COMP 1

The effects of active site solvation and protein conformational flexibility on protein-ligand binding

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Both the distribution and free energies of solvent molecules and the induced fit conformation of the protein receptor have a profound effect upon the thermodynamics of protein-ligand binding. We will discuss a methodology to map out the distribution of quasi-localized water clusters, based on molecular dynamics simulations, in the active site, and to assign these water clusters excess enthalpies and entropies in relation to bulk solvent. Displacement of these water molecules is a principal driving force of ligand binding, and the method described above can thus be used to approximately compute differential ligand binding in the receptor, based on displacement of water molecules by the ligand. Such estimates can be combined with other scoring terms, including estimates of protein reorganization energy due to induced fit effects, to provide a comprehensive description of ligand binding thermodynamics. Our most recent methods achieve an average error of 1 kcal/mole for on the order of 30 targets, with the data set comprising 700 complexes in all.

COMP 2

Gated binding of ligands to proteins

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The binding of a ligand to a protein often requires that the protein adopt an "open binding site" conformation. The kinetics of binding can therefore be coupled to the kinetics of the conformational transitions of the protein. This talk will outline a number of such situations that have been studied by computer simulation, including substrate and inhibitor (drug) binding to enzymes. More information, including images and animations, can be found at http://mccammon.ucsd.edu/

COMP 3

Following biomolecular recognition and association at the microsecond/atomic scale

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Fundamental questions on biomolecular recognition and association are addressed by

microsecond explicit solvent molecular dynamics simulations of a de novo design test system.

To improve sampling statistics and capture rare/transient events multiple independent simulations

are also employed, together with novel techniques that allow enhancing searching and sampling

of the potential energy surface. Computer simulations provide relevant insight to understand the

relationship among peptide folding, crowding, and association. The search problem in biomolecular

recognition and association can be overcome by using accurate computer simulations, if sufficient

sampling statistics is achieved. The results are discussed in the more general case of biological

protein-protein association.

COMP 4

Dynamics and conformational changes in DNA-binding proteins

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Dynamics of proteins are closely related to their functions. We present two examples of DNA-binding proteins showing the link between dynamics and conformational changes upon DNA binding. The first example is restriction endonuclease EcoO109I that cleaves DNA with a specific sequence pattern. EcoO109I undergoes large conformational changes of the backbone upon DNA binding. Molecular dynamics simulations of EcoO109I in the DNA-free form indicate that this enzyme is considerably flexible and its intrinsic dynamics are suitable for the functional motions upon DNA binding. The second example is a DNA-binding domain of transcription factor PhoB. In contrast to EcoO109I, PhoB undergoes no significant conformational change in its backbone upon DNA binding. Instead, dynamics of side chains are significantly altered upon DNA binding, shown by molecular dynamics simulations and NMR experiments. Even in the DNA-free form, side-chain conformations similar to the DNA-bound form already exist prior to DNA binding. DNA binding shifts population toward the DNA-bound side-chain conformations. This clearly corresponds to the so-called population-shift mechanism.

COMP 5

Functionally important conformations of enzymes are populated by rapid thermal fluctuations

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The large-scale conformational changes in proteins are often related to their function. These changes can be induced by the interaction with a ligand or another protein. The key challenges are to understand how the binding of a substrate leads to large-scale protein motions and to determine the corresponding mechanistic pathway as well as the energetics of the conformational change. In this talk, we will discuss the application of the potential of mean force simulations to elucidate the atomically detailed pathway of two biologically important enzymes, adenylate kinase and dihydrofolate reductase. Our energetic and dynamics analysis suggests conformational changes in these enzymes that are consistent with the selected-fit hypothesis of ligand binding. In dihydrofolate reductase the dynamics of the Met20 loop can be effectively described as diffusion along one-dimensional reaction coordinate. The computational methods to be discussed can be applied to investigate the dynamics of other proteins or protein-nucleic acid complexes.

