tokushima Graduate School], and Hiroshi Chuman

J. Phys. Chem. B., **116**, 10283–10289, 2012.

We previously proposed a novel QSAR (quantitative structure–activity relationship) procedure called LERE (linear expression by representative energy terms)-QSAR involving molecular calculations such as an ab initio fragment molecular orbital ones. In the present work, we applied LERE-QSAR to complex formation of matrix metalloproteinase-9 (MMP-9) with a series of substituted biphenylsulfonamides. The results shows that the overall free-energy change accompanying complex formation is due to predominantly the contribution from the electrostatic interaction with the zinc atom in the active site of MMP-9.

Carbon Nanoparticles

Density functional investigation of hydrogen gas adsorption on Fe-doped pristine and Stone–Wales defected single-walled carbon nanotubes

Chanukorn Tabtimsai, Somchai Keawwangchai, Nadtanet Nunthaboot, Vithaya Ruangpornvisuti and Banchob Wanno [Mahasarakham University]

J. Mol.Mod., **18**, 3941-3949, 2012.

The adsorptions of hydrogen molecule of the Fe – doped pristine and Stone – Wales defected armchair (5,5) single – walled carbon nanotubes (SWCNTs) compared with the pristine SWCNT were investigated by using the density functional theory at the B3LYP/LanL2DZ level. The doping of Fe atom into SWCNTs occurring via an exothermic process was found. The adsorptions of hydrogen molecule on the Fe – doped structures of either perfect or SW defected SWCNTs are stronger than on their corresponding undoped structures.

Carbon Nanoparticles (Cont'd)

Parametric Study of ReaxFF Simulation Parameters for Molecular Dynamics Modeling of Reactive Carbon Gases

Benjamin D. Jensen, Ananyo Bandyopadhyay, Kristopher E. Wise, and Gregory M. Odegard [Michigan Technological University]

J. Chem. Theor. and Comp., **8**, 3003–3008, 2012.

The development of innovative carbon-based materials can be greatly facilitated by molecular modeling techniques. Although the Reax Force Field (ReaxFF) can be used to simulate the chemical behavior of carbon-based systems, the simulation settings required for accurate predictions have not been fully explored. Using the ReaxFF, molecular dynamics (MD) simulations are used to simulate the chemical behavior of pure carbon and hydrocarbon reactive gases that are involved in the formation of carbon structures such as graphite, buckyballs, amorphous carbon, and carbon nanotubes.

1.2. Biopolymers

Bioinformatics and Cheminformatics

Computational prediction of N-linked glycosylation incorporating structural properties and patterns

Gwo-Yu Chuang, Jeffrey C. Boyington, M. Gordon Joyce, Jiang Zhu, Gary J. Nabel, Peter D. Kwong, and Ivelin Georgiev [National Institutes of Health, Bethesda]

Bioinformatics. **28**, 2249–2255, 2012.

N-linked glycosylation occurs predominantly at the N-X-T/S motif, where X is any amino acid except proline. Not all N-X-T/S sequons are glycosylated, and a number of web servers for predicting N-linked glycan occupancy using sequence and/or residue pattern information have been developed. None of the currently available servers, however, utilizes protein structural information for the prediction of N-glycan occupancy. Here, we describe a novel classifier algorithm, NGlycPred, for the prediction of glycan occupancy at the N-X-T/S sequons. The algorithm utilizes both structural as well as residue pattern information and was trained on a set of glycosylated protein structures using the Random Forest algorithm.

Dendrimer building toolkit: Model building and characterization of various dendrimer architectures

Vishal Maingi, Vaibhav Jain, Prasad V. Bharatam [NIPER, India] and Prabal K. Maiti

J. Comp. Chem. **33**, 1997–2011, 2012.

We have developed a graphical user interface based dendrimer builder toolkit (DBT) which can be used to generate the dendrimer configuration of desired generation for various dendrimer architectures. The validation of structures generated by this tool was carried out by studying the structural properties of two well known classes of dendrimers: ethylenediamine cored poly(amidoamine) (PAMAM) dendrimer, diaminobutyl cored poly(propylene imine) (PPI) dendrimer. Using full atomistic molecular dynamics (MD) simulation we have calculated the radius of gyration, shape tensor and monomer density distribution for PAMAM and PPI dendrimer at neutral and high pH.

Bioinformatics and Cheminformatics (Cont'd)

Molecular docking studies of protein-nucleotide complexes using MOLSDOCK (mutually orthogonal Latin squares DOCK)

Shankaran Nehru Viji, Nagarajan Balaji and Namasivayam Gautham [University of Madras]

J. Mol.Mod., **18**, 3705-3722, 2012.

Understanding the principles of protein receptor recognition, interaction, and association with molecular substrates and inhibitors is of principal importance in the drug discovery process. MOLSDOCK is a molecular docking method that we have recently developed. It uses mutually orthogonal Latin square sampling (together with a variant of the mean field technique) to identify the optimal docking conformation and pose of a small molecule ligand in the appropriate receptor site. Here we report the application of this method to simultaneously identify both the low energy conformation and the one with the best pose in the case of 62 protein-bound nucleotide ligands.

Protein Structure Prediction

Computational structural analysis of proteins of Mycobacterium tuberculosis and a resource for identifying off-targets

Sameer Hassan, Abhimita Debnath, Vasantha Mahalingam and Luke Elizabeth Hanna [National Institute for Research in Tuberculosis, Chetpet]

J. Mol.Mod., **18**, 3993-4004, 2012.

Advancement in technology has helped to solve structures of several proteins including *M. tuberculosis* (MTB) proteins. Identifying similarity between protein structures could not only yield valuable clues to their function, but can also be employed for motif finding, protein docking and off-target identification. The current study has undertaken analysis of structures of all MTB gene products with available structures was analyzed. Majority of the MTB proteins belonged to the α/β class. 23 different protein folds are used in the MTB protein structures.

Comparative or Homology Modeling

A Kinetic Model for Type I and II IP₃R Accounting for Mode Changes

Ivo Siekmann [The University of Auckland], Larry E. Wagner, David Yule, Edmund J. Crampin, James Sneyd

Biophysical Journal. **103**, 658-668, 2012.

Based upon an extensive single-channel data set, a Markov model for types I and II inositol trisphosphate receptors (IP₃R) is developed. The model aims to represent accurately the kinetics of both receptor types of IP₃R depending on the concentrations of inositol trisphosphate (IP₃), adenosine trisphosphate (ATP), and intracellular calcium (Ca²⁺). In particular, the model takes into account that for some combinations of ligands the IP₃R switches between extended periods of inactivity alternating with intervals of bursting activity (mode changes).

Comparative or Homology Modeling (Cont'd)

Computational study on new natural polycyclic compounds of H1N1 influenza virus neuraminidase

Ye Wang, Di Wu, Dahai Yu, Xuexun Fang [Jilin University], Zhiyong Wang and Li Tian, et al.

J. Mol.Mod., **18**, 3445-3453, 2012.

A new strain of influenza A (H1N1) virus is a major cause of morbidity and mortality around the world. The neuraminidase of the influenza virus has been the most potential target for the anti-influenza drugs such as oseltamivir and zanamivir. However, the emergence of drug-resistant variants of these drugs makes a pressing need for the development of new neuraminidase inhibitors for controlling illness and transmission. Here a 3D structure model of H1N1 avian influenza virus neuraminidase type 1 (N1) was constructed based on the structure of the template H5N1 avian influenza virus N1.

In silico investigation of interactions between human cannabinoid receptor-1 and its antagonists

Guanglin Kuang, Guoping Hu, Xianqiang Sun, Yun Tang [East China University of Science and Technology], Weihua Li and Guixia Liu, et al.

J. Mol.Mod., **18**, 3831-3845, 2012.

Cannabinoid receptor-1 (CB1) is widely expressed in the central nervous system and plays a vital role in regulating food intake and energy expenditure. CB1 antagonists such as Rimonabant have been used in clinic to inhibit food intake, and therefore reduce body weight in obese animals and humans. To investigate the binding modes of CB1 antagonists to the receptor, both receptor- and ligand-based methods were implemented in this study. At first, a pharmacophore model was generated based on 31 diverse CB1 antagonists collected from literature.

Protein Conformational Analysis

Coarse-Grained Simulations of Transitions in the E2-to-E1 Conformations for Ca ATPase (SERCA) Show Entropy–Enthalpy Compensation

Anu Nagarajan, Jens Peter Andersen, Thomas B. Woolf [Johns Hopkins University]

J. Molec. Bio. **420**, 575-593, 2012.

SERCA is a membrane transport protein that has been extensively studied. There are a large number of highly resolved X-ray structures and several hundred mutations that have been characterized functionally. Despite this, the molecular details of the catalytic cycle, a cycle that includes large conformational changes, is not fully understood. In this computational study, we provide molecular dynamics descriptions of conformational changes during the E2 → E1 transitions. The motivating point for these calculations was a series of insertion mutants in the A-M3 linker region that led to significant shifts in measured rates between the E2 and E1 states, as shown by experimental characterization.

Assessing Polyglutamine Conformation in the Nucleating Event by Molecular Dynamics Simulations

Markus S. Miettinen, Volker Knecht, Luca Monticelli, and Zoya Ignatova [University of Potsdam]

J. Phys. Chem. B., **116**, 10259–10265, 2012.

Polyglutamine (polyQ) diseases comprise a group of dominantly inherited pathology caused by an expansion of an unstable polyQ stretch which is presumed to form β -sheets. Similar to other amyloid pathologies, polyQ amyloidogenesis occurs via a nucleated polymerization mechanism, and proceeds through energetically unfavorable nucleus whose existence and structure are difficult to detect. Here, we use atomistic molecular dynamics simulations in explicit solvent to assess the conformation of the polyQ stretch in the nucleus that initiates polyQ fibrillization.

Protein Conformational Analysis (Cont'd)

Role of the Subunit Interactions in the Conformational Transitions in Adult Human Hemoglobin: An Explicit Solvent Molecular Dynamics Study

Olaniyi K. Yusuff, Jonathan O. Babalola, Giovanni Bussi [International School for Advanced Studies (SISSA)], and Simone Raugei

J. Phys. Chem. B., **116**, 11004–11009, 2012.

Hemoglobin exhibits allosteric structural changes upon ligand binding due to the dynamic interactions between the ligand binding sites, the amino acids residues and some other solutes present under physiological conditions. In the present study, the dynamical and quaternary structural changes occurring in two unligated (deoxy-) T structures and two fully ligated (oxy-) R, R2 structures of adult human hemoglobin were investigated with molecular dynamics. It is shown that, in the submicrosecond time scale, there is no marked difference in the global dynamics of the amino acid residues in both the oxy- and the deoxy-forms of the individual structures.

A dynamic model of long-range conformational adaptations triggered by nucleotide binding in GroEL-GroES

Lars Skjaerven [The European Molecular Biology Laboratory], Arturo Muga, Nathalie Reuter and Aurora Martinez

Proteins: Stru. Fun. & Bioinf., **80**, 2333–2346, 2012.

The molecular chaperone, GroEL, essential for correct protein folding in *E. coli*, is composed of 14 identical subunits organized in two interacting rings, each providing a folding chamber for non-native substrate proteins. The oligomeric assembly shows positive cooperativity within each ring and negative cooperativity between the rings. . Here we present multiple all-atom molecular dynamics simulations of the GroEL-GroES assemblies at different stages of the functional cycle.

Protein Dynamics

Protein domain recurrence and order can enhance prediction of protein functions

Mario Abdel Messih, Meghana Chitale, Vladimir B. Bajic, Daisuke Kihara, and Xin Gao [King Abdullah University of Science and Technology]

Bioinformatics. **28**, i444-i450, 2012.

Burgeoning sequencing technologies have generated massive amounts of genomic and proteomic data. Annotating the functions of proteins identified in this data has become a big and crucial problem. Various computational methods have been developed to infer the protein functions based on either the sequences or domains of proteins. We developed two new methods to infer protein functions based on protein domain recurrence and domain order. Our first method, DRDO, calculates the posterior probability of the Gene Ontology terms based on domain recurrence and domain order information, whereas our second method, DRDO-NB, relies on the naïve Bayes methodology using the same domain architecture information.

Protein Dynamics (Cont'd)

Identification of Minimally Interacting Modules in an Intrinsically Disordered Protein

Anurag Sethi, Jianhui Tian, Dung M. Vu, S. Gnanakaran [Los Alamos National Laboratory]

Biophysical Journal. **103**, 748-757, 2012.

The conformational characterization of intrinsically disordered proteins (IDPs) is complicated by their conformational heterogeneity and flexibility. If an IDP could somehow be divided into smaller fragments and reconstructed later, theoretical and spectroscopic studies could probe its conformational variability in detail. Here, we used replica molecular-dynamics simulations and network theory to explore whether such a divide-and-conquer strategy is feasible for α -synuclein, a prototypical IDP. We characterized the conformational variability of α -synuclein by conducting >100 unbiased all-atom molecular-dynamics simulations, for a total of >10 μ s of trajectories.

Solvating atomic level fine-grained proteins in supra-molecular level coarse-grained water for molecular dynamics simulations

Sereina Riniker, Andreas P. Eichenberger and Wilfred F. van Gunsteren [Laboratory of Physical Chemistry, ETH Zurich]

Europ. Biophys. Jou., **41**, 647-661, 2012.

Simulation of the dynamics of a protein in aqueous solution using an atomic model for both the protein and the many water molecules is still computationally extremely demanding considering the time scale of protein motions. The use of supra-atomic or supra-molecular coarse-grained (CG) models may enhance the computational efficiency, but inevitably at the cost of reduced accuracy. . Here, the use of a supra-molecular coarse-grained water model that largely preserves the thermodynamic and dielectric properties of atomic level fine-grained (FG) water in molecular dynamics simulations of an atomic model for four proteins is investigated.

Direct Simulation of Early-Stage Sec-Facilitated Protein Translocation

Bin Zhang and Thomas F. Miller [California Institute of Technology]

J. Am. Chem. Soc., **134**, 13700–13707, 2012.

Direct simulations reveal key mechanistic features of early-stage protein translocation and membrane integration via the Sec-translocon channel. We present a novel computational protocol that combines non-equilibrium growth of the nascent protein with microsecond timescale molecular dynamics trajectories. Analysis of multiple, long timescale simulations elucidates molecular features of protein insertion into the translocon, including signal-peptide docking at the translocon lateral gate (LG), large lengthscale conformational rearrangement of the translocon LG helices, and partial membrane integration of hydrophobic nascent-protein sequences.

Protein Dynamics (Cont'd)

Multistate Organization of Transmembrane Helical Protein Dimers Governed by the Host Membrane

Anton A. Polyansky [Russian Academy of Sciences], Pavel E. Volynsky, and Roman G. Efremov

J. Am. Chem. Soc., **134**, 14390–14400, 2012.

Association of transmembrane (TM) helices taking place in the cell membrane has an important contribution to the biological function of bitopic proteins, among which receptor tyrosine kinases represent a typical example and a potent target for medical applications. Since this process depends on a complex interplay of different factors, it is still far from being fully understood. Here, we present a computational modeling framework, which we have applied to systematically analyze dimerization of 18 TM helical homo- and heterodimers of different bitopic proteins, including the family of epidermal growth factor receptors (ErbBs).

p53 Searches on DNA by Rotation-Uncoupled Sliding at C-Terminal Tails and Restricted Hopping of Core Domains

Tsuyoshi Terakawa, Hiroo Kenzaki, and Shoji Takada [Kyoto University]

J. Am. Chem. Soc., **134**, 14555–14562, 2012.

The tumor suppressor p53 is a transcription factor that searches its cognate sites on DNA. During the search, the roles and interplay of its two DNA binding domains, the folded core domain and the disordered C-terminal domain (CTD), have been controversial. Here, we performed molecular simulations of p53 at various salt concentrations finding that, at physiological salt concentration, p53 diffuses along nonspecific DNA via rotation-uncoupled sliding with its CTD, whereas the core domain repeats dissociation and association.

Ab Initio Dynamics of Cellulose Pyrolysis: Nascent Decomposition Pathways at 327 and 600 °C

Vishal Agarwal, Paul J. Dauenhauer, George W. Huber, and Scott M. Auerbach [University of Massachusetts]

J. Am. Chem. Soc., **134**, 14958–14972, 2012.

We modeled nascent decomposition processes in cellulose pyrolysis at 327 and 600 °C using Car–Parrinello molecular dynamics (CPMD) simulations with rare events accelerated with the metadynamics method. We used a simulation cell comprised of two unit cells of cellulose I β periodically repeated in three dimensions to mimic the solid cellulose. CPMD-metadynamics implemented with various sets of collective variables, such as coordination numbers of the glycosidic oxygen, yielded a variety of chemical reactions such as depolymerization, fragmentation, ring opening, and ring contraction.

Insights into the mechanisms of the selectivity filter of Escherichia coli aquaporin Z

Guodong Hu [University of Texas at San Antonio], Liao Y. Chen and Jihua Wang

J. Mol. Mod., **18**, 3731–3741, 2012.

Aquaporin Z (AQPZ) is a tetrameric protein that forms water channels in the cell membrane of Escherichia coli. The histidine residue (residue 174) in the selectivity filter (SF) region plays an important role in the transport of water across the membrane. In this work, we perform equilibrium molecular dynamics (MD) simulations to illustrate the gating mechanism of the SF and the influences of residue 174 in two different protonation states: Hsd174 with the proton at N δ , and Hse174 with the proton at N ϵ .

Protein Dynamics (Cont'd)

Theoretical study of the decomposition mechanisms and kinetics of the ingredients RDX in composition B

Jian-Guo Zhang [Beijing Institute of Technology, Beijing], Kun Wang, Xiao-Qing Niu, Shao-Wen Zhang and Xiao-Jun Feng, et al.

J. Mol.Mod., **18**, 3915-3926, 2012.

RDX as a component in composition B (TNT + RDX) was first studied by us on its mechanism and kinetics of decomposition reactions in this paper. We have pointed out three possible pathways and found a new low-energy process of its decomposition. The N—N bond cleavage in composition B has higher dissociation energies than the monomer, but it is also the initial step. The optimized structures and the frequencies of all the stationary points were calculated at the B3LYP/6-31G(d) level.

Concerted Movement in pH-Dependent Gating of FocA from Molecular Dynamics Simulations

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

J.Chem. Infor. and Mod. **52**, 2119–2131, 2012.

FocA, a member of the formate-nitrite transporter (FNT) family, transports formate and nitrite across biological membranes in cellular organisms. The export and uptake of formate in bacteria are both mediated by FocA, which undergoes a pH-dependent functional switch. Recently, the crystal structures of *Escherichia coli* FocA (EcFocA), *Vibrio cholerae* FocA (VcFocA), and *Salmonella typhimurium* FocA (StFocA) were reported. We performed molecular dynamics (MD) on StFocA and EcFocA with different states of His209 (protonated and unprotonated), representing different pH conditions of FocA.

Molecular simulation and docking studies of Gal1p and Gal3p proteins in the presence and absence of ligands ATP and galactose: implication for transcriptional activation of GAL genes

Sanjay K. Upadhyay and Yellamraju U. Sasidhar [Indian Institute of Technology Bombay]

J. Comp. Aided Mol. Des. **26**, 847-864, 2012.

The Gal4p mediated transcriptional activation of GAL genes requires the interaction between Gal3p bound with ATP and galactose and Gal80p. Though numerous studies suggest that galactose and ATP activate Gal3p/Gal1p interaction with Gal80p, neither the mechanism of activation nor the interacting surface that binds to Gal80p is well understood. In this study we investigated the dynamics of Gal3p and Gal1p in the presence and absence of ligands ATP and galactose to understand the role played by dynamics in the function of these proteins through molecular dynamics simulation and protein-protein docking studies.

Molecular Dynamics and Umbrella Sampling Study of Stabilizing Factors in Cyclic Peptide-Based Nanotubes

R. Vijayaraj, S. Van Damme, P. Bultinck, and V. Subramanian [CSIR-Central Leather Research Institute]

J. Phys. Chem. B., **116**, 9922–9933, 2012.

In this study, the dissociation mechanism of self-assembled cyclic peptides (CPs) has been investigated using classical/steered molecular dynamics simulations combined with umbrella sampling techniques in a polar and a nonpolar solvent. The stability of cyclic peptide nanotubes (CPNTs) with different surface polarity, {cyclo-[(d-Trp-l-Leu)₄]}₈ and {cyclo-[(l-Gln-d-Ala-l-Glu-d-Ala)₂]}₈, are explored in detail. It is observed from the results that the CPNTs are less dynamic in the nonpolar solvent than in the polar solvent.

Protein Dynamics (Cont'd)

Concentration and Temperature Dependences of Polyglutamine Aggregation by Multiscale Coarse-Graining Molecular Dynamics Simulations

Li Deng, Yanting Wang [Chinese Academy of Sciences], and Zhong-can Ou-yang

J. Phys. Chem. B., **116**, 10135–10144, 2012.

The solvent-free multiscale coarse-graining model of polyglutamine was employed to study polyglutamine aggregation at different concentrations and temperatures by means of molecular dynamics simulation. The heterogeneity order parameter (HOP) was used to quantify the polyglutamine aggregation. Our simulation results demonstrate that polyglutamine aggregation is sensitive to concentration and temperature changes. In equilibrium states, polyglutamine molecules fluctuate between aggregating tightly and distributing uniformly.

Free Energy Calculations

Regularizing Binding Energy Distributions and the Hydration Free Energy of Protein Cytochrome C from All-Atom Simulations

Valéry Weber and D. Asthagiri [Johns Hopkins University, Baltimore]

J. Chem. Theor. and Comp., **8**, 3409–3415, 2012.

By introducing an external field to temper short-range protein water interactions, we regularize the statistical problem of calculating the hydration free energy, μ^{ex} , of the protein cytochrome C using the potential distribution theorem. Using this approach, we calculate the nonelectrostatic (dispersion) and electrostatic contributions to μ^{ex} . The nonelectrostatic contribution interpreted within an accessible surface area approach leads to a surface energy parameter that is about twice the value based on the hydration of small alkanes: at the size scale of the protein, hydrophobic hydration is more stronger relative to small alkanes.

Ligand Binding/Docking

Toward a better understanding of the interaction between TGF- β family members and their ALK receptors

Valentina Romano, Domenico Raimondo, Luisa Calvanese, Gabriella D'Auria and Anna Tramontano, Lucia Falcigno [Federico II University of Naples]

J. Mol.Mod., **18**, 3617-3625, 2012.

Transforming growth factor-beta (TGF- β) proteins are a family of structurally related extracellular proteins that trigger their signaling functions through interaction with the extracellular domains of their cognate serine/threonine kinase receptors. The specificity of TGF- β /receptor binding is complex and gives rise to multiple functional roles. Additionally, it is not completely understood at the atomic level. Here, we use the most reliable computational methods currently available to study systems involving activin-like kinase (ALK) receptors ALK4 and ALK7 and their multiple TGF- β ligands.

Ligand Binding / Docking (Cont'd)

Binding of rhodamine B and kiton red S to cucurbit[7]uril: density functional investigations

Jayshree K. Khedkar, Krishna K. Jagtap, Rahul V. Pinjari, Alok Kumar Ray and Shridhar P. Gejji [University of Pune]

J. Mol.Mod., **18**, 3743-3750, 2012.

The binding of the laser dyes rhodamine B (RhB) and sulforhodamine B (kiton red S or KRS) to a cucurbit[7]uril (CB[7]) host has been investigated using density functional theory. Both guests (RhB and KRS) contain two N,N-diethylamino groups on a xanthene core. The lowest-energy structure of these host-guest complexes has one of the N,N-diethylamino groups encapsulated within the host cavity, that engenders C-H...O interactions with portals, while the remaining noninteracting diethylamino group resides outside the cavity.

Theoretical studies on the interaction of biphenyl inhibitors with Mycobacterium tuberculosis protein tyrosine phosphatase MtpB

Lihua Dong, Junyou Shi and Yongjun Liu [Chinese Academy of Sciences]

J. Mol.Mod., **18**, 3847-3856, 2012.

MtpB is an essential secreted virulence factor for *M. tuberculosis*. Inhibition of MtpB impairs mycobacterial survival in host macrophages and thus helps reduce tuberculosis infections. However, the binding mode of the biphenyl inhibitors, which are known as some of the most potent MtpB inhibitors, remains unclear. In this study, to understand the interactions between biphenyl inhibitors and MtpB, docking and molecular dynamics simulations were carried out using AutoDock and GROMACS softwares.

Insights from comprehensive multiple receptor docking to HDAC8

Michael Brunsteiner and Pavel A. Petukhov [University of Illinois at Chicago]

J. Mol.Mod., **18**, 3927-3939, 2012.

A systematic investigation of the available crystal structures of HDAC8 and of the influence of different receptor structures and docking protocols is presented. The study shows that the open conformation of HDAC8 may be preferred by ligands with flexible surface binding groups, as such a conformation allows the ligands to minimize their exposure to solvent upon binding. This observation allowed us to rationalize the excellent potency of pyrazole-based inhibitors compared to that of isoxazole-based inhibitors.

Molecular Dynamics Approach to Probe the Allosteric Inhibition of PTP1B by Chlorogenic and Cichoric Acid

Sarath Kumar Baskaran, Nabajyoti Goswami, Sudhagar Selvaraj, Velusamy Shanmuganathan Muthusamy, and Baddireddi Subhadra Lakshmi [Anna University]

J.Chem. Infor. and Mod. **52**, 2004-2012, 2012.

Protein tyrosine phosphatase 1B (PTP1B), a major negative regulator of the insulin and leptin signaling pathway, is a potential target for therapeutic intervention against diabetes and obesity. The current study investigates the molecular interactions between the allosteric site of PTP1B with two caffeoyl derivatives, chlorogenic acid (CGA) and cichoric acid (CHA), using computational strategies. Molecular docking analysis with CGA and CHA at the allosteric site of PTP1B were performed and the resulting protein-ligand complexes used for molecular dynamics simulation studies for a time scale of 10 ns.

Ligand Binding / Docking (Cont'd)

Understanding the Inhibitory Effect of Highly Potent and Selective Archazolides Binding to the Vacuolar ATPase

Sandra Dreisigacker, Dorota Latek, Svenja Bockelmann, Markus Huss, Helmut Wiczorek, Slawomir Filipek, Holger Gohlke, Dirk Menche, and Teresa Carlomagno [Structural and Computational Biology Unit, EMBL, Mayerhofstrasse 1]

J.Chem. Infor. and Mod. **52**, 2265–2272, 2012.

Vacuolar ATPases are a potential therapeutic target because of their involvement in a variety of severe diseases such as osteoporosis or cancer. Archazolide A (**1**) and related analogs have been previously identified as selective inhibitors of V-ATPases with potency down to the subnanomolar range. Herein we report on the determination of the ligand binding mode by a combination of molecular docking, MD simulations, and biochemical experiments, resulting in a sound model for the inhibitory mechanism of this class of putative anticancer agents. The binding site of archazolides was confirmed to be located in the equatorial region of the membrane-embedded V_0 -rotor, as recently proposed on the basis of site-directed mutagenesis.

Curcumin Binds to $A\beta_{1-40}$ Peptides and Fibrils Stronger Than Ibuprofen and Naproxen

Son Tung Ngo and Mai Suan Li [Institute for Computational Science and Technology, 6 Quarter, Linh Trung Ward]

J. Phys. Chem. B., **116**, 10165–10175, 2012.

Binding of curcumin, naproxen, and ibuprofen to $A\beta_{1-40}$ peptide and its fibrils is studied by docking method and all-atom molecular dynamics simulations. The Gromos96 43a1 force field and simple point charge model of water have been used for molecular dynamics simulations. It is shown that if the receptor is a monomer then naproxen and ibuprofen are bound to the same place that is different from the binding position of curcumin. However all of three ligands have the same binding pocket in fibrillar structures.

Probing Ligand-Binding Modes and Binding Mechanisms of Benzoxazole-Based Amide Inhibitors with Soluble Epoxide Hydrolase by Molecular Docking and Molecular Dynamics Simulation

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

J. Phys. Chem. B., **116**, 10219–10233, 2012.

Soluble epoxide hydrolase (sEH) has become a new therapeutic target for treating a variety of human diseases. The inhibition of human sEH hydrolase activity was studied by MD simulation techniques. A set of six benzoxazole-based amide inhibitors binding to sEH has been studied through molecular docking, MD simulation, free energy calculations, and energy decomposition analysis. On the basis of molecular mechanics-generalized Born/surface area (MM-GB/SA) computation and normal-mode analysis (NMA), the obtained results indicate that the rank of calculated binding free energies ($\Delta\Delta G_{TOT}$) of these inhibitors is in excellent agreement with that of experimental bioactivity data (IC_{50}).

How Strongly Does Trehalose Interact with Lysozyme in the Solid State? Insights from Molecular Dynamics Simulation and Inelastic Neutron Scattering

Adrien Lerbret [Université Lille Nord de France], Frédéric Affouard, Alain Hédoux, Stefanie Krenzlin, Jürgen Siepmann, Marie-Claire Bellissent-Funel, and Marc Descamps

J. Phys. Chem. B., **116**, 11103–11116, 2012.

Therapeutic proteins are usually conserved in glassy matrixes composed of stabilizing excipients and a small amount of water, which both control their long-term stability, and thus their potential use in medical treatments. To shed some light on the protein–matrix interactions in such systems, we performed molecular dynamics (MD) simulations on matrixes of (i) the model globular protein lysozyme (L), (ii) the well-known bioprotectant trehalose (T), and (iii) the 1:1 (in weight) lysozyme/trehalose mixture (LT), at hydration levels h of 0.0, 0.075, and 0.15 (in g of water/g of protein or sugar).

Enzyme Catalysis

Study on the enantioselectivity inhibition mechanism of acetyl-coenzyme A carboxylase toward haloxyfop by homology modeling and MM-PBSA analysis

Jin Tao, Guirong Zhang, Aijun Zhang, Liangyu Zheng [Jilin University] and Shugui Cao

J. Mol.Mod., **18**, 3783-3792, 2012.

Acetyl-coenzyme A carboxylase (ACCase) has been identified as one of the most important targets of herbicide Aryloxyphenoxypropionates (APPs). ACCase shows different enantioselectivity toward APPs, and only (R)-enantiomers of APPs have the herbicidal activity. In order to deeply understand the enantioselective recognition mechanism of ACCase, (R)-haloxyfop, which is a typical commercial herbicide from APPs, is selected and the relative binding free energy between ACCase and (R)-haloxyfop is investigated and compared with that between ACCase and (S)-haloxyfop by homology modeling and molecular mechanics-Poisson-Boltzmann surface area (MM-PBSA) method.

Targeting imidazoline site on monoamine oxidase B through molecular docking simulations

Fernanda Pretto Moraes and Walter Filgueira de Azevedo Jr [Pontificia Universidade Católica do Rio Grande do Sul]

J. Mol.Mod., **18**, 3877-3886, 2012.

Monoamine oxidase (MAO) is an enzyme of major importance in neurochemistry, because it catalyzes the inactivation pathway for the catecholamine neurotransmitters, noradrenaline, adrenaline and dopamine. In the last decade it was demonstrated that imidazoline derivatives were able to inhibit MAO activity. Furthermore, crystallographic studies identified the imidazoline-binding domain on monoamine oxidase B (MAO-B), which opens the possibility of molecular docking studies focused on this binding site. The goal of the present study is to identify new potential inhibitors for MAO-B.

Free Energy Calculations Give Insight into the Stereoselective Hydroxylation of α -Ionones by Engineered Cytochrome P450 BM3 Mutants

Stephanie B.A. de Beer, Harini Venkataraman, Daan P. Geerke, Chris Oostenbrink [Vrije Universiteit], and Nico P.E. Vermeulen

J.Chem. Infor. and Mod. **52**, 2139–2148, 2012.

Previously, stereoselective hydroxylation of α -ionone by Cytochrome P450 BM3 mutants M01 A82W and M11 L437N was observed. While both mutants hydroxylate α -ionone in a regioselective manner at the C3 position, M01 A82W catalyzes formation of trans-3-OH- α -ionone products whereas M11 L437N exhibits opposite stereoselectivity, producing trans-(3S,6S)-OH- α -ionone and cis-(3S,6R)-OH- α -ionone. Here, we explore the stereoselective C3 hydroxylation of α -ionone by Cytochrome P450 BM3 mutants M01 A82W and M11 L437N using molecular dynamics-based free energy calculations to study the interaction between the enzyme and both the substrates and the products.

Enzyme Catalysis (Cont'd)

Mechanism of Taq DNA Polymerase Inhibition by Fullerene Derivatives: Insight from Computer Simulations

Praveen Nedumpully Govindan, Luca Monticelli, and Emppu Salonen [Aalto University]

J. Phys. Chem. B., **116**, 10676–10683, 2012.

Experiments have shown that two water-soluble fullerene C₆₀ derivatives, fullerenol and fullerene trimalonate, inhibit duplication of DNA via polymerase chain reaction (PCR). It has further been shown that the target of this inhibition is the DNA polymerase protein routinely used in PCR. We have used a combination of molecular docking and molecular dynamics simulations to study the possible DNA polymerase inhibition mechanisms in atomistic detail.

Initial Events in the Degradation of Hyaluronan Catalyzed by Hyaluronate Lyase from *Spectrooccus pneumoniae*: QM/MM Simulation

Min Zheng, Hongling Zhang, and Dingguo Xu [Sichuan University]

J. Phys. Chem. B., **116**, 11166–11172, 2012.

Hyaluronate lyase from *Spectrooccus pneumoniae* can degrade hyaluronic acid, which is one of the major components in the extracellular matrix. The major functions of hyaluronan are to regulate water balance and osmotic pressure and act as an ion-exchange resin. In this work, we focus on the prerequisite issue of the enzymatic reaction, i.e., the initial reactive conformer. Based on the quantum mechanical and molecular mechanical molecular dynamic simulations and free energy profiles, a near attack conformer was obtained for the degradation of hyaluronan catalyzed by the hyaluronate lyase.

Protein-Protein Interactions

Techniques to cope with missing data in host–pathogen protein interaction prediction

Meghana Kshirsagar, Jaime Carbonell, and Judith Klein-Seetharaman [Carnegie Mellon University]

Bioinformatics. **28**, i466–i472, 2012.

Approaches that use supervised machine learning techniques for protein–protein interaction (PPI) prediction typically use features obtained by integrating several sources of data. Often certain attributes of the data are not available, resulting in missing values. In particular, our host–pathogen PPI datasets have a large fraction, in the range of 58–85% of missing values, which makes it challenging to apply machine learning algorithms. We show that specialized techniques for missing value imputation can improve the performance of the models significantly. We use cross species information in combination with machine learning techniques like Group lasso with ℓ_1/ℓ_2 regularization. We demonstrate the benefits of our approach on two PPI prediction problems.

Protein-Protein Interactions (Cont'd)

Coarse-Grained Simulations of Protein-Protein Association: An Energy Landscape Perspective

Krishnakumar M. Ravikumar, Wei Huang, Sichun Yang
[Case Western Reserve University]

Biophysical Journal. **103**, 837-845, 2012.

Understanding protein-protein association is crucial in revealing the molecular basis of many biological processes. Here, we describe a theoretical simulation pipeline to study protein-protein association from an energy landscape perspective. First, a coarse-grained model is implemented and its applications are demonstrated via molecular dynamics simulations for several protein complexes. Second, an enhanced search method is used to efficiently sample a broad range of protein conformations. Third, multiple conformations are identified and clustered from simulation data and further projected on a three-dimensional globe specifying protein orientations and interacting energies.

Relationship between Hot Spot Residues and Ligand Binding Hot Spots in Protein-Protein Interfaces

Brandon S. Zerbe, David R. Hall, Sandor Vajda [Boston University], Adrian Whitty, and Dima Kozakov

J.Chem. Infor. and Mod. **52**, 2236–2244, 2012.

In the context of protein-protein interactions, the term “hot spot” refers to a residue or cluster of residues that makes a major contribution to the binding free energy, as determined by alanine scanning mutagenesis. In contrast, in pharmaceutical research, a hot spot is a site on a target protein that has high propensity for ligand binding and hence is potentially important for drug discovery. Here we examine the relationship between these two hot spot concepts by comparing alanine scanning data for a set of 15 proteins with results from mapping the protein surfaces for sites that can bind fragment-sized small molecules.

Predicting the effects of amino acid replacements in peptide hormones on their binding affinities for class B GPCRs and application to the design of secretin receptor antagonists

Jerez A. Te, Maoqing Dong, Laurence J. Miller and Andrew J. Bordner [Mayo Clinic]

J. Comp. Aided Mol. Des. **26**, 835-845, 2012.

Computational prediction of the effects of residue changes on peptide-protein binding affinities, followed by experimental testing of the top predicted binders, is an efficient strategy for the rational structure-based design of peptide inhibitors. In this study we apply this approach to the discovery of competitive antagonists for the secretin receptor, the prototypical member of class B G protein-coupled receptors (GPCRs). Proteins in this family are involved in peptide hormone-stimulated signaling and are implicated in several human diseases, making them potential therapeutic targets.

Computational design, construction, and characterization of a set of specificity determining residues in protein-protein interactions

Chioko Nagao [National Institute of Biomedical Innovation, 7-6-8 Saito-Asagi], Nozomi Izako, Shinji Soga, Samia Haseeb Khan, Shigeki Kawabata, Hiroki Shirai and Kenji Mizuguchi

Proteins: Stru. Fun. & Bioinf., **80**, 2426–2436, 2012.

Proteins interact with different partners to perform different functions and it is important to elucidate the determinants of partner specificity in protein complex formation. Although methods for detecting specificity determining positions have been developed previously, direct experimental evidence for these amino acid residues is scarce, and the lack of information has prevented further computational studies. In this article, we constructed a dataset that is likely to exhibit specificity in protein complex formation, based on available crystal structures and several intuitive ideas about interaction profiles and functional subclasses.

Membrane Proteins and Lipid Peptide Interactions

New description of protein–ligand interactions using a spherical self-organizing map

Kiyoshi Hasegawa, Kimito Funatsu [The University of Tokyo]

Bioorg. and Med.Chem., **20**, 5410-5415, 2012.

In a previous report, we studied the mapping ability of the spherical self-organizing map (SSOM). The original 3D structure of the active site of the $\beta 2$ protein structure was well reproduced by the SSOM. To validate the geometrical transformation and the resulting molecular electrostatic potential (MEP) distribution, the molecular surfaces of 20 $\beta 2$ ligands were mapped onto the protein SSOM sphere. In this study, we perform a quantitative structure–activity relationship (QSAR) study of caspase-3 inhibitors based on the SSOM technique. Initially, the active site of the protein structure ‘caspase-3’ was characterized by the SSOM using the MEP values. Each inhibitor was then projected onto the protein SSOM sphere and the chemical descriptors were derived from the ligand SSOM sphere.

Computational Study of Room-Temperature Ionic Liquids Interacting with a POPC Phospholipid Bilayer

Richard J. Bingham [University of Leeds] and Pietro Ballone

J. Phys. Chem. B., **116**, 11205–11216, 2012.

Molecular dynamics simulations based on an empirical force field have been carried out to investigate the properties of a zwitter-ionic phospholipid (POPC) bilayer in contact with a water solution of [bmim][Cl], [bmim][PF₆] and [bmim][Tf₂N] at concentration $c = 0.5$ M. The results reveal important and specific interactions of cations and anions with the bilayer. The [bmim]⁺ cation, in particular, shows a clear tendency to be incorporated tail-first into the bilayer.

Protein Folding

Multidomain Protein Solves the Folding Problem by Multifunnel Combined Landscape: Theoretical Investigation of a Y-Family DNA Polymerase

Yong Wang, Xiakun Chu, Zucui Suo, Erkang Wang, and Jin Wang [Chinese Academy of Sciences, Changchun]

J. Am. Chem. Soc., **134**, 13755–13764, 2012.

Approximately three-fourths of eukaryotic proteins are composed of multiple independently folded domains. The degrees of freedom for proteins with multiple domains are many orders of magnitude larger than that for single domain proteins. Now, the question arises: How do the multidomain proteins solve the “protein folding problem”? Here, we specifically address this issue by exploring the structure folding relationship of *Sulfolobus solfataricus* DNA polymerase IV (DPO4), a prototype Y-family DNA polymerase which contains a polymerase core consisting of a palm (P domain), a finger (F domain), and a thumb domain (T domain) in addition to a little finger domain (LF domain).

Protein Folding (Cont'd)

Folding and Self-Assembly of a Small Protein Complex

Adam K. Sieradzan, Adam Liwo, and Ulrich H. E. Hansmann
[Oklahoma University, Norman]

J. Chem. Theor. and Comp., **8**, 3416–3422, 2012.

The synthetic homotetrameric $\beta\beta\alpha$ (BBAT1) protein possesses a stable quaternary structure with a $\beta\beta\alpha$ fold. Because of its small size (a total of 84 residues), the homotetramer is an excellent model system with which to study the self-assembly and protein–protein interactions. We find from replica exchange MD simulations with the coarse-grain UNRES force field that the folding and association pathway consists of three well-separated steps, where association to a tetramer precedes and facilitates folding of the four chains.

Evaluation and Optimization of Discrete State Models of Protein Folding

Elizabeth H. Kellogg, Oliver F. Lange, and David Baker
[University of Washington, Seattle]

J. Phys. Chem. B., **116**, 11405–11413, 2012.

The space accessed by a folding macromolecule is vast, and how to best project computer simulations of protein folding trajectories into an interpretable sequence of discrete states is an open research problem. Here we introduce a trajectory likelihood measure for assessing alternative discrete state models of protein folding. We find that widely used rmsd-based clustering methods require large numbers of initial states and a second agglomeration step based on kinetic connectivity to produce models with high predictive power; this is the approach taken in elegant recent work with Markov State Models of protein folding.

Temperature and pressure denaturation of chignolin: Folding and unfolding simulation by multibaric-multithermal molecular dynamics method

Hisashi Okumura [Institute for Molecular Science, Okazaki]

Proteins: Stru. Fun. & Bioinf., **80**, 2397–2416, 2012.

A multibaric-multithermal molecular dynamics (MD) simulation of a 10-residue protein, chignolin, was performed. All-atom model with the Amber parm99SB force field was used for the protein and the TIP3P model was used for the explicit water molecules. This MD simulation covered wide ranges of temperature between 260 and 560 K and pressure between 0.1 and 600 MPa and sampled many conformations without getting trapped in local-minimum free-energy states. Folding events to the native β -hairpin structure occurred five times and unfolding events were observed four times.

Protein-Nucleic acid Interactions

Dynamics of Forced Nucleosome Unraveling and Role of Nonuniform Histone-DNA Interactions

Irina V. Dobrovolskaia, Gaurav Arya [University of California at San Diego]

Biophysical Journal. **103**, 989-998, 2012.

A coarse-grained model of the nucleosome is introduced to investigate the dynamics of force-induced unwrapping of DNA from histone octamers. In this model, the DNA is treated as a charged, discrete worm-like chain, and the octamer is treated as a rigid cylinder carrying a positively charged superhelical groove that accommodates 1.7 turns of DNA. The groove charges are parameterized to reproduce the nonuniform histone/DNA interaction free energy profile and the loading rate-dependent unwrapping forces, both obtained from single-molecule experiments. Brownian dynamics simulations of the model under constant loading conditions reveal that nucleosome unraveling occurs in three distinct stages.

Protein-Nucleic acid Interactions (Cont'd)

Single-Stranded DNA within Nanopores: Conformational Dynamics and Implications for Sequencing; a Molecular Dynamics Simulation Study

Andrew T. Guy, Thomas J. Piggot, Syma Khalid [University of Southampton, Southampton]

Biophysical Journal. **103**, 1028-1036, 2012.

Engineered protein nanopores, such as those based on α -hemolysin from *Staphylococcus aureus* have shown great promise as components of next-generation DNA sequencing devices. However, before such protein nanopores can be used to their full potential, the conformational dynamics and translocation pathway of the DNA within them must be characterized at the individual molecule level. Here, we employ atomistic molecular dynamics simulations of single-stranded DNA movement through a model α -hemolysin pore under an applied electric field.

Nucleic Acids

Strikingly Different Effects of Hydrogen Bonding on the Photodynamics of Individual Nucleobases in DNA: Comparison of Guanine and Cytosine

Tomáš Zelený, Matthias Ruckebauer, Adelia J.A. Aquino, Thomas Müller, Filip Lankaš, Tomáš Dršata, William L. Hase, Dana Nachtigallova [Academy of Sciences of the Czech Republic], and Hans Lischka

J. Am. Chem. Soc., **134**, 10959–10965, 2012.

Ab initio surface hopping dynamics calculations were performed to study the photophysical behavior of cytosine and guanine embedded in DNA using a quantum mechanical/molecular mechanics (QM/MM) approach. It was found that the decay rates of photo excited cytosine and guanine were affected in a completely different way by the hydrogen bonding to the DNA environment. In case of cytosine, the geometrical restrictions exerted by the hydrogen bonds did not influence the relaxation time of cytosine significantly due to the generally small cytosine ring puckering required to access the crossing region between excited and ground state.

Role of wobble base pair geometry for codon degeneracy: purine-type bases at the anticodon wobble position

Gunajyoti Das and R. H. Duncan Lyngdoh [North-Eastern Hill University]

J. Mol.Mod., **18**, 3805-3820, 2012.

Codon degeneracy is a key feature of the genetic code, explained by Crick (*J Mol Biol* 19:548-555, 1966) in terms of imprecision of base pairing at the codon third position (the wobble position) of the codon-anticodon duplex. The Crick wobble rules define, but do not explain, which base pairs are allowed/disallowed at the wobble position of this duplex. This work examines whether the H-bonded configurations of solitary RNA base pairs can in themselves help decide which base pairs are allowed at the wobble position during codon-anticodon pairing.

Surfaces, Catalysts, and Materials Subjects

2. METHODOLOGY

Quantitative Structure-Activity Relations

3D-QSAR study of Chk1 kinase inhibitors based on docking

Lingzhou Zhao, Yongjuan Liu, Shiyuan Hu and Huabei Zhang [Beijing Normal University]

J. Mol.Mod., **18**, 3669-3694, 2012.

Checkpoint kinase 1 (Chk1), a kind of a serine/threonine protein kinase, plays a significant role in DNA damage-induced checkpoints. . In this paper, in order to understand the structure-activity relationship of macrocyclic urea Chk1 inhibitors, a study combined molecular docking and 3D-QSAR modeling was carried out, which resulted in two substructure-based 3D-QSAR models, including the CoMFA model (r^2 , 0.873; q^2 , 0.572) and CoMSIA model (r^2 , 0.897; q^2 , 0.599).

In silico development, validation and comparison of predictive QSAR models for lipid peroxidation inhibitory activity of cinnamic acid and caffeic acid derivatives using multiple chemometric and cheminformatics tools

Indrani Mitra, Achintya Saha and Kunal Roy [Jadavpur University]

J. Mol.Mod., **18**, 3951-3967, 2012.

The design and development of antioxidant molecules have lately gained a great deal of focus which is attributed to their immense biomedical importance in combating the free radical associated health hazards. In a situation to replenish the endogenous antioxidant loss, synthetic molecules with potent antioxidant activity is demanded. The present work thus aims at in silico modeling of antioxidant molecules that may facilitate in searching and designing of new chemical entities with enhanced activity profile. A series of cinnamic acid and caffeic acid derivatives having the ability to inhibit lipid peroxidation have been modeled in the present work.

R-group template CoMFA combines benefits of “ad hoc” and topomer alignments using 3D-QSAR for lead optimization

Richard D. Cramer [Tripos DE]

J. Comp. Aided Mol. Des. **26**, 805-819, 2012.

Template CoMFA methodologies extend topomer CoMFA by allowing user-designated templates, for example the experimental receptor-bound conformation of a prototypical ligand, to help determine the alignment of training and test set structures for 3D-QSAR. The algorithms that generate its new structural modality, template-constrained topomers, are described. Template CoMFA's resolution of certain topomer CoMFA concerns, by providing user control of topological consistency and structural acceptability, is demonstrated for sixteen 3D-QSAR training sets, in particular the Selwood dataset.

Potentials and Parameters

Force field development for cofactors in the photosystem II

Lu Zhang, Daniel-Adriano Silva, YiJing Yan and Xuhui Huang [Hong Kong University of Science and Technology]

J. Comp. Chem. **33**, 1969–1980, 2012.

We present a set of force field (FF) parameters compatible with the AMBER03 FF to describe five cofactors in photosystem II (PSII) of oxygenic photosynthetic organisms: plastoquinone-9 (three redox forms), chlorophyll-a, pheophytin-a, heme-b, and β -carotene. The development of a reliable FF for these cofactors is an essential step for performing molecular dynamics simulations of PSII. Such simulations are important for the calculation of absorption spectrum and the further investigation of the electron and energy transfer processes.

Molecular Dynamics

Ion-Controlled Conformational Dynamics in the Outward-Open Transition from an Occluded State of LeuT

Chunfeng Zhao, Sebastian Stolzenberg, Luis Gracia, Harel Weinstein, Sergei Noskov [University of Calgary, Calgary], Lei Shi

Biophysical Journal. **103**, 878-888, 2012.

Neurotransmitter:sodium symporter (NSS) proteins are secondary Na^+ -driven active transporters that terminate neurotransmission by substrate uptake. Despite the availability of high-resolution crystal structures of a bacterial homolog of NSSs—Leucine Transporter (LeuT)—and extensive computational and experimental structure-function studies, unanswered questions remain regarding the transport mechanisms. We used microsecond atomistic molecular-dynamics (MD) simulations and free-energy computations to reveal ion-controlled conformational dynamics of LeuT in relation to binding affinity and selectivity of the more extracellularly positioned Na^+ binding site (Na1 site).

Simulation of Metal–Ligand Self-Assembly into Spherical Complex M_6L_8

Makoto Yoneya, Tomohiko Yamaguchi, Sota Sato, and Makoto Fujita [University of Tokyo]

J. Am. Chem. Soc., **134**, 14401–14407, 2012.

Molecular dynamics simulations were performed to study the self-assembly of a spherical complex through metal–ligand coordination interactions. M_6L_8 , a nanosphere with six palladium ions and eight pyridine-capped tridentate ligands, was selected as a target system. We successfully observed the spontaneous formation of spherical shaped M_6L_8 cages over the course of our simulations, starting from random initial placement of the metals and ligands. To simulate spontaneous coordination bond formations and breaks, the cationic dummy atom method was employed to model nonbonded metal–ligand interactions.

Molecular Dynamics (Cont'd)

Transportation behavior of alkali ions through a cell membrane ion channel. A quantum chemical description of a simplified isolated model

Ferenc Billes [Budapest University of Technology and Economics], Ildikó Mohammed-Ziegler and Hans Mikosch

J. Mol.Mod., **18**, 3627-3637, 2012.

Quantum chemical model calculations were carried out for modeling the ion transport through an isolated ion channel of a cell membrane. An isolated part of a natural ion channel was modeled. The model channel was a calixarene derivative, hydrated sodium and potassium ions were the models of the transported ion. The electrostatic potential of the channel and the energy of the channel-ion system were calculated as a function of the alkali ion position. Both attractive and repulsive ion-channel interactions were found. The calculations – namely the dependence of the system energy and the atomic charges of the water molecules with respect to the position of the alkali ion in the channel – revealed the molecular-structural background of the potassium selectivity of this artificial ion channel.

Local and global effects of Mg²⁺ on Ago and miRNA-target interactions

Zhi Ma, Zhenghua Xue, Huixiao Zhang, Yan Li and Yonghua Wang [Northwest A&F University]

J. Mol.Mod., **18**, 3769-3781, 2012.

Three magnesium ions (Mg²⁺), named Mg1 (in Mid domain), Mg2 and Mg3 (both in PIWI domain), located at the small RNA binding domain of Argonaute (Ago) protein, are important for sequence-specific miRNA-target interactions. Such conjunction between the Ago protein and miRNA raises the question: How do Mg²⁺ ions participate in the recognition process of miRNA by Ago or its target. Furthermore, it is still unclear whether the Mg²⁺ ions contribute to the local or global stability of the miRNA complex. In this work, we have performed a series of 16 independent molecular dynamic simulations (MD) to characterize the functions of Mg²⁺, hydration patterns and the conformational events involved in the miRNA-target interactions.

Reaction Dynamics of ATP Hydrolysis in Actin Determined by ab Initio Molecular Dynamics Simulations

Holly Freedman [University of Algarve], Teodoro Laino, and Alessandro Curioni

J. Chem. Theor. and Comp., **8**, 3373–3383, 2012.

Energy released by the hydrolysis of the high-energy phosphate bond of nucleoside triphosphate (NTP) cofactors is the driving force behind most biological processes. To understand how this energy is used to induce differences in protein structure and function, we examine the transfer of vibrational energy into the nucleotide-bound actin active site immediately after reaction activation. To this end, we perform Born–Oppenheimer molecular dynamics simulations of the active site at the level of density functional theory (DFT) starting at the calculated transition state (TS) structure.

QM and QM/MM

Hybrid Dynamics Simulation Engine for Metalloproteins

Manuel Sparta, David Shirvanyants, Feng Ding, Nikolay V. Dokholyan, Anastassia N. Alexandrova [University of California, Los Angeles]

Biophysical Journal. **103**, 767-776, 2012.

Quality computational description of metalloproteins is a great challenge due to the vast span of time- and lengthscales characteristic of their existence. We present an efficient new method that allows for robust characterization of metalloproteins. It combines quantum mechanical (QM) description of the metal-containing active site, and extensive dynamics of the protein captured by discrete molecular dynamics (DMD) (QM/DMD). DMD samples the entire protein, including the backbone, and most of the active site, except for the immediate coordination region of the metal.

Binding of piano-stool Ru(II) complexes to DNA; QM/MM study

Zdeněk Futera, James A. Platts and Jaroslav V. Burda [Charles University]

J. Comp. Chem. **33**, 2092–2101, 2012.

Ru(II) “piano-stool” complexes belong to group of biologically active metallocomplexes with promising anticancer activity. In this study, we investigate the reaction mechanism of $[(\eta^6\text{-benzene})\text{Ru(II)(en)(H}_2\text{O)}]^{2+}$ (en = ethylenediamine) complex binding to DNA by hybrid QM/MM computational techniques. The reaction when the Ru(II) complex is coordinated on N7-guanine from major groove is explored. Two reaction pathways, direct binding to N7 position and two-step mechanism passing through O6 position, are considered. It was found that the reaction is exothermic and the direct binding process is preferred kinetically.

Interfacing the GROMOS (bio)molecular simulation software to quantum-chemical program packages

Katharina Meier, Nathan Schmid and Wilfred F. van Gunsteren [Swiss Federal Institute of Technology Zürich ETH]

J. Comp. Chem. **33**, 2108–2117, 2012.

The newly implemented quantum-chemical/molecular-mechanical (QM/MM) functionality of the Groningen molecular simulation (GROMOS) software for (bio)molecular simulation is described. The implementation scheme is based on direct coupling of the GROMOS C++ software to executables of the quantum-chemical program packages MNDO and TURBOMOLE, allowing for an independent further development of these packages.

Density functional study on the derivatives of purine

Wei-Jie Chi [Shanxi Normal University], Lu-Lin Li, Bu-Tong Li and Hai-Shun Wu

J. Mol.Mod., **18**, 3501-3506, 2012.

The derivatives of purine are designed through substituting the hydrogen atoms on it for nitro and amino functional groups. Geometries and frequency are analyzed at the B3LYP/6-31 G** level of density functional theory (DFT). Heats of formation (HOF), bond dissociation energy (BDE) and detonation parameters (detonation velocity and detonation pressure) are obtained in detail at the same level. It is found that the BDE values of all derivatives are over 120KJ•mol⁻¹, and have high positive heats of formation.

QM and QM/MM (Cont'd)

Non-Gaussian Statistics and Nanosecond Dynamics of Electrostatic Fluctuations Affecting Optical Transitions in Proteins

Daniel R. Martin and Dmitry V. Matyushov [Arizona State University]

J. Phys. Chem. B., **116**, 10294–10300, 2012.

We show that electrostatic fluctuations of the protein–water interface are globally non-Gaussian. The electrostatic component of the optical transition energy (energy gap) in a hydrated green fluorescent protein is studied here by classical molecular dynamics simulations. The distribution of the energy gap displays a high excess in the breadth of electrostatic fluctuations over the prediction of the Gaussian statistics. The energy gap dynamics include a nanosecond component. When simulations are repeated with frozen protein motions, the statistics shifts to the expectations of linear response and the slow dynamics disappear.

Exploring, Refining, and Validating the Paradynamics QM/MM Sampling

Nikolay V. Plotnikov and Arieh Warshel [University of Southern California]

J. Phys. Chem. B., **116**, 10342–10356, 2012.

The performance of the paradynamics (PD) reference potential approach in QM/MM calculations is examined. It is also clarified that, in contrast to some possible misunderstandings, this approach provides a rigorous strategy for QM/MM free energy calculations. In particular, the PD approach provides a gradual and controlled way of improving the evaluation of the free energy perturbation associated with moving from the EVB reference potential to the target QM/MM surface.

DFT-Based Simulations of Amide I' IR Spectra of a Small Protein in Solution Using Empirical Electrostatic Map with a Continuum Solvent Model

William R. W. Welch and Jan Kubelka [University of Wyoming]

J. Phys. Chem. B., **116**, 10739–10747, 2012.

A continuum solvent model was tested for simulations of amide I' IR spectra for a 40-residue subdomain of P22 viral coat protein in aqueous solution. Spectra obtained using DFT (BPW91/6-31G**) parameters for a reduced all-Ala representation of the protein were corrected by an electrostatic potential map obtained from the solvent cavity surface and AMBER99 side-chain atom partial charges. Various cavity sizes derived from van der Waals atomic radii with an added effective solvent radius up to 2.0 Å were tested. The interplay of the side-chain and solvent electrostatic effects was investigated by considering the side chains and solvent separately as well as together.

Electronic Properties of Water in Liquid Environment. A Sequential QM/MM Study Using the Free Energy Gradient Method

Herbert C. Georg [Universidade Federal de Goiás] , Sylvio Canuto

J. Phys. Chem. B., **116**, 11247–11254, 2012.

There is a continuous search for theoretical methods that are able to describe the effects of the liquid environment on molecular systems. Different methods emphasize different aspects, and the treatment of both the local and bulk properties is still a great challenge. In this work, the electronic properties of a water molecule in liquid environment is studied by performing a relaxation of the geometry and electronic distribution using the free energy gradient method. This is made using a series of steps in each of which we run a purely molecular mechanical (MM) Monte Carlo Metropolis simulation of liquid water and subsequently perform a QM/MM calculation of the ensemble averages of the charge distribution, atomic forces, and second derivatives.

Comparative or Homology Modeling

Homology modeling of the human 5-HT1A, 5-HT2A, D1, and D2 receptors: model refinement with molecular dynamics simulations and docking evaluation

Beow Keat Yap, Michael J. C. Buckle and Stephen W. Doughty [University of Nottingham Malaysia Campus]

J. Mol.Mod., **18**, 3639-3655, 2012.

5-HT1A serotonin and D1 dopamine receptor agonists have been postulated to be able to improve negative and cognitive impairment symptoms of schizophrenia, while partial agonists and antagonists of the D2 and 5-HT2A receptors have been reported to be effective in reducing positive symptoms. In this study, homology models were built based on the high-resolution crystal structure of the β 2-adrenergic receptor (2RH1) and further refined via molecular dynamics simulations in a 1-palmitoyl-2-oleoyl-sn-glycero-3-phosphocholine (POPC) lipid bilayer system with the GROMOS96 53A6 united atom force field.

Molecular modeling and computational simulation of the photosystem-II reaction center to address isoproturon resistance in *Phalaris minor*

Durg Vijay Singh, Shikha Agarwal, Rajesh Kumar Kesharwani and Krishna Misra [Indian Institute of Information Technology, Allahabad]

J. Mol.Mod., **18**, 3903-3913, 2012.

Isoproturon is the only herbicide that can control *Phalaris minor*, a competitive weed of wheat that developed resistance in 1992. Resistance against isoproturon was reported to be due to a mutation in the psbA gene that encodes the isoproturon-binding D1 protein. Previously in our laboratory, a triazole derivative of isoproturon (TDI) was synthesized and found to be active against both susceptible and resistant biotypes at 0.5 kg/ha but has shown poor specificity. In the present study, both susceptible D1(S), resistant D1(R) and D2 proteins of the PS-II reaction center of *P. minor* have been modeled and simulated, selecting the crystal structure of PS-II from *Thermosynechococcus elongatus* (2AXT.pdb) as template.

Comprehensive model of wild-type and mutant HIV-1 reverse transcriptases

Flavio Ballante, Ira Musmuca, Garland R. Marshall and Rino Ragno [Sapienza Università di Roma]

J. Comp. Aided Mol. Des. **26**, 907-919, 2012.

An enhanced version of COMBINE that uses both ligand-based and structure-based alignment of ligands has been used to build a comprehensive 3-D QSAR model of wild-type HIV-1 reverse transcriptase and drug-resistant mutants. The COMBINER model focused on 7 different RT enzymes complexed with just two HIV-RT inhibitors, niverapine (NVP) and efavirenz (EFV); therefore, 14 inhibitor/enzyme complexes comprised the training set. An external test set of chiral 2-(alkyl/aryl)amino-6-benzylpyrimidin-4(3H)-ones (DABOs) was used to test predictability.

Ligand Docking

MARS: Computing Three-Dimensional Alignments for Multiple Ligands Using Pairwise Similarities

Thomas Klabunde, Clemens Giegerich, and Andreas Evers
[Sanofi-Aventis Deutschland GmbH]

J.Chem. Infor. and Mod. **52**, 2022–2030, 2012.

The three-dimensional (3D) superimposition of molecules of one biological target reflecting their relative bioactive orientation is key for several ligand-based drug design studies (e.g., QSAR studies, pharmacophore modeling). However, with the lack of sufficient ligand-protein complex structures, an experimental alignment is difficult or often impossible to obtain. Here, we present a new approach, MARS (Multiple Alignments by ROCS-based Similarity), that is based on the pairwise alignment of all molecules within the data set using the tool ROCS (Rapid Overlay of Chemical Structures).

Combination of Resonance Raman Spectroscopy and Docking Simulations to Study the Nonspecific Binding of a Free-Base Porphyrin to a Globular Protein

James E. Parker, Robert J. Thomas, Dayla Morisson, and Lorenzo Brancalion [The University of Texas at San Antonio]

J. Phys. Chem. B., 116, 11032–11040, 2012.

Understanding the conformational changes induced by small ligands noncovalently bound to proteins is a central problem in biophysics. We focus on the binding location of the water-soluble porphyrin, meso-tetrakis (p-sulfonatophenyl) porphyrin, to a globular protein, β -lactoglobulin, which has been observed to partially unfold when irradiated by laser light. Identifying the binding location is necessary to determine the mechanism of action as well as the atoms and residues involved in the photoinduced partial unfolding.

3. JOURNAL REVIEWS

Journal of Computational Chemistry, 33(25), September, 2012.

1969–1980 **Force field development for cofactors in the photosystem II**, Lu Zhang, Daniel-Adriano Silva, YiJing Yan and Xuhui Huang [Hong Kong University of Science and Technology]

See Methodology / Potentilas and Parameters.

1981–1996 **A hierarchical algorithm for fast debye summation with applications to small angle scattering**, Nail A. Gumerov, Konstantin Berlin, David Fushman and Ramani Duraiswami [University of Maryland]

Debye summation, which involves the summation of sinc functions of distances between all pair of atoms in three-dimensional space, arises in computations performed in crystallography, small/wide angle X-ray scattering (SAXS/WAXS), and small angle neutron scattering (SANS).

1997–2011 **Dendrimer building toolkit: Model building and characterization of various dendrimer architectures**, Vishal Maingi, Vaibhav Jain, Prasad V. Bharatam [NIPER, India] and Prabal K. Maiti

See Applications / Bioinformatics.

2012–2022 **On the importance of excited state dynamic response electron correlation in polarizable embedding methods**, Janus J. Eriksen, Stephan P. A. Sauer, Kurt V. Mikkelsen, Hans J. Aa. Jensen and Jacob Kongsted [University of Southern Denmark]

We investigate the effect of including a dynamic reaction field at the lowest possible ab initio wave function level of theory, namely the Hartree-Fock (HF) self-consistent field level within the polarizable embedding (PE) formalism.

2023–2031 **Implementation of empirical dispersion corrections to density functional theory for periodic systems**, Werner Reckien, Florian Janetzko, Michael F. Peintinger and Thomas Bredow [Universität Bonn]

A recently developed empirical dispersion correction (Grimme et al., J. Chem. Phys. 2010, 132, 154104) to standard density functional theory (DFT-D3) is implemented in the plane-wave program package VASP.

2032–2042 **Prediction of hydrocarbon enthalpies of formation by various thermochemical schemes**, Brent R. Wilson, Nathan J. DeYonker and Angela K. Wilson [University of North Texas]

The correlation consistent composite approach (ccCA) has been used to compute the enthalpies of formation (ΔH_f° 's) for 60 closed-shell, neutral hydrocarbon molecules selected from an established set (Cioslowski et al., J. Chem. Phys. **2000**, 113, 9377). This set of thermodynamic values includes ΔH_f° 's for hydrocarbons that span a range of molecular sizes, degrees of aromaticity, and geometrical configurations, and, as such, provides a rigorous assessment of ccCA's applicability to a variety of hydrocarbons.

Journal of Computational Chemistry, 33(26), October, 2012.

- 2049–2057 **Development and testing of a compact basis set for use in effective core potential calculations on rhodium complexes**, Otello M. Roscioni [Università di Bolgna], Edmond P. F. Lee and John M. Dyke

We present a set of effective core potential (ECP) basis sets for rhodium atoms which are of reasonable size for use in electronic structure calculations. In these ECP basis sets, the Los Alamos ECP is used to simulate the effect of the core electrons while an optimized set of Gaussian functions, which includes polarization and diffuse functions, is used to describe the valence electrons.

- 2058–2066 **On orthogonality constrained multiple core-hole states and optimized effective potential method**, V. N. Glushkov [Dnipropetrovsk National University] and X. Assfeld

An attempt to construct a multiple core-hole state within the optimized effective potential (OEP) methodology is presented.

- 2067–2072 **Accurate and fast treatment of large molecular systems: Assessment of CEPA and pCCSD within the local pair natural orbital approximation**, Tobias Schwabe [University of Hamburg]

The local pair natural orbital approach, which has been combined with two post-Hartree–Fock methods, CEPA-1 and pCCSD-1a, recently, is assessed for its applicability to large real-world problems without abundant computing resources.

- 2073–2082 **An electronic structure theory investigation of the physical chemistry of the intermolecular complexes of cyclopropenylidene with hydrogen halides**, Pradeep R. Varadwaj [Concordia University], Arpita Varadwaj and Gilles H. Peslherbe

The proton accepting and donating abilities of cyclopropenylidene ($c\text{-C}_3\text{H}_2$) on its complexation with hydrogen halides $\text{H}-\text{X}$ ($\text{X} = \text{F}, \text{Cl}, \text{Br}$) are analyzed using density-functional theory with three functionals (PBE0, B3LYP, and B3LYP-D) and benchmarked against second-order Møller–Plesset (MP2) theory.

- 2083–2091 **Structure and stability of coinage metal fluoride and chloride clusters (M_nF_n and M_nCl_n , $\text{M} = \text{Cu}, \text{Ag}, \text{or Au}$; $n = 1\text{--}6$)**, F. Rabilloud [Université de Lyon]

Calculations in the framework of the density functional theory are performed to study the lowest-energy isomers of coinage metal fluoride and chloride clusters (M_nF_n , M_nCl_n , $\text{M} = \text{Cu}, \text{Ag}, \text{or Au}$, $n = 1\text{--}6$).

- 2092–2101 **Binding of piano-stool Ru(II) complexes to DNA; QM/MM study**, Zdeněk Futera, James A. Platts and Jaroslav V. Burda [Charles University]

See Methodology / QM and QM/MM.

- 2102–2107 **Electronic structure and thermodynamics of V_2O_3 polymorphs**, C. Wessel, C. Reimann, A. Müller, D. Weber, M. Lerch, T. Ressler, T. Bredow and R. Dronskowski [RWTH Aachen University]

A metastable bixbyite-type polymorph of vanadium sesquioxide, V_2O_3 , has recently been synthesized, and it transforms to the corundum-type phase at temperatures around 550 °C.

- 2108–2117 **Interfacing the GROMOS (bio)molecular simulation software to quantum-chemical program packages**, Katharina Meier, Nathan Schmid and Wilfred F. van Gunsteren [Swiss Federal Institute of Technology Zürich ETH]

See Methodology / QM and QM/MM.

- 2118–2123 **Density functional theory study of 1,2-dioxetanone decomposition in condensed phase**, Luís Pinto da Silva and Joaquim C.G. Esteves da Silva [Faculdade de Ciências da Universidade do Porto]

The decomposition of 1,2-dioxetanone into a CO_2 molecule and into an excited state formaldehyde molecule was studied in condensed phase, using a density functional theory approach.

Journal of Molecular Modeling, 18(8), August, 2012.

- 3445–3453 **Computational study on new natural polycyclic compounds of H1N1 influenza virus neuraminidase**, Ye Wang, Di Wu, Dahai Yu, Xuexun Fang [Jilin University], Zhiyong Wang and Li Tian, et al.

See Applications / Homology Modeling.

- 3455–3466 **A test of improved force field parameters for urea: molecular-dynamics simulations of urea crystals**, Gül Altınbaş Özpınar, Frank R. Beierlein, Wolfgang Peukert, Dirk Zahn and Timothy Clark [Friedrich-Alexander Universität Erlangen-Nürnberg]

Molecular-dynamics (MD) simulations of urea crystals of different shapes (cubic, rectangular prismatic, and sheet) have been performed using our previously published force field for urea.

- 3467–3479 **Characterization of nitrogen-bridged 1,2,4,5-tetrazine-, furazan-, and 1H-tetrazole-based polyheterocyclic compounds: heats of formation, thermal stability, and detonation properties**, Tao Wei, Jianzhang Wu, Weihua Zhu [Nanjing University of Science and Technology], Chenchen Zhang and Heming Xiao

The heats of formation (HOFs), thermal stability, and detonation properties for a series of nitrogen-bridged 1,2,4,5-tetrazine-, furazan-, and 1H-tetrazole-based polyheterocyclic compounds (3,6-bis(1H-1,2,3,4-tetrazole-5-ylamino)-1,2,4,5-tetrazine (TST), 3,6-bis(furazan-5-ylamino)-1,2,4,5-tetrazine (FSF), 3,4-bis(1,2,4,5-tetrazine-3-ylamino)-furazan (SFS), 3,4-bis(1H-1,2,3,4-tetrazole-5-ylamino)-furazan (TFT), 1,5-bis(1,2,4,5-tetrazine-3-ylamino)-1H-1,2,3,4-tetrazole (STS), and 1,5-bis(furazan-3-ylamino)-1H-1,2,3,4-tetrazole (FTF) derivatives) were systematically studied by using density functional theory.

3481-3487 Characteristics of beryllium bonds; a QTAIM study, K. Eskandari [Damghan University]

The nature of beryllium bonds formed between BeX₂ (X is H, F and Cl) and some Lewis bases have been investigated.

3489-3499 Theoretical studies on the Mo-catalyzed asymmetric intramolecular Pauson-Khand-type [2 + 2 + 1] cycloadditions of 3-allyloxy-1-propynylphosphonates, Qingxi Meng and Ming Li [Southwest University, Chongqing]

Density functional theory (DFT) was used to investigate the Mo-catalyzed intramolecular Pauson-Khand reaction of 3-allyloxy-1-propynylphosphonates. All intermediates and transition states were optimized completely at the B3LYP/6-31 G(d,p) level [LANL2DZ(f) for Mo].

3501-3506 Density functional study on the derivatives of purine, Wei-Jie Chi [Shanxi Normal University], Lu-Lin Li, Bu-Tong Li and Hai-Shun Wu

See Methodology / QM and QM/MM.