COMP 6

Modeling of synergistic regulation and ligand-induced conformational changes of tryptophan synthase

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Biological nanomachines, such as the tryptophan synthase complex, couple chemical and mechanical processes to achieve biological function. The alpha- and beta-subunits of the enzyme complex catalyzes the last two steps in the biosynthesis of L-tryptophan. The enzymatic function of tryptophan synthase depends on switching the two subunits between open conformations of low catalytic activity and closed conformations of high activity. Switching between conformations is modulated by binding of the substrate and/or covalent transformations at the active site. Moreover, to avoid the metabolite escapes during the processes, the metabolite, indole, is transferred between a 25 Å-long channel which connects the subunits. The work shows important interactions between the ligand-protein and the alpha- and beta-subunits that contribute changes of protein conformations and flexibility. Our simulations also suggest the shift of populations of some protein conformations between the free and the bound states.

COMP 7

Human glutathione synthetase (hGS) and its mechanism of negative cooperativity

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Glutathione synthetase is an enzyme which catalyzes the formation of glutathione (GSH) from γ-glutamylcysteine and glycine. GSH is an important natural antioxidant, protects cells from damage by reactive oxygen species, is involved in the metabolism of mutagens and carcinogens, and plays a role in amino acid transport. Human glutathione synthetase (hGS) is a negatively cooperative enzyme, as the binding of the first substrate molecule in one subunit

inhibits the binding of a second substrate molecule in the other subunit. This allows hGS to respond less strongly to the widely varying concentrations of its substrates. Despite the importance of hGS, its mechanism of negative cooperativity is not well understood. Molecular dynamics simulations have been used to investigate the manner of the negative cooperativity of hGS. The results suggest that amino acid sidechain interactions are responsible for communication between the subunits of the dimer, and are the cause of the negative cooperativity of hGS.

COMP 8

Detection, assignment, and analysis of multiple scaffolds for medicinal chemistry project databases

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Analysis of structure-activity data for lead optimization often involves simultaneously classifying several series of analogous compounds according to scaffolds and R-group substituents. We have developed new algorithms for detection and analysis of multiple common scaffolds, and an interactive web-based report for examining the relationship between structure and activity.

The method for scaffold analysis advances the state of the art in the following ways:

• The scaffold detection method finds multiple related common scaffolds, which will be aligned to each other in order to estimate common orientation

• The assignment of scaffolds to molecules takes into account degeneracy, such as is the case for symmetrical scaffolds, in order to minimize the resulting R-group diversity

• If partial information about the scaffolds is already available, this can be used to influence or override the automated methods

The results of this analysis are used to create a report, in which:

• Molecules are rendered in 2D showing aligned scaffolds and implied R-groups

• Tools for structure-activity analysis include correlation tables, activity estimation, fragment analysis, property graphs and navigation of similarity space

• The report uses standard cross-platform HTML/JavaScript features which can be rendered by all modern browsers

COMP 9

Online chemical modeling environment: models

***Iurii Sushko**, Sergii Novotarskyi, Anil Kumar Pandey, Robert Körner, and **Igor V. Tetko**, itetko@vcclab.org, Helmholtz Zentrum Muenchen German Research Center for Environmental Health, Institute of Bioinformatics and Systems Biology, Ingolstaedter Landstrasse 1, Neuherberg D-85764, Germany*

The modeling framework is being developed to complement the Wiki-style database of chemical structures available at http://qspr.eu (see also our presentation at CINF). It's main goal is to provide a flexible and expandable calculation environment, that would allow a user to create and manipulate QSAR and QSPR models on-line. The modeling framework is integrated with the database web-interface, that allows easy transfer of database data to the models. The web interface of the modeling environment is aimed to provide to the Web users easy means to create high-quality prediction models and estimate their accuracy of prediction and applicability domain. The developed models can be published on the Web and be accessed by other users to predict new molecules on-line. This tool is aimed to generate a new paradigm for structure activity relationship knowledgebases, making QSAR/QSPR models active, user-contributed and easily accessible for benchmarking, general use and educational purposes.