3507-3522 Ab initio and density functional theoretical design and screening of model crown ether based ligand (host) for extraction of lithium metal ion (guest): effect of donor and electronic induction, Anil Boda, Sk. Musharaf Ali [Bhabha Atomic Research Centre], Hanmanth Rao and Sandip K. Ghosh

The structures, energetic and thermodynamic parameters of model crown ethers with different donor, cavity and electron donating/ withdrawing functional group have been determined with ab initio MP2 and density functional theory in gas and solvent phase.

3523-3533 Consequences of one-electron oxidation and one-electron reduction for 4-aminopyrimidine—DFT studies, Ewa D. Raczynska [Warsaw University of Life Sciences (SGGW)], Katarzyna Kolczyńska and Tomasz M. Stępniewski

The consequences of one-electron oxidation and one-electron reduction were studied for 4-aminopyrimidine (4APM), which displays prototropic tautomerism.

3535-3540 Cation- π interaction of alkali metal ions with C₂₄ fullerene: a DFT study, Morteza Moradi, Ali Ahmadi Peyghan [Islamic Azad University], Zargham Bagheri and Mohammad Kamfiroozi

Using first principle calculations, we investigated cation- π interactions between alkali cations (Li⁺, Na⁺, and K⁺) and pristine C₂₄ or doped fullerenes of BC₂₃, and NC₂₃.

3541-3552 Modeling the weak hydrogen bonding of pyrrole and dichloromethane through Raman and DFT study, Dheeraj Kumar Singh, Birendra Pratap Asthana and Sunil Kumar Srivastava [Guru Ghasidas University]

Raman spectra of neat pyrrole (C₄H₅N) and its binary mixtures with dichloromethane (CH₂Cl₂, DCM) with varying mole fractions of C₄H₅N from 0.1 to 0.9 were recorded in order to monitor the influence of molecular interaction on spectral features of selected vibrational bands of pyrrole in the region 600-1600 cm⁻¹.

- 3553-3562 **Equilibrium geometries, stabilities, and electronic properties of the cationic AuBe^+ ($n = 1-8$) clusters: comparison with pure gold clusters**, Peng Shao [Sichuan University], Xiao-Yu Kuang, Ya-Ru Zhao, Yan-Fang Li and Su-Juan Wang

Ab initio method based on density functional theory at PW91PW91 level has been applied in studying the geometrical structures, relative stabilities, and electronic properties of small bimetallic Au_nBe^+ ($n = 1-8$) cluster cations.

- 3563-3576 **Mechanisms and kinetics of thiotepa and tepa hydrolysis: DFT study**, Hedieh Torabifard and Alireza Fattahi [Sharif University of Technology]

See Applications / Medicinal Chemistry and Drug Design.

- 3577-3586 **Theoretical studies on all-metal binuclear sandwich-like complexes $\text{M}_2(\eta^4\text{-E}_4)_2$ ($\text{M}=\text{Al, Ga, In; E}=\text{Sb, Bi}$)**, Congzhi Wang, Xiuhui Zhang [Beijing Institute of Technology, Beijing], Jian Lu and Qianshu Li

A series of all-metal binuclear sandwich-like complexes with the formula $\text{M}_2(\eta^4\text{-E}_4)_2$ ($\text{M}=\text{Al, Ga, In; E}=\text{Sb, Bi}$) was studied by density functional theory (DFT).

- 3587-3608 **Spectroscopic investigation and hydrogen-bonding analysis of triazinones**, Devadhas Arul Dhas, Isaac Hubert Joe [Mar Ivanios College], Solomon Dawn Dharma Roy and Sreedharan Balachandran

NIR FT-Raman, FTIR and UV-vis spectra of the herbicide metamitron were recorded and analyzed.

- 3609-3615 **Donor-enhanced bridge effect on the electronic properties of triphenylamine based dyes: density functional theory investigations**, Ahmad Irfan [King Khalid University], Abdullah G. Al-Sehemi and Abdullah M. Asiri

The geometries have been optimized by using density functional theory. The highest occupied molecular orbitals are delocalized on triphenylamine moiety while lowest unoccupied molecular orbital are localized on anchoring group.

- 3617-3625 **Toward a better understanding of the interaction between TGF- β family members and their ALK receptors**, Valentina Romano, Domenico Raimondo, Luisa Calvanese, Gabriella D'Auria and Anna Tramontano, Lucia Falcigno [Federico II University of Naples]

See Applications / Ligand Binding.

- 3627-3637 **Transportation behavior of alkali ions through a cell membrane ion channel. A quantum chemical description of a simplified isolated model**, Ferenc Billes [Budapest University of Technology and Economics], Ildikó Mohammed-Ziegler and Hans Mikosch

See Methodology / Molecular Dynamics.

- 3639-3655 **Homology modeling of the human 5-HT_{1A}, 5-HT_{2A}, D₁, and D₂ receptors: model refinement with molecular dynamics simulations and docking evaluation**, Beow Keat Yap, Michael J. C. Buckle and Stephen W. Doughty [University of Nottingham Malaysia Campus]

See Methodology / Homology Modeling.

- 3657-3667 **Theoretical study of two-photon absorption properties and up-conversion efficiency of new symmetric organic π -conjugated molecules for photovoltaic devices**, Zhong Hu [South Dakota State University], Vedbar S. Khadka, Wei Wang, David W. Galipeau and Xingzhong Yan

Organic material with high intensity of two-photon absorption (TPA) induced fluorescence can be used as the frequency up-converter materials for improving efficiency of the solar cells. In this work, the organic molecular structures were designed by symmetrically grafting two elongated conjugated linkers on a conjugated core and then adding donor groups at both terminals.

- 3669-3694 **3D-QSAR study of Chk1 kinase inhibitors based on docking**, Lingzhou Zhao, Yongjuan Liu, Shiyuan Hu and Huabei Zhang [Beijing Normal University]

See Methodology / QSAR.

- 3695-3704 **Density functional calculations for a high energy density compound of formula $C_6H_6-n(NO_2)_n$** , Wei-Jie Chi, Lu-Lin Li, Bu-Tong Li [Shanxi Normal University] and Hai-Shun Wu

A series of polynitroprismanes, $C_6H_6-n(NO_2)_n$ ($n=1-6$) intended for use as high energy density compounds (HEDCs) were designed computationally.

- 3705-3722 **Molecular docking studies of protein-nucleotide complexes using MOLSDOCK (mutually orthogonal Latin squares DOCK)**, Shankaran Nehru Viji, Nagarajan Balaji and Namasivayam Gautham [University of Madras]

See Applications / Bioinformatics.

- 3723-3729 **Cooperativity effects in linear formaldehyde oligomers using density functional theory calculations**, Vinayak Deshmukh, Shyi-Long Lee and Ajay Chaudhari [The Institute of Science, FORT]

This work reports hydrogen bonding interaction in linear formaldehyde oligomers using density functional theory method.

- 3731-3741 **Insights into the mechanisms of the selectivity filter of Escherichia coli aquaporin Z**, Guodong Hu [University of Texas at San Antonio], Liao Y. Chen and Jihua Wang

See Applications / Protein Dynamics.

- 3743-3750 **Binding of rhodamine B and kiton red S to cucurbit[7]uril: density functional investigations**, Jayshree K. Khedkar, Krishna K. Jagtap, Rahul V. Pinjari, Alok Kumar Ray and Shridhar P. Gejji [University of Pune]

See Applications / Ligand Binding.

- 3751-3768 **Odd-electron molecular theory of graphene hydrogenation**, Elena F. Sheka [Peoples' Friendship University of Russia] and Nadezhda A. Popova

This paper highlights the molecular essence of graphene and presents its hydrogenation from the viewpoint of the odd-electron molecular theory. This chemical transformation was performed computationally, using a particular algorithm, through the stepwise addition of either hydrogen molecules or hydrogen atoms to a pristine graphene molecule.

- 3769-3781 **Local and global effects of Mg²⁺ on Ago and miRNA-target interactions**, Zhi Ma, Zhenghua Xue, Huixiao Zhang, Yan Li and Yonghua Wang [Northwest A&F University]

See Methodology / Molecular Dynamics.

- 3783-3792 **Study on the enantioselectivity inhibition mechanism of acetyl-coenzyme A carboxylase toward haloxyfop by homology modeling and MM-PBSA analysis**, Jin Tao, Guirong Zhang, Aijun Zhang, Liangyu Zheng [Jilin University] and Shugui Cao

See Applications / Enzyme Catalysis.

- 3793-3804 **Selective oxidation of propylamine on oxygen-covered Au(111): a DFT study**, Xian-Yong Pang [Taiyuan University of Technology], Juan-Juan Wang and Gui-Chang Wang

The reaction mechanism for selective oxidation of propylamine on oxygen-covered gold has been studied by the density functional theory (DFT) and generalized gradient approximation (GGA) with slab model.

- 3805-3820 **Role of wobble base pair geometry for codon degeneracy: purine-type bases at the anticodon wobble position**, Gunajyoti Das and R. H. Duncan Lyngdoh [North-Eastern Hill University]

See Applications / Nucleic Acids.

- 3821-3830 **The degradation mechanism of phenol induced by ozone in wastes system**, Sun Youmin, Ren Xiaohua, Cui Zhaojie [Shandong University] and Zhang Guiqin

A distinct understanding for the degradation mechanism of phenol induced by ozone is very essential because the ozonation process, one of the advanced oxidation processes (AOPs), is attractive and popular in wastewater treatment. In the present work, the detailed reactions of ozone and phenol are investigated employing the density functional theory B3LYP method with the 6-311++G (d, p) basis set.

- 3831-3845 **In silico investigation of interactions between human cannabinoid receptor-1 and its antagonists**, Guanglin Kuang, Guoping Hu, Xianqiang Sun, Yun Tang [East China University of Science and Technology], Weihua Li and Guixia Liu, et al.

See Applications / Homology Modeling.

- 3847-3856 **Theoretical studies on the interaction of biphenyl inhibitors with Mycobacterium tuberculosis protein tyrosine phosphatase MptpB**, Lihua Dong, Junyou Shi and Yongjun Liu [Chinese Academy of Sciences]

See Applications / Ligand Binding.

- 3857-3866 **First principles studies of the graphene-phenol interactions**, José M. Galicia Hernández [Benemérita Universidad Autónoma de Puebla], Ernesto Chigo Anot, María T. Romero de la Cruz, Minerva González Melchor and Gregorio Hernández Cocoltzi

Studies of the interaction between phenol and intrinsic graphene, as well as phenol and aluminum doped graphene layer are performed using first principles total energy calculations within the periodic density functional theory. A 4x4 periodic structure is used to explore the adsorption of a phenol molecule on the intrinsic graphene and on aluminum doped graphene layer.

- 3867-3875 **A novel halogen bond and a better-known hydrogen bond cooperation of neonicotinoid and insect nicotinic acetylcholine receptor recognition**, Hongxia Duan [China Agricultural University], Weiwei Zhang, Jin Zhao, Desheng Liang and Xinling Yang, et al.

See Applications / Medicinal Chemistry and Drug Design.

- 3877-3886 **Targeting imidazoline site on monoamine oxidase B through molecular docking simulations**, Fernanda Pretto Moraes and Walter Filgueira de Azevedo Jr [Pontifícia Universidade Católica do Rio Grande do Sul]

See Applications / Enzyme Catalysis.

- 3887-3902 **Architectures, electronic structures, and stabilities of Cu-doped Gen clusters: density functional modeling**, Debashis Bandyopadhyay [Birla Institute of Technology and Science]

The present study reports the geometries, electronic structures, growth behavior, and stabilities of neutral and ionized copper-doped germanium clusters containing 1–20 Ge atoms within the framework of linear combination of atomic orbitals density functional theory (DFT) under the spin-polarized generalized gradient approximation.

- 3903-3913 **Molecular modeling and computational simulation of the photosystem-II reaction center to address isoproturon resistance in *Phalaris minor***, Durg Vijay Singh, Shikha Agarwal, Rajesh Kumar Kesharwani and Krishna Misra [Indian Institute of Information Technology, Allahabad]

See Methodology / Homology Modeling.

- 3915-3926 **Theoretical study of the decomposition mechanisms and kinetics of the ingredients RDX in composition B**, Jian-Guo Zhang [Beijing Institute of Technology, Beijing], Kun Wang, Xiao-Qing Niu, Shao-Wen Zhang and Xiao-Jun Feng, et al.

See Applications / Protein Dynamics.

- 3927-3939 **Insights from comprehensive multiple receptor docking to HDAC8**, Michael Brunsteiner and Pavel A. Petukhov [University of Illinois at Chicago]

See Applications / Ligand Binding.

- 3941-3949 **Density functional investigation of hydrogen gas adsorption on Fe-doped pristine and Stone–Wales defected single-walled carbon nanotubes**, Chanukorn Tabtimsai, Somchai Keawwangchai, Nadtanet Nunthaboot, Vithaya Ruangpornvisuti and Banchob Wanno [Mahasarakham University]

See Applications / Carbon Nanotubes.

- 3951-3967 **In silico development, validation and comparison of predictive QSAR models for lipid peroxidation inhibitory activity of cinnamic acid and caffeic acid derivatives using multiple chemometric and cheminformatics tools**, Indrani Mitra, Achintya Saha and Kunal Roy [Jadavpur University]

See Methodology / QSAR.

- 3969-3980 **Chemical reactivity analysis of deoxyribonucleosides and deoxyribonucleoside analogues (NRTIs): a first-principles density functional approach**, Vipin Kumar [J. V. College, Baraut], Shyam Kishor and Lavanya M. Ramaniah

See Applications / Medicinal Chemistry and Drug Design.

- 3981-3992 **Computational chemistry calculations of stability for bismuth nanotubes, fullerene-like structures and hydrogen-containing nanostructures**, Oxana V. Kharissova, Mario Osorio, Mario Sánchez Vázquez and Boris I. Kharisov [Universidad Autónoma de Nuevo León]

Using molecular mechanics (MM+), semi-empirical (PM6) and density functional theory (DFT) (B3LYP) methods we characterized bismuth nanotubes. In addition, we predicted the bismuth clusters {Bi₂₀(C₅V), Bi₂₄(C₆V), Bi₂₈(C₁), Bi₃₂(D₃H), Bi₆₀(C₁)} and calculated their conductor properties.

- 3993-4004 **Computational structural analysis of proteins of Mycobacterium tuberculosis and a resource for identifying off-targets**, Sameer Hassan, Abhimita Debnath, Vasantha Mahalingam and Luke Elizabeth Hanna [National Institute for Research in Tuberculosis, Chetpet]

See Applications / Protein Structure Prediction.

4. ADDRESSES OF PRINCIPAL AUTHORS

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1. APPLICATIONS

1.1. Small Molecules

Water and Solvation

Structural and Spectroscopic Properties of Water around Small Hydrophobic Solutes

Maria Montagna, Fabio Sterpone, and Leonardo Guidoni
[Università degli studi dell'Aquila]

J. Phys. Chem. B., **116**, 11695–11700, 2012.

We investigated the structural, dynamical and spectroscopic properties of water molecules around a solvated methane by means of Car–Parrinello molecular dynamics simulations. Despite their mobility, in the first shell, water molecules are dynamically displaced in a clathrate-like cage around the hydrophobic solute. No significant differences in water geometrical parameters, in molecular dipole moments or in hydrogen bonding properties, are observed between in-shell and out-shell molecules, indicating that liquid water can accommodate a small hydrophobic solute without altering its structural properties.

Medicinal Chemistry and Drug Design

Inhibitory activities and possible anticancer targets of Ru(II)-based complexes using computational docking method

Adebayo A. Adeniyi, Peter A. Ajibade [University of Fort Hare]

J. Mol.Graph. and Mod., **38**, 60-69, 2012.

In an effort to search for better alternatives to cis-platin and its derivatives that are non-selective cytotoxic anticancer agents, many metal based complexes especially that of Ru(II) that will have alternate targets other than universal target such as DNA have been suggested. This paper focus more on finding an alternative protein targets other DNA for some Ru(II)-based complexes using computational docking as a means of addressing commonly reported research challenges with regards to the lack of proper understanding of the anticancer targets of Ru-based complexes.



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Medicinal Chemistry and Drug Design (Cont'd)

Design, modification and 3D QSAR studies of novel 2,3-dihydrobenzo[b][1,4]dioxin-containing 4,5-dihydro-1H-pyrazole derivatives as inhibitors of B-Raf kinase

Yu-Shun Yang, Qing-Shan Li, Shuai Sun, Yan-Bin Zhang, Xiao-Liang Wang, Fei Zhang, Jian-Feng Tang, Hai-Liang Zhu [Nanjing University]

Bioorg. and Med.Chem., **20**, 6048-6058, 2012.

Two series of novel 2,3-dihydrobenzo[b][1,4]dioxin-containing 4,5-dihydro-1H-pyrazole derivatives **C1–C15** and **D1–D15** have been synthesized and evaluated for their B-Raf inhibitory and anti-proliferation activities. Compound **C14** ((3-(4-bromophenyl)-5-(2-fluorophenyl)-4,5-dihydro-1H-pyrazol-1-yl)(2,3-dihydrobenzo[b][1,4]dioxin-6-yl)methanone) showed the most potent biological activity against B-Raf^{V600E} (IC₅₀ = 0.11 μM) and WM266.4 human melanoma cell line (GI₅₀ = 0.58 μM), being comparable with the positive control Erlotinib and more potent than our previous best compound, while **D10** ((2,3-dihydrobenzo[b][1,4]dioxin-2-yl)(5-(3-fluorophenyl)-3-phenyl-4,5-dihydro-1H-pyrazol-1-yl)methanone) performed the best in the **D** series (IC₅₀ = 1.70 μM; GI₅₀ = 1.45 μM).

Fitting the complexity of GPCRs modulation into simple hypotheses of ligand design

Chiara Custodi, Roberto Nuti, Tudor I. Oprea, Antonio Macchiarulo [Università di Perugia]

J. Mol.Graph. and Mod., **38**, 70-81, 2012.

G-protein coupled receptors (GPCRs) are a large family of membrane-bound receptors that mediate a wide range of physiologic responses to hormones, neurotransmitters and dietary lipids, which represent an important class of drug targets. Significant chemical space regions have been explored both in the academia and by pharmaceutical companies, in the quest for new GPCR modulators as potential therapeutic agents. In this study, the chemical space covered within the WOMBAT database by GPCRs modulators was investigated with the aim of identifying specific molecular determinants that distinguish GPCR agonists from antagonists.

Binding pattern of the long acting neuraminidase inhibitor laninamivir towards influenza A subtypes H5N1 and pandemic H1N1

Arthitaya Meeprasert, Wasinee Khuntawee, Kittiwat Kamlungsua, Nadtanet Nunthaboot, Thanyada Rungrotmongkol [Chulalongkorn University], Supot Hannongbua

J. Mol.Graph. and Mod., **38**, 148-154, 2012.

Influenza A H5N1 and pH1N1 viruses have broadly emerged and become widespread in various countries around the world. Oseltamivir, the most commonly used antiviral drug against the seasonal and pandemic influenza viruses, is targeted at the viral neuraminidase (NA), but some isolates of this virus have become highly resistant to this drug. The novel long-acting drug, laninamivir, was recently developed to inhibit influenza A and B viruses of either the wild-type (WT) or the oseltamivir resistant mutant of NA. To understand the high efficiency of laninamivir, all-atom molecular dynamics simulations were performed on the WT and H274Y mutant of H5N1 and pH1N1 NAs with laninamivir bound.

Medicinal Chemistry and Drug Design (Cont'd)

Targeting essential cell wall lipase Rv3802c for potential therapeutics against tuberculosis

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J. Mol.Graph. and Mod., **38**, 235-242, 2012.

Cell wall and lipid metabolism plays a vital role in the survival and infection of *Mycobacterium tuberculosis*. Increase in the incidences of life-threatening multidrug-resistant (MDR) and extreme drug-resistant (XDR) tuberculosis worsens the existing scenario and urge the need of new druggable targets and new drugs. Targeting Rv3802c, an essential cell wall lipase, can open up a new arsenal to fight the dreadful opportunistic pathogen. Our current study highlights the essentiality of Rv3802c. Its 3D structure is predicted for the first time which provides insight in identifying the ligand binding sites.

Identification of structural determinants of ligand selectivity in 5-HT₂ receptor subtypes on the basis of protein–ligand interactions

Jae Wan Jang, Min Sup Kim, Yong Seo Cho, Art E. Cho, Ae Nim Pae [Korea Institute of Science and Technology]

J. Mol.Graph. and Mod., **38**, 342-353, 2012.

Drug selectivity is one of the most critical improvement steps in drug development. The 5-hydroxytryptamine 2 (5-HT₂) receptor has 3 subtypes that exhibit different pharmacological functions. Because of their high amino acid sequence similarity, designing small molecules that selectively activate only 1 receptor among the 3 subtypes is difficult. We performed homology modeling of the 5-HT₂ receptor subtypes using the β_2 -adrenergic receptor as a template to identify differences in active sites that may influence 5-HT₂ receptor agonist selectivity.

Structural Sweet Spot for A₁ Adenosine Receptor Activation by Truncated (N)-Methanocarba Nucleosides: Receptor Docking and Potent Anticonvulsant Activity

Dilip K. Tosh, Silvia Paoletta, Francesca Deflorian, Khai Phan, Steven M. Moss, Zhan-Guo Gao, Xiaohui Jiang, and Kenneth A. Jacobson [National Institutes of Health, Bethesda]

J.Med.Chem., **55**, 8075–8090, 2012.

A₁ adenosine receptor (AR) agonists display antiischemic and antiepileptic neuroprotective activity, but peripheral cardiovascular side effects impeded their development. SAR study of N⁶-cycloalkylmethyl 4'-truncated (N)-methanocarba-adenosines identified **10** (MRS5474, N⁶-dicyclopropylmethyl, K_i = 47.9 nM) as a moderately A₁AR-selective full agonist. Two stereochemically defined N⁶-methynyl group substituents displayed narrow SAR; groups larger than cyclobutyl greatly reduced AR affinity, and those larger or smaller than cyclopropyl reduced A₁AR selectivity. Nucleoside docking to A₁AR homology model characterized distinct hydrophobic cyclopropyl subpockets, the larger "A" forming contacts with Thr270 (7.35), Tyr271 (7.36), Ile274 (7.39), and carbon chains of glutamates (EL2) and the smaller subpocket "B" forming contacts between TM6 and TM7.

Quantitative Structure-Activity Relations

Quantitative structure–activity relationships (QSARs) using the novel marine algal toxicity data of phenols

M. Doğa Ertürk, Melek Türker Saçan [Boğaziçi University],
Marjana Novic, Nikola Minovski

J. Mol.Graph. and Mod., **38**, 90-100, 2012.

The present study reports for the first time in its entirety the toxicity of 30 phenolic compounds to marine alga *Dunaliella tertiolecta*. Toxicity of polar narcotics and respiratory uncouplers was strongly correlated to hydrophobicity as described by the logarithm of the octanol/water partition coefficient (Log P). Compounds expected to act by more reactive mechanisms, particularly hydroquinones, were shown to have toxicity in excess of that predicted by Log P. A quality quantitative structure–activity relationship (QSAR) was obtained with Log P and a 2D autocorrelation descriptor weighted by atomic polarizability (MATS3p) only after the removal of hydroquinones from the data set.

Exploring the structure determinants of pyrazinone derivatives as PDE5 3HC8 inhibitors: An in silico analysis

Yan Li [Dalian University of Technology], Wenzhao Wu,
Hong Ren, Jinghui Wang, Shuwei Zhang, Guohui Li, Ling
Yang

J. Mol.Graph. and Mod., **38**, 112-122, 2012.

Phosphodiesterase type 5 (PDE5) inhibitors are clinically indicated for the treatment of erectile dysfunction, pulmonary hypertension and various other diseases. In this work, both ligand- and receptor-based three-dimensional quantitative structure–activity relationship (3D-QSAR) studies were carried out using comparative molecular field analysis (CoMFA) and comparative molecular similarity indices analysis (CoMSIA) techniques on 122 pyrazinone derivatives as PDE inhibitors. The resultant optimum 3D-QSAR model exhibits a proper predictive ability as indicated by the statistical results of Q^2 of 0.584, R^2_{ncv} of 0.884 and R^2_{pre} of 0.817, respectively.

Profile-QSAR and Surrogate AutoShim Protein-Family Modeling of Proteases

Prasenjit Mukherjee [Novartis Institutes for Biomedical
Research] and Eric Martin

J.Chem. Infor. and Mod. **52**, 2430–2440, 2012.

The 2D Profile-QSAR and 3D Surrogate AutoShim protein-family virtual screening methods were originally developed for kinases. They are the key components of an iterative medium-throughput screening alternative to expensive and time-consuming experimental high-throughput screening. A validation study on 24 S1-serine protease assay data sets from 16 unique proteases gave very promising results. Profile-QSAR gave a median $R_{ext}^2 = 0.60$ for 24 assay data sets, and pairwise selectivity modeling on 60 protease pairs gave a median $R_{ext}^2 = 0.64$, comparable to the performance for kinases. A 17-structure universal ensemble S1-serine protease surrogate receptor for Autoschim was developed from a collection of ~1500 X-ray structures.

Carbon Nanoparticles

Single-walled Carbon Nanotube Growth from Chiral Carbon Nanorings: Prediction of Chirality and Diameter Influence on Growth Rates

Hai-Bei Li, Alister J. Page, Stephan Irle, and Keiji Morokuma [Kyoto University]

J. Am. Chem. Soc., **134**, 15887–15896, 2012.

Catalyst-free, chirality-controlled growth of chiral and zigzag single-walled carbon nanotubes (SWCNTs) from organic precursors is demonstrated using quantum chemical simulations. Growth of (4,3), (6,5), (6,1), (10,1) and (8,0) SWCNTs was induced by ethynyl radical (C_2H) addition to organic precursors. These simulations show a strong dependence of the SWCNT growth rate on the chiral angle, θ . The SWCNT diameter however does not influence the SWCNT growth rate under these conditions.

Phase transition study of confined water molecules inside carbon nanotubes: Hierarchical multiscale method from molecular dynamics simulation to ab initio calculation

Soheila Javadian [Tarbiat Modares University], Fariba Taghavi, Faramarz Yari, Seyed Majid Hashemianzadeh

J. Mol. Graph. and Mod., **38**, 40–49, 2012.

In this study, the mechanism of the temperature-dependent phase transition of confined water inside a (9,9) single-walled carbon nanotube (SWCNT) was studied using the hierarchical multi-scale modeling techniques of MD and density functional theory (DFT). The MD calculations verify the formation of hexagonal ice nanotubes at the phase transition temperature $T_c = 275$ K by a sharp change in the location of the oxygen atoms inside the SWCNT. Natural bond orbital (NBO) analysis provides evidence of considerable intermolecular charge transfer during the phase transition and verifies that the ice nanotube contains two different forms of hydrogen bonding due to confinement.

Crystal Growth

Crystal Structure of a Preacylation Complex of the β -Lactamase Inhibitor Sulbactam Bound to a Sulfenamide Bond-Containing Thiol- β -lactamase

Elizabeth A. Rodkey, Sarah M. Drawz, Jared M. Sampson, Christopher R. Bethel, Robert A. Bonomo, and Focco van den Akker [Case Western Reserve University]

J. Am. Chem. Soc., **134**, 16798–16804, 2012.

The rise of inhibitor-resistant and other β -lactamase variants is generating an interest in developing new β -lactamase inhibitors to complement currently available antibiotics. To gain insight into the chemistry of inhibitor recognition, we determined the crystal structure of the inhibitor preacylation complex of sulbactam, a clinical β -lactamase inhibitor, bound in the active site of the S70C variant of SHV-1 β -lactamase, a resistance enzyme that is normally present in *Klebsiella pneumoniae*. The S70C mutation was designed to affect the reactivity of that catalytic residue to allow for capture of the preacylation complex.

Investigation of a predicted N-terminal amphipathic α -helix using atomistic molecular dynamics simulation of a complete prototype poliovirus virion

Jason A. Roberts [Victorian Infectious Diseases Reference Laboratory], Michael J. Kuiper, Bruce R. Thorley, Peter M. Smooker, Andrew Hung

J. Mol. Graph. and Mod., **38**, 165–173, 2012.

The wild type 1 poliovirus capsid was first described in atomic detail in 1985 using X-ray crystallography. Numerous poliovirus capsid structures have been produced since, but none resolved the spatial positioning and conformation of a predicted N-terminal α -helix of the capsid protein VP1, which is considered critical to virus replication. We studied the helical structure under varying conditions using in silico reconstruction and atomistic MD simulation methods based on the available poliovirus capsid atom coordinate data.

1.2. Biopolymers

Bioinformatics and Cheminformatics

Development of a Computational Tool to Rival Experts in the Prediction of Sites of Metabolism of Xenobiotics by P450s

Valérie Campagna-Slater, Joshua Pottel, Eric Therrien, Louis-David Cantin, and Nicolas Moitessier [McGill University]

J.Chem. Infor. and Mod. **52**, 2471–2483, 2012.

The metabolism of xenobiotics—and more specifically drugs—in the liver is a critical process controlling their half-life. Although there exist experimental methods, which measure the metabolic stability of xenobiotics and identify their metabolites, developing higher throughput predictive methods is an avenue of research. It is expected that predicting the chemical nature of the metabolites would be an asset for designing safer drugs and/or drugs with modulated half-lives. We have developed IMPACTS (In-silico Metabolism Prediction by Activated Cytochromes and Transition States), a computational tool combining docking to metabolic enzymes, transition state modeling, and rule-based substrate reactivity prediction to predict the site of metabolism (SoM) of xenobiotics.

A Flexible, Grid-Enabled Web Portal for GROMACS Molecular Dynamics Simulations

Marc van Dijk, Tsjerk A. Wassenaar, and Alexandre M.J.J. Bonvin [Utrecht University]

J. Chem. Theor. and Comp., **8**, 3463–3472, 2012.

Molecular dynamics simulations are becoming a standard part of workflows in structural biology. However, performing a successful simulation requires sufficient computational resources, familiarity with the simulation software, and experience in the setup of a system and the analysis of the resulting trajectories. Here, we present the GROMACS grid-enabled Web portal for the setup and execution of molecular dynamics simulation on the WeNMR grid infrastructure, a distributed network of computational resources within the European Grid Initiative.

Protein Structure Prediction

Structural analysis of Ca²⁺ dependent and Ca²⁺ independent type II antifreeze proteins: A comparative molecular dynamics simulation study

Sangeeta Kundu, Debjani Roy [Bose Institute, Kolkata]

J. Mol.Graph. and Mod., **38**, 211-219, 2012.

Comparative MD simulations of Ca²⁺ dependent psychrophilic type II antifreeze protein (AFP) from herring (*Clupea harengus*) (hAFP) and Ca²⁺ independent type II antifreeze protein from long snout poacher (*Brachyopsis rostratus*) (lpAFP) have been performed for 10 ns each at five different temperatures. We have tried to investigate whether the Ca²⁺ dependent protein obtains any advantage in nature over the independent one. To this end the dynamic properties of these two proteins have been compared in terms of secondary structure content, solvent accessibility, intra molecular hydrogen bonds and protein–solvent interactions.

Comparative or Homology Modeling

Membrane Binding and Self-Association of the Epsin N-Terminal Homology Domain

Chun-Liang Lai, Christine C. Jao, Edward Lyman, Jennifer L. Gallop, Brian J. Peter, Harvey T. McMahon, Ralf Langen, Gregory A. Voth [University of Chicago]

J. Molec. Bio. **420**, 800-817, 2012.

Epsin possesses a conserved epsin N-terminal homology (ENTH) domain that acts as a phosphatidylinositol 4,5-bisphosphate- lipid- targeting and membrane- curvature- generating element. Upon binding phosphatidylinositol 4,5- bisphosphate, the N-terminal helix (H_0) of the ENTH domain becomes structured and aids in the aggregation of ENTH domains, which results in extensive membrane remodeling. In this article, atomistic and coarse-grained (CG) molecular dynamics (MD) simulations are used to investigate the structure and the stability of ENTH domain aggregates on lipid bilayers.

Comparative study on activation mechanism of carboxypeptidase A1, A2 and B: First insights from steered molecular dynamics simulations

Jitrayut Jitnonnom [University of Phayao], Christoph Sontag

J. Mol.Graph. and Mod., **38**, 298-303, 2012.

Different forms of procarboxypeptidases (PCPs) zymogens are observed experimentally to show different rates and modes of activation: PCPA1 shows a slow, biphasic, activation pathway compared to PCPA2 and PCPB which have a faster, monotonic activation behavior. Detailed mechanisms involved in activating these zymogen forms to the active enzymes are not well understood yet. In this work, three PCP zymogens (subtypes A1, A2 and B) were in silico converted into the primary cleavage state of zymogens using available X-ray structures. Based on these cleaved forms of zymogen, we are able to investigate their spontaneous dissociation process of the prosegment from its associated enzyme domain using steered molecular dynamics simulation.

Validation of a novel secretion modification region (SMR) of HIV-1 Nef using cohort sequence analysis and molecular modeling

Patrick E. Campbell, Olexandr Isayev, Syed A. Ali, William W. Roth, Ming-Bo Huang, Michael D. Powell, Jerzy Leszczynski, Vincent C. Bond [Morehouse School of Medicine]

J. Mol.Mod., **18**, 4603-4613, 2012.

The HIV-1 accessory protein Nef plays an active role in the pathogenesis of AIDS by its numerous cellular interactions that facilitate the release of virus particles. This 27 kDa protein is required for maintenance of the viral replication in HIV, and is also known to contribute to immune evasion, blocking of apoptosis in virus-infected cells and enhancement of virus infectivity. Nef has been shown to be secreted and is present on the surface of virus-infected cells. Recent studies from our laboratory have shown that the Nef protein is secreted from nef-transfected and HIV-1-infected cells in small exosome-like vesicles (40–100 nm diam.) that do not contain virions.

Comparative or Homology Modeling (Cont'd)

Binding mechanism between Hsp90 and Sgt1 explored by homology modeling and molecular dynamics simulations in rice

Jun-jie Yan, Yu-bo Zhang, Yi Ding [Wuhan University]

J. Mol.Mod., **18**, 4665-4673, 2012.

The Hsp90 (for heat shock protein90) and the Sgt1 (for suppressor of the G2 allele of *skp1*) are widely distributed in animals, yeast, and plants. The former functions as molecular chaperon activating a series of client proteins, the latter functions as an adaptor protein participating in multiple biological processes such as immunity response through interactions with different protein complexes. In the present study, we have constructed a homology model of Hsp90-Sgt1 complex in rice based on a recently resolved structure from barley and Arabidopsis to explore its binding mechanisms and to understand the detailed interaction profile.

Protein Conformational Analysis

Surveying Capsid Assembly Pathways through Simulation-Based Data Fitting

Lu Xie, Gregory R. Smith, Xian Feng, Russell Schwartz [Carnegie Mellon University, Pittsburgh]

Biophysical Journal. **103**, 1545-1554, 2012.

Virus capsid assembly has attracted considerable interest from the biophysical modeling community as a model system for complicated self-assembly processes. Simulation methods have proven valuable for characterizing the space of possible kinetics and mechanisms of capsid assembly, but they have so far been able to say little about the assembly kinetics or pathways of any specific virus. Here, we apply the improved data-fitting approach to three capsid systems—human papillomavirus (HPV), hepatitis B virus (HBV), and cowpea chlorotic mottle virus (CCMV)—to assess both the range of pathway types the methods can learn and the diversity of assembly strategies in use between these viruses.

Molecular Dynamics of β -Hairpin Models of Epigenetic Recognition Motifs

Xiang Zheng, Chuanjie Wu, Jay W. Ponder, and Garland R. Marshall [Washington University, St. Louis]

J. Am. Chem. Soc., **134**, 15970–15978, 2012.

The conformations and stabilities of the β -hairpin model peptides of Waters (Riemen, A. J.; Waters, M. L. *Biochemistry* 2009, 48, 1525; Hughes, R. M.; Benshoff, M. L.; Waters, M. L. *Chemistry* 2007, 13, 5753) have been experimentally characterized as a function of lysine ϵ -methylation. These models were developed to explore molecular recognition of known epigenetic recognition motifs. This system offered an opportunity to computationally examine the role of cation- π interactions, desolvation of the ϵ -methylated ammonium groups, and aromatic/aromatic interactions on the observed differences in NMR spectra.

Protein Conformational Analysis (Cont'd)

Structural and Conformational Dynamics of Self-Assembling Bioactive β -Sheet Peptide Nanostructures Decorated with Multivalent RNA-Binding Peptides

Sanghun Han, Donghun Kim, So-hee Han, Nam Hee Kim, Sun Hee Kim [Yonsei University], and Yong-beom Lim

J. Am. Chem. Soc., **134**, 16047–16053, 2012.

Understanding the dynamic behavior of nanostructural systems is important during the development of controllable and tailor-made nanomaterials. This is particularly true for nanostructures that are intended for biological applications because biomolecules are usually highly dynamic and responsive to external stimuli. In this Article, we investigated the structural and conformational dynamics of self-assembling bioactive β -sheet peptide nanostructures using electron paramagnetic resonance (EPR) spectroscopy. Our results provide an overall picture of β -sheet peptide nanostructure dynamics, which should be useful in the development of dynamic self-assembled peptide nanostructures.

Preferential Solvation of Triglycine in Aqueous Urea: An Open Boundary Simulation Approach

Debashish Mukherji, Nico F. A. van der Vegt, Kurt Kremer [Max-Planck Institut für Polymerforschung]

J. Chem. Theor. and Comp., **8**, 3536–3541, 2012.

Solvation free energies of peptides in water decrease with increasing urea concentration and therefore lead to increased solubility. In this work, we study the solvation thermodynamics of a triglycine in aqueous urea solutions at room temperature $T = 300$ K. We perform our analysis within the framework of the Kirkwood–Buff theory of liquid mixtures, developed for open systems. For this purpose, we use a recently proposed approach to study liquid mixtures within an “effective” open boundary simulation scheme (AdResS).

Coarse-Grained and Atomistic Simulations of the Salt-Stable Cowpea Chlorotic Mottle Virus (SS-CCMV) Subunit 26–49: β -Barrel Stability of the Hexamer and Pentamer Geometries

Tristan Bereau [Carnegie Mellon University], Christoph Globisch, Markus Deserno, and Christine Peter

J. Chem. Theor. and Comp., **8**, 3750–3758, 2012.

A combination of coarse-grained (CG) and atomistic simulations provides a suitable computational framework to study unstructured regions of proteins, for which experimental data are often lacking or limited. In this work, we combine CG and atomistic simulations with clustering algorithms and free energy reweighting methods to explore the conformational equilibrium of certain regions of the salt-stable cowpea chlorotic mottle virus (SS-CCMV). In particular, we focus on the geometry of converging strands (residues 26–49) from contacting subunits at the 3-fold (hexamer) and 5-fold (pentamer) symmetry points of the capsid.

On the Contribution of Linear Correlations to Quasi-harmonic Conformational Entropy in Proteins

Anton A. Polyansky, Antonija Kuzmanic, Mario Hlevnjak, and Bojan Zagrovic [University of Vienna]

J. Chem. Theor. and Comp., **8**, 3820–3829, 2012.

We study the contribution of linear, pairwise atom-positional correlations (covariances) to absolute and relative conformational entropy as calculated by quasi-harmonic analysis of MD trajectories (S_{QH} and ΔS_{QH}). By analyzing a total of 25 μ s of MD simulations of ubiquitin and six of its binding partners in bound and unbound states, and 2.4 μ s of simulations of eight different proteins in phosphorylated and unphosphorylated states, we show that ΔS_{QH} represents a remarkably constant fraction of a quasi-harmonic entropy change obtained if one ignores the contribution of covariance terms and uses mass-weighted atom-positional variances only (ΔS_{VAR}).

Protein Conformational Analysis (Cont'd)

Event detection and sub-state discovery from biomolecular simulations using higher-order statistics: Application to enzyme adenylate kinase

Arvind Ramanathan, Andrej J. Savol, Pratul K. Agarwal and Chakra S. Chennubhotla [University of Pittsburgh]

Proteins: Stru. Fun. & Bioinf., **80**, 2536–2551, 2012.

Biomolecular simulations at millisecond and longer time-scales can provide vital insights into functional mechanisms. Because post-simulation analyses of such large trajectory datasets can be a limiting factor in obtaining biological insights, there is an emerging need to identify key dynamical events and relating these events to the biological function online, that is, as simulations are progressing. Recently, we have introduced a novel computational technique, quasi-anharmonic analysis (QAA) (Ramanathan et al., PLoS One 2011;6:e15827), for partitioning the conformational landscape into a hierarchy of functionally relevant sub-states.

Protein Dynamics

Robust Driving Forces for Transmembrane Helix Packing

Ayelet Benjamini, Berend Smit [University of California, Berkeley]

Biophysical Journal. **103**, 1227-1235, 2012.

The packing structures of transmembrane helices are traditionally attributed to patterns in residues along the contact surface. In this view, besides keeping the helices confined in the membrane, the bilayer has only a minor effect on the helices structure. Here, we use two different approaches to show that the lipid environment has a crucial effect in determining the cross-angle distribution of packed helices. We analyzed structural data of a membrane proteins database. We show that the distribution of cross angles of helix pairs in this database is statistically indistinguishable from the cross-angle distribution of two noninteracting helices imbedded in the membrane.

Coarse-Graining Provides Insights on the Essential Nature of Heterogeneity in Actin Filaments

Jun Fan, Marissa G. Saunders, Gregory A. Voth [University of Chicago]

Biophysical Journal. **103**, 1334-1342, 2012.

Experiments have shown that actin is structurally polymorphic, but knowledge of the details of molecular level heterogeneity in both the dynamics of a single subunit and the interactions between subunits is still lacking. Here, using atomistic molecular dynamics simulations of the actin filament, we identify domains of atoms that move in a correlated fashion, quantify interactions between these domains using coarse-grained (CG) analysis methods, and perform CG simulations to explore the importance of filament heterogeneity.

Protein Dynamics (Cont'd)

Simulations of HIV Capsid Protein Dimerization Reveal the Effect of Chemistry and Topography on the Mechanism of Hydrophobic Protein Association

Naiyin Yu, Michael F. Hagan [Brandeis University, Waltham]

Biophysical Journal, **103**, 1363-1369, 2012.

Recent work has shown that the hydrophobic protein surfaces in aqueous solution sit near a drying transition. The tendency for these surfaces to expel water from their vicinity leads to self-assembly of macromolecular complexes. In this article, we show with a realistic model for a biologically pertinent system how this phenomenon appears at the molecular level. We focus on the association of the C-terminal domain (CA-C) of the human immunodeficiency virus capsid protein. By combining all-atom simulations with specialized sampling techniques, we measure the water density distribution during the approach of two CA-C proteins as a function of separation and amino acid sequence in the interfacial region.

Differential Flap Dynamics in Wild-Type and a Drug Resistant Variant of HIV-1 Protease Revealed by Molecular Dynamics and NMR Relaxation

Yufeng Cai, Nese Kurt Yilmaz, Wazo Myint, Rieko Ishima, and Celia A. Schiffer [University of Massachusetts Medical School]

J. Chem. Theor. and Comp, **8**, 3452–3462, 2012.

Drug resistance has been extensively studied in HIV-1 protease where resistance occurs when the balance between enzyme inhibition and substrate recognition and turnover is perturbed to favor catalytic activity. Flap+ is a multidrug-resistant variant of HIV-1 protease with a combination of mutations at the edge of the active site, within the active site, and in the flaps (L10I, G48V, I54V, and V82A).). The impact of these mutations on the dynamics in the unliganded form in comparison with the wild-type protease was elucidated with Molecular Dynamic simulations and NMR relaxation experiments.

Molecular Mechanism for the Preferential Exclusion of TMAO from Protein Surfaces

Deepak R. Canchi, Pruthvi Jayasimha, Donald C. Rau, George I. Makhatadze, and Angel E. Garcia [Rensselaer Polytechnic Institute, Troy]

J. Phys. Chem. B., **116**, 12095–12104, 2012.

Trimethylamine N-oxide (TMAO) is a naturally occurring protecting osmolyte that stabilizes the folded state of proteins and also counteracts the destabilizing effect of urea on protein stability. Experimentally, it has been inferred that TMAO is preferentially excluded from the vicinity of protein surfaces. Here, we combine computer modeling and experimental measurements to gain an understanding of the mechanism of the protecting effect of TMAO on proteins. We have developed an all-atom molecular model for TMAO that captures the exclusion of TMAO from model compounds and protein surfaces.

pH-dependent molecular dynamics of vesicular stomatitis virus glycoprotein G

Pia Rücker, Silke A. Wieninger, G. Matthias Ullmann and Heinrich Sticht [Friedrich-Alexander-Universität Erlangen-Nürnberg]

Proteins: Stru. Fun. & Bioinf., **80**, 2601–2613, 2012.

Vesicular stomatitis virus glycoprotein G (VSV-G) belongs to a new class of viral fusion proteins (Class III). The structure of VSV-G has been solved in two different conformations and fusion is known to be triggered by low pH. To investigate Class III fusion mechanisms, molecular dynamics simulations were performed on the VSV-G prefusion structure in two different protonation states: at physiological pH (pH 7) and low pH present in the endosome (pH 5). Domain IV containing the fusion loops, which need to interact with the target membrane, exhibits the highest mobility.

Free Energy Calculations

Computational prediction of monosaccharide binding free energies to lectins with linear interaction energy models

Sushil Kumar Mishra, Johan Sund, Johan Åqvist and Jaroslav Koča [Masaryk University]

J. Comp. Chem. **33**, 2340–2350, 2012.

The linear interaction energy (LIE) method to compute binding free energies is applied to lectin-monosaccharide complexes. Here, we calculate the binding free energies of monosaccharides to the *Ralstonia solanacearum* lectin (RSL) and the *Pseudomonas aeruginosa* lectin-II (PA-IIL). The standard LIE model performs very well for RSL, whereas the PA-IIL system, where ligand binding involves two calcium ions, presents a major challenge. To overcome this, we explore a new variant of the LIE model, where ligand–metal ion interactions are scaled separately.

Ligand Binding/Docking

Predictions for Cholesterol Interaction Sites on the A_{2A} Adenosine Receptor

Ji Young Lee and Edward Lyman [University of Delaware, Newark]

J. Am. Chem. Soc., **134**, 16512–16515, 2012.

Molecular dynamics simulations of the A_{2A} adenosine receptor totaling 1.4 μ s show clear evidence for specific sites mediating interactions between adenosine-bound A_{2A} and cholesterol. The strongest evidence is for three binding sites. Two are in the extracellular leaflet, with one site interacting with helices VII and I, and the other with helices II and III. One site is located in the intracellular leaflet, interacting with helices III and IV. One of our three predicted binding sites is confirmed by a just-published high-resolution structure of A_{2A} cocrystallized with an antagonist.

Membrane-Binding Mechanism of a Peripheral Membrane Protein through Microsecond Molecular Dynamics Simulations

Brent Rogaski, Jeffery B. Klauda [University of Maryland]

J. Molec. Bio. **420**, 847-861, 2012.

A homologue oxysterol binding protein of yeast (Osh4) peripherally binds to organelle and plasma membranes and promotes lipid transport and membrane contact. Extensive molecular dynamics simulations of Osh4 are used to characterize the structure and mechanism of protein attachment to various model lipid membranes. A high density of negatively charged lipids (phosphatidylserine and phosphatidylinositol-4,5-biphosphate) or a low density of phosphatidylinositol- 4,5- biphosphate results in a single binding conformation consisting of interactions with several loops and a portion of the mouth to the lipid binding pocket.

 Ligand Binding / Docking (Cont'd)

Molecular dynamics simulation of the interaction between protein tyrosine phosphatase 1B and aryl diketoacid derivatives

Qiang Wang, Jun Gao, Yongjun Liu, Chengbu Liu
[Shandong University]

J. Mol. Graph. and Mod., **38**, 186-193, 2012.

The protein tyrosine phosphatase 1B (PTP-1B) is acknowledged as an outstanding therapeutic target for the treatment of diabetes, obesity and cancer. In this work, six aryl diketoacid compounds have been studied on the basis of molecular dynamics simulations. Hydrogen bonds, binding energies and conformation changes of the WPD loop have been analyzed. The results indicated that their activation model falls into two parts: the target region of the monomeric aryl diketoacid compounds is the active site, whereas the target region of the dimeric aryl diketoacid compounds is the WPD loop or the R loop.

Autoinhibitory Mechanism for the Mutation-Induced Impaired FGF9 Signaling

Ying Wang, Xiao-Lin Wu, Dong-Qing Wei, Yi-Xue Li, and Jing-Fang Wang [Shanghai Jiao Tong University]

J. Chem. Infor. and Mod. **52**, 2422–2429, 2012.

Fibroblast growth factor 9 (FGF9), an important member of the fibroblast growth factor (FGF) family, can bind with high affinity to FGFR3 in a heparin-dependent approach. In humans, the deletions and mutations resulting in dysfunction of the FGF9 signaling can cause human skeletal dysplasia and cancers. However, the detailed mechanism for this observation still remains unknown. In this study, we used molecular dynamics simulations and free energy calculations to study the interactions of FGF9^{WT/S99N}, FGFR3c, and heparin, with an aim of providing atomic sights into the detailed mechanism for the impaired FGF signaling caused by the S99N mutation.

Some insights into the binding mechanism of Aurora B kinase gained by molecular dynamics simulation

Rui Xiong, Xiao-Mei Cai, Jing Wei, Peng-Yu Ren
[University of Texas, Austin]

J. Mol. Mod., **18**, 4591-4601, 2012.

Aurora B kinase is essential in the process of mitosis, and its overexpression has been reported to be associated with a number of solid tumors. We therefore carried out molecular docking, molecular dynamics, and molecular mechanics Poisson–Boltzmann/surface area (MM-PBSA) calculations on several structurally diverse inhibitors (pentacyclic, pyrimidine, quinazoline, and pyrrolopyridine derivatives) and Aurora B kinase to explore the structural and chemical features responsible for the binding recognition mechanism. Molecular simulations reveal that the binding site mainly consists of six binding regions (sites A–F).

Dynamics and Binding Affinity of Spin-Labeled Stearic Acids in β -Lactoglobulin: Evidences from EPR Spectroscopy and Molecular Dynamics Simulation

Rita Guzzi [University of Calabria, Bruno Rizzuti, and Rosa Bartucci]

J. Phys. Chem. B., **116**, 11608–11615, 2012.

β -Lactoglobulin (β -LG) is a member of the lipocalin protein family involved in the transport of fatty acids and other small hydrophobic molecules. The main binding site is at a central cavity, referred to as “calyx”, formed by the protein β -barrel sandwich. Continuous-wave and pulsed Fourier transform electron spin resonance (cw- and FT-EPR) spectroscopy and molecular dynamics (MD) simulation were combined to investigate the interaction of fatty acids with bovine β -LG. Stearic acid bearing the nitroxide label at different positions, n, along the acyl chain (n-SASL, n = 5, 7, 10, 12, 16) were used.

Ligand Binding / Docking (Cont'd)

Adsorption Behavior of Hydrophobic Proteins on Polydimethylsiloxane Substrates

Yingzhe Liu, Ming Wu, Xizeng Feng, Xueguang Shao, and Wensheng Cai [Nankai University]

J. Phys. Chem. B., **116**, 12227–12234, 2012.

The design of a bioactive surface with appropriate wettability for effective protein immobilization has attracted much attention. Previous experiments showed that the adsorption of hydrophobic protein HFBI onto a polydimethylsiloxane (PDMS) substrate surface can reverse the inherent hydrophobicity of the surface, hence making it suitable for immobilization of a secondary protein. In this study, atomistic molecular dynamics simulations have been conducted to elucidate the adsorption mechanism of HFBI on the PDMS substrate in an aqueous environment.

Peptide binding to the PDZ domain by conformational selection

Sandra Steiner and Amedeo Caflisch [University of Zürich]

Proteins: Stru. Fun. & Bioinf., **80**, 2562–2572, 2012.

The PDZ domains, a large family of peptide recognition proteins, bind to the C-terminal segment of membrane ion channels and receptors thereby mediating their localization. The peptide binding process is not known in detail and seems to differ among different PDZ domains. For the third PDZ domain of the synaptic protein PSD-95 (PDZ3), a lock-and-key mechanism was postulated on the basis of the almost perfect overlap of the crystal structures in the presence and absence of its peptide ligand. Here, peptide binding to PDZ3 is investigated by explicit solvent molecular dynamics (MD) simulations (for a total of 1.3 μ s) and the cut-based free energy profile method for determining free energy barriers and basins.

Enzyme Catalysis

Understanding the binding of daunorubicin and doxorubicin to NADPH-dependent cytosolic reductases by computational methods

Davide Pirolli, Bruno Giardina, Alvaro Mordente, Silvana Ficarra, Maria Cristina De Rosa [Università Cattolica del Sacro Cuore]

Europ. Jou. Med. Chem., **56**, 145-154, 2012.

The anthracycline anticancer agents daunorubicin (DAUN) and doxorubicin (DOX) are reduced by different NADPH-dependent cytosolic reductases into their corresponding alcohol metabolites daunorubicinol (DAUNol) and doxorubicinol (DOXol), which have been implicated in the development of chronic cardiomyopathy. To better understand the individual importance of each enzyme in the reduction and to provide deeper insight into the binding at atomic level we performed molecular docking and dynamics simulations of DAUN and DOX into the active sites of human carbonyl reductase 1 (CBR1) and human aldehyde reductase (AKR1A1).

Enzyme Catalysis (Cont'd)

Revelation of a Catalytic Calcium-Binding Site Elucidates Unusual Metal Dependence of a Human Apyrase

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J. Am. Chem. Soc., **134**, 15595–15603, 2012.

Human soluble calcium-activated nucleotidase 1 (hSCAN-1) represents a new family of apyrase enzymes that catalyze the hydrolysis of nucleotide di- and triphosphates, thereby modulating extracellular purinergic and pyrimidinergic signaling. Among well-characterized phosphoryl transfer enzymes, hSCAN-1 is unique not only in its unusual calcium-dependent activation, but also in its novel phosphate-binding motif. By employing a state-of-the-art computational approach, we have revealed a previously uncharacterized catalytic calcium-binding site in hSCAN-1, which elucidates the unusual calcium-dependence of its apyrase activity.

Modulation of a Pre-existing Conformational Equilibrium Tunes Adenylate Kinase Activity

Jörgen Ådén, Abhinav Verma, Alexander Schug, and Magnus Wolf-Watz [Umeå University]

J. Am. Chem. Soc., **134**, 16562–16570, 2012.

Structural plasticity is often required for distinct microscopic steps during enzymatic reaction cycles. Adenylate kinase from *Escherichia coli* (AK_{eco}) populates two major conformations in solution; the open (inactive) and closed (active) state, and the overall turnover rate is inversely proportional to the lifetime of the active conformation. Therefore, structural plasticity is intimately coupled to enzymatic turnover in AK_{eco}. Here, we probe the open to closed conformational equilibrium in the absence of bound substrate with NMR spectroscopy and molecular dynamics simulations.

Coupled motions during dynamics reveal a tunnel toward the active site regulated by the N-terminal α -helix in an acylaminoacyl peptidase

Elena Papaleo [University of Milano-Bicocca], Giulia Renzetti

J. Mol. Graph. and Mod., **38**, 226–234, 2012.

Acylaminoacyl peptidase (AAP) subfamily belongs to the prolyl oligopeptidase (POP) family of serine-proteases. The active site relies at the interface between the C-terminal catalytic domain and the β -propeller domain, whose N-terminal region acts as a bridge to the hydrolase domain. In AAP, the N-terminal extension is characterized by a structurally conserved α 1-helix, which is known to affect thermal stability and thermal dependence of the catalytic activity. In the present contribution, results from hundreds nanosecond all-atom molecular dynamics simulations, along with analyses of the networks of cross-correlated motions of a member of the AAP subfamily are discussed.

Molecular modeling of the lipase-catalyzed hydrolysis of acetoxymethyl(i-propoxy)phenylphosphine oxide and its P-borane analogue

Grzegorz Krasinski, Marek Cypryk [Polish Academy of Sciences], Małgorzata Kwiatkowska, Marian Mikołajczyk, Piotr Kielbasiński

J. Mol. Graph. and Mod., **38**, 290–297, 2012.

The molecular modeling of the CAL-B-promoted hydrolysis reactions of acetoxymethyl(i-propoxy)phenylphosphine oxide and its P-borane analogue, acetoxymethyl(i-propoxy)-phenylphosphine P-borane, confirms that the reactions proceed with the same stereochemistry and in both cases the (S)-enantiomers are preferentially transformed by the enzyme. Molecular mechanics calculations show that the main reason for the particular stereoselectivity of the substrates is the steric effect of the phenyl. The results helped to revise the previously published erroneous conclusions concerning absolute configuration of the phosphine–borane complex.

Enzyme Catalysis (Cont'd)

Insights into the Role of Magnesium Triad in myo-Inositol Monophosphatase: Metal Mechanism, Substrate Binding, and Lithium Therapy

Shaoyong Lu, Wenkang Huang, Xiaobai Li, Zhimin Huang, Xinyi Liu, Yingyi Chen, Ting Shi, and Jian Zhang [Shanghai Jiaotong University]

J.Chem. Infor. and Mod. **52**, 2398–2409, 2012.

myo-Inositol monophosphatase (IMPase) plays a pivotal role in the intracellular phosphatidylinositol cell signaling pathway. It has attracted considerable attention as a putative therapeutic target for lithium therapy in the treatment of bipolar disorder. A trio of activated cofactor Mg^{2+} ions is required for inositol monophosphate hydrolysis by IMPase. In the present study, computational studies, including two-layered ONIOM-based quantum mechanics/mechanical mechanics (QM/MM) calculations, molecular modeling, and molecular dynamics (MD) simulations, were performed to ascertain the role of the Mg^{2+} triad in the IMPase active site.

Comparison of QM-Only and QM/MM Models for the Mechanism of Tungsten-Dependent Acetylene Hydratase

Rong-Zhen Liao and Walter Thiel [Kaiser-Wilhelm-Platz 1]

J. Chem. Theor. and Comp. **8**, 3793–3803, 2012.

We report a comparison of QM-only and QM/MM approaches for the modeling of enzymatic reactions. For this purpose, we present a QM/MM case study on the formation of vinyl alcohol in the catalytic cycle of tungsten-dependent acetylene hydratase. Three different QM regions ranging from 32 to 157 atoms are designed for the reinvestigation of the previously suggested one-water attack mechanism. The QM/MM calculations with the minimal QM region **M1** (32 atoms) yield a two-step reaction profile, with an initial nucleophilic attack followed by the protonation of the formed vinyl anion intermediate, as previously proposed on the basis of QM-only calculations on cluster model **M2** (116 atoms); however, the overall QM/MM barrier with **M1** is much too high, mainly due to an overestimate of the QM/MM electrostatic repulsions.

Molecular Dynamics Simulation of Autotaxin: Roles of the Nuclease-like Domain and the Glycan Modification

Michio Koyama, Hiroshi Nishimasu, Ryuichiro Ishitani, and Osamu Nureki [The University of Tokyo]

J. Phys. Chem. B., **116**, 11798–11808, 2012.

Autotaxin (ATX) is a secreted lysophospholipase D that produces lysophosphatidic acid, a lipid mediator that activates G protein-coupled receptors to evoke various cellular responses. The nuclease-like domain of ATX and the Asn524-linked glycan are reportedly critical for the catalytic activity. Recently, the crystal structures of ATX were determined, but the means by which the nuclease-like domain and the N-glycosylation participate in the catalytic activity still remain undetermined. To address this question, we conducted molecular dynamics simulations of ATX. The simulation trajectories starting from the full-length structure and from structures lacking the nuclease-like domain and/or the glycan were compared.

Enzyme Catalysis (Cont'd)

Aging Mechanism of Soman Inhibited Acetylcholinesterase

Gulseher Sarah Sirin, Yanzi Zhou, Lee Lior-Hoffmann, Shenglong Wang, and Yingkai Zhang [New York University]

J. Phys. Chem. B., **116**, 12199–12207, 2012.

Acetylcholinesterase (AChE) is a crucial enzyme in the cholinergic nervous system that hydrolyzes neurotransmitter acetylcholine (ACh) and terminates synaptic signals. The catalytic serine of AChE can be phosphorylated by soman, one of the potent nerve agents, and subsequently undergo an aging reaction. This phosphorylation and aging process leads to irreversible AChE inhibition, results in increase of excess ACh at the synaptic clefts, and causes neuromuscular paralysis. By using Born–Oppenheimer *ab initio* QM/MM MD simulations with umbrella sampling, a state-of-the-art approach to simulate enzyme reactions, we have described the aging mechanism of soman phosphorylated AChE and determined its free energy profile.

Theoretical Analysis of the Catalytic Mechanism of Helicobacter pylori Glutamate Racemase

Edgar Mixcoha, Mireia Garcia-Viloca, José M. Lluch, and Àngels González-Lafont [Universitat Autònoma de Barcelona]

J. Phys. Chem. B., **116**, 12406–12414, 2012.

One of the most challenging open key questions behind the stereoinversion of d-glutamate and l-glutamate catalyzed by glutamate racemases is how those enzymes manage to generate the thermodynamically unfavorable reverse protonation state of the catalytic residue cysteine required for the proton abstraction from the α -carbon of glutamate. In this paper, we have used molecular dynamics (MD) simulations with a molecular mechanics force field along with QM/MM calculations starting from the crystal structure and from different MD snapshots to study the enantiomeric conversion of d-glutamate to l-glutamate catalyzed by the *Helicobacter pylori* glutamate racemase.

Protein-Protein Interactions

Application of asymmetric statistical potentials to antibody–protein docking

Ryan Brenke, David R. Hall, Gwo-Yu Chuang, Stephen R. Comeau, Tanggis Bohnuud, Dmitri Beglov, Ora Schueler-Furman, Sandor Vajda [Boston University], and Dima Kozakov

Bioinformatics. **28**, 2608–2614, 2012.

An effective docking algorithm for antibody–protein antigen complex prediction is an important first step toward design of biologics and vaccines. We have recently developed a new class of knowledge-based interaction potentials called Decoys as the Reference State (DARS) and incorporated DARS into the docking program PIPER based on the fast Fourier transform correlation approach. Since this asymmetry cannot be adequately modeled using a symmetric pairwise potential, we have removed the usual assumption of symmetry. Interaction statistics were extracted from antibody–protein complexes under the assumption that a particular atom on the antibody is different from the same atom on the antigen protein.

Membrane Proteins and Lipid Peptide Interactions

Interfacial Tension and Surface Pressure of High Density Lipoprotein, Low Density Lipoprotein, and Related Lipid Droplets

O. H. Samuli Ollila [Lund University], Antti Lamberg, Maria Lehtivaara, Artturi Koivuniemi, Ilpo Vattulainen

Biophysical Journal. **103**, 1236-1244, 2012.

Lipid droplets play a central role in energy storage and metabolism on a cellular scale. Their core is comprised of hydrophobic lipids covered by a surface region consisting of amphiphilic lipids and proteins. Here we use coarse-grained molecular-dynamics simulations to consider a number of related issues by calculating the interfacial tension in protein-free lipid droplets, and in HDL and LDL particles mimicking physiological conditions.

Peptide-Lipid Interactions of the Stress-Response Peptide TisB That Induces Bacterial Persistence

Thomas Steinbrecher, Sebastian Prock, Johannes Reichert, Parvesh Wadhvani, Benjamin Zimpfer, Jochen Bürck, Marina Berditsch, Marcus Elstner, Anne S. Ulrich [Karlsruhe Institute of Technology]

Biophysical Journal. **103**, 1460-1469, 2012.

The bacterial stress-response peptide TisB in *Escherichia coli* has been suggested to dissipate the transmembrane potential, such that the depletion of ATP levels induces the formation of dormant persister cells which can eventually form biofilms. We studied the structure and membrane interactions of TisB to find out whether it forms pores or other proton-selective channels. Circular dichroism revealed an amphiphilic α -helical structure when reconstituted in lipid vesicles, and oriented circular dichroism showed that the helix assumes a transmembrane alignment.

N-Ras Forms Dimers at POPC Membranes

Jörn Güldenhaupt, Till Rudack, Peter Bachler, Daniel Mann, Gemma Triola, Herbert Waldmann, Carsten Kötting, Klaus Gerwert [Ruhr-Universität Bochum]

Biophysical Journal. **103**, 1585-1593, 2012.

Ras is a central regulator of cellular signaling pathways. It is mutated in 20–30% of human tumors. To perform its function, Ras has to be bound to a membrane by a posttranslationally attached lipid anchor. Surprisingly, we identified here dimerization of membrane anchored Ras by combining attenuated total reflectance Fourier transform infrared spectroscopy, biomolecular simulations, and Förster resonance energy transfer experiments.

Molecular Dynamics Simulations of the Interactions of DMSO with DPPC and DOPC Phospholipid Membranes

Zak E. Hughes, Alan E. Mark, and Ricardo L. Mancera [Curtin University]

J. Phys. Chem. B., **116**, 11911–11923, 2012.

Molecular dynamics simulations have been used to investigate the effect of DMSO on 1,2-dipalmitoyl-sn-glycero-3-phosphatidylcholine (DPPC) and 1,2-dioleoyl-sn-glycero-3-phosphocholine (DOPC) phospholipid bilayers. The concentration of DMSO was varied between 0 and 25.0 mol %. For both lipids, DMSO causes the membrane to expand in the plane of the membrane while thinning normal to that plane. Above a critical concentration, pores in the membrane form spontaneously, and if the concentration is increased further, then the bilayer structure is destroyed.

Protein Folding

Design Strategies for the Sequence-Based Mimicry of Side-Chain Display in Protein β -Sheets by α/β -Peptides

George A. Lengyel and W. Seth Horne [University of Pittsburgh, Pittsburgh]

J. Am. Chem. Soc., **134**, 15906–15913, 2012.

The sophistication of folding patterns and functions displayed by unnatural-backbone oligomers has increased tremendously in recent years. Design strategies for the mimicry of tertiary structures seem within reach; however, a general method for the mimicry of sheet segments in the context of a folded protein is an unmet need preventing realization of this goal. Here, we evaluate four different substitution strategies based on replacement of $\alpha\alpha$ dipeptide segments for the ability to retain both sheet folding encoded by a parent α -peptide sequence as well as natively-like side-chain display in the vicinity of the β -residue insertion point.

Identifying Metastable States of Folding Proteins

Abhinav Jain and Gerhard Stock [Albert Ludwigs University]

J. Chem. Theor. and Comp., **8**, 3810–3819, 2012.

Recent molecular dynamics simulations of biopolymers have shown that in many cases the global features of the free energy landscape can be characterized in terms of the metastable conformational states of the system. To identify these states, a conceptionally and computationally simple approach is proposed. It consists of (i) an initial preprocessing via principal component analysis to reduce the dimensionality of the data, followed by k-means clustering to generate up to 10^4 microstates, (ii) the most probable path algorithm to identify the metastable states of the system, and (iii) boundary corrections of these states via the introduction of cluster cores in order to obtain the correct dynamics.

Folding-Reaction Coupling in a Self-Cleaving Protein

Göran Wallin, Torleif Härd, and Johan Åqvist [Uppsala University]

J. Chem. Theor. and Comp., **8**, 3871–3879, 2012.

Backbone torsional strain has been implicated as a cause of rate enhancement in a class of autoproteolytic proteins performing proteolysis and protein splicing. In the autoproteolytic protein domain SEA, folding and proteolytic activity have experimentally been shown to be coupled with about 7 kcal/mol of folding free energy available for catalysis. Here, we have examined the catalytic strategy of SEA with molecular dynamics simulations, potential of mean force free energy profiles, and B3LYP/6-311G(d,p) density functional calculations.

Confinement-Induced States in the Folding Landscape of the Trp-cage Miniprotein

Kristen A. Marino and Peter G. Bolhuis [University of Amsterdam]

J. Phys. Chem. B., **116**, 11872–11880, 2012.

Although protein folding is typically studied in dilute solution, folding in a cell will be affected by interactions with other biomolecules and excluded volume effects. Here, we examine the effect of hydrophobic confinement on folding of the Trp-cage miniprotein. We used replica exchange molecular dynamics simulations to probe the differences between folding in the bulk, on a hydrophobic surface, and confined between two hydrophobic walls. In addition to promotion of helix formation due to reduced conformational entropy of the unfolded state upon confinement, adsorption of Trp-cage to a hydrophobic surface stabilizes intermediate structures not present in the bulk.

Protein-Nucleic acid Interactions

Structure-Based Simulations of the Translocation Mechanism of the Hepatitis C Virus NS3 Helicase along Single-Stranded Nucleic Acid

Wenjun Zheng [University at Buffalo], Mustafa Tekpinar

Biophysical Journal. **103**, 1343-1353, 2012.

The NS3 helicase of Hepatitis C virus is an ATP-fueled molecular motor that can translocate along single-stranded (ss) nucleic acid, and unwind double-stranded nucleic acids. It makes a promising antiviral target and an important prototype system for helicase research. Despite recent progress, the detailed mechanism of NS3 helicase remains unknown. In this study, we have combined coarse-grained (CG) and atomistic simulations to probe the translocation mechanism of NS3 helicase along ssDNA.

Early stage intercalation of doxorubicin to DNA fragments observed in molecular dynamics binding simulations

Hongxing Lei, Xiaofeng Wang, Chun Wu [University of California, Santa Barbara]

J. Mol.Graph. and Mod., **38**, 279-289, 2012.

The intercalation mode between doxorubicin (an anticancer drug) and two 6-base-pair DNA model fragments (d(CGATCG)₂ and d(CGTACG)₂) has been well studied by X-ray crystallography and NMR experimental methods. Yet, the detailed intercalation pathway at molecular level remains elusive. In this study, we conducted molecular dynamics binding simulations of these two systems using AMBER DNA (parmbsc0) and drug (GAFF) force fields starting from the unbound state. We observed outside binding (minor groove binding or end-binding) in all six independent binding simulations (three for each DNA fragment), followed by the complete intercalation of a drug molecule in two simulations (one for each DNA fragment).

Influence of Hyperthermophilic Protein Cren7 on the Stability and Conformation of DNA: Insights from Molecular Dynamics Simulation and Free Energy Analysis

Lin Chen, Ji-Long Zhang, Li-Ying Yu, Qing-Chuan Zheng, Wen-Ting Chu, Qiao Xue, Hong-Xing Zhang [Jilin University], and Chia-Chung Sun

J. Phys. Chem. B., **116**, 12415–12425, 2012.

Cren7, a novel chromatin protein highly conserved among crenarchaea, plays an important role in genome packaging and gene regulation. However, the detail dynamical structural characteristic of the Cren7–DNA complex and the detail study of the DNA in the complex have not been done. Focused on two specific Cren7–DNA complexes (PDB codes [3LWH](#) and [3LWI](#)), we applied molecular dynamics (MD) simulations at four different temperatures (300, 350, 400, and 450 K) and the molecular mechanics Poisson–Boltzmann surface area (MM-PBSA) free energy calculation at 300 and 350 K to examine the role of Cren7 protein in enhancing the stability of DNA duplexes via protein–DNA interactions, and to study the structural transition in DNA.

Motion of transfer RNA from the A/T state into the A-site using docking and simulations

Thomas Caulfield [Mayo Clinic, Jacksonville] and Batsal Devkota

Proteins: Stru. Fun. & Bioinf., **80**, 2489–2500, 2012.

The ribosome catalyzes peptidyl transfer reactions at the growing nascent polypeptide chain. Here, we present a structural mechanism for selecting cognate over near-cognate A/T transfer RNA (tRNA). In part, the structural basis for the fidelity of translation relies on accommodation to filter cognate from near-cognate tRNAs. To examine the assembly of tRNAs within the ribonucleic–riboprotein complex, we conducted a series of all-atom MD simulations of the entire solvated 70S *Escherichia coli* ribosome, along with its associated cofactors, proteins, and messenger RNA (mRNA).

Nucleic Acids

Transcription Stochasticity of Complex Gene Regulation Models

Anne Schwabe, Katja N. Rybakova, Frank J. Bruggeman [Centre for Mathematics and Computer Science (Centrum Wiskunde & Informatica)]

Biophysical Journal. **103**, 1152–1161, 2012.