COMP 10

In silico profiling based on Aureus Global Pharmacology Space Knowledgebase

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In the past years Aureus Pharma scientists assembled from structure-activity relationship literature a considerable amount of pharmacological data integrated into a unique knowledge management system. In Aureus Global Pharmacology Space (GPS) more than 500 000 chemical structures are linked to over 2 million quantitative biological activities for major therapeutic drug targets such as GPCRs, Kinases, Ion Channels, Proteases, and Nuclear receptors. Mining this GPS helps revealing potentially interesting polypharmacology compounds and rapidly generate in silico drug profiles based on chemical and biological annotations. Considering typical medicinal chemistry scaffolds such as

phenothiazines, butyrophenones, benzodiazepines, dihydroperidines and others we analyzed the target activity profiles available for corresponding ligands and described in the GPS platform. For most of these structures we identified active representative compounds in several target protein classes. Using a newly developed application named AurPROFILER and thanks to our highly structured data schema and biological activities normalization, the target profiles obtained are easily visualized, analyzed, and reported. Several other examples of in silico generated profiles to build hypotheses on drug action mechanisms as well as off-target risk assessment will demonstrate the powerful approach of in silico profiling based on a strongly structured pharmacological knowledge database.

COMP 11

BIDATA: An SAR Knowledgebase for data retrieval and new compound suggestions

***Scott Oloff**, Research Chemistry Systems, Boehringer-Ingelheim Pharmaceuticals Inc, 900 Ridgebury Road, PO Box 368, Ridgefield, CT 06877*

Having a thorough understanding of the published SAR, internal data, and available IP is an absolutely necessity in the pharmaceutical industry. Many of these data sources however are scattered across multiple applications and in different formats making it difficult to interpret the data in the same context. This presentation will discuss approaches and technologies we have used to incorporate commercial SAR DB's with our own internal DB. There will also be discussions surrounding how this SAR is compared with patent DB's to identify available IP space.

COMP 12

Using knowledgebases of structure-activity-data, receptor-site and protein structural similarity to generate new matter ideas

***Steven M Muskal**, smuskal@eidogen-sertanty.com, Eidogen-Sertanty, Inc, 3460 Marron St #103-475, Oceanside, CA 92056*

For several years, researchers have leveraged SAR, protein sequence and structural similarity in numerous ways, including but not limited to target hypothesis, target prioritization, ligand design, and lead optimization.

Strong synergies can be realized when coupling a large body of ligand-based structure-activity content with the growing body of target-based structural information. For example, given over 55,000 publicly available apo- and co-complex protein structures, very reliable models can be proliferated within and

across many species. With this expanded structural view of the proteome, larger than expected conservation of receptor site-similarity can be identified and leveraged. We show how an automated design of novel matter by LigandCross or ligand hybridization using receptor-site similarity can be a very productive workflow.

COMP 13

Density matrix renormalization group self consistent field: Canonical transformation calculation on conjugated polyenes

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Density Matrix Renormalization Group with orbital optimization (DMRG-SCF) has recently enabled us to carry out CASSCF calculations in conjugated organic systems with fully correlated multireference active-spaces of up to 24 electrons in 24 orbitals in conjugated polyenes and also on beta-carotene[1]. In order to incorporate the effect of dynamic correlation we have coupled the DMRG-SCF theory to Canonical transformation theory[2]. Excitation energies of polyenes with complete valence active space have been calculated with DMRGSCF-CT. There are still questions about the ordering of excited states in butadiene and the accurate vertical excitation energy in ethylene and our method can throw some light in this area. We have calculated the vertical and non-vertical excitation energies of small polyenes in complete valence and bigger active space and vertical excitation energies of long polyenes in complete valence active space.

[1] D. Ghosh, J. Hachmann, T. Yanai, G. K-L. Chan, J. Chem. Phys., 128 ,144117(2008)

[2] T. Yanai, G. K-L. Chan, J. Chem. Phys., 124, 194106 (2006).

COMP 14

Continuous and smooth potential energy surface for conductor-like screening solvation model using fixed points with variable areas

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Rigorously continuous and smooth potential energy surfaces, as well as exact analytic gradients, are obtained for a conductor-like screening solvation model (CPCM, a variant of the general COSMO) with Hartree-Fock (RHF, ROHF, UHF and MCSCF) and density functional theory (R-DFT, RO-DFT and U-DFT) methods using a new tessellation scheme, fixed points with variable areas (FIXPVA). In FIXPVA, spheres centered at atoms are used to define the molecular cavity and surface. The surface of each sphere is divided into 60, 240 or 960 tesserae, which have positions fixed relative to the sphere center and areas scaled by switching functions of their distances to neighboring spheres. Analytic derivatives of the positions and areas of the surface tesserae with respect to atomic coordinates can be obtained and used to evaluate the solvation energy gradients. Due to the accurate analytic gradients and smooth potential energy surface, geometry optimization processes using these methods are stable and convergent.