Transcription is regulated by a multitude of factors that concertedly induce genes to switch between activity states. Eukaryotic transcription involves a multitude of complexes that sequentially assemble on chromatin under the influence of transcription factors and the dynamic state of chromatin. Prokaryotic transcription depends on transcription factors, sigma-factors, and, in some cases, on DNA looping. We present a stochastic model of transcription that considers these complex regulatory mechanisms. We coarse-grain the molecular details in such a way that the model can describe a broad class of gene-regulation mechanisms.

Structural Variations of Single and Tandem Mismatches in RNA Duplexes: A Joint MD Simulation and Crystal Structure Database Analysis

Sukanya Halder and Dhananjay Bhattacharyya [Saha Institute of Nuclear Physics]

J. Phys. Chem. B., **116**, 11845–11856, 2012.

Internal loops within RNA duplex regions are formed by single or tandem basepairing mismatches with flanking canonical Watson–Crick basepairs on both sides. They are the most common motif observed in RNA secondary structures and play integral functional and structural roles. In this report, we have studied the structural features of 1×1 , 2×2 , and 3×3 internal loops using all-atom MD simulation technique with explicit solvent model. As MD simulation is intricately dependent on the choice of force-field and these are often rather approximate, we have used both the most popular force-fields for nucleic acids—CHARMM27 and AMBER94—for a comparative analysis.

DNA Base Dimers Are Stabilized by Hydrogen-Bonding Interactions Including Non-Watson–Crick Pairing Near Graphite Surfaces

Akshaya Shankar, Anand Jagota, and Jeetain Mittal [Lehigh University, Bethlehem]

J. Phys. Chem. B., **116**, 12088–12094, 2012.

Single- and double-stranded DNA are increasingly being paired with surfaces and nanoparticles for numerous applications, such as sensing, imaging, and drug delivery. Unlike the majority of DNA structures in bulk that are stabilized by canonical Watson–Crick pairing between Ade-Thy and Gua-Cyt, those adsorbed on surfaces are often stabilized by noncanonical base pairing, quartet formation, and base–surface stacking. Not much is known about these kinds of interactions. All-atom molecular simulations of DNA bases in two cases—in bulk water and strongly adsorbed on a graphite surface—are conducted to study the relative strengths of stacking and hydrogen bond interactions for each of the 10 possible combinations of base pairs.

Nucleic Acids (Cont'd)

Molecular Mechanism of Direct Proflavine–DNA Intercalation: Evidence for Drug-Induced Minimum Base-Stacking Penalty Pathway

Wilbee D. Sasikala and Arnab Mukherjee [Indian Institute of Science Education and Research]

J. Phys. Chem. B., **116**, 12208–12212, 2012.

DNA intercalation, a biophysical process of enormous clinical significance, has surprisingly eluded molecular understanding for several decades. With appropriate configurational restraint (to prevent dissociation) in all-atom metadynamics simulations, we capture the free energy surface of direct intercalation from minor groove-bound state for the first time using an anticancer agent proflavine. Mechanism along the minimum free energy path reveals that intercalation happens through a minimum base stacking penalty pathway where nonstacking parameters (Twist→Slide/Shift) change first, followed by base stacking parameters (Buckle/Roll→Rise).

Surfaces, Catalysts, and Materials Subjects

Coarse-Grained Molecular Simulation of Self-Assembly for Nonionic Surfactants on Graphene Nanostructures

Dan Wu and Xiaoning Yang [Nanjing University of Technology]

J. Phys. Chem. B., **116**, 12048–12056, 2012.

Self-assembly of amphiphilic molecules on the surfaces of nanoscale materials has an important application in a variety of nanotechnology. Here, we report a coarse-grained molecular dynamics simulation on the structure and morphology of the nonionic surfactant, n-alkyl poly(ethylene oxide) (PEO), adsorbed on planar graphene nanostructures. The effects of concentration, surfactant structure, and size of graphene sheet are explored. Because of the finite dimension effect, various morphological hemimicelles can be formed on nanoscale graphene surfaces, which is somewhat different from the self-assembly structures on infinite carbon surfaces.

2. METHODOLOGY

Quantitative Structure-Activity Relations

The 3D-QSAR study of 110 diverse, dual binding, acetylcholinesterase inhibitors based on alignment independent descriptors (GRIND-2). The effects of conformation on predictive power and interpretability of the models

Maja D. Vitorović-Todorović [University of Belgrade], Ilija N. Cvijetić, Ivan O. Juranić, Branko J. Drakulić

J. Mol. Graph. and Mod., **38**, 194-210, 2012.

The 3D-QSAR analysis based on alignment independent descriptors (GRIND-2) was performed on the set of 110 structurally diverse, dual binding AChE reversible inhibitors. Three separate models were built, based on different conformations, generated following next criteria: (i) minimum energy conformations, (ii) conformation most similar to the co-crystallized ligand conformation, and (iii) docked conformation. We found that regardless on conformation used, all the three models had good statistic and predictivity. The models revealed the importance of protonated pyridine nitrogen of tacrine moiety for anti AChE activity, and recognized HBA and HBD interactions as highly important for the potency.

Quantitative Structure-Activity Relations (Cont'd)

GA(M)E-QSAR: A Novel, Fully Automatic Genetic-Algorithm-(Meta)-Ensembles Approach for Binary Classification in Ligand-Based Drug Design

Yunierkis Pérez-Castillo, Cosmin Lazar, Jonatan Taminau, Mathy Froeyen, Miguel Ángel Cabrera-Pérez, and Ann Nowé [Vrije Universiteit Brussel]

J.Chem. Infor. and Mod. **52**, 2366–2386, 2012.

Computer-aided drug design has become an important component of the drug discovery process. Despite the advances in this field, there is not a unique modeling approach that can be successfully applied to solve the whole range of problems faced during QSAR modeling. Feature selection and ensemble modeling are active areas of research in ligand-based drug design. Here we introduce the GA(M)E-QSAR algorithm that combines the search and optimization capabilities of Genetic Algorithms with the simplicity of the Adaboost ensemble-based classification algorithm to solve binary classification problems.

3D-QSAR Based on Quantum-Chemical Molecular Fields: Toward an Improved Description of Halogen Interactions

Stefan Güssregen, Hans Matter, Gerhard Hessler, Marco Müller, Friedemann Schmidt, and Timothy Clark [Friedrich-Alexander-Universität Erlangen-Nürnberg]

J.Chem. Infor. and Mod. **52**, 2441–2453, 2012.

Current 3D-QSAR methods such as CoMFA or CoMSIA make use of classical force-field approaches for calculating molecular fields. Thus, they can not adequately account for noncovalent interactions involving halogen atoms like halogen bonds or halogen- π interactions. We have now replaced classical force field derived molecular fields by local properties such as the local ionization energy, local electron affinity, or local polarizability, calculated using quantum-mechanical (QM) techniques that do not suffer from the above limitation for 3D-QSAR. We first investigate the characteristics of QM-based local property fields to show that they are suitable for statistical analyses after suitable pretreatment.

QSAR Models for P-Glycoprotein Transport Based on a Highly Consistent Data Set

Fabio Broccatelli [University of Perugia]

J.Chem. Infor. and Mod. **52**, 2462–2470, 2012.

P-Glycoprotein (Pgp) is involved in the elimination and in the disposition of a significant portion of marketed drugs. So far, publicly available data sets used for modeling Pgp transport included compounds tested in different assays, different cell lines, and different protocols. In this work, we present a collection of 478 Efflux Ratios (ERs) in MDCK-MDR1 cell lines, and from this collection we define a data set of 187 compounds that were tested in the Borst-derived MDCK-MDR1 cell lines.

The receptor-dependent LQTA-QSAR: application to a set of trypanothione reductase inhibitors

uzébio G. Barbosa, Kerly Fernanda M. Pasqualoto, Márcia M. C. Ferreira [University of Campinas]

J. Comp. Aided Mol. Des., **26**, 1055-1065, 2012.

A new Receptor-Dependent LQTA-QSAR approach, RD-LQTA-QSAR, is proposed as a new 4D-QSAR method. It is an evolution of receptor independent LQTA-QSAR. This approach uses the free GROMACS package to carry out molecular dynamics simulations and generates a conformational ensemble profile for each compound. Such an ensemble is used to build molecular interaction field-based QSAR models, as in CoMFA. To show the potential of this methodology, a set of 38 phenothiazine derivatives that are specific competitive T. cruzi trypanothione reductase inhibitors, was chosen.

Molecular Dynamics

Computational and Experimental Analyses Reveal the Essential Roles of Interdomain Linkers in the Biological Function of Chemotaxis Histidine Kinase CheA

Xiqing Wang, Chun Wu, Anh Vu, Joan-Emma Shea, and Frederick W. Dahlquist [University of California Santa Barbara]

J. Am. Chem. Soc., **134**, 16107–16110, 2012.

A two-component signal transduction pathway underlies the phenomenon of bacterial chemotaxis that allows bacteria to modulate their swimming behavior in response to environmental stimuli. The dimeric five-domain histidine kinase, CheA, plays a central role in the pathway, converting sensory signals to a chemical signal via trans-autophosphorylation between the P1 and P4 domains. We performed replica exchange molecular dynamics simulations on the CheA kinase core and found that while individual domains maintained their structural fold, these domains exhibited a variety of interdomain orientations due to two interdomain linkers.

Insights from molecular dynamics: The binding site of cocaine in the dopamine transporter and permeation pathways of substrates in the leucine and dopamine transporters

Bonnie A. Merchant, Jeffry D. Madura [Duquesne University]

J. Mol. Graph. and Mod., **38**, 1-12, 2012.

The dopamine transporter (DAT) facilitates the regulation of synaptic neurotransmitter levels. As a target for therapeutic and illicit psycho-stimulant drugs like antidepressants and cocaine, DAT has been studied intensively. Despite a wealth of mutational and physiological data regarding DAT, the structure remains unsolved and details of the transport mechanism, binding sites and conformational changes remain debated. A bacterial homolog of DAT, the leucine transporter (LeuT_{Aa}) has been used as a template and framework for modeling and understanding DAT.

Implementation of the force decomposition machine for molecular dynamics simulations

Urban Borštnik [National Institute of Chemistry, Hajdrihova], Benjamin T. Miller, Bernard R. Brooks, Dušanka Janežič

J. Mol. Graph. and Mod., **38**, 243-247, 2012.

We present the design and implementation of the force decomposition machine (FDM), a cluster of personal computers (PCs) that is tailored to running molecular dynamics (MD) simulations using the distributed diagonal force decomposition (DDFD) parallelization method. The cluster interconnect architecture is optimized for the communication pattern of the DDFD method. Our implementation of the FDM relies on standard commodity components even for networking. An analysis of several MD simulation runs on both the FDM and a standard PC cluster demonstrates that the FDM's interconnect architecture provides a greater performance compared to a more general cluster interconnect.

The Solvation Structure of Na⁺ and K⁺ in Liquid Water Determined from High Level ab Initio Molecular Dynamics Simulations

Christopher N. Rowley and Benoît Roux [The University of Chicago]

J. Chem. Theor. and Comp., **8**, 3526–3535, 2012.

Knowledge of the hydration structure of Na⁺ and K⁺ in the liquid phase has wide ranging implications in the field of biological chemistry. Despite numerous experimental and computational studies, even basic features such as the coordination number of these alkali ions in liquid water, thought to play a critical role in selectivity, continue to be the subject of intensive debates. In this article, we report the results from molecular dynamics simulations of Na⁺ and K⁺ hydration based on a novel and rigorous strategy designed to overcome the challenges of QM/MM simulations of solvent molecules in the liquid phase.

Molecular Dynamics (Cont'd)

Molecular Dynamics Simulations of Star Polymeric Molecules with Diblock Arms, a Comparative Study

William C. Swope [IBM Almaden Research Center], Amber C. Carr, Amanda J. Parker, Joseph Sly, Robert D. Miller, and Julia E. Rice

J. Chem. Theor. and Comp., **8**, 3733–3749, 2012.

We have performed all atom explicit solvent molecular dynamics simulations of three different star polymeric systems in water, each star molecule consisting of 16 diblock copolymer arms bound to a small adamantane core. The arms of each system consist of an inner “hydrophobic” block (either polylactide, polyvalerolactone, or polyethylene) and an outer hydrophilic block (polyethylene oxide, PEO). These models exhibit unusual structure very close to the core (clearly an artifact of our model) but which we believe becomes “normal” or bulk-like at relatively short distances from this core. We report on a number of temperature-dependent thermodynamic (structural/energetic) properties as well as kinetic properties.

Mixing Atomistic and Coarse Grain Solvation Models for MD Simulations: Let WT4 Handle the Bulk

Leonardo Darré, Alex Tek, Marc Baaden, and Sergio Pantano [Institut Pasteur de Montevideo]

J. Chem. Theor. and Comp., **8**, 3880–3894, 2012.

Accurate simulation of biomolecular systems requires the consideration of solvation effects. The arrangement and dynamics of water close to a solute are strongly influenced by the solute itself. However, as the solute–solvent distance increases, the water properties tend to those of the bulk liquid. This suggests that bulk regions can be treated at a coarse grained (CG) level, while keeping the atomistic details around the solute. We show here that mixing the popular SPC water model with a CG model for solvation (called WatFour) can effectively mimic the hydration, structure, and dynamics of molecular systems composed of pure water, simple electrolyte solutions, and solvated macromolecules.

Nature of Protein–CO₂ Interactions as Elucidated via Molecular Dynamics

Michael L. Drummond [University of North Texas, Denton], Angela K. Wilson, and Thomas R. Cundari

J. Phys. Chem. B., **116**, 11578–11593, 2012.

Rising global temperatures require innovative measures to reduce atmospheric concentrations of CO₂. The most successful carbon capture technology on Earth is the enzymatic capture of CO₂ and its sequestration in the form of glucose. Efforts to improve upon or mimic this naturally occurring process will require a rich understanding of protein–CO₂ interactions. Toward that end, extensive all-atom molecular dynamics (MD) simulations were performed on the CO₂-utilizing enzyme phosphoenolpyruvate carboxykinase (PEPCK).

QM and QM/MM

Catalytic Mechanism in Artificial Metalloenzyme: QM/MM Study of Phenylacetylene Polymerization by Rhodium Complex Encapsulated in apo-Ferritin

Zhuofeng Ke, Satoshi Abe, Takafumi Ueno, and Keiji Morokuma [Kyoto University]

J. Am. Chem. Soc., **134**, 15418–15429, 2012.

Artificial metalloenzyme, composed of metal complex(es) and a host protein, is a promising way to mimic enzyme catalytic functions or develop novel enzyme-like catalysis. However, it is highly challenging to unveil the active site and exact reaction mechanism inside artificial metalloenzyme, which is the bottleneck in its rational design. We present a QM/MM study of the complicated reaction mechanism for the recently developed artificial metalloenzyme system, **(Rh(nbd)·apo-Fr)** (nbd = norbornadiene), which is composed of a rhodium complex [Rh(nbd)Cl]₂ and the recombinant horse L-chain apo-Ferritin.

Context and Force Field Dependence of the Loss of Protein Backbone Entropy upon Folding Using Realistic Denatured and Native State Ensembles

Michael C. Baxa, Esmael J. Haddadian, Abhishek K. Jha, Karl F. Freed [The University of Chicago], and Tobin R. Sosnick

J. Am. Chem. Soc., **134**, 15929–15936, 2012.

The loss of conformational entropy is the largest unfavorable quantity affecting a protein's stability. We calculate the reduction in the number of backbone conformations upon folding using the distribution of backbone dihedral angles (ϕ, ψ) obtained from an experimentally validated denatured state model, along with all-atom simulations for both the denatured and native states. The average loss of entropy per residue is $T\Delta S_{U-N}^{BB} = 0.7, 0.9, \text{ or } 1.1 \text{ kcal}\cdot\text{mol}^{-1}$ at $T = 298 \text{ K}$, depending on the force field used, with a $0.6 \text{ kcal}\cdot\text{mol}^{-1}$ dispersion across the sequence.

Substrate-Assisted Catalytic Mechanism of O-GlcNAc Transferase Discovered by Quantum Mechanics/Molecular Mechanics Investigation

Igor Tvaroška [Slovak Academy of Sciences], Stanislav Kozmon, Michaela Wimmerová, and Jaroslav Koča

J. Am. Chem. Soc., **134**, 15563–15571, 2012.

In higher eukaryotes, a variety of proteins are post-translationally modified by adding O-linked N-acetylglucosamine (GlcNAc) residue to serine or threonine residues. Misregulation of O-GlcNAcylation is linked to a wide variety of diseases, such as diabetes, cancer, and neurodegenerative diseases, including Alzheimer's disease. GlcNAc transfer is catalyzed by an inverting glycosyltransferase O-GlcNAc transferase (uridine diphospho-N-acetylglucosamine:polypeptide β -N-acetylaminyltransferase, OGT) that belongs to the GT-B superfamily. The catalytic mechanism of this metal-independent glycosyltransferase is of primary importance and is investigated here using QM(DFT)/MM methods.

Ab Initio QM/MM Free Energy Simulations of Peptide Bond Formation in the Ribosome Support an Eight-Membered Ring Reaction Mechanism

Jun Xu, John Z. H. Zhang, and Yun Xiang [East China Normal University]

J. Am. Chem. Soc., **134**, 16424–16429, 2012.

Ab initio QM/MM free-energy simulations were carried out to study the peptide bond formation reaction in the peptidyl transferase center of the ribosome. The QM part of the reaction was treated by density functional theory at the B3LYP/6-31G* level, while the MM part including the solvent and RNA environment was described by molecular force field. The calculated free-energy surfaces for the two popular reaction mechanisms, the six- and eight-membered ring reactions, exhibited large energetic differences which favor the eight-membered reaction mechanism.

QM and QM/MM (Cont'd)

Combining a Dissociative Water Model with a Hybrid QM/MM Approach—A Simulation Strategy for the Study of Proton Transfer Reactions in Solution

Thomas S. Hofer [University of Innsbruck], Manuel Hitzenberger, and Bernhard R. Randolf

J. Chem. Theor. and Comp., **8**, 3586–3595, 2012.

An implementation strategy for a dissociative water potential in hybrid QM/MM simulations is outlined. As the knowledge of the time-dependent topology is crucial for the assignment of solvent molecules to the QM or MM subregion, proton transfer events and the associated change of the molecular composition have to be monitored as the simulation is progressing. A simple and effective update criterion is proposed, which was found to be an efficient tool to identify sustained proton transfer reactions. The resulting topology data enable the application of the dissociative solvent model in QM/MM simulations and serve as a reference for the analysis of time-dependent properties such as the proton hopping rate and the diffusion coefficient.

Exploring the Multidimensional Free Energy Surface of Phosphoester Hydrolysis with Constrained QM/MM Dynamics

Wenjin Li, Till Rudack, Klaus Gerwert, Frauke Gräter [Chinese Academy of Sciences], and Jürgen Schlitter

J. Chem. Theor. and Comp., **8**, 3596–3604, 2012.

The mechanism of the hydrolysis of phosphate monoesters, a ubiquitous biological reaction, has remained under debate. We here investigated the hydrolysis of a nonenzymatic model system, the monomethyl phosphate dianion, by hybrid QM/MM simulations. The solvation effects were taken into account with explicit water. Detailed free energy landscapes in two-dimensional and three-dimensional space were resolved using the multidimensional potential of mean constraint force, a newly developed method that was demonstrated to be powerful for free energy calculations along multiple coordinates.

QM/MM-Based Fitting of Atomic Polarizabilities for Use in Condensed-Phase Biomolecular Simulation

C. Ruben Vosmeer, Ariën S. Rustenburg, Julia E. Rice, Hans W. Horn, William C. Swope, and Daan P. Geerke [VU University Amsterdam]

J. Chem. Theor. and Comp., **8**, 3839–3853, 2012.

Accounting for electronic polarization effects in biomolecular simulation (by using a polarizable force field) can increase the accuracy of simulation results. However, the use of gas-phase estimates of atomic polarizabilities α_i usually leads to overpolarization in condensed-phase systems. In the current work, a combined QM/MM approach has been employed to obtain condensed-phase estimates of atomic polarizabilities for water and methanol (QM) solutes in the presence of (MM) solvents of different polarity. In a next step, the validity of the linear response and isotropy assumptions were evaluated based on the observed condensed-phase distributions of α_i values.

Catalytic Mechanism of Porphobilinogen Synthase: The Chemical Step Revisited by QM/MM Calculations

Bo-Xue Tian, Edvin Erdtman, and Leif A. Eriksson [University of Gothenburg]

J. Phys. Chem. B., **116**, 12105–12112, 2012.

Porphobilinogen synthase (PBGS) catalyzes the asymmetric condensation and cyclization of two 5-aminolevulinic acid (5-ALA) substrate molecules to give porphobilinogen (PBG). The chemical step of PBGS is herein revisited using QM/MM (ONIOM) calculations. Two different protonation states and several different mechanisms are considered. Previous mechanisms based on DFT-only calculations are shown unlikely to occur. According to these new calculations, the deprotonation step rather than ring closure is rate-limiting.

QM and QM/MM (Cont'd)

Ab Initio Quantum Chemistry for Protein Structures

Heather J. Kulik, Nathan Luehr, Ivan S. Ufimtsev, and Todd J. Martinez [Stanford University]

J. Phys. Chem. B., **116**, 12501–12509, 2012.

Structural properties of over 55 small proteins have been determined using both density-based and wave-function-based electronic structure methods in order to assess the ability of ab initio “force fields” to retain the properties described by experimental structures measured with crystallography or nuclear magnetic resonance. The efficiency of the GPU-based quantum chemistry algorithms implemented in our TeraChem program enables us to carry out systematic optimization of ab initio protein structures, which we compare against experimental and molecular mechanics force field references.

Comparative or Homology Modeling

Homology modeling, docking and molecular dynamics of the *Leishmania mexicana* arginase: A description of the catalytic site useful for drug design

Carlos A. Méndez-Cuesta, Oscar Méndez-Lucio, Rafael Castillo [Universidad Nacional Autónoma de México]

J. Mol.Graph. and Mod., **38**, 50-59, 2012.

The crystallographic structure of the *Leishmania mexicana* arginase, an attractive target for the design of leishmanicidal agents, is still unknown. For this reason, we report a computer-assisted homology study conducted to build its three-dimensional structure based on the known sequence of amino acids of this enzyme. In this study, the amino acid sequence in the arginase of the parasite was compared with the sequence of the amino acids in the crystallographic structure of rat and human liver arginases. The best similarity was found with the rat liver arginase. These results provide important information for the design of new inhibitors.

Ligand-specific homology modeling of human cannabinoid (CB1) receptor

Rizi Ai, Chia-en A. Chang [University of California Riverside]

J. Mol.Graph. and Mod., **38**, 155-164, 2012.

Cannabinoid (CB1) receptor is a therapeutic drug target, and its structure and conformational changes after ligand binding are of great interest. The known CB1 ligands are highly diverse structurally, so CB1 receptor may undergo considerable conformational changes to accept different ligands, which is challenging for molecular docking methods. To account for the flexibility of CB1 receptor, we constructed four CB1 receptor models based on four structurally distinct ligands, HU-210, ACEA, WIN55212-2 and SR141716A, using the newest X-ray crystal structures of human β_2 adrenergic receptor and adenosine A_{2A} receptor as templates.

Ligand Docking

Impact of the CXCR4 structure on docking-based virtual screening of HIV entry inhibitors

Jesús M. Planesas, Violeta I. Pérez-Nueno, José I. Borrell, Jordi Teixidó [Universitat Ramon Llull]

J. Mol.Graph. and Mod., **38**, 123-136, 2012.

Herein we analyze in depth the receptor-based virtual screening (VS) performance of the five recent crystallized CXCR4 structures along with a CXCR4 rhodopsin-based homology model. All CXCR4 Protein Data Bank (PDB) structures are co-crystallized with a small organic antagonist except structure 3OE0, which is co-crystallized with a cyclic peptide analog. Evaluation of the CXCR4 models was done by retrospective docking-based VS using a test set of 248 known CXCR4 inhibitors from 4 different chemotype families and 4696 different presumed inactives. The performance of the docking protocol using the five different protein structures was assessed in terms of pose prediction and hits detection using 12 different docking scoring functions and a scoring function with rescoring.

Water-Driven Cavity–Ligand Binding: Comparison of Thermodynamic Signatures from Coarse-Grained and Atomic-Level Simulations

Riccardo Baron [The University of Utah] and Valeria Molinero

J. Chem. Theor. and Comp, **8**, 3696–3704, 2012.

The role of water (thermo)dynamics is crucial in molecular recognition and self-assembly. Here, we study a prototype cavity–ligand system as a model for hydrophobic noncovalent binding. Two alternative molecular dynamics simulation resolutions are employed and the resulting structural, dynamic, and thermodynamic properties compared: first, a coarse-grained (CG) resolution based on the previously reported and validated methane-like M solute and mW water models; second, an atomic-level (AL) resolution based on the popular OPLS united atom methane and the TIP4P water models.

3. JOURNAL REVIEWS

Journal of Molecular Graphics and Modelling, 38, September, 2012.

- 1-12 **Insights from molecular dynamics: The binding site of cocaine in the dopamine transporter and permeation pathways of substrates in the leucine and dopamine transporters**, Bonnie A. Merchant, Jeffry D. Madura [Duquesne University]

See Methodology / Molecular Dynamics.

- 13-25 **Preferential heterochiral cyclic trimerization of 5-(aminoethyl)-2-furancarboxylic acid (AEFC) driven by non-covalent interactions**, N.V. Suresh Kumar, Harjinder Singh, Kiran Kumar Pulkuri, Tushar Kanti Chakraborty [International Institute of Information Technology-Hyderabad]

Theoretical justification for preferential heterochiral cyclic trimerization of 5-(aminoethyl)-2-furancarboxylic acid (AEFC) is attempted using density functional theory (DFT) calculations.

- 26-30 **Computed NMR shielding of phosphorus-containing conjugated five-membered ring heterocycles as a measure of aromaticity**, Ned H. Martin [University of North Carolina Wilmington], Jonathan D. Robinson

The GIAO-HF method in Gaussian 03 was used to calculate the isotropic shielding value of the proximal hydrogen of a diatomic hydrogen probe oriented perpendicular to the plane and moved in a square grid 2.5 Å above the plane of conjugated five-membered ring heterocyclic compounds: pyrrole, furan, phosphole and thiophene and their phosphorus containing analogs.

- 31-39 **Solvent effect on halogen bonding: The case of the I...O interaction**, Alessandra Forni, Stefano Rendine, Stefano Pieraccini, Maurizio Sironi [Istituto di Scienze e Tecnologie Molecolari del CNR (CNR-ISTM) and INSTM UdR]

The solvent effect on the I...O halogen bonding in complexes of iodobenzene derivatives with formaldehyde has been investigated by systematically varying the substituents on the iodobenzene ring.

- 40-49 **Phase transition study of confined water molecules inside carbon nanotubes: Hierarchical multiscale method from molecular dynamics simulation to ab initio calculation**, Soheila Javadian [Tarbiat Modares University], Fariba Taghavi, Faramarz Yari, Seyed Majid Hashemianzadeh

See Applications / Carbon Nanoparticles.

- 50-59 **Homology modeling, docking and molecular dynamics of the Leishmania mexicana arginase: A description of the catalytic site useful for drug design**, Carlos A. Méndez-Cuesta, Oscar Méndez-Lucio, Rafael Castillo [Universidad Nacional Autónoma de México]

See Methodology / Homology Modeling.

- 60-69 **Inhibitory activities and possible anticancer targets of Ru(II)-based complexes using computational docking method**, Adebayo A. Adeniyi, Peter A. Ajibade [University of Fort Hare]

See Applications / Medicinal Chemistry and Drug Design.

- 70-81 **Fitting the complexity of GPCRs modulation into simple hypotheses of ligand design**, Chiara Custodi, Roberto Nuti, Tudor I. Oprea, Antonio Macchiarulo [Università di Perugia]

See Applications / Medicinal Chemistry and Drug Design.

- 82-89 **Substituent effects on zinc phthalocyanine derivatives: A theoretical calculation and screening of sensitizer candidates for dye-sensitized solar cells**, Linlin Yang, Lianshun Guo, Qianqian Chen, Huafei Sun, Hui Yan, Qinghua Zeng, Xianxi Zhang [Liaocheng University], Xu Pan, Songyuan Dai

A series of unsymmetrical phthalocyanine sensitizer candidates with different donor and acceptor substituents, namely ZnPcB—Ph, ZnPcB—OPh, ZnPcB—tBu, ZnPcB—N(Ph)₂, ZnPcB—NHPh, ZnPcB—NH₂, ZnPcB—NHCH₃ and ZnPcB—N(CH₃)₂, were designed and calculated using density functional theory (DFT) and time-dependent DFT calculations.

- 90-100 **Quantitative structure–activity relationships (QSARs) using the novel marine algal toxicity data of phenols**, M. Doğa Ertürk, Melek Türker Saçan [Boğaziçi University], Marjana Novic, Nikola Minovski

See Applications / QSAR.

- 112-122 **Exploring the structure determinants of pyrazinone derivatives as PDE5 3HC8 inhibitors: An in silico analysis**, Yan Li [Dalian University of Technology], Wenzhao Wu, Hong Ren, Jinghui Wang, Shuwei Zhang, Guohui Li, Ling Yang

See Applications / QSAR.

- 123-136 **Impact of the CXCR4 structure on docking-based virtual screening of HIV entry inhibitors**, Jesús M. Planesas, Violeta I. Pérez-Nueno, José I. Borrell, Jordi Teixidó [Universitat Ramon Llull]

See Methodology / Ligand Docking.

- 137-147 **Novel descriptors from main and side chains of high-molecular-weight polymers applied to prediction of glass transition temperatures**, Damián Palomba, Gustavo Esteban Vazquez, Mónica Fátima Díaz [Development in Scientific Computing (LIDeCC)]

New descriptors of main and side chains for polymers with high molecular weight are presented in order to predict the glass-transition temperature (T_g) by means of T_g/M ratio.

- 148-154 **Binding pattern of the long acting neuraminidase inhibitor laninamivir towards influenza A subtypes H5N1 and pandemic H1N1**, Arthitaya Meeprasert, Wasinee Khuntawee, Kittiwat Kamlungsua, Nadtanet Nunthaboot, Thanyada Rungrotmongkol [Chulalongkorn University], Supot Hannongbua

See Applications / Medicinal Chemistry and Drug Design.

- 155-164 **Ligand-specific homology modeling of human cannabinoid (CB1) receptor**, Rizi Ai, Chia-en A. Chang [University of California Riverside]

See Methodology / Homology Modeling.

- 165-173 **Investigation of a predicted N-terminal amphipathic α -helix using atomistic molecular dynamics simulation of a complete prototype poliovirus virion**, Jason A. Roberts [Victorian Infectious Diseases Reference Laboratory], Michael J. Kuiper, Bruce R. Thorley, Peter M. Smooker, Andrew Hung

See Applications / Crystal growth.

- 174-185 **Structural significance of hypermodified nucleic acid base hydroxywybutine (OHyW) which occur at 37th position in the anticodon loop of yeast tRNA^{Phe}**, Navanath M. Kumbhar, Bajarang V. Kumbhar, Kailas D. Sonawane [Shivaji University]

Conformational preferences of hypermodified nucleic acid base hydroxywybutine (OHyW) have been studied using quantum chemical single point semi-empirical PM3 method.

- 186-193 **Molecular dynamics simulation of the interaction between protein tyrosine phosphatase 1B and aryl diketoacid derivatives**, Qiang Wang, Jun Gao, Yongjun Liu, Chengbu Liu [Shandong University]

See Applications / Ligand Binding.

- 194-210 **The 3D-QSAR study of 110 diverse, dual binding, acetylcholinesterase inhibitors based on alignment independent descriptors (GRIND-2). The effects of conformation on predictive power and interpretability of the models**, Maja D. Vitorović-Todorović [University of Belgrade], Ilija N. Cvijetić, Ivan O. Juranić, Branko J. Drakulić

See Methodology / QSAR.

- 211-219 **Structural analysis of Ca²⁺ dependent and Ca²⁺ independent type II antifreeze proteins: A comparative molecular dynamics simulation study**, Sangeeta Kundu, Debjani Roy [Bose Institute, Kolkata]

See Applications / Protein Structure Prediction.

- 220-225 **First principle investigation of transport properties of Lindqvist derivatives based molecular junction**, Shizheng Wen, Wei Guan, Zhongmin Su [Northeast Normal University], Likai Yan, Stefano Sanvito

The transport properties of Lindqvist type-polyoxometalates $H_2M_6O_{19}$ ($M = Mo, W$) sandwiched between carbon nanotube electrodes are investigated by using density functional theory combined with the non-equilibrium Green's function method.

- 226-234 **Coupled motions during dynamics reveal a tunnel toward the active site regulated by the N-terminal α -helix in an acylaminoacyl peptidase**, Elena Papaleo [University of Milano-Bicocca], Giulia Renzetti

See Applications / Enzyme Catalysis.

- 235-242 **Targeting essential cell wall lipase Rv3802c for potential therapeutics against tuberculosis**, Parameswaran Saravanan, Hindupur Avinash, Vikash Kumar Dubey, Sanjukta Patra [Indian Institute of Technology Guwahati]

See Applications / Medicinal Chemistry and Drug Design.

- 243-247 **Implementation of the force decomposition machine for molecular dynamics simulations**, Urban Borštnik [National Institute of Chemistry, Hajdrihova], Benjamin T. Miller, Bernard R. Brooks, Dušanka Janežič

See Methodology / Molecular Dynamics.

- 248-255 **Computational study: How redox affect the nonlinear optical properties of donor substituted heteroleptic bis-tridentate Ru(II) complexes?**, Xiu-Xin Sun, Na-Na Ma, Xiao-Juan Li, Shi-Ling Sun, Hai-Ming Xie, Yong-Qing Qiu [Northeast Normal University]

Donor substituted heteroleptic bis-tridentate Ru(II) complexes with different deprotonated forms exhibit larger alterations of the first hyperpolarizabilities in oxidized process and are promising to become redox-switchable nonlinear optical (NLO) molecular materials.

- 279-289 **Early stage intercalation of doxorubicin to DNA fragments observed in molecular dynamics binding simulations**, Hongxing Lei, Xiaofeng Wang, Chun Wu [University of California, Santa Barbara]

See Applications / Nucleic Acids-Protein Interactions.

- 290-297 **Molecular modeling of the lipase-catalyzed hydrolysis of acetoxymethyl(i-propoxy)phenylphosphine oxide and its P-borane analogue**, Grzegorz Krasinski, Marek Cypryk [Polish Academy of Sciences], Małgorzata Kwiatkowska, Marian Mikołajczyk, Piotr Kielbasiński

See Applications / Enzyme Catalysis.

- 298-303 **Comparative study on activation mechanism of carboxypeptidase A1, A2 and B: First insights from steered molecular dynamics simulations**, Jitrayut Jitnorn [University of Phayao], Christoph Sontag

See Applications / Homology Modeling.

- 304-313 **Toward panchromatic organic functional molecules: Density functional theory study on the nature of the broad UV–Vis–NIR spectra of substituted tetra(azulene)porphyrins**, Dongdong Qi, Lijuan Zhang, Jianzhuang Jiang [University of Science and Technology Beijing]

To achieve full solar spectrum absorption of organic dyes for organic solar cells and organic solar antenna collectors, a series of tetra(azulene)porphyrin derivatives including $H_2(TAzP)$, $H_2(\alpha-F_4TAzP)$, $H_2(\beta-F_4TAzP)$, $H_2(\gamma-F_4TAzP)$, $H_2(\delta-F_4TAzP)$, $H_2(\epsilon-F_4TAzP)$, $H_2(\zeta-F_4TAzP)$, $H_2[\alpha-(NH_2)_4TAzP]$, $H_2[\beta-(NH_2)_4TAzP]$, $H_2[\gamma-(NH_2)_4TAzP]$, $H_2[\delta-(NH_2)_4TAzP]$, $H_2[\epsilon-(NH_2)_4TAzP]$, and $H_2[\zeta-(NH_2)_4TAzP]$ were designed and their electronic absorption spectra were systematically studied on the basis of TDDFT calculations.

- 314-323 **Quantitative analysis of molecular surface based on improved Marching Tetrahedra algorithm**, Tian Lu, Feiwu Chen [University of Science and Technology Beijing]

Quantitative analysis of molecular surface is a valuable technique for analyzing non-covalent interaction, studying molecular recognition mode, predicting reactive site and reactivity. An efficient way to realize the analysis was first proposed by Bulat et al. (J. Mol. Model., 16, 1679), in which Marching Tetrahedra (MT) approach commonly used in computer graphics is employed to generate vertices on molecular surface.

- 324-333 **Toward understanding the molecular basis for chemical allosteric modulator design**, Qi Wang, Mingyue Zheng, Zhimin Huang, Xinyi Liu, Huchen Zhou, Yingyi Chen, Ting Shi, Jian Zhang [Shanghai JiaoTong University]

Among the regulation mechanisms of cellular function, allosteric regulation is the most direct, rapid and efficient. Due to the wider receptor selectivity and lower target-based toxicity, compared with orthosteric ligands, allosteric modulators are expected to play a larger role in pharmaceutical research and development. In this study, we compared known allosteric modulators with various compounds from different databases to unveil the structural and qualitative characteristics of allosteric modulators.

- 334-341 **A theoretical study of structural and electronic properties of pentacene/Al(1 0 0) interface**, G. Saranya, Shiny Nair, V. Natarajan, P. Kolandaivel, K. Senthilkumar [Bharathiar University]

The first principle calculations within the framework of density functional theory have been performed for the pentacene molecule deposited on the aluminum Al(1 0 0) substrate to study the structural and electronic properties of the pentacene/Al(1 0 0) interface.

- 342-353 **Identification of structural determinants of ligand selectivity in 5-HT₂ receptor subtypes on the basis of protein–ligand interactions**, Jae Wan Jang, Min Sup Kim, Yong Seo Cho, Art E. Cho, Ae Nim Pae [Korea Institute of Science and Technology]

See Applications / Medicinal Chemmistry and Drug Design.

- 354-359 **A DFT study on the interaction between adsorbed silver on C₆₀ and disulfide bond**, Khaled Azizi [University of Kurdistan], Ali Sohrabinia

Adsorption of a silver atom on the surface of Buckyball (C₆₀) was investigated using density functional theory (DFT).

- 360-362 **Teach–Discover–Treat (TDT): Collaborative computational drug discovery for neglected diseases**, Johanna M. Jansen [Novartis Institutes for Biomedical Research], Wendy Cornell, Y. Jane Tseng, Rommie E. Amaro

Teach–Discover–Treat (TDT) is an initiative to promote the development and sharing of computational tools solicited through a competition with the aim to impact education and collaborative drug discovery for neglected diseases.

- 363-368 **In silico studies toward the recognition of fluoride ion by substituted borazines**, Manoj K. Kesharwani, Bishwajit Ganguly [Central Salt and Marine Chemicals Research Institute (Council of Scientific and Industrial Research), Bhavnagar]

The substituted borazines have been computationally investigated as new type of receptors for the recognition of fluoride ion. Fluorine, methyl and phenyl groups have been selected as electron-withdrawing, electron-releasing and aromatic substituents for the study employing DFT (B3LYP/6-311 + G**) and ab initio (MP2/6-311 + G**) levels of calculations.

- 369-374 **Comparative electronic structures and UV–vis spectra of tribenzosubporphyrin, tribenzomonoazasubporphyrin, tribenzodiazasubporphyrin, and subphthalocyanine: Insight from DFT and TDDFT calculations**, Yunling Gao, Pavlo V. Solntsev, Victor N. Nemykin [University of Minnesota-Duluth]

Electronic structures, geometries, and vertical excitation energies of chloroboron subphthalocyanine, tribenzodiazasubporphyrin, tribenzomonoazasubporphyrin, and tribenzosubporphyrin were calculated using density functional theory (DFT) and time-dependent (TD) DFT coupled with polarized continuum model (PCM) approach.

- 375-381 **New statistical boundary conditions for argon–tungsten interactions**, M.S. Ozhgibesov [National Cheng Kung University], T.S. Leu, C.H. Cheng, A.V. Utkin

In this study, scattering processes of argon beam impinging on tungsten surface are investigated numerically by applying molecular dynamics (MD) simulations.

- 382-388 **Structure-based de novo design of Eya2 phosphatase inhibitors**, Hwangseo Park [Sejong University], Seong Eon Ryu, Seung Jun Kim

Although Eyes absent protein tyrosine phosphatases proved to be involved in various human cancers by a series of persuasive experimental evidence, only a very few number of small-molecule inhibitors have been reported so far. We have been able to identify 29 novel inhibitors of Eyes absent homologue 2 (Eya2) by means of a structure-based de novo design with the two known inhibitor scaffolds that contain a proper chelating group for the active-site Mg^{2+} ion.

- 389-395 **Computational algorithms for fast-building 3D carbon nanotube models with defects**, M. Leonor Contreras, Diego Ávila, José Alvarez, Roberto Rozas [University of Santiago de Chile]

Algorithms for generating defective carbon nanotubes have been developed and implemented in software. The algorithms were designed to create arrays of carbon atoms that form layers and interconnect.

- 396-410 **Partial physicochemical properties and relative stability of polyhydroxylated dibenzofurans: Theoretical and experimental study**, Jia-Qi Shi, Jing Qiu, Li Sun, Meng Wang, Fu-Yang Wang, Zun-Yao Wang [Nanjing University]

Polyhydroxylated dibenzofuran (PHODF) is an important degradation product of polychlorinated dibenzofuran (PCDF). Four types of hydrogen bonds (the one between a hydroxyl and the oxygen atom in the matrix, between hydroxyls at ortho positions, between the oxygen atom of hydroxyl at position 1 and the hydrogen atom of the matrix at position 9, and between hydroxyls at positions 1 and 9) exist in PHODFs. The energies of the hydrogen bonds were ascertained by comparing the two configurational isomers as approximately $8\text{--}11\text{ kJ mol}^{-1}$, $16\text{--}21\text{ kJ mol}^{-1}$, $5\text{--}8\text{ kJ mol}^{-1}$ and $23\text{--}25\text{ kJ mol}^{-1}$, respectively.

Journal of Computational Chemistry, 33(28), October, 2012.

- 2211-2224 **Transition state theory thermal rate constants and RRKM-based branching ratios for the $\text{N}(2\text{D}) + \text{CH}_4$ reaction based on multi-sState and multi-reference Ab Initio calculations of interest for the titan's chemistry**, Chanda-Malis Ouk, Natalia Zvereva-Loëte [CNRS-Université de Franche-Comté], Yohann Scribano and Béatrice Bussery-Honvault

Multireference single and double configuration interaction (MRCI) calculations including Davidson (+Q) or Pople (+P) corrections have been conducted in this work for the reactants, products, and extrema of the doublet ground state potential energy surface involved in the $\text{N}(^2\text{D}) + \text{CH}_4$ reaction.

- 2225-2232 **Evaluating nonpolarizable nucleic acid force fields: A systematic comparison of the nucleobases hydration free energies and chloroform-to-water partition coefficients**, Maarten G. Wolf [Max-Planck-Institute for Biophysical Chemistry] and Gerrit Groenhof

Nucleic acid force fields have been shown to reproduce structural properties of DNA and RNA very well, but comparative studies with respect to thermodynamic properties are rare. As a test for thermodynamic properties, we have computed hydration free energies and chloroform-to-water partition coefficients of nucleobases using the AMBER-99, AMBER-gaff, CHARMM-27, GROMOS-45a4/53a6 and OPLS-AA force fields.

- 2233-2242 **BLUF Hydrogen network dynamics and UV/Vis spectra: A combined molecular dynamics and quantum chemical study**, Jan P. Götzke [Max-Planck-Institut für Kohlenforschung], Claudio Greco, Roland Mitrić, Vlasta Bonačić-Koutecký and Peter Saalfrank

Blue light sensing using flavin (BLUF) protein photoreceptor domains change their hydrogen bond network after photoexcitation. To explore this phenomenon, BLUF domains from *R. sphaeroides* were simulated using Amber99 molecular dynamics (MD).

- 2243-2249 **Electron-pair density decomposition for core-valence separable systems**, Jian Wang [Huzhou University], Yu Wang and Jesus M. Ugalde

The electron pair density of a core-valence separable system can be decomposed into three parts: core-core, core-valence, and valence-valence. The core-core part has a Hartree-Fock like structure. The valence-valence part is left to be determined from the reduced frozen-core type wave function, which often contains the essential information on the electron correlation and the chemical bond. We demonstrate the analysis to the ground state of negative ion Li^- and $2^1\Sigma_u^+$ excited state of the Li_2 molecule.

- 2250–2275 **Comparing normal modes across different models and scales: Hessian reduction versus coarse-graining**, An Ghysels [Ghent University], Benjamin T. Miller, Frank C. Pickard IV and Bernard R. Brooks

Dimension reduction is often necessary when attempting to reach longer length and time scales in molecular simulations. It is realized by constraining degrees of freedom or by coarse-graining the system. When evaluating the accuracy of a dimensional reduction, there is a practical challenge: the models yield vectors with different lengths, making a comparison by calculating their dot product impossible. This article investigates mapping procedures for normal mode analysis.

Journal of Computational Chemistry, 33(29), November, 2012.

- 2285–2291 **RMC_POT: A computer code for reverse monte carlo modeling the structure of disordered systems containing molecules of arbitrary complexity**, Orsolya Gereben and László Pusztai [Hungarian Academy of Sciences]

An approach has been devised and tested for preserving the molecular dynamics molecular geometry taking into account energetic considerations during Reverse Monte Carlo (RMC) modeling.

- 2292–2302 **The role of the basis set and the level of quantum mechanical theory in the prediction of the structure and reactivity of cisplatin**, Diego Paschoal, Bruna L. Marcial, Juliana Fedoce Lopes, Wagner B. De Almeida and Hélio F. Dos Santos [Universidade Federal de Juiz de Fora]

In this article, we conducted an extensive ab initio study on the importance of the level of theory and the basis set for theoretical predictions of the structure and reactivity of cisplatin [cis-diamminedichloroplatinum(II) (cDDP)].

- 2303–2309 **Intermolecular hydrogen bond energies in crystals evaluated using electron density properties: DFT computations with periodic boundary conditions**, M. V. Vener [Mendeleev University of Chemical Technology], A. N. Egorova, A. V. Churakov and V. G. Tsirelson

The hydrogen bond (H-bond) energies are evaluated for 18 molecular crystals with 28 moderate and strong $\text{O} \cdots \text{H} \cdots \text{O}$ bonds using the approaches based on the electron density properties, which are derived from the B3LYP/6-311G** calculations with periodic boundary conditions.

- 2310–2317 **Binding energies of five molecular pincers calculated by explicit and implicit solvent models**, Jiří Kessler, Milan Jakubek, Bohumil Dolenský and Petr Bouř [Academy of Sciences, 166 10 Prague]

Molecular pincers or tweezers are designed to hold and release the target molecule. Potential applications involve drug distribution in medicine, environment technologies, or microindustrial techniques. . In this study, density functional theory (DFT) computations combined with dielectric continuum solvent model are compared with the potential of mean force approach using umbrella sampling and the weighted histogram analysis method (WHAM) with molecular dynamics (MD) simulations.

- 2318–2331 **Probing the electronic structure, chemical bonding, and excitation spectra of [CuE]^{+0/-} (E = 14 group element) diatomics employing DFT and ab initio methods**, Athanassios C. Tsipis [University of Ioannina] and Dimitrios N. Gkarpounis

The electronic structure, chemical bonding, and excitation spectra of neutral, cationic, and anionic diatomic molecules of Cu and 14 group elements formulated as [CuE]^{+0/-} (E = C, Si, Ge, Sn, Pb) were investigated by density functional theory (DFT) and time-dependent (TD)-DFT methods.

- 2332–2339 **Quantum monte carlo study of the retinal minimal model C₅H₆NH₂⁺**, Emanuele Coccia and Leonardo Guidoni [Università degli Studi dell'Aquila]

In this work, we study the electronic and geometrical properties of the ground state of the Retinal Minimal Model C₅H₆NH₂⁺ using the variational Monte Carlo (VMC) method by means of the Jastrow antisymmetrized geminal power (JAGP) wavefunction.

- 2340–2350 **Computational prediction of monosaccharide binding free energies to lectins with linear interaction energy models**, Sushil Kumar Mishra, Johan Sund, Johan Åqvist and Jaroslav Koča [Masaryk University]

See Applications / Free energy calculations.

- 2351–2356 **GPU-accelerated computation of electron transfer**, Siegfried Höfner [Università di Bologna], Angela Acocella, Sergiu C. Pop, Tetsu Narumi, Kenji Yasuoka, Titus Beu and Francesco Zerbetto

Electron transfer is a fundamental process that can be studied with the help of computer simulation. The underlying quantum mechanical description renders the problem a computationally intensive application. In this study, we probe the graphics processing unit (GPU) for suitability to this type of problem.

Journal of Computational Chemistry, 33(30), November, 2012.

- 2363–2379 **Natural bond orbital analysis: A critical overview of relationships to alternative bonding perspectives**, Frank Weinhold [University of Wisconsin, Madison]

We sketch the basic principles of natural bond orbital (NBO) theory, including critical discussion of its relationship to alternative bonding concepts and selected illustrations of its application to a broad spectrum of chemical bonding motifs.

- 2380–2387 **Vibrational frequency scale factors for density functional theory and the polarization consistent basis sets**, Marie L. Laury, Matthew J. Carlson and Angela K. Wilson [University of North Texas, Denton]

Calculated harmonic vibrational frequencies systematically deviate from experimental vibrational frequencies. The observed deviation can be corrected by applying a scale factor. Scale factors for: (i) harmonic vibrational frequencies [categorized into low (<1000 cm⁻¹) and high (>1000 cm⁻¹)], (ii) vibrational contributions to enthalpy and entropy, and (iii) zero-point vibrational energies (ZPVEs) have been determined for widely used density functionals in combination with polarization consistent basis sets (pc-n, n = 0,1,2,3,4).

- 2388–2399 **Calculating pK_a values for substituted phenols and hydration energies for other compounds with the first-order fuzzy-border continuum solvation model**, Ity Sharma and George A. Kaminski [Worcester Polytechnic Institute]

We have computed pK_a values for 11 substituted phenol compounds using the continuum Fuzzy-Border (FB) solvation model. Hydration energies for 40 other compounds, including alkanes, alkenes, alkynes, ketones, amines, alcohols, ethers, aromatics, amides, heterocycles, thiols, sulfides, and acids have been calculated.

- 2400–2411 **Electronic fluxes during diels-alder reactions involving 1,2-benzoquinones: mechanistic insights from the analysis of electron localization function and catastrophe theory**, Patricio González-Navarrete, Luis R. Domingo, Juan Andrés [Universitat Jaume I], Slawomir Berski and Bernard Silvi

By means of the joint use of electron localization function (ELF) and Thom's catastrophe theory, a theoretical analysis of the energy profile for the hetero-Diels-Alder reaction of 4-methoxy-1,2-benzoquinone **1** and methoxyethylene **2** has been carried out.

- 2412–2439 **MesoBioNano explorer—A universal program for multiscale computer simulations of complex molecular structure and dynamics**, Ilia A. Solov'yov [Allée des Noisetiers], Alexander V. Yakubovich, Pavel V. Nikolaev, Ilya Volkovets and Andrey V. Solov'yov

We present a multipurpose computer code MesoBioNano Explorer (MBN Explorer). The package allows to model molecular systems of varied level of complexity.

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1. APPLICATIONS

1.1. Small Molecules

Organic Solvents

Molecular Recognition in Different Environments: β -Cyclodextrin Dimer Formation in Organic Solvents

Haiyang Zhang, Tianwei Tan, Wei Feng, and David van der Spoel [Uppsala University, Husargatan 3]

J. Phys. Chem. B., **116**, 12684–12693, 2012.

Electrostatic and van der Waals interactions as well as entropy contribute to the energetics governing macromolecular complexation in biomolecules. Hydrogen bonds play a particularly important role in such interactions. Here we use molecular dynamics (MD) simulations to investigate the hydrogen bond (HB) orientations of free beta-cyclodextrin (β -CD) and head-to-head dimerization of β -CD monomers with and without guest molecules in different environments, namely, in 10 different solvents covering a wide range of polarity. Potentials of mean force for the dimer dissociation are derived from umbrella sampling simulations, allowing determination of the binding affinity between monomers.



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Medicinal Chemistry and Drug Design

The Basis for Carbapenem Hydrolysis by Class A β -Lactamases: A Combined Investigation using Crystallography and Simulations

Fátima Fonseca, Ewa I. Chudyk, Marc W. van der Kamp, António Correia, Adrian J. Mulholland, and James Spencer [University of Bristol Medical Sciences Building]

J. Am. Chem. Soc., **134**, 18275–18285, 2012.

Carbapenems are the most potent β -lactam antibiotics and key drugs for treating infections by Gram-negative bacteria. In such organisms, β -lactam resistance arises principally from β -lactamase production. Although carbapenems escape the activity of most β -lactamases, due in the class A enzymes to slow deacylation of the covalent acylenzyme intermediate, carbapenem-hydrolyzing class A β -lactamases are now disseminating in clinically relevant bacteria. The reasons why carbapenems are substrates for these enzymes, but inhibit other class A β -lactamases, remain to be fully established. Here, we present crystal structures of the class A carbapenemase SFC-1 from *Serratia fonticola* and of complexes of its Ser70 Ala (Michaelis) and Glu166 Ala (acylenzyme) mutants with the carbapenem meropenem.

Effect of atomic charge, solvation, entropy, and ligand protonation state on MM-PB(GB)SA binding energies of HIV protease

Daniel P. Oehme, Robert T. C. Brownlee and David J. D. Wilson [La Trobe University, Bundoora]

J. Comp. Chem. **33**, 2566–2580, 2012.

The molecular mechanics-Poisson-Boltzmann surface area (MM-PBSA) and MM-generalized-Born surface area (MM-GBSA) approaches are commonly used in molecular modeling and drug design. Four critical aspects of these approaches have been investigated for their effect on calculated binding energies: (1) the atomic partial charge method used to parameterize the ligand force field, (2) the method used to calculate the solvation free energy, (3) inclusion of entropy estimates, and (4) the protonation state of the ligand. HIV protease has been used as a test case with six structurally different inhibitors covering a broad range of binding strength to assess the effect of these four parameters.

GRID-Based Three-Dimensional Pharmacophores I: FLAPpharm, a Novel Approach for Pharmacophore Elucidation

Simon Cross [Molecular Discovery Limited], Massimo Baroni, Laura Goracci, and Gabriele Cruciani

J. Chem. Infor. and Mod. **52**, 2587–2598, 2012.

Pharmacophore elucidation approaches are routinely used in drug discovery, primarily with the aim of determining the three-dimensional arrangement of common features shared by ligands interacting at the site of interest; these features can then be used to investigate the structure–activity relationship between the ligands and also to screen for other molecules possessing the relevant features. Here we present a novel approach based on GRID molecular interaction fields and the derivative method FLAP that has been previously described, which provides a common reference framework to compare both small molecule ligands and macromolecular protein targets.

Medicinal Chemistry and Drug Design (Cont'd)

Molecular Basis of Drug Resistance in A/H1N1 Virus

Ariela Vergara-Jaque, Horacio Poblete, Eric H. Lee, Klaus Schulten, Fernando González-Nilo, and Christophe Chipot [Nancy Université BP 239]

J.Chem. Infor. and Mod. **52**, 2650–2656, 2012.

New mutants of human influenza virus (A/H1N1) exhibit resistance to antiviral drugs. The mechanism whereby they develop insensitivity to these medications is, however, not yet completely understood. A crystallographic structure of A/H1N1 neuraminidase has been published recently. Using MD simulations, it is now possible to characterize at the atomic level the mechanism that underlies the loss of binding affinity of the drugs. In this study, free-energy perturbation was used to evaluate the relative binding free energies of Tamiflu and Relenza with H274Y, N294S, and Y252H neuraminidase mutants.

Validation of computational approach to study monomer selectivity toward the template Gallic acid for rational molecularly imprinted polymer design

Sushma Pardeshi, Rajendra Patrikar, Rita Dhodapkar, Anupama Kumar [Visvesvaraya National Institute of Technology]

J. Mol.Mod., **18**, 4797-4810, 2012.

Gallic acid (GA) is important for pharmaceutical industries as an antioxidant. It also finds use in tanning, ink dyes and manufacturing of paper. Molecularly imprinted polymers (MIP), which are tailor made materials, can play an excellent role in separation of GA from complex matrices. Molecular recognition being the most important property of MIP, the present work proposes a methodology based on density functional theory (DFT) calculations for selection of suitable functional monomer for a rational design of MIP with a high binding capacity for GA.

Docking and molecular dynamics studies of new potential inhibitors of the human epidermal receptor 2

Wilian Augusto Cortopassi [Pontifical Catholic University of Rio de Janeiro], Rafael José Cavalieri Feital, Diogo de Jesus Medeiros, Teobaldo Ricardo Cuya Guizado, Tanos Celmar Costa França & André Silva Pimentel

Molecular Simulation, **38**, 1132-1142, 2012.

Compounds similar to lapatinib and gefitinib have been investigated as potential inhibitors of the intracellular receptor tyrosine kinase (RTK) domain of the human epidermal receptor 2 (HER2), which is a promising molecular target to the drug design of new chemotherapies for breast, lung, ovarian and colorectal cancers. In this study, we have searched potential HER2 inhibitors used for treatment of other illnesses such as hepatitis, bacterial infections and sexual impotence screened in the DrugBank. The compounds selected were subjected to virtual screening docking in order to evaluate the main interactions between them and the RTK domain of HER2.

Quantitative Structure-Activity Relations

Exploring the Role of Water Molecules for Docking and Receptor Guided 3D-QSAR Analysis of Naphthyridine Derivatives as Spleen Tyrosine Kinase (Syk) Inhibitors

Maninder Kaur, Malkeet Singh Bahia, and Om Silakari [Punjabi University, Patiala]

J.Chem. Infor. and Mod. **52**, 2619–2630, 2012.

In the present study, 3D-QSAR analysis was performed utilizing docking based alignment of [1,6]-naphthyridine derivatives as Syk enzyme inhibitors. The role of the water molecules was explored for the docking based alignment that revealed two conserved water molecules important for proper orientation and alignment of naphthyridine inhibitors in the active site of Syk enzyme. The QSAR model was selected having highest value of Q^2 (0.624) and Pearson-r (0.862). The selected model also displayed the highest values of R^2 (0.978) and F-value (184.5) and the lowest SD (0.862).

Host-Guest Systems

Effect of thiol-functionalised silica on cisplatin adsorption

Andres Díaz Compañy [Universidad Nacional del Sur],
Graciela Brizuela & Sandra Simonetti

Molecular Simulation, **38**, 1055-1060, 2012.

This study contributes to the investigation related to guest–host interactions between the chemotherapeutic agent cisplatin and a functionalised silica matrix in order to improve and find new materials such as drug carriers. The adsorption of cisplatin and its complexes, $\text{cis-}[\text{PtCl}(\text{NH}_3)_2]^+$ and $\text{cis-}[\text{Pt}(\text{NH}_3)_2]^{2+}$, on a SH-functionalised $\text{SiO}_2(111)$ surface has been studied by the atom superposition and electron delocalisation method. The adiabatic energy curves for the adsorption of the drug and its products on the delivery system were considered. The electronic structure and bonding analysis were also performed.

Zeolites

The effects of structural parameters of zeolite on the adsorption of hydrogen: a molecular simulation study

Mahmoud Rahmati [Amirkabir University of Technology (Tehran Polytechnic)] & Hamid Modarress

Molecular Simulation, **38**, 1038-1047, 2012.

The adsorption isotherm of hydrogen in zeolites FAU, LTA, KFI, RWY, RHO and TSC has been simulated employing grand canonical Monte Carlo procedure for a temperature range of 77 to 95 K and different pressures. The effects of structural composition, unit cell volume, framework density and specific surface area of zeolite on hydrogen adsorption in zeolites were investigated. The results clearly show that the adsorption of hydrogen in zeolites with the same silica density is a function of oxygen density at low pressures, and it is approximately the same at intermediate pressures.

Carbon Nanoparticles

Computational study of Au₄ cluster on a carbon nanotube with and without defects using QM/MM methodology

Diana Barraza-Jimenez [Centro de Investigacion en Alimentacion y Desarrollo A.C. Unidad Delicias], D. H. Galvan, Alvaro Posada-Amarillas, Manuel Alberto Flores-Hidalgo, Daniel Glossman-Mitnik, Miguel Jose-Yacaman

J. Mol.Mod., **18**, 4885-4891, 2012.

We use ONIOM (QM/MM) methodology to carry out geometry calculations in a 4-atom nanocluster supported by an (8, 8) armchair carbon nanotube with and without defects employing LSDA/SDD for the QM system and UFF for MM. In two particular cases, defects were added in the carbon nanotube wall. These defects are a double oxygenated vacancy (Vac_2O_2) and a double vacancy but without oxygen which creates two pentagons and an octagon. Our results show how geometries using QM/MM and energies calculations carried out with QM, change on both the gold nanocluster and the carbon nanotube. A comparison is made with the binding energy resulting values as well as with the orbital energies such as the frontier orbitals HOMO and LUMO.

Carbon Nanoparticles (Cont'd)

Embedded Single-Walled Carbon Nanotubes Locally Perturb DOPC Phospholipid Bilayers

R. Parthasarathi, N. R. Tummala, and A. Striolo [The University of Oklahoma, Norman]

J. Phys. Chem. B., **116**, 12769–12782, 2012.

Understanding and controlling how carbon nanotubes (CNTs) interact with phospholipid membranes is necessary for preventing adverse effects of these relatively new, but still exciting, materials. Futuristic applications envision incorporating CNTs in liposomes for personalized medicine, controlled delivery, and imaging. Because of their ability to penetrate phospholipid bilayers, nanotubes could serve as nanoscale syringes to deliver molecular cargo and develop gene therapy.

Brittle ductile transition in carbon nanotube bundles

Charles F. Cornwell [US Army Engineer Research and Development Center] & Charles R. Welch

Molecular Simulation, **38**, 1032-1037, 2012.

The superior strength and stiffness of carbon nanotubes (CNTs) make them attractive for many structural applications. Although the strength and stiffness of CNTs are extremely high, fibres of aligned CNTs have been found to date to be far weaker than the constituent CNTs. The intermolecular interactions between the CNTs in the fibres are governed by weak van der Waals forces, resulting in slippage between CNTs which occurs at tensions well below the breaking strength of the CNTs. Both theoretical and experimental studies show that by introducing chemical bonds between the CNTs increases load transfer and prevents the CNTs from slipping.

Changes in CNT-confined water structural properties induced by the variation in water molecule orientation

Ximing Wu [Nanjing University of Technology], Linghong Lu, Yudan Zhu, Mingjie Wei, Xiaojing Guo & Xiaohua Lu

Molecular Simulation, **38**, 1094-1102, 2012.

Using a (8, 8) carbon nanotube (CNT) as a model for nanochannel, we studied the effects of carbonyl (–CO) groups and external electric field on the properties of confined water molecules by MD simulation. We analysed the density profiles, the distribution of orientation and the hydrogen bonds of water molecules in the axial and radial directions of the CNT. The results show that –CO groups are more powerful than electric fields on controlling water properties, and property changes induced by –CO groups are less affected by electric fields.

Crystal Growth

Uncovering Molecular Details of Urea Crystal Growth in the Presence of Additives

Matteo Salvalaglio, Thomas Vetter, Federico Giberti, Marco Mazzotti, and Michele Parrinello [ETH Zurich]

J. Am. Chem. Soc., **134**, 17221–17233, 2012.

Controlling the shape of crystals is of great practical relevance in fields like pharmacology and fine chemistry. Here we examine the paradigmatic case of urea which is known to crystallize from water with a needle-like morphology. To prevent this undesired effect, inhibitors that selectively favor or discourage the growth of specific crystal faces can be used. In urea the most relevant faces are the {001} and the {110} which are known to grow fast and slow, respectively. We study the growth of fast {001} and slow {110} faces in water solution and the effect of shape controlling inhibitors like biuret.

1.2. Biopolymers

Bioinformatics and Cheminformatics

SAPIN: A framework for the structural analysis of protein interaction networks

Jae-Seong Yang, Anne Campagna, Javier Delgado, Peter Vanhee, Luis Serrano, and Christina Kiel[EMBL/CRG, Design of Biological Systems]

Bioinformatics. **28**, 2998-2999, 2012.

Protein interaction networks are widely used to depict the relationships between proteins. These networks often lack the information on physical binary interactions, and they do not inform whether there is incompatibility of structure between binding partners. Here, we introduce SAPIN, a framework dedicated to the structural analysis of protein interaction networks. SAPIN first identifies the protein parts that could be involved in the interaction and provides template structures. Next, SAPIN performs structural superimpositions to identify compatible and mutually exclusive interactions. Finally, the results are displayed using Cytoscape Web.

Protein Flexibility in Virtual Screening: The BACE-1 Case Study

Sandro Cosconati, Luciana Marinelli, Francesco Saverio Di Leva, Valeria La Pietra, Angela De Simone, Francesca Mancini, Vincenza Andrisano, Ettore Novellino, David S. Goodsell, and Arthur J. Olson [The Scripps Research Institute]

J.Chem. Infor. and Mod. **52**, 2697–2704, 2012.

Simulating protein flexibility is a major issue in the docking-based drug-design process for which a single methodological solution does not exist. In our search of new anti-Alzheimer ligands, we were faced with the challenge of including receptor plasticity in a virtual screening campaign aimed at finding new β -secretase inhibitors. To this aim, we incorporated protein flexibility in our simulations by using an ensemble of static X-ray enzyme structures to screen the National Cancer Institute database. A unified description of the protein motion was also generated by computing and combining a set of grid maps using an energy weighting scheme.

Comparative or Homology Modeling

NS2B/NS3 protease: allosteric effect of mutations associated with the pathogenicity of tick-borne encephalitis virus

Ulyana V. Potapova [Siberian Branch of the Russian Academy of Sciences], Sergey I. Feranchuk, Vladimir V. Potapov, Nina V. Kulakova, Ilya G. Kondratov, Galina N. Leonova & Sergey I. Belikov

J. Biomol. Stru. and Dyn., **30**, 638-651, 2012.

The sequences of the protease domain of the tick-borne encephalitis (TBE) virus NS3 protein have two amino acid substitutions, 16 R→K and 45 S→F, in the highly pathogenic and poorly pathogenic strains of the virus, respectively. Two models of the NS2B-NS3 protease complex for the highly pathogenic and poorly pathogenic strains of the virus were constructed by homology modeling using the crystal structure of West Nile virus NS2B-NS3 protease as a template; 20 ns molecular dynamic simulations were performed for both models, the trajectories of the dynamic simulations were compared, and the averaged distance between the two models was calculated for each residue.

Comparative or Homology Modeling (Cont'd)

Homology modeling and structural analysis of human γ -glutamylcysteine ligase catalytic subunit for antitumor drug development

Hideaki Yamaguchi [Meijo University], Tatsuo Akitaya, Yumi Kidachi, Katsuyoshi Kamiie, Hironori Umetsu

Jour. Bioph. Chem., **03**, 238-248, 2012.

Homology modeling and structural analysis of human glutamate cysteine ligase catalytic subunit (hGCLC) were performed with a software package the Molecular Operating Environment. A yeast GCLC (yGCLC; PDB code: 3LVV) was selected as a template for the 3D structure modeling of hGCLC. The modeled hGCLC showed significant 3D similarities at the ligand binding site (LBS) to the yGCLC structure. The contact energy profiles of the hGCLC model were in good agreement with those of the yGCLC structure. Ramachandran plots revealed that only 1.4% of the amino acid residues were in the disfavored region for hGCLC.

Homology Models of Human All-Trans Retinoic Acid Metabolizing Enzymes CYP26B1 and CYP26B1 Spliced Variant

Patricia Saenz-Méndez, Ali Ateia Elmabsout, Helena Sävenstrand, Mohamed Khalid Alhaj Awadalla, Åke Strid, Allan Sirsjö, and Leif A. Eriksson [University of Gothenburg]

J.Chem. Infor. and Mod. **52**, 2631–2637, 2012.

Homology models of CYP26B1 (cytochrome P450RA12) and CYP26B1 spliced variant were derived using the crystal structure of cyanobacterial CYP120A1 as template for the model building. The quality of the homology models generated were carefully evaluated, and the natural substrate all-trans-retinoic acid (atRA), several tetralone-derived retinoic acid metabolizing blocking agents (RAMBAs), and a well-known potent inhibitor of CYP26B1 (R115866) were docked into the homology model of full-length cytochrome P450 26B1. The results show that in the model of the full-length CYP26B1, the protein is capable of distinguishing between the natural substrate (atRA), R115866, and the tetralone derivatives.

Protein Conformational Analysis

The Conformational Ensembles of α -Synuclein and Tau: Combining Single-Molecule FRET and Simulations

Abhinav Nath, Maria Sammalkorpi, David C. DeWitt, Adam J. Trexler, Shana Elbaum-Garfinkle, Corey S. O'Hern, Elizabeth Rhoades [Yale University, New Haven]

Biophysical Journal. **103**, 1940-1949, 2012.

Intrinsically disordered proteins (IDPs) are increasingly recognized for their important roles in a range of biological contexts, both in normal physiological function and in a variety of devastating human diseases. However, their structural characterization by traditional biophysical methods, for the purposes of understanding their function and dysfunction, has proved challenging. Here, we investigate the model IDPs α -Synuclein (α S) and tau, that are involved in major neurodegenerative conditions including Parkinson's and Alzheimer's diseases, using excluded volume Monte Carlo simulations constrained by pairwise distance distributions from single-molecule fluorescence measurements.

Protein Conformational Analysis (Cont'd)

Collapse of Unfolded Proteins in a Mixture of Denaturants

Zhen Xia, Payel Das, Eugene I. Shakhnovich, and Ruhong Zhou [IBM Thomas J. Watson Research Center]

J. Am. Chem. Soc., **134**, 18266–18274, 2012.

Both urea and guanidinium chloride (GdmCl) are frequently used as protein denaturants. Given that proteins generally adopt extended or unfolded conformations in either aqueous urea or GdmCl, one might expect that the unfolded protein chains will remain or become further extended due to the addition of another denaturant. However, a collapse of denatured proteins is revealed using atomistic molecular dynamics simulations when a mixture of denaturants is used. Both hen egg-white lysozyme and protein L are found to undergo collapse in the denaturant mixture.

Efficient sampling of protein conformational space using fast loop building and batch minimization on highly parallel computers

Michael D. Tyka [University of Washington, Seattle], Kenneth Jung and David Baker

J. Comp. Chem. **33**, 2483–2491, 2012.

All-atom sampling is a critical and compute-intensive end stage to protein structural modeling. Because of the vast size and extreme ruggedness of conformational space, even close to the native structure, the high-resolution sampling problem is almost as difficult as predicting the rough fold of a protein. Here, we present a combination of new algorithms that considerably speed up the exploration of very rugged conformational landscapes and are capable of finding heretofore hidden low-energy states. The algorithm is based on a hierarchical workflow and can be parallelized on supercomputers with up to 128,000 compute cores with near perfect efficiency.

Effects of Lysine Substitution on Stability of Polyalanine α Helix

Sergei Y. Ponomarev, Qina Sa, and George A. Kaminski [Worcester Polytechnic Institute, Worcester]

J. Chem. Theor. and Comp., **8**, 4691–4706, 2012.

We have studied the stability of polyalanine α -helices with lysine residues added at C- and N-termini in the gas phase and aqueous solution. Monte Carlo simulations with the fixed-charge OPLS-AA and our polarizable POSSIM force fields were carried out. The results of the simulations confirm previously observed phenomena of the helix being stable with the LYS residue on the C-terminus and losing its helical structure if the charged LYS residue is located at the N-terminus of the polypeptide in the gas phase.