COMP 15

Energy decomposition analysis of bonding and nonbonding interactions

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An energy decomposition analysis algorithm is implemented for the analysis of both bonding and nonbonding interactions on the basis of single determinantal Hartree-Fock (RHF, ROHF and UHF) wavefunctions and their density functional theory analogies. For HF methods, the total interaction energy from a supermolecule calculation is decomposed into electrostatic, exchange, repulsion and polarization terms. Dispersion energy is obtained from second-order perturbation theory (MP2) and coupled-cluster methods such as CCSD and CCSD(T). Similar to HF methods, density functional Kohn-Sham interaction energy is decomposed into electrostatic, exchange, repulsion, polarization and dispersion terms. Tests on various systems show that this algorithm is simple and robust. Insights into covalent bond formation, internal rotational barrier, hydrogen bonding, van der Waals interaction, DNA base pair formation, coordinate bond formation, metal-ligand interaction and ionic interactions are obtained using this energy decomposition analysis algorithm.

COMP 16

Heterogeneous conductor-like screening solvation model for quantum chemical calculation: Implementation and application

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For the first time, a heterogeneous conductor-like screening solvation model (COSMO) is implemented for quantum chemical calculations of protein active sites consisting of ~100 atoms: the solvent-exposed atoms are screened by a dielectric of 80 while the inner atoms are screened by lower dielectrics varying from 4 to 20. Special symmetrization treatment is used to form the heterogeneous COSMO operator in variational Hartree-Fock and density functional Kohn-Sham calculations and a simple analytic expression of the energy gradients, which are vital for geometry optimization and molecular dynamics simulation, is derived and implemented. Using our new FIXPVA surface tessellation scheme, rigorously continuous and smooth potential energy surfaces, as well as exact gradients, are obtained for this heterogeneous quantum COSMO. Using active site models consisting of ~100 atoms and the heterogeneous COSMO, the reduction potential of eight type-1 copper proteins are calculated and compared well to experimental values.

COMP 17

Excitation energy in solution at EOM-CCSD level, a state specific approach within the polarizable continuum model

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Coupled cluster theory is one the most successful approaches in quantum chemistry for the study of transition phenomena, because it combines a well defined ab initio expression for the wave function and high accuracy. However, although most of the experimental spectroscopy is done in solution, there are only few examples of coupled cluster calculations of excitation energies in solution. Among them, the majority use a hybrid approach, where the solute is treated at quantum mechanical level and the solvent at molecular mechanical level. Only Christiansen and Mikkelsen proposed an approach that employs a continuum dielectric description of the solvent, within the linear response of the solute wave funtion. In this study we retain the continuum dielectric description of the solvent, but we employ a state specific approach, in which the solvent response depends on the total state density of the solute, whereas in the linear response the solvent interacts with the solute transition density. We investigate various approximations in the definition of the excited state solute density at the EOM-CCSD level, and the effect on various solvents and solutes, in order to gather useful information for the formulation of a production strategy.

COMP 18

O+ethylene potential energy surface: Theoretical study at the MCSCF and MRMP2 levels

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The $O(^3P, ^1D)+C_2H_4$ reaction provides a crucial, initial understanding of hydrocarbon combustion. The lowest lying triplet and singlet potential energy surfaces were extensively explored at the MCSCF and MRMP2 levels with an initial surface crossing investigation. In particular, a careful determination of an active space along the intrinsic reaction pathway is necessary; and in some cases, more than one active space must be explored for computational feasibility. Challenges and areas of further exploration will be discussed.

COMP 19

Orbital ordering in density matrix renormalization group methods

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The Density Matrix Renormalization Group (DMRG) method has shown to be a powerful method as applied to quantum chemistry, but still many questions remain unanswered when one considers applications to molecules. DMRG was developed to treat one dimensional systems with primarily local interactions, however, a problem arises of how to represent and map a higher dimensional system to the 1D lattice structure inherent to the current algorithm. We study the use of the Natural Bonding Orbitals and the Lewis structure that arises from these orbitals to propose a simple, chemically intuitive method for defining this mapping. We compare our ordering of orbitals to those previously proposed, such as band width minimization of the one-electron integral matrix.

COMP 20

DFT and ONIOM(DFT:MM) computational studies of *myo*-inositol oxygenase: Insights into the (superoxo)diiron(III/III) intermediate and reaction mechanism

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Accumulated evidence indicates that depletion of the intracellular level of *myo*-inositol is associated with various diabetic complications such as nephropathy, retinopathy, neuropathy, and cataract. A nonheme diiron enzyme *myo*-inositol oxygenase (MIOX) catalyzes the oxidative conversion of *myo*-inositol to D-glucuronate, which is the first committed step in *myo*-inositol catabolism. MIOX has thus been implicated to play a critical role in the pathogenesis of those diabetic diseases. Recently, significant progress has been made experimentally in understanding the mechanistic, electronic, and structural details of MIOX. However, many fundamental aspects of the enzyme, particularly those which are not readily tractable by experimental means, still remain unclear. We therefore performed computational studies using density functional theory and hybrid ONIOM(DFT:MM) methods. Our calculations provided new insights into the (superoxo)diiron(III/III) intermediate formation and subsequent substrate oxidation reaction. The effect of protein environment on these events was found to be important.

COMP 21

Quantum mechanics-coupled AMBER ff99 compatible heme parameters for the P450 catalytic cycle

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The lack of a consistent set of atomic parameters for the key heme species during the P450 catalytic cycle has limited the accuracy of computational methods for predicting drug metabolism. Our research focuses on elucidating the contribution of electronic, conformational and thermodynamic factors to competing P450-catalyzed reaction mechanisms during the metabolism of tamoxifen -the current drug of choice for the treatment of breast cancer. We

present the results of our quantum mechanics calculations for key heme species during the P450 catalytic cycle at the UB3LYP/LACVP level. These results have been further used to develop a consistent set of AMBER ff99-compatible parameters for the P450 catalytic cycle. We will discuss the contribution of these parameters towards the improved accuracy of our combined empirical and computational approach which uses coupled QM-based force field development, flexible docking, and extensive MD in explicit solvent to study the biophysical factors involved in P450-mediated drug metabolism.

COMP 22

Substrate hydroxylation by the P450s: Is there any consensus mechanism?

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There is an ongoing controversy regarding the mechanism of C-H hydroxylation by cytochrome P450 enzymes (Auclaire, K.; Hu, Z.; Little, D.M.; Oritz de Montellano, P.R.; Groves, J.T. J. Am. Chem. Soc. 2002, 124, 6020-6027. Newcomb, M.; Aebisher, D.; Shen, R.; Esala, R.; Chadrasena, P.; Hollenberg, P.F.; Coon, M.J. J. Am. Chem. Soc. 2003, 125, 6064-6065). To address this controversy we have carried out extensive theoretical study with two experimental ring strained probes, bicyclopentane (1) and norcarane (2). The present study revealed that the low energy pathway for C-H hydroxylation is the two state rebound mechanism described earlier for methane hydroxylation (Ogliaro, F.; Harris, N.; Cohen, S.; Filatov, M.; de Visser, S.P.; Shaik, S. J. Am. Chem. Soc. 2000, 122, 8977-8989). The C-H hydroxylation is found to follow a new principle which can be called as "dielectromeric effect" according to which the reactivity of substrates are controlled by two different elctromers that emerges from two oxidation potentials of Fe i.e. Fe(IV) and Fe(III). Cpd I is the main reactive species from where P450 hydroxylation starts and later it bifurcates along two reaction channels depending on the oxidation potential of Fe i.e. Fe(IV) and Fe(III). The Fe(IV) channel mainly yields unarranged product while Fe(III) channel yields rearranged product. The present study well accommodates relative experimental yield of various reaction products and the rearrangement patterns. It is found that substrates 1 and 2 will mainly follow radical rearrangement.

COMP 23

2'-F-2'-C-Methyl nucleosides for the treatment of HCV: From discovery to the clinic

***Michael J. Sofia**, Pharmasset Inc, 303-A College Road East, Princeton, NJ 08540*

Hepatitis C is a global health problem with over 170 million individuals infected with the hepatitis C virus (HCV). Infection with HCV has been shown to lead to chronic liver disease, cirrhosis and eventually hepatocellular carcinoma. Currently, the standard of care is a combination of interferon-alpha and ribavirin, however, this regimen has limited effectiveness and is associated with debilitating side-effects. The search for direct acting antiviral agents has lead to the discovery of R7128 a nucleoside prodrug that inhibits the HCV NS5B polymerase. R7128 has demonstrated exceptional potency and safety in the clinic against genotype 1, 2 and 3 patients. In addition, PSI-7851, a nucleotide prodrug, showed increased liver exposure of the active triphosphate metabolite in laboratory animals and has also entered clinical evaluation. The discovery and current state of development for these two agents will be presented.

COMP 24

Modeling binding modes of HIV integrase inhibitors

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Although significant progress has been made in HIV integrase inhibitor drug discovery, as demonstrated by FDA approval of Merck's raltegravir, there is still very limited understanding of inhibitor binding modes due to the lack of relevant crystal structures. In order to gain insight into the mechanism of inhibition and aid drug discovery effort, we have constructed an active site model of HIV-1 integrase complexed to both viral DNA and inhibitor. Our model suggests a common binding mode for potent integrase inhibitors that involves interactions with an induced active site hydrophobic pocket, formed upon viral DNA binidng. In addition, based on analysis of large number of nucleotidyltransferase, substrate, and Mg complex structures, we hypothesized that potent integrase inhibitors interact with only one of two bound active site Mg cations. To further validate the model, we made specific compounds and mutated key residues predicted to play an important role in inhibitor binding. These predictions were subsequently confirmed experimentally.

COMP 25

Identifying novel anthrax toxin lethal factor inhibitors via topomeric searching and docking/scoring

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Anthrax is an acute infectious disease caused by the spore-forming, Gram-positive, rod-shaped bacterium Bacillus anthracis. The lethal factor (LF) enzyme is a zinc metalloenzyme secreted by B. anthracis as part of a tripartite exotoxin and is chiefly responsible for anthrax-related cytotoxicity. As LF can remain in the system for long after antibiotics have eradicated B. anthracis from the body, the preferred therapeutic modality is the administration of antibiotics together with an effective LF inhibitor. Such inhibitors must not only bind strongly to the receptor but must also possess excellent ADMET profiles. Although LF has attracted much attention as a drug target, few published inhibitors have demonstrated activity in cell-based assays and no LF inhibitor is currently available as a therapeutic or preventive agent. Here we present a novel virtual screening protocol which, together with experimental high-throughput screening, was able to identify nine new non-hydroxamic acid small molecules functioning as LF inhibitors with low micromolar-level inhibition against that target. A key topomeric searching component of this protocol was able to prioritize twenty-two thousand compounds from an initial dataset of approximately thirty-five million non-redundant structures. Compounds identified by this method were subsequently subjected to docking and scoring and drug-like (ADME-related) filtering protocols. Among the nine new hits, none of which was previously identified as a LF inhibitors, seven demonstrated experimental activity against LF less than 50 micromolar. Three of the top hits that exhibited single-digit IC50 values may potentially serve as scaffolds for lead optimization. Each of these three hits demonstrates a different zinc-binding mechanism predicted by docking and scoring; future work is planned to experimentally assess predicted binding modes by means of X-ray crystallography.

COMP 26

Fragment-based molecular docking in inhibitor discovery against CTX-M class A β-lactamase

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Fragment screens have successfully identified new scaffolds in drug discovery, often with relatively high hit rates (5%) using small screening libraries (1,000-10,000 compounds). This raises two questions: would other interesting chemotypes be found were one to screen all commercially available fragments (>300,000), and does the success rate imply low specificity of fragments? We used molecular docking to screen large libraries of fragments against CTX-M beta-lactamase, one of the most common extended-spectrum beta-lactamases in many regions of the world and also a challenging target for inhibitor discovery. Ten mM-range inhibitors were identified from the 69 compounds tested. The docking poses corresponded closely to the crystallographic structures subsequently determined. Intriguingly, these initial low affinity hits showed little specificity between CTX-M and an unrelated beta-lactamase, AmpC, which is unusual among beta-lactamase inhibitors. This is consistent with the idea that the high hit rates among fragments correlate to a low initial specificity. As the inhibitors were progressed, both specificity and affinity rose together, leading to the first micromolar-range non-covalent inhibitors against a class A beta-lactamase.

COMP 27

Design and optimization of novel peptide deformylase inhibitors as new antibacterial agents

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Polypeptide Deformylase (PDF) is a metalloenzyme that has garnered much attention within the pharmaceutical industry as a promising target for the development of novel antibacterial agents. This enzyme catalyzes the removal of a formyl group from the N-terminal methionine of newly synthesized bacterial proteins, a deformylation process that is essential for bacterial survival. PDF is a relatively small protein (20-25 kD) that has proven to be amenable to X-ray crystallography studies. We have capitalized on this readily available structural information to design multiple series of novel non-peptidic inhibitors. The design and successful optimization of these PDF inhibitors will be discussed.

COMP 28

De novo design of novel polypeptide deformylase (PDF) inhibitor templates with broad spectrum antibacterial activity

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A broad-spectrum antimicrobial target must be conserved across all pathogens of interest within a therapeutic product profile, essential for bacterial growth, and either absent, substantially different or non-essential in humans. PDF meets all of these criteria and is one of the most promising unexploited bacterial targets in the search for new antibiotics with a novel mode of action. PDF (EC 3.5.1.88) is a metalloprotease that removes the N-formyl group of the polypeptides as they emerge from the ribosome during or immediately after completion of the elongation process.

Structure-based design studies in conjunction with de novo design studies using Allegrow was employed to find novel backup templates with broad-spectrum activity for the PDF program. The results from these studies will be presented.

COMP 29

Discovery of novel small-molecule inhibitors of P. falciparum using the hybrid structure based method

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A key component of host cell invasion by Apicomplexan parasites is the interaction between the carboxy terminal tail of myosin A and the myosin tail interacting protein-MTIP. Based on the co-crystal structure of P. knowlesi MTIP and a MyoA tail peptide and using Hybrid Structure Based virtual screening approach, a series of small molecules were identified as having potential to inhibit MyoA-MTIP interactions. Of the initial 15 compounds tested, a pyrazole urea compound inhibited P. falciparum growth with an EC50 of ~250 nM. Screening of an additional 51 compounds belonging to the same chemical class identified eight compounds with EC50 of ~300 nM and one with an IC50 of ~50 nM. Interestingly, the compounds appear to act at several stages of the parasite life cycle to block growth and development. Thermal melting studies of MTIP in the presence and absence of the compounds show that many of the compounds bind and stabilize MTIP. The pyrazole urea compounds identified in this study could be effective antimalarials since they competitively inhibit a key protein-protein interaction between MTIP and MyoA responsible for the gliding motility and invasive features of the malarial parasite.

COMP 30

Visualizing lowly-populated regions of the free energy landscape of macromolecular complexes by paramagnetic relaxation enhancement

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Many biological macromolecular interactions proceed via lowly-populated, highly transient species that arise from rare excursions between the minimum free energy configuration and other local minima of the free energy landscape. Little is known about the structural properties of such lowly-occupied states since they are difficult to trap and hence inaccessible to conventional structural and

biophysical techniques. Yet these states play a crucial role in a variety of dynamical processes including molecular recognition and binding, allostery, induced-fit and self-assembly. Here we highlight recent progress in paramagnetic nuclear magnetic resonance to detect, visualize and characterize lowly-populated transient species at equilibrium. We have used the PRE (a) to detect and characterize the stochastic target search process whereby a sequence-specific transcription factor binds to non-cognate DNA sites as a means of enhancing the rate of specific association via intramolecular sliding and intermolecular translocation1; (b) to