Protein Dynamics

Counterion Effects on the Denaturing Activity of Guanidinium Cation to Protein

Qiang Shao, Yubo Fan, Lijiang Yang, and Yi Qin Gao [Beijing National Laboratory of Molecular Sciences]

J. Chem. Theor. and Comp., **8**, 4364–4373, 2012.

The denaturation of a three- α -helix bundle, the B domain of protein A, by guanidinium is studied by molecular dynamics simulations. The simulation results showed that in GdmCl solution, guanidinium cations accumulate around the protein surface, whereas chloride anions are expelled from the protein. In contrast, in GdmSCN solution, both cations and anions accumulate around the protein surface and the degree of Gdm⁺ accumulation is higher than that in GdmCl, suggesting the cooperativity between the cations and anions in preferential binding.

Protein Dynamics (Cont'd)

Toward the Characterization of Fractional Stochastic Processes Underlying Methyl Dynamics in Proteins

Paolo Calligari and Daniel Abergel [Ecole Normale Supérieure]

J. Phys. Chem. B., **116**, 12955–12965, 2012.

In this article, we investigate the multiple-scale structure of methyl side chain dynamics in proteins. We show that the orientational correlation functions of CH₃ methyl groups are well described by a fractional Brownian dynamics model. Typical angular correlation functions involved in NMR relaxation were computed from MD simulations performed on two different proteins. These correlation functions were shown to be very well fitted by a fractional Ornstein–Uhlenbeck process in the presence of effective local potentials at the C–H and C–C methyl bonds.

Dynamical Stability and Assembly Cooperativity of β -Sheet Amyloid Oligomers – Effect of Polarization

Yang Li, Changge Ji, Weixin Xu, and John Z.H. Zhang [East China Normal University]

J. Phys. Chem. B., **116**, 13368–13373, 2012.

The soluble intermediate oligomers of amyloidogenic proteins are suspected to be more cytotoxic than the mature fibrils in neurodegenerative disorders. Here, the dynamic stability and assembly cooperativity of a model oligomer of human islet amyloid polypeptide (hIAPP) segments were explored by means of all-atom molecular dynamics (MD) simulations under different force fields including AMBER99SB, OPLS, and polarized protein-specific charge (PPC) model. Simulation results show that the dynamic stability of β -sheet oligomers is seriously impacted by electrostatic polarization.

Interactions between lignin and urea researched by molecular simulation

Wenzhuo Li[Nanjing Forestry University] & Jianlong Wang

Molecular Simulation, **38**, 1048-1054, 2012.

Molecular simulations of interactions between urea molecules and lignin polymer have been carried out with the aim of understanding the mechanism of urea slow-release behaviours in lignin–urea materials. It has been found, by docking technology and natural bond orbital analysis, that H-bonds and π -electronic conjugation effect are the main driving forces to keep urea molecules adsorbed on the lignin. In the NPT (isothermal–isobaric ensemble) simulations, mean-squared displacement results show that water molecules can promote the urea molecules gradually away from the lignin.

Ligand Binding/Docking

Molecular Dynamics of Class A β -lactamases—Effects of Substrate Binding

Olivier Fiset, Stéphane Gagné, Patrick Lagüe [Université Laval and PROTEO and IBIS]

Biophysical Journal. **103**, 1790-1801, 2012.

The effects of substrate binding on class A β -lactamase dynamics were studied using molecular dynamics simulations of two model enzymes; 40 100-ns trajectories of the free and substrate-bound forms of TEM-1 (with benzylpenicillin) and PSE-4 (with carbenicillin) were recorded (totaling 4.0 μ s). Substrates were parameterized with the CHARMM General Force Field. In both enzymes, the Ω loop exhibits a marked flexibility increase upon substrate binding, supporting the hypothesis of substrate gating.

Ligand Binding / Docking (Cont'd)

Modeling loop backbone flexibility in receptor-ligand docking simulations

Johannes Flick, Frank Tristram and Wolfgang Wenzel
[Karlsruhe Institute of Technology]

J. Comp. Chem. **33**, 2504–2515, 2012.

The relevance of receptor conformational change during ligand binding is well documented for many pharmaceutically relevant receptors, but is still not fully accounted for in in silico docking methods. Here, we investigate an efficient multistage backbone reconstruction algorithm for large loop regions in the receptor and demonstrate that treatment of backbone receptor flexibility significantly improves binding mode prediction starting from apo structures and in cross docking simulations.

Steered molecular dynamics simulations on the binding of the appendant structure and helix- β 2 in domain-swapped human cystatin C dimer

Manli Shen [Liaoning University], Jing Guan, Linan Xu, Yuanyuan Yu, Jianwei He, Gary W. Jones & Youtao Song

J. Biomol. Stru. and Dyn., **30**, 652-661, 2012.

We have performed steered molecular dynamics (SMD) simulations to investigate the dissociation process between the appendant structure (AS) and helix- β 2 in human cystatin C dimer. Energy change during SMD showed that electrostatic interactions, including hydrogen bonds and salt bridges, were the dominant interactions to stabilize the two parts of the dimer. Furthermore, our data indicated that residues, Asn35, Asp40, Ser44, Lys75, and Arg93 play significant roles in the formation of these electrostatic interactions.

Computation of relative binding free energy for an inhibitor and its analogs binding with Erk kinase using thermodynamic integration MD simulation

Kuan-Wei Wu, Po-Chin Chen, Jun Wang, Ying-Chieh Sun
[National Taiwan Normal University]

J. Comp. Aided Mol. Des., **26**, 1159-1169, 2012.

In the present study, we carried out thermodynamic integration molecular dynamics simulation for a pair of analogous inhibitors binding with Erk kinase to investigate how computation performs in reproducing the relative binding free energy. The computation with BCC-AM1 charges for ligands gave -1.1 kcal/mol, deviated from experimental value of -2.3 kcal/mol by 1.2 kcal/mol, in good agreement with experimental result. The error of computed value was estimated to be 0.5 kcal/mol. To obtain convergence, switching vdw interaction on and off required approximately 10 times more CPU time than switching charges.

Explicit Solvent Molecular Dynamics Simulations of A β Peptide Interacting with Ibuprofen Ligands

Christopher Lockhart, Seongwon Kim, and Dmitri K. Klimov
[George Mason University, Manassas]

J. Phys. Chem. B., **116**, 12922–12932, 2012.

Using all-atom explicit water model and replica exchange molecular dynamics, we study the interactions between A β monomer and nonsteroidal anti-inflammatory drug ibuprofen, which is known to reduce the risk of Alzheimer's disease. Ibuprofen binding to A β is largely governed by hydrophobic effect, and its binding site in A β peptide is entirely composed of hydrophobic amino acids. Electrostatic interactions between negatively charged ibuprofen ligands and positively charged side chains make a relatively small contribution to binding. This outcome is explained by the competition of ligand-peptide electrostatic interactions with intrapeptide salt bridges.

Ligand Binding / Docking (Cont'd)

Identification of Cholesterol Binding Sites in the Serotonin_{1A} Receptor

Durba Sengupta [Council of Scientific and Industrial Research] and Amitabha Chattopadhyay

J. Phys. Chem. B., **116**, 12991–12996, 2012.

The serotonin_{1A} receptor is a representative member of the G protein-coupled receptor (GPCR) superfamily and serves as an important drug target in the development of therapeutic agents for neuropsychiatric disorders. Previous work has shown the requirement of membrane cholesterol in the organization, dynamics, and function of the serotonin_{1A} receptor. We show here that membrane cholesterol binds preferentially to certain sites on the serotonin_{1A} receptor by performing multiple, long time scale MARTINI coarse-grain molecular dynamics simulations.

Enzyme Catalysis

Conformational dynamics of threonine 195 and the S1 subsite in functional trypsin variants

Trevor Gokey, Teaster T. Baird Jr., Anton B. Guliaev [San Francisco State University]

J. Mol.Mod., **18**, 4941-4954, 2012.

Replacing the catalytic serine in trypsin with threonine (S195T variant) leads to a nearly complete loss of catalytic activity, which can be partially restored by eliminating the C42-C58 disulfide bond. The 0.69 μ s of combined explicit solvent MD simulations revealed continuous rearrangement of T195 with different conformational preferences between five trypsin variants tested. Among three conformational families observed for the T195 residue, one showed the T195 hydroxyl in a conformation analogous to that of the serine residue in wild-type trypsin, positioning the hydroxyl oxygen atom for attack on the carbonyl carbon of the peptide substrate.

The Catalytic Machinery of Rhomboid Proteases: Combined MD and QM Simulations

Neta Uritsky, Michael Shokhen, and Amnon Albeck [Bar Ilan University]

J. Chem. Theor. and Comp., **8**, 4663–4671, 2012.

Rhomboid proteases are a ubiquitous family of intramembrane serine proteases in prokaryotic and eukaryotic organisms that cleave membrane proteins in their transmembrane region. Their catalytic activity is centered at a His–Ser catalytic dyad. We applied molecular dynamics and quantum mechanics calculations in order to clarify the protonation state of the catalytic residues of *E. coli* GlpG rhomboid protease and how it is affected by the immersion of the enzyme in the membrane. We identified (N ϵ)H150^{dpr}_H254^{dpr}_S201^{pr} as the protonation (and H150 tautomeric) state of free GlpG in both lipid-solubilized and membrane environments.

Enzyme Catalysis (Cont'd)

How Does Pin1 Catalyze the Cis–Trans Prolyl Peptide Bond Isomerization? A QM/MM and Mean Reaction Force Study

Esteban Vöhringer-Martinez [Universidad de Concepción],
Fernanda Duarte, and Alejandro Toro-Labbé

J. Phys. Chem. B., **116**, 12972–12979, 2012.

Pin1 represents an enzyme that specifically catalyzes the isomerization of peptide bonds between phosphorylated threonine or serine residues and proline. Despite its relevance as molecular timer in a number of biological processes related to cancer and Alzheimer disease, a detailed understanding of the factors contributing to the catalysis is still missing. In this study, we employ extensive QM/MM molecular dynamics simulations in combination with the mean reaction force (MRF) to discern the influence of the enzyme on the reaction mechanism and the origin of the catalysis. As a recently introduced method, the MRF separates the activation free energy barrier to reach the transition state into structural and electronic contributions providing a more detailed description of the enzyme's function.

Molecular dynamics simulation of the gGAPDH–NAD⁺ complex from Trypanosoma cruzi

Osmair Vital de Oliveira [Universidade Federal de São Carlos], José Divino dos Santos & Luiz C.G. Freitas

Molecular Simulation, **38**, 1124–1131, 2012.

A 50-ns molecular dynamics simulation has been used to study the homotetramer of the enzyme glycosomal glyceraldehyde 3-phosphate dehydrogenase (gGAPDH) complexes, from *Trypanosoma cruzi*, with nicotinamide adenine dinucleotide (NAD⁺) cofactors in aqueous solution. The root mean square deviation indicates that the overall structure of the homotetramer does not undergo significant change. The largest structural change observed was in the NAD⁺ binding domain of subunit (chain) D; as a consequence, the NAD⁺ cofactor was dislocated from its initial position. However, the other subunits were not affected, suggesting that the gGAPDH enzyme exhibits non-cooperative behaviour.

Protein-Protein Interactions

Correlating Protein Hot Spot Surface Analysis Using ProBiS with Simulated Free Energies of Protein–Protein Interfacial Residues

Nejc Carl, Milan Hodošček, Blaž Vehar, Janez Konc, Bernard R. Brooks, and Dušanka Janežič [National Institute of Chemistry, Hajdrihova 19]

J.Chem. Infor. and Mod. **52**, 2541–2549, 2012.

A protocol was developed for the computational determination of the contribution of interfacial amino acid residues to the free energy of protein–protein binding. Thermodynamic integration, based on molecular dynamics simulation in CHARMM, was used to determine the free energy associated with single point mutations to glycine in a protein–protein interface. The hot spot amino acids found in this way were then correlated to structural similarity scores detected by the ProBiS algorithm for local structural alignment.

Membrane Proteins and Lipid Peptide Interactions

Design of Peptide-Membrane Interactions to Modulate Single-File Water Transport through Modified Gramicidin Channels

Guillem Portella, Tanja Polupanow, Florian Zocher, Danila A. Boytsov, Peter Pohl, Ulf Diederichsen, Bert L. de Groot [Max Planck Institute for Biophysical Chemistry]

Biophysical Journal. **103**, 1698-1705, 2012.

Water permeability through single-file channels is affected by intrinsic factors such as their size and polarity and by external determinants like their lipid environment in the membrane. Previous computational studies revealed that the obstruction of the channel by lipid headgroups can be long-lived, in the range of nanoseconds, and that pore-length-matching membrane mimetics could speed up water permeability. To test the hypothesis of lipid-channel interactions modulating channel permeability, we designed different gramicidin A derivatives with attached acyl chains.

Structure and Orientation of Bovine Lactoferrampin in the Mimetic Bacterial Membrane as Revealed by Solid-State NMR and Molecular Dynamics Simulation

Atsushi Tsutsumi, Namsrai Javkhlantugs, Atsushi Kira, Masako Umeyama, Izuru Kawamura, Katsuyuki Nishimura, Kazuyoshi Ueda, Akira Naito [Yokohama National University]

Biophysical Journal. **103**, 1735-1743, 2012.

Bovine lactoferrampin (LFampinB) is a newly discovered antimicrobial peptide found in the N1-domain of bovine lactoferrin (268–284), and consists of 17 amino-acid residues. It is important to determine the orientation and structure of LFampinB in bacterial membranes to reveal the antimicrobial mechanism. We therefore performed ^{13}C and ^{31}P NMR, ^{13}C - ^{31}P rotational echo double resonance (REDOR), potassium ion-selective electrode, and quartz-crystal microbalance measurements for LFampinB with mimetic bacterial membrane and molecular-dynamics simulation in acidic membrane.

Sorting of Lipidated Peptides in Fluid Bilayers: A Molecular-Level Investigation

Trevor A. Daly, Paulo F. Almeida, and Steven L. Regen [Lehigh University, Bethlehem]

J. Am. Chem. Soc., **134**, 17245–17252, 2012

Nearest-neighbor recognition (NNR) measurements have been made for two lipidated forms of GlyCys, interacting with analogues of cholesterol and 1,2-dipalmitoyl-sn-glycero-3-phosphocholine (DPPC) in the liquid-ordered (l_o) and liquid-disordered (l_d) phases. Interaction free energies that have been determined from these measurements have been used in Monte Carlo simulations to quantify the distribution of the peptides between liquid-ordered and liquid-disordered regions.

Formation and Domain Partitioning of H-ras Peptide Nanoclusters: Effects of Peptide Concentration and Lipid Composition

Zhenlong Li, Lorant Janosi, and Alemayehu A Gorfe [The University of Texas Health Science Center at Houston]

J. Am. Chem. Soc., **134**, 17278–17285, 2012.

Experiments have shown that homologous Ras proteins containing different lipid modification, which is required for membrane binding, form nonoverlapping nanoclusters on the plasma membrane. However, the physical basis for clustering and lateral organization remains poorly understood. We have begun to tackle this issue using coarse-grained molecular dynamics simulations of the H-ras lipid anchor (tH), a triply lipid-modified heptapeptide embedded in a domain-forming mixed lipid bilayer [Janosi L. et al. *Proc. Natl. Acad. Sci. U.S.A.* **2012**, 109, 8097].

Membrane Proteins and Lipid Peptide Interactions (Cont'd)

Molecular View of Phase Coexistence in Lipid Monolayers

Svetlana Baoukina, Eduardo Mendez-Villuendas, and D. Peter Tieleman [University of Calgary]

J. Am. Chem. Soc., **134**, 17543–17553, 2012.

We used computer simulations to study the effect of phase separation on the properties of lipid monolayers. This is important for understanding the lipid–lipid interactions underlying lateral heterogeneity (rafts) in biological membranes and the role of domains in the regulation of surface tension by lung surfactant. Molecular dynamics simulations with the coarse-grained MARTINI force field were employed to model large length (~80 nm in lateral dimension) and time (tens of microseconds) scales. Lipid mixtures containing saturated and unsaturated lipids and cholesterol were investigated under varying surface tension and temperature.

Fast force field-based optimization of protein–ligand complexes with graphics processor

Lennart Heinzerling, Robert Klein and Matthias Rarey [University of Hamburg, Germany]

J. Comp. Chem. **33**, 2554–2565, 2012.

Usually based on molecular mechanics force fields, the post-optimization of ligand poses is typically the most time-consuming step in protein–ligand docking procedures. In return, it bears the potential to overcome the limitations of discretized conformation models. Because of the parallel nature of the problem, recent graphics processing units (GPUs) can be applied to address this dilemma. We present a novel algorithmic approach for parallelizing and thus massively speeding up protein–ligand complex optimizations with GPUs.

Integrating Ligand-Based and Protein-Centric Virtual Screening of Kinase Inhibitors Using Ensembles of Multiple Protein Kinase Genes and Conformations

Anshuman Dixit and Gennady M. Verkhivker [Chapman University, One University Drive]

J. Chem. Infor. and Mod. **52**, 2501–2515, 2012.

The rapidly growing wealth of structural and functional information about kinase genes and kinase inhibitors that is fueled by a significant therapeutic role of this protein family provides a significant impetus for development of targeted computational screening approaches. In this work, we explore an ensemble-based, protein-centric approach that allows for simultaneous virtual ligand screening against multiple kinase genes and multiple kinase receptor conformations. We systematically analyze and compare the results of ligand-based and protein-centric screening approaches using both single-receptor and ensemble-based docking protocols.

Statistical analyses and computational prediction of helical kinks in membrane proteins

Y.-H. Huang, C.-M. Chen [National Taiwan Normal University]

J. Comp. Aided Mol. Des., **26**, 1171–1185, 2012.

We have carried out statistical analyses and computer simulations of helical kinks for TM helices in the PDBTM database. About 59 % of 1562 TM helices showed a significant kink, and 38 % of these kinks are associated with prolines in a range of ± 4 residues. Our analyses show that helical kinks are more populated in the central region of helices, particularly in the range of 1–3 residues away from the helix center. Among 1,053 helical kinks analyzed, 88 % of kinks are bends (change in helix axis without loss of helical character) and 12 % are disruptions (change in helix axis and loss of helical character).

Membrane Proteins and Lipid Peptide Interactions (Cont'd)

Molecular Dynamics Simulations of Phosphatidylcholine Membranes: A Comparative Force Field Study

Thomas J. Piggot, Ángel Piñeiro, and Syma Khalid
[University of Southampton]

J. Chem. Theor. and Comp, **8**, 4593–4609, 2012.

Molecular dynamics simulations provide a route to studying the dynamics of lipid bilayers at atomistic or near atomistic resolution. Over the past 10 years or so, molecular dynamics simulations have become an established part of the biophysicist's tool kit for the study of model biological membranes. As simulation time scales move from tens to hundreds of nanoseconds and beyond, it is timely to re-evaluate the accuracy of simulation models. We describe a comparative analysis of five freely available force fields that are commonly used to model lipid bilayers.

Molecular Dynamics Simulations of a Characteristic DPC Micelle in Water

Stéphane Abel [Commissariat à l'Energie Atomique et aux Energies Alternatives], François-Yves Dupradeau, and Massimo Marchi

J. Chem. Theor. and Comp, **8**, 4610–4623, 2012.

We present the first comparative molecular dynamics investigation for a dodecylphosphocholine (DPC) micelle performed in condensed phase using the CHARMM36, GROMOS53A6, GROMOS54A7, and GROMOS53A6/Berger force fields and a set of parameters developed anew. Our potential consists of newly derived RESP atomic charges, which are associated with the Amber99SB force field developed for proteins. This new potential is expressly designed for simulations of peptides and transmembrane proteins in a micellar environment. To validate this new ensemble, molecular dynamics simulations of a DPC micelle composed of 54 monomers were carried out in explicit water using a "self-assembling" approach.

GPU-Based Massive Parallel Kawasaki Kinetics in the Dynamic Monte Carlo Simulations of Lipid Nanodomains

Mateusz Lis, Lukasz Pital, Jerzy Swiatek, and Lukasz Cwiklik [Academy of Sciences of the Czech Republic]

J. Chem. Theor. and Comp, **8**, 4758–4765, 2012.

Multicomponent lipid membranes in the liquid phase exhibit dynamic lateral heterogeneities which play an important role in specific cell membrane functions. A GPU-based parallel algorithm for two-dimensional lattice Dynamic Monte Carlo simulations of nanodomain formation in binary lipid membranes was developed and tested. Speedups of up to 50-times over CPU-based calculations were achieved, and simulations employing lattices of up to 1800×1800 sites were performed. The existence of large nonregular lipid domains of sizes up to 160 nm was demonstrated.

Lipid Bilayers: The Effect of Force Field on Ordering and Dynamics

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

J. Chem. Theor. and Comp, **8**, 4807–4817, 2012.

The sensitivity of the structure and dynamics of a fully hydrated pure bilayer of 1,2-dipalmitoyl-sn-glycero-3-phosphocholine (DPPC) in molecular dynamics simulations to changes in force-field and simulation parameters has been assessed. Three related force fields (the Gromos 54A7 force field, a Gromos 53A6-derived parameter set and a variant of the Berger parameters) in combination with either particle-mesh Ewald (PME) or a reaction field (RF) were compared. Structural properties such as the area per lipid, carbon–deuterium order parameters, electron density profile and bilayer thicknesses, are reproduced by all the parameter sets within the uncertainty of the available experimental data.

Membrane Proteins and Lipid Peptide Interactions (Cont'd)

Accommodation of a Central Arginine in a Transmembrane Peptide by Changing the Placement of Anchor Residues

Vitaly V. Vostrikov, Benjamin A. Hall, Mark S. P. Sansom, and Roger E. Koeppe, II [University of Arkansas, Fayetteville]

J. Phys. Chem. B., **116**, 12980–12990, 2012.

Both Trp and Arg in transmembrane protein domains make important interactions with lipids at the membrane/water interface, but at different depths. Derivatives of the designed peptide GWALP23, acetyl-GGALW⁵LALALALALALW¹⁹LAGA-amide, with single Trp anchors, have proven useful for characterizing such interactions. Indeed, previous work revealed quite different effects emanating from Arg substitutions at positions 12 and 14 within GWALP23, with the R12 peptide exhibiting multiple positions and orientations with respect to DOPC bilayer membranes (Vostrikov et al. *J. Am. Chem. Soc.* **2010**, 132, 5803–5811). To gain further understanding of the multistate behavior, we moved the Trp “anchor” residues to more outer positions 3 and 21 in GWALP23 itself, and in the R12 and R14 derivatives.

Atomistic Simulations of a Multicomponent Asymmetric Lipid Bilayer

Anirban Polley, Satyavani Vemparala, and Madan Rao [C. V. Raman Avenue, Bangalore]

J. Phys. Chem. B., **116**, 13403–13410, 2012.

The cell membrane is inherently asymmetric and heterogeneous in its composition, a feature that is crucial for its function. Using atomistic molecular dynamics simulations, the physical properties of a 3-component asymmetric mixed lipid bilayer system comprising an unsaturated POPC (palmitoyl-oleoylphosphatidylcholine), a saturated PSM (palmitoylsphingomyelin), and cholesterol are investigated. Our simulations explore both the dynamics of coarsening following a quench from the mixed phase and the final phase-segregated regime obtained by equilibrating a fully segregated configuration.

Protein Folding

Prediction of Protein Relative Enthalpic Stability from Molecular Dynamics Simulations of the Folded and Unfolded States

Voichita M. Dadarlat, Lev A. Gorenstein, Carol Beth Post [Purdue University]

Biophysical Journal. **103**, 1762–1773, 2012.

For proteins of known structure, the relative enthalpic stability with respect to wild-type, $\Delta\Delta H^U$, can be estimated by direct computation of the folded and unfolded state energies. We propose a model by which the change in stability upon mutation can be predicted from all-atom molecular dynamics simulations for the folded state and a peptide-based model for the unfolded state. The unfolding enthalpies are expressed in terms of environmental and hydration-solvent reorganization contributions that readily allow a residue-specific analysis of $\Delta\Delta H^U$.

Protein Folding (Cont'd)

A Highly Compliant Protein Native State with a Spontaneous-like Mechanical Unfolding Pathway

Pétur O. Heidarsson, Immanuel Valpapuram, Carlo Camilloni, Alberto Imparato, Guido Tiana, Flemming M. Poulsen, Birthe B. Kragelund, and Ciro Cecconi [University of Modena and Reggio Emilia]

J. Am. Chem. Soc., **134**, 17068–17075, 2012.

The mechanical properties of proteins and their force-induced structural changes play key roles in many biological processes. Previous studies have shown that natively folded proteins are brittle under tension, unfolding after small mechanical deformations, while partially folded intermediate states, such as molten globules, are compliant and can deform elastically a great amount before crossing the transition state barrier. Moreover, under tension proteins appear to unfold through a different sequence of events than during spontaneous unfolding. Here, we describe the response to force of the four- α -helix acyl-CoA binding protein (ACBP) in the low-force regime using optical tweezers and ratcheted MD simulations.

Fast Photochemical Oxidation of Proteins and Mass Spectrometry Follow Submillisecond Protein Folding at the Amino-Acid Level

Jiawei Chen, Don L. Rempel, Brian C. Gau, and Michael L. Gross [Washington University in St. Louis]

J. Am. Chem. Soc., **134**, 18724–18731, 2012.

We report a study of submillisecond protein folding with amino-acid residue resolution achieved with a two-laser pump/probe experiment with analysis by mass spectrometry. The folding of a test protein, barstar, can be triggered by a laser-induced temperature jump (T jump) from $\sim 0^\circ\text{C}$ to $\sim$ room temperature. Subsequent reactions via fast photochemical oxidation of proteins (FPOP) at various fractional millisecond points after the T jump lead to oxidative modification of solvent-accessible side chains whose “protection” changes with time and extent of folding. The modifications are identified and quantified by LC-MS/MS following proteolysis.

Further Optimization of a Hybrid United-Atom and Coarse-Grained Force Field for Folding Simulations: Improved Backbone Hydration and Interactions between Charged Side Chains

Wei Han and Klaus Schulten [University of Illinois at Urbana-Champaign]

J. Chem. Theor. and Comp., **8**, 4413–4424, 2012.

PACE, a hybrid force field that couples united-atom protein models with coarse-grained (CG) solvent (*J. Chem. Theory Comput.* **2010**, 6, 3373), has been further optimized, aiming to improve its efficiency for folding simulations. Backbone hydration parameters have been reoptimized based on hydration free energies of polyalanyl peptides through atomistic simulations. Also, atomistic partial charges from all-atom force fields were combined with PACE to provide a more realistic description of interactions between charged groups.

Coarse-Grained Simulations of Protein Backbone Dynamics. 1. Local Sterics Define the Dihedral Angles

Andreas Wagenmann [Universität des Saarlandes] and Tihamér Geyer

J. Chem. Theor. and Comp., **8**, 4732–4745, 2012.

Here, we present a coarse-grained model targeted for implicit solvent simulations of unfolded or intrinsically disordered proteins. The hierarchical model with its nonspherical building blocks allows one to reproduce the local dynamics of the backbone with simple harmonic bonds and steric collisions between a small number of atoms at the correct off-center positions on the building blocks. We also describe the implementation of the global shape of the protein chain and the extended local interactions that add a first secondary structure bias, which will subsequently be augmented by additional hydrophobic interactions, hydrogen bonds, and dipole-dipole couplings along the backbone.

Protein Folding (Cont'd)

Folding of multidomain proteins: Biophysical consequences of tethering even in apparently independent folding

Oshrit Arviv and Yaakov Levy [The Weizmann Institute of Science]

Proteins: Stru. Fun. & Bioinf., **80**, 2780–2798, 2012.

Most eukaryotic and a substantial fraction of prokaryotic proteins are composed of more than one domain. The tethering of these evolutionary, structural, and functional units raises, among others, questions regarding the folding process of conjugated domains. Studying the folding of multidomain proteins *in silico* enables one to identify and isolate the tethering-induced biophysical determinants that govern crosstalks generated between neighboring domains. For this purpose, we carried out coarse-grained and atomistic molecular dynamics simulations of two two-domain constructs from the immunoglobulin-like β -sandwich fold.

Protein-Nucleic acid Interactions

Insights into the thermal stabilization and conformational transitions of DNA by hyperthermophile protein Sso7d: molecular dynamics simulations and MM-PBSA analysis

Lin Chen [Jilin University, Changchun], Qing-Chuan Zheng, Li-Ying Yu, Wen-Ting Chu, Ji-Long Zhang, Qiao Xue, Hong-Xing Zhang & Chia-Chung Sun

J. Biomol. Stru. and Dyn., **30**, 716-727, 2012.

In the assembly of DNA-protein complex, the DNA kinking plays an important role in nucleoprotein structures and gene regulation. Molecular dynamics (MD) simulations were performed on specific protein-DNA complexes in this study to investigate the stability and structural transitions of DNA depending on temperature. Furthermore, we introduced the molecular mechanics/Poisson–Boltzmann surface area (MM-PBSA) approach to analyze the interactions between DNA and protein in hyperthermophile. Focused on two specific Sso7d-DNA complexes (PDB codes: 1BNZ and 1BF4), we performed MD simulations at four temperatures (300, 360, 420, and 480 K) and MM-PBSA at 300 and 360 K to illustrate detailed information on the changes of DNA.

Nucleic Acids

Proton affinities of deoxyribonucleosides via the ONIOM-ccCA methodology

Amanda G. Riojas, Joshua R. John, T. Gavin Williams and Angela K. Wilson [University of North Texas, Denton]

J. Comp. Chem. **33**, 2590–2601, 2012.

Utilizing the recently developed ONIOM-ccCA methodology, the proton affinities (PAs) of small biomolecules (~15 nonhydrogen atoms) were determined. The ONIOM-ccCA method was used to predict the PAs of eight amine-containing molecules and these predictions were then compared with experiment. In these comparisons, a protocol for the determination of the model system size was established, and the low level method and basis set for the real system component of ONIOM-ccCA were considered. Several possible density functionals were investigated for description of the real system (low layer), including B3LYP, B97-1, B97-2, B98, BMK, M06, and M06-2X.

Nucleic Acids (Cont'd)

Binding effects of Mn^{2+} and Zn^{2+} ions on the vibrational properties of guanine-cytosine base pairs in the Watson-Crick and Hoogsteen configurations

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

J. Mol.Mod., **18**, 4781-4786, 2012.

The binding effects of Mn^{2+} and Zn^{2+} ions on the vibrational properties of guanine-cytosine base pairs have been performed using density functional theory investigations. The calculations were carried out on Watson-Crick and Hoogsteen configurations of the base pairs. We have found, that in Watson-Crick configuration, the metal is coordinated to N7 atom of guanine while, in the case of Hoogsteen configuration, the coordination is at N3 atom of guanine. We have pointed out the vibrational bands that can be used to detect the presence of metallic ions in the Watson-Crick and Hoogsteen structures.

Molecular Mechanism of preQ₁ Riboswitch Action: A Molecular Dynamics Study

Pavel Banáš, Petr Sklenovský, Joseph E. Wedekind, Jiří Šponer, and Michal Otyepka [Palacky University Olomouc]

J. Phys. Chem. B., **116**, 12721–12734, 2012.

Riboswitches often occur in the 5'-untranslated regions of bacterial mRNA where they regulate gene expression. The preQ₁ riboswitch controls the biosynthesis of a hypermodified nucleoside queuosine in response to binding the queuosine metabolic intermediate. Structures of the ligand-bound and ligand-free states of the preQ₁ riboswitch from *Thermoanaerobacter tengcongensis* were determined recently by X-ray crystallography. We used multiple, microsecond-long molecular dynamics simulations (29 μ s in total) to characterize the structural dynamics of preQ₁ riboswitches in both states.

Competitive Binding of Cations to Duplex DNA Revealed through Molecular Dynamics Simulations

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

J. Phys. Chem. B., **116**, 12946–12954, 2012.

The concept of “ion atmosphere” is prevalent in both theoretical and experimental studies of nucleic acid systems, yet the spatial arrangement and the composition of ions in the ion atmosphere remain elusive, in particular when several ionic species (e.g., Na^+ , K^+ , and Mg^{2+}) compete to neutralize the charge of a nucleic acid polyanion. Complementing the experimental study of Bai and co-workers (*J. Am. Chem. Soc.***2007**, 129, 14981), here we characterize ion atmosphere around double-stranded DNA through all-atom molecular dynamics simulations. We demonstrate that our improved parametrization of the all-atom model can quantitatively reproduce the experimental ion-count data.

Surfaces, Catalysts, and Materials Subjects

Transesterification Catalyzed by Ionic Liquids on Superhydrophobic Mesoporous Polymers: Heterogeneous Catalysts That Are Faster than Homogeneous Catalysts

Fujian Liu, Liang Wang, Qi Sun, Longfeng Zhu, Xiangju Meng, and Feng-Shou Xiao [Zhejiang University]

J. Am. Chem. Soc., **134**, 16948–16950, 2012.

Homogeneous catalysts usually show higher catalytic activities than heterogeneous catalysts because of their high dispersion of catalytically active sites. We demonstrate here that heterogeneous catalysts of ionic liquids functionalized on superhydrophobic mesoporous polymers exhibit much higher activities in transesterification to form biodiesel than homogeneous catalysts of the ionic liquids themselves. This phenomenon is strongly related to the unique features of high enrichment and good miscibility of the superhydrophobic mesoporous polymers for the reactants.

Thermodynamic Investigations Using Molecular Dynamics Simulations with Potential of Mean Force Calculations for Cardiotoxin Protein Adsorption on Mixed Self-Assembled Monolayers

Shih-Wei Hung, Pai-Yi Hsiao, Ming-Chang Lu, and Ching-Chang Chieng [National Tsing Hua University, Hsinchu]

J. Phys. Chem. B., **116**, 12661–12668, 2012.

Understanding protein adsorption onto solid surfaces is of critical importance in the field of bioengineering, especially for applications such as medical implants, diagnostic biosensors, drug delivery systems, and tissue engineering. This study proposed the use of molecular dynamics simulations with potential of mean force (PMF) calculations to identify and characterize the mechanisms of adsorption of a protein molecule on a designed surface. A set of model systems consisting of a cardiotoxin (CTX) protein and mixed self-assembled monolayer (SAM) surfaces were used as examples.

Temperature Influence on the Structure and Interfacial Properties of Surfactin Micelle: A Molecular Dynamics Simulation Study

An-Qi She, Hong-Ze Gang, and Bo-Zhong Mu [East China University of Science and Technology]

J. Phys. Chem. B., **116**, 12735–12743, 2012.

Surfactin is an efficient biosurfactant excreted by different strains of *Bacillus subtilis*. Our study provides a molecular view of the temperature dependence of the structure and the interfacial properties of un-ionized surfactin micelles. The overall size and shape, the surface area, the radial density distribution of the micelles, the conformation of the hydrocarbon chain, and the intramolecular/intermolecular hydrogen bonds formed in surfactin molecules were investigated. The micelles were mostly in sphere shapes, and the radii of surfactin micelle were estimated to be around 2.2 nm. The peptide rings occupied most of the surface of the micelles.

2. METHODOLOGY

Quantitative Structure-Activity Relations

QSAR Classification Model for Antibacterial Compounds and Its Use in Virtual Screening

Narender Singh [DoD Biotechnology High Performance Software Applications Institute], Sidhartha Chaudhury, Ruifeng Liu, Mohamed Diwan M. AbdulHameed, Gregory Tawa, and Anders Wallqvist

J.Chem. Infor. and Mod. **52**, 2559–2569, 2012.

As novel and drug-resistant bacterial strains continue to present an emerging health threat, the development of new antibacterial agents is critical. This includes making improvements to existing antibacterial scaffolds as well as identifying novel ones. The aim of this study is to apply a Bayesian classification QSAR approach to rapidly screen chemical libraries for compounds predicted to have antibacterial activity. Toward this end we assembled a data set of 317 known antibacterial compounds as well as a second data set of diverse, well-validated, non-antibacterial compounds from 215 PubChem Bioassays against various bacterial species.

Does Rational Selection of Training and Test Sets Improve the Outcome of QSAR Modeling?

Todd M. Martin [United States Environmental Protection Agency], Paul Harten, Douglas M. Young, Eugene N. Muratov, Alexander Golbraikh, Hao Zhu, and Alexander Tropsha

J.Chem. Infor. and Mod. **52**, 2570–2578, 2012.

Prior to using a quantitative structure activity relationship (QSAR) model for external predictions, its predictive power should be established and validated. In the absence of a true external data set, the best way to validate the predictive ability of a model is to perform its statistical external validation. In statistical external validation, the overall data set is divided into training and test sets. Commonly, this splitting is performed using random division. Rational splitting methods can divide data sets into training and test sets in an intelligent fashion. The purpose of this study was to determine whether rational division methods lead to more predictive models compared to random division.

Classical and 3D QSAR studies on inverse agonists of human histamine H1 receptor

Sundarapandian Thangapandian [Gyeongsang National University (GNU)], Shalini John & Keun Woo Lee

Molecular Simulation, **38**, 1143-1156, 2012.

Human histamine H1 receptor (HHR1) is one of the receptors through which histamine exerts its allergic reactions, and inhibition of this receptor is an important strategy in treatment of inflammatory diseases. In this study, classical and 3D quantitative structure–activity relationship (QSAR) studies were carried out using 36 inverse agonists of which 27 diverse compounds were used in training set. The MOE[®] and SYSTAT[®] programs were used in descriptor calculation and step-wise multiple regression analysis. A predictive and statistically significant QSAR model based on four descriptors was developed and cross-validated with the leave-one-out (LOO) method.

Molecular Dynamics

Long-Timescale Molecular Dynamics Simulations Elucidate the Dynamics and Kinetics of Exposure of the Hydrophobic Patch in Troponin C

Steffen Lindert [University of California San Diego], Peter M. Keken-Huskey, J. Andrew McCammon

Biophysical Journal. **103**, 1784-1789, 2012.

Troponin (Tn) is an important regulatory protein in the thin-filament complex of cardiomyocytes. Calcium binding to the troponin C (TnC) subunit causes a change in its dynamics that leads to the transient opening of a hydrophobic patch on TnC's surface, to which a helix of another subunit, troponin I (TnI), binds. This process initiates contraction, making it an important target for studies investigating the detailed molecular processes that underlie contraction. Here we use microsecond-timescale Anton molecular dynamics simulations to investigate the dynamics and kinetics of the opening transition of the TnC hydrophobic patch.

Design, synthesis and 3D-QSAR analysis of novel 2-hydrazinyl-4-morpholinothieno[3,2-d]pyrimidine derivatives as potential antitumor agents

Wufu Zhu, Yajing Liu, Xin Zhai, Xiao Wang, Yan Zhu, Di Wu, Hongyu Zhou, Ping Gong, Yanfang Zhao [Shenyang Pharmaceutical University]

Europ. Jou. Med. Chem., **57**, 162-175, 2012.

A series of 2-hydrazinyl-4-morpholinothieno[3,2-d]pyrimidine derivatives were synthesized and evaluated for their cytotoxic activities against five cancer cell lines. Most of them exhibited moderate to significant cytotoxic activities and high-selectivity against one or more cell lines, and nearly all of them had higher potency than positive controls against MDA-MB-231 cell line. The most promising compound **15f** showed strong cytotoxic activities against H460, HT-29 and MDA-MB-231 cell lines, which were 1.7- to 66.5-folds more active than 2-(1*H*-Indazol-4-yl)-6-((4-(methylsulfonyl)-1-piperazinyl)methyl)-4-(4-morpholinyl)thieno[3,2-d]pyrimidine(GDC-0941).

LAMBADA and InflateGRO2: Efficient Membrane Alignment and Insertion of Membrane Proteins for Molecular Dynamics Simulations

Thomas H. Schmidt and Christian Kandt [University of Bonn]

J.Chem. Infor. and Mod. **52**, 2657–2669, 2012.

At the beginning of each molecular dynamics membrane simulation stands the generation of a suitable starting structure which includes the working steps of aligning membrane and protein and seamlessly accommodating the protein in the membrane. Here we introduce two efficient and complementary methods based on pre-equilibrated membrane patches, automating these steps. Using a voxel-based cast of the coarse-grained protein, LAMBADA computes a hydrophilicity profile-derived scoring function based on which the optimal rotation and translation operations are determined to align protein and membrane.

Enhancing Conformation and Protonation State Sampling of Hen Egg White Lysozyme Using pH Replica Exchange Molecular Dynamics

Jason M. Swails and Adrian E. Roitberg [University of Florida, Gainesville]

J. Chem. Theor. and Comp, **8**, 4393–4404, 2012.

We evaluate the efficiency of the pH replica exchange molecular dynamics (pH-REMD) method proposed by Itoh et al. (Proteins**2011**, 79, 3420–3436) by using it to predict the pK_a values of the titratable residues in hen egg white lysozyme (HEWL). pK_a values predicted using pH-REMD converge significantly faster than those calculated using constant pH molecular dynamics (CpHMD). Furthermore, increasing the frequency between exchange attempts in pH-REMD simulations improves protonation and conformational state sampling.

Monte Carlo

Local Sampling in Steered Monte Carlo Simulations Decreases Dissipation and Enhances Free Energy Estimates via Nonequilibrium Work Theorems

Riccardo Chelli [Università di Firenze]

J. Chem. Theor. and Comp., **8**, 4040–4052, 2012.

Configurational freezing (J. Chem. Theory Comput.**2011**, 7, 582) is a method devised for steered Monte Carlo simulations aimed at improving free energy estimates via nonequilibrium work theorems (see Jarzynski in Phys. Rev. Lett.**1997**, 78, 2690 and Crooks in J. Stat. Phys.**1998**, 90, 1481). The basic idea is to limit the sampling to particles located in the region of space where dissipation occurs, while leaving the other particles fixed. Therefore, the method is based on the reasonable assumption that dissipation is a local phenomenon in single-molecule nonequilibrium processes, a statement which holds for many processes including, for example, folding of biopolymers and protein–ligand binding/unbinding.

QM and QM/MM

Quantum chemical study in the direction to design efficient donor-bridge-acceptor triphenylamine sensitizers with improved electron injection

Ahmad Irfan [King Khalid University], Abdullah G. Al-Sehemi

J. Mol.Mod., **18**, 4893-4900, 2012.

The ground state geometries have been computed by using density functional theory. The excitation energies for dye sensitizers were performed by using time dependant density functional theory. The polarizable continuum model (PCM) has been used for evaluating bulk solvent effects at all stages. The calculations have been carried out in methanol according to the experimental set up. The long-range-corrected functional (PCM-TD-LC-BLYP) underestimate the absorption spectrum of parent molecule while PCM-TDBHandHLYP is in good agreement with the experimental data.

Dehydration of a polyether type extraction agent and of the corresponding K^+ complex: insights into liquid-liquid extraction mechanisms by quantum chemical methods

Mário Valente, Sérgio Filipe Sousa, Alexandre L. Magalhães, Cristina Freire [Faculdade de Ciências da Universidade do Porto]

J. Mol.Mod., **18**, 4909-4915, 2012.

In this paper we report a quantum chemical study performed at the B3LYP/6-311G++(d,p) level of theory on structural and energetic aspects of the sequential dehydration of a tetra-hydrated polyethylene-glycol type podand (1,2-bis-{2-[2-(2-methoxy-ethoxy)-ethoxy]-benzene, hereafter b33) and its complex with the K^+ cation. Thermodynamical parameters were determined by hessian quantum calculations performed using a self-consistent reaction field (SCRF) method, taking into account solvent (dichloromethane) effects. The results allowed the estimation of dehydration enthalpies, entropies and free energies for the hydrated free b33 podand and its corresponding K^+ cation complex in dichloromethane.

QM and QM/MM (Cont'd)

Correlation between biological activity and binding energy in systems of integrin with cyclic RGD-containing binders: a QM/MM molecular dynamics study

Mingli Xiang [Sichuan University], Yuchun Lin, Gu He, Lijuan Chen, Mingli Yang, Shengyong Yang, Yirong Mo

J. Mol.Mod., **18**, 4917-4927, 2012.

We here report a combined quantum mechanical/molecular mechanical (QM/MM) molecular dynamics (MD) study on the binding interactions between the $\alpha_v\beta_3$ integrin and eight cyclic arginine-glycine-aspartate (RGD) containing peptides. The initial conformation of each peptide within the binding site of the integrin was determined by docking the ligand to the reactive site of the integrin crystal structure with the aid of docking software FRED. The subsequent QM/MM MD simulations of the complex structures show that these eight cyclic RGD-peptides have a generally similar interaction mode with the binding site of the integrin to the cyclo(RGDf-N[M]V) analog found in the crystal structure.

Asymptotic Expansion for Electrostatic Embedding Integrals in QM/MM Calculations

Aurelio Alvarez-Ibarra [CINVESTAV, Avenida Instituto Politécnico Nacional 2508], Andreas M. Köster, Rui Zhang, and Dennis R. Salahub

J. Chem. Theor. and Comp., **8**, 4232–4238, 2012.

In QM/MM studies with large MM regions, the calculation of electrostatic embedding integrals can become a computational bottleneck. To overcome this problem, an asymptotic expansion for nuclear attraction-type integrals is developed. As a result, the long-range interactions between the QM and MM atoms reduce to atom-centered multipole moment-like expansions. The algorithm uses a natural spatial division of the molecular structure. To further improve the computational performance, a cutoff radius for the multipole moment-like expansion is introduced. The new code was validated and benchmarked with deMon2k/CHARMM QM/MM calculations on an RNA polymerase II model with almost 350 000 atoms.

A Modified QM/MM Hamiltonian with the Self-Consistent-Charge Density-Functional-Tight-Binding Theory for Highly Charged QM Regions

Guanhua Hou, Xiao Zhu, Marcus Elstner, and Qiang Cui [University of Wisconsin, Madison]

J. Chem. Theor. and Comp., **8**, 4293–4304, 2012.

To improve the description of electrostatic interaction between QM and MM atoms when the QM is SCC-DFTB, we adopt a Klopman–Ohno (KO) functional form which considers the finite size of the QM and MM charge distributions. Compared to the original implementation that used a simple Coulombic interaction between QM Mulliken and MM point charges, the KO-based QM/MM scheme takes the charge penetration effect into consideration and therefore significantly improves the description of QM/MM interaction at short range, especially when the QM region is highly charged. To be consistent with the third-order formulation of SCC-DFTB, the Hubbard parameter in the KO functional is dependent on the QM charge.

QM and QM/MM (Cont'd)

Solvent Boundary Potentials for Hybrid QM/MM Computations Using Classical Drude Oscillators: A Fully Polarizable Model

Eliot Boulanger and Walter Thiel [Max-Planck-Institut für Kohlenforschung]

J. Chem. Theor. and Comp., **8**, 4527–4538, 2012.

Accurate quantum mechanical/molecular mechanical (QM/MM) treatments should account for MM polarization and properly include long-range electrostatic interactions. We report on a development that covers both these aspects. Our approach combines the classical Drude oscillator (DO) model for the electronic polarizability of the MM atoms with the generalized solvent boundary Potential (GSBP) and the solvated macromolecule boundary potential (SMBP). These boundary potentials (BP) are designed to capture the long-range effects of the outer region of a large system on its interior.

Effects of Dispersion in Density Functional Based Quantum Mechanical/Molecular Mechanical Calculations on Cytochrome P450 Catalyzed Reactions

Richard Lonsdale, Jeremy N. Harvey, and Adrian J. Mulholland [University of Bristol]

J. Chem. Theor. and Comp., **8**, 4637–4645, 2012.

Density functional theory (DFT) based quantum mechanical/molecular mechanical (QM/MM) calculations have provided valuable insight into the reactivity of the cytochrome P450 family of enzymes (P450s). A failure of commonly used DFT methods, such as B3LYP, is the neglect of dispersion interactions. An empirical dispersion correction has been shown to improve the accuracy of gas phase DFT calculations of P450s. The current work examines the effect of the dispersion correction in QM/MM calculations on P450s.

Computational Study of Absorption Spectra of the Photoconvertible Fluorescent Protein EosFP in Different Protonation States

Petra Imhof [University of Heidelberg]

J. Chem. Theor. and Comp., **8**, 4828–4836, 2012.

Absorption spectra of the green-to-red convertible fluorescent protein EosFP have been computed in a hybrid quantum mechanical/molecular mechanical (QM/MM) framework. The experimentally observed absorption maximum at ~390 nm is well reproduced by the protein with a neutral chromophore, and the anionic form is computed to absorb close to the experimentally determined maximum at ~500 nm. Absorption of a zwitterionic form is calculated to lie in the same spectral region; however, this species cannot be unambiguously assigned to the experimental spectra.

Amino Acid Tautomerization Reactions in Aqueous Solution via Concerted and Assisted Mechanisms Using Free Energy Curves from MD Simulation

Santiago Tolosa [Universidad de Extremadura], Antonio Hidalgo, and Jorge A. Sansón

J. Phys. Chem. B., **116**, 13033–13044, 2012.

A theoretical study is described of chemical reactions in solution by means of molecular dynamics simulations, with solute–solvent interaction potentials derived from AMBER van der Waals parameters and QM/MM electrostatic charges in solution. The solvent is used as the reaction coordinate, and the free energy curves to calculate the properties related to the reaction mechanism. The proposed scheme is applied to the tautomerization process in aqueous solution for some amino acids H₂NCHR–COOH (with R = H being glycine, R = CH₃ alanine, R = CH₂OH serine, and R = CH₂COOH aspartic acid), focusing on the role of the solvent in the reaction (assisted versus unassisted mechanisms) and on the effect of the hydrophilic/hydrophobic character of the radical R on the activation and reaction energies.

Comparative or Homology Modeling

Modeling of Open, Closed, and Open-Inactivated States of the hERG1 Channel: Structural Mechanisms of the State-Dependent Drug Binding

Serdar Durdagi, Sumukh Deshpande, Henry J Duff, and Sergei Y. Noskov [University of Calgary, Alberta]

J.Chem. Infor. and Mod. **52**, 2760–2774, 2012.

The human ether-a-go-go related gene 1 (hERG1) K ion channel is a key element for the rapid component of the delayed rectified potassium current in cardiac myocytes. Since there are no crystal structures for hERG channels, creation and validation of its reliable atomistic models have been key targets in molecular cardiology for the past decade. In this study, we developed and vigorously validated models for open, closed, and open-inactivated states of hERG1 using a multistep protocol. The conserved elements were derived using multiple-template homology modeling utilizing available structures for Kv1.2, Kv1.2/2.1 chimera, and KcsA channels.

Computational Analysis of Human OGA Structure in Complex with PUGNAc and NAG-Thiazoline Derivatives

Nelson Alberto N. de Alencar, Paulo Robson M. Sousa, José Rogério A. Silva, Jerônimo Lameira [Universidade Federal do Pará], Cláudio Nahum Alves, Sergio Martí, and Vicent Moliner

J.Chem. Infor. and Mod. **52**, 2775–2783, 2012.

The substitution of serine and threonine residues in nucleocytoplasmic proteins with 2-acetamido-2-deoxy- β -d-glucopyranose (O-GlcNAc) residues is an essential post-translational modification found in many multicellular eukaryotes. O-glycoprotein 2-acetamido-2-deoxy- β -d-glucopyranosidase (O-GlcNAcase) hydrolyzes O-GlcNAc residues from post-translationally modified serine/threonine residues of nucleocytoplasmic protein. O-GlcNAc has been implicated in several disease states such as cancer, Alzheimer's disease, and type II diabetes. For this paper, a model of the human O-GlcNAcase (hOGA) enzyme based on the X-ray structures of bacterial *Clostridium perfringens* (CpNagJ) and *Bacteroides thetaiotaomicrometer* (BtOGA) homologues has been generated through molecular homology modeling.

Ligand Docking

Application of docking-based comparative intermolecular contacts analysis to validate Hsp90 α docking studies and subsequent in silico screening for inhibitors

Mahmoud A. Al-Sha'er [Zarqa University], Mutasem O. Taha

J. Mol.Mod., **18**, 4843-4863, 2012.

Heat shock protein (Hsp90 α) has been recently implicated in cancer, prompting several attempts to discover and optimize new Hsp90 α inhibitors. Towards this end, we docked 83 diverse Hsp90 α inhibitors into the ATP-binding site of this chaperone using several docking-scoring settings. Subsequently, we applied our newly developed computational tool—docking-based comparative intramolecular contacts analysis (dbCICA)—to assess the different docking conditions and select the best settings. dbCICA is based on the number and quality of contacts between docked ligands and amino acid residues within the binding pocket.

Ligand Docking (Cont'd)

Structural insights into interacting mechanism of ID1 protein with an antagonist ID1/3-PA7 and agonist ETS-1 in treatment of ovarian cancer: molecular docking and dynamics studies

Kannan Muthu, Manivel Panneerselvam, Muthukumaran Jayaraman, Nishith Saurav Topno, Arindam Atanu Das, Krishna Ramadas [Pondicherry University]

J. Mol.Mod., 18, 4865-4884, 2012.

Among the many abnormally expressed proteins in ovarian cancer, the prominent cancer in women, ID1 (inhibitors of DNA binding protein 1) is a potential one among other several targets. Interaction of ID1 with ETS-1 (transcriptional activator of p16^{INK4a}) suppresses the transcription of p16^{INK4a} and causes abnormal cell proliferation. A peptide aptamer (ID1/3-PA7) has been designed to prevent this interaction and thereby leading to the transcription of p16^{INK4a}. However, the structural basis behind the molecular interaction of ID1 with ETS-1 (agonist) and ID1/3-PA7 (antagonist) is poorly understood. In order to understand this structural recognition and their interaction mechanism, in silico methods were used.

Docking and DFT Studies to explore the Topoisomerase II ATP Pocket employing 3-Substituted 2,6-Piperazindiones for drug design

J. Correa-Basurto [Escuela Superior de Medicina IPN], F. R. Ramos-Morales, M. H. Matus, M. C. Rosales-Hernández, T. Mancilla-Percino, J. Trujillo-Ferrara & I. Ilizaliturri-Flores

Molecular Simulation, 38, 1072-1084, 2012.

Topoisomerases (Topos) are very important protein targets for drug design in cancer treatment. Human Topo type II α (hTopo II α) has been widely studied experimentally and theoretically. Here, we performed protein rigid/flexible side-chain docking to study a set of thirty-nine 3-substituted-2,6-piperazindiones (labelled **1a**, (R)-[(2-20)**a**] and (S)-[(2-20)**b**]) derived from α -amino acids. To explain the ligand-protein complexes at the electronic level [using the highest occupied and the lowest unoccupied molecular orbitals (HOMO and LUMO) energies], density functional theory calculations were carried out. Finally, to show adenosine triphosphate (ATP) binding-site constituents, the Q-SiteFinder program was used.

3. JOURNAL REVIEWS

Journal of Computational Chemistry, 33(31), December, 2012.

- 2451–2468 **Extension of the CHARMM general force field to sulfonyl-containing compounds and its utility in biomolecular simulations**, Wenbo Yu, Xibing He, Kenno Vanommeslaeghe and Alexander D. MacKerell Jr. [University of Maryland]

Presented is an extension of the CHARMM General Force Field (CGenFF) to enable the modeling of sulfonyl-containing compounds. Model compounds containing chemical moieties such as sulfone, sulfonamide, sulfonate, and sulfamate were used as the basis for the parameter optimization.

- 2469–2482 **A reliable and efficient first principles-based method for predicting pK_a values. 4. organic bases**, Shuming Zhang [University of Arkansas, Fayetteville]

The ionization (dissociation) constant (pK_a) is one of the most important properties of a drug molecule. It is reported that almost 68% of ionized drugs are weak bases. To be able to predict accurately the pK_a value(s) for a drug candidate is very important, especially in the early stages of drug discovery, as calculations are much cheaper than determining pK_a values experimentally. In this study, we derive two linear fitting equations ($pK_a = a \times \Delta E + b$; where a and b are constants and ΔE is the energy difference between the cationic and neutral forms, i.e., $\Delta E = E_{\text{neutral}} - E_{\text{cationic}}$) for predicting pK_as for organic bases in aqueous solution based on a training/test set of almost 500 compounds using our previously developed protocol (OLYP/6-311+G**//3-21G(d) with the the conductor-like screening model solvation model, water as solvent; see Zhang, Baker, Pulay, J. Phys. Chem. A **2010**, 114, 432).

- 2483–2491 **Efficient sampling of protein conformational space using fast loop building and batch minimization on highly parallel computers**, Michael D. Tyka [University of Washington, Seattle], Kenneth Jung and David Baker

See Applications / Protein Confirmation Analysis.

- 2492–2497 **Relationship between dye–iodine binding and cell voltage in dye-sensitized solar cells: A quantum-mechanical look**, Abu Md. Asaduzzaman, Guy A. G. Chappellaz and Georg Schreckenbach [University of Manitoba, Winnipeg]

It has been proposed that iodine binding to dyes may actually decrease the cell efficiency of a dye-sensitized solar cell. A previous experimental study showed that a two-atom change from oxygen to sulfur increased recombination of iodine with injected electrons by a factor of approximately 2. Here, it is shown that iodine binding is a plausible explanation for this effect.

- 2498–2503 **The valence and Rydberg excited states of CH₂: A theoretical exploration**, Bu-Tong Li [Shanxi Normal University], Zi-Zhang Wei and Hai-Shun Wu

Using the completed active space second-order perturbation (CASPT2) method, valence and Rydberg excited states of CH₂ molecule are probed with the large atomic natural orbital (ANO-L) basis set. Five states are optimized and the geometric parameters are in good agreement with the available data in literatures, furthermore, the state of 2¹B₁ is obtained for the first time.

- 2504–2515 **Modeling loop backbone flexibility in receptor-ligand docking simulations**, Johannes Flick, Frank Tristram and Wolfgang Wenzel [Karlsruhe Institute of Technology]

See Applications / Ligand Binding.

- 2516–2525 **Comprehensive method based on model free method and IKP method for evaluating kinetic parameters of solid state reactions**, Yunqing Han, Tianxiang Li and Kozo Saito [University of Kentucky, Lexington]

This article presents, firstly, a short review of methods for evaluating kinetic parameters of solid state reactions and a critical analysis of the isoconversional principle of model free methods. It shows theoretically that the activation energy for complex reactions is not only a function of the reaction degree but also of heating programs, and points out that any method that attempts to extract the dependences of activation energy on conversion degree without considering the dependences of heating programs is problematic.

Journal of Computational Chemistry, 33(32), December, 2012.

- 2533–2543 **A QTAIM-based energy partitioning for understanding the physical origin of conformational preferences: Application to the Z effect in O=C-X-R and related units**, David Ferro-Costas, Nicolás Otero, Ana M. Graña and Ricardo A. Mosquera [Universidade de Vigo]

A quantum theory of atoms in molecules-based energy partitioning was carried out for **Z** and **E** conformers of a series of O=C-X-R containing compounds.

- 2544–2553 **Static hyperpolarizability of the van der Waals complex CH₄—N₂**, Yulia N. Kalugina, Mikhail A. Buldakov and Victor N. Cherepanov [Tomsk State University]

The static first hyperpolarizability of the van der Waals CH₄—N₂ complex was calculated. The calculations were carried out in the approximation of the rigid interacting molecules for a broad range of intermolecular separations ($R = 6\text{--}40\ a_0$) and for six configurations at CCSD(T) level of theory using the correlation consistent aug-cc-pVTZ basis set with the basis set superposition error correction.

- 2554–2565 **Fast force field-based optimization of protein–ligand complexes with graphics processor**, Lennart Heinzerling, Robert Klein and Matthias Rarey [University of Hamburg, Germany]

See Applications / Membrane proteins.

- 2566–2580 **Effect of atomic charge, solvation, entropy, and ligand protonation state on MM-PB(GB)SA binding energies of HIV protease**, Daniel P. Oehme, Robert T. C. Brownlee and David J. D. Wilson [La Trobe University, Bundoora]

See Applications / Medicinal Chemistry and Drug Design.

- 2581–2589 **Accelerating VASP electronic structure calculations using graphic processing units**, Mohamed Hacene, Ani Anciaux-Sedrakian, Xavier Rozanska, Diego Klahr, Thomas Guignon and Paul Fleurat-Lessard [IFP Energies Nouvelles]

We present a way to improve the performance of the electronic structure Vienna Ab initio Simulation Package (VASP) program. We show that high-performance computers equipped with graphics processing units (GPUs) as accelerators may reduce drastically the computation time when offloading these sections to the graphic chips.

- 2590–2601 **Proton affinities of deoxyribonucleosides via the ONIOM-ccCA methodology**, Amanda G. Riojas, Joshua R. John, T. Gavin Williams and Angela K. Wilson [University of North Texas, Denton]

See Applications / Nucleic Acids.

Journal of Molecular Modeling, 18(11), November, 2012.

- 4761-4780 **A comparative proteomic approach to analyse structure, function and evolution of rice chitinases: a step towards increasing plant fungal resistance**, Kishore Sarma, Budheswar Dehury, Jagajjit Sahu, Ranjan Sarmah, Smita Sahoo, Mousumi Sahu, Priyabrata Sen, Mahendra Kumar Modi, Madhumita Barooah [Assam Agricultural University]

Glycoside hydrolase family 19 chitinases (EC 3.2.1.14) widely distributed in plants, bacteria and viruses catalyse the hydrolysis of chitin and play a major role in plant defense mechanisms and development. Rice possesses several classes of chitinase, out of which a single structure of class I has been reported in PDB to date. In the present study an attempt was made to gain more insight into the structure, function and evolution of class I, II and IV chitinases of GH family 19 from rice.

- 4781-4786 **Binding effects of Mn^{2+} and Zn^{2+} ions on the vibrational properties of guanine-cytosine base pairs in the Watson-Crick and Hoogsteen configurations**, Cristian Morari, Diana Bogdan, Cristina M. Muntean [National Institute for Research and Development of Isotopic and Molecular Technologies]

See Applications / Nucleic Acids.

- 4787-4795 **Theoretical study on the mechanism of cycloaddition reaction between silylene silylene($H_2Si=Si:$) and acetaldehyde**, Xiuhui Lu [University of Jinan, Jinan], Leyi Shi, Hua Ji

The mechanism of the cycloaddition reaction between singlet silylene silylene ($H_2Si=Si:$) and acetaldehyde has been investigated with CCSD(T)//MP2/6-31G* and CCSD(T)//MP2/6-31G** method, from the potential energy profile, we could predict that the reaction has three competitive dominant reaction pathways.

- 4797-4810 **Validation of computational approach to study monomer selectivity toward the template Gallic acid for rational molecularly imprinted polymer design**, Sushma Pardeshi, Rajendra Patrikar, Rita Dhodapkar, Anupama Kumar [Visvesvaraya National Institute of Technology]

See Applications / Medicinal Chemistry and Drug Design.

- 4811-4818 **Thermal conductivity of silicon and carbon hybrid monolayers: a molecular dynamics study**, Lin Wang, Huai Sun [Shanghai Jiao Tong University]

Thermal conductivities of graphene-like silicon and carbon hybrid nanostructures with silicon atom percentages varying from 0 % (graphene) to 100 % (silicene) are investigated using the reserve non-equilibrium molecular dynamic (RNEMD) method and Tersoff bond order potentials.

- 4819-4830 **Computational investigation of the adsorption of carbon dioxide onto zirconium oxide clusters**, Pascal Boulet [Aix-Marseille Université et CNRS], Christina Knöfel, Bogdan Kuchta, Virginie Hornebecq, Philip L. Llewellyn

A theoretical investigation of the adsorption of CO₂ onto ZrO₂ is presented. Various cluster models were used to mimic different basic and acidic sites on the surface. The method used was the density functional theory with the generalized gradient approximation and including Grimme's empirical model in order to properly describe the weak interactions that may occur between the adsorbate and the surface.

- 4831-4841 **Charge transfer in TATB and HMX under extreme conditions**, Chaoyang Zhang [China Academy of Engineering Physics (CAEP)], Yu Ma, Daojian Jiang

Charge transfer is usually accompanied by structural changes in materials under different conditions. However, the charge transfer in energetic materials that are subjected to extreme conditions has seldom been explored by researchers. In the work described here, the charge transfer in single molecules and unit cells of the explosives TATB and HMX under high temperatures and high pressures was investigated by performing static and dynamic calculations using three DFT methods, including the PWC functional of LDA, and the BLYP and PBE functionals of GGA.

- 4843-4863 **Application of docking-based comparative intermolecular contacts analysis to validate Hsp90 α docking studies and subsequent in silico screening for inhibitors**, Mahmoud A. Al-Sha'er [Zarqa University], Mutasem O. Taha

See Methodology / Ligand Docking.

- 4865-4884 **Structural insights into interacting mechanism of ID1 protein with an antagonist ID1/3-PA7 and agonist ETS-1 in treatment of ovarian cancer: molecular docking and dynamics studies**, Kannan Muthu, Manivel Panneerselvam, Muthukumaran Jayaraman, Nishith Saurav Topno, Arindam Atanu Das, Krishna Ramadas [Pondicherry University]

See Methodology / Ligand Docking.

- 4885-4891 **Computational study of Au₄ cluster on a carbon nanotube with and without defects using QM/MM methodology**, Diana Barraza-Jimenez [Centro de Investigacion en Alimentacion y Desarrollo A.C. Unidad Delicias], D. H. Galvan, Alvaro Posada-Amarillas, Manuel Alberto Flores-Hidalgo, Daniel Glossman-Mitnik, Miguel Jose-Yacaman

See Applications / Carbon Nanoparticles.

- 4893-4900 **Quantum chemical study in the direction to design efficient donor-bridge-acceptor triphenylamine sensitizers with improved electron injection**, Ahmad Irfan [King Khalid University], Abdullah G. Al-Sehemi

See Methodology / QM and QM/MM.

- 4901-4907 **Effect of dehydrogenation/hydrogenation on the linear and nonlinear optical properties of Li@porphyrins**, Heng-Qing Wu, Shi-Ling Sun, Rong-Lin Zhong, Hong-Liang Xu, Zhong-Min Su [Northeast Normal University]

In the present work, Li@porphyrins and their derivatives were designed in order to explore the effect of dehydrogenation/hydrogenation on linear and nonlinear optical properties. Their stable structures were obtained by the M06-2X method.

- 4909-4915 **Dehydration of a polyether type extraction agent and of the corresponding K⁺ complex: insights into liquid-liquid extraction mechanisms by quantum chemical methods**, Mário Valente, Sérgio Filipe Sousa, Alexandre L. Magalhães, Cristina Freire [Faculdade de Ciências da Universidade do Porto]

See Methodology / QM and QM/MM.

- 4917-4927 **Correlation between biological activity and binding energy in systems of integrin with cyclic RGD-containing binders: a QM/MM molecular dynamics study**, Mingli Xiang [Sichuan University], Yuchun Lin, Gu He, Lijuan Chen, Mingli Yang, Shengyong Yang, Yirong Mo

See Methodology / QM and QM/MM.

- 4929-4939 **The structural, electronic, and optical properties of ladder-type polyheterofluorenes: a theoretical study**, Chao Zheng, Ye Tao, Jin-Zhu Cao, Run-Feng Chen, Ping Zhao, Xiao-Jun Wu, Wei Huang [Nanjing University of Posts & Telecommunications]

The ladder-type polyheterofluorenes were investigated theoretically by using density functional theory (DFT) to reveal their optical and electronic properties for applications in organic optoelectronic devices.

- 4941-4954 **Conformational dynamics of threonine 195 and the S1 subsite in functional trypsin variants**, Trevor Gokey, Teaster T. Baird Jr., Anton B. Guliaev [San Francisco State University]

See Applications / Enzyme Catalysis.

Molecular Simulation, 38(13), 2012.

- 1032-1037 **Brittle ductile transition in carbon nanotube bundles**, Charles F. Cornwell [US Army Engineer Research and Development Center] & Charles R. Welch

See Applications / Carbon Nanoparticles.

- 1038-1047 **The effects of structural parameters of zeolite on the adsorption of hydrogen: a molecular simulation study**, Mahmoud Rahmati [Amirkabir University of Technology (Tehran Polytechnic)] & Hamid Modarress

See Applications / Zeolites.

- 1048-1054 **Interactions between lignin and urea researched by molecular simulation**, Wenzhuo Li [Nanjing Forestry University] & Jianlong Wang

See Applications / Protein Dynamics.

- 1055-1060 **Effect of thiol-functionalised silica on cisplatin adsorption**, Andres Díaz Compañy [Universidad Nacional del Sur], Graciela Brizuela & Sandra Simonetti

See Applications / Host-Guest Systems.

- 1061-1071 **Theoretical investigation of the use of doped graphene as a membrane support for effective CO removal in hydrogen fuel cells**, D. J. Durbin [Royal Military College of Canada] & C. Malardier-Jugroot

Carbon monoxide poisoning of the anode catalyst is currently a big problem facing the use of hydrogen fuel cells. This study uses density functional theory to model the interaction between a filter membrane and carbon monoxide to optimise the removal of CO from the H₂ feed gas.

- 1072-1084 **Docking and DFT Studies to explore the Topoisomerase II ATP Pocket employing 3-Substituted 2,6-Piperazindiones for drug design**, J. Correa-Basurto [Escuela Superior de Medicina IPN], F. R. Ramos-Morales, M. H. Matus, M. C. Rosales-Hernández, T. Mancilla-Percino, J. Trujillo-Ferrara & I. Ilizaliturri-Flores

See Methodology / Ligand Docking.

- 1085-1093 **Simulations of nuclear spin relaxation in liquid acetonitrile**, J. T. Gerig [University of California-Santa Barbara]

Molecular dynamics simulations at 298 and 273 K were carried out in order to explore the ability of calculations to predict NMR spin-lattice relaxation rates of the protons of liquid acetonitrile.

- 1094-1102 **Changes in CNT-confined water structural properties induced by the variation in water molecule orientation**, Ximing Wu [Nanjing University of Technology], Linghong Lu, Yudan Zhu, Mingjie Wei, Xiaojing Guo & Xiaohua Lu

See Applications / Carbon Nanoparticles.

- 1103-1113 **Intermolecular electrostatics via molecular fragmentation: an application to crystal structure prediction**, Matthew Habgood [University College London]

Molecular fragmentation is an attractive approach to the simulation of large molecules, in which calculations are carried out on small segments of the molecule, achieving linear scaling but reduced accuracy. Its application to crystal structure prediction (CSP) is challenged by high accuracy requirements. In this study, the applicability of a fragmentation scheme is tested for distributed multipoles, which are used in CSP to model intermolecular electrostatic interactions.

- 1114-1123 **Confined fluids in a Janus pore: influence of surface asymmetry on structure and solvation forces**, Ateeque Malani [, Indian Institute of Science, Bangalore] & K. G. Ayappa

Density distribution, fluid structure and solvation forces for fluids confined in Janus slit-shaped pores are investigated using grand canonical Monte Carlo simulations.

- 1124-1131 **Molecular dynamics simulation of the gGAPDH–NAD⁺ complex from Trypanosoma cruzi**, Osmair Vital de Oliveira [Universidade Federal de São Carlos], José Divino dos Santos & Luiz C.G. Freitas

See Applications / Enzyme Catalysis.

- 1132-1142 **Docking and molecular dynamics studies of new potential inhibitors of the human epidermal receptor 2**, Wilian Augusto Cortopassi [Pontifical Catholic University of Rio de Janeiro], Rafael José Cavaliere Feital, Diogo de Jesus Medeiros, Teobaldo Ricardo Cuya Guizado, Tanos Celmar Costa França & André Silva Pimentel

See Applications / Medicinal Chemistry and Drug Design.

- 1143-1156 **Classical and 3D QSAR studies on inverse agonists of human histamine H1 receptor**, Sundarapandian Thangapandian [Gyeongsang National University (GNU)], Shalini John & Keun Woo Lee

See Methodology / QSAR.

- 1157-1168 **Shear rate dependence of free energy barrier height for phenyl ring rotations in polystyrene based on non-equilibrium molecular dynamics simulations**, Wen-Yen Chang [National Tsing Hua University] & Rong-Yeu Chang

Polystyrene properties are influenced by ring motions in side groups. The main chain conformation and interaction with the surroundings dominate the ring rotations. It is known that shear flow affects linear chain conformation and molecular distribution. However, shear-induced variations in the ring rotations have yet to be studied. This study presents a shear flow system of polystyrene via non-equilibrium molecular dynamics simulations.

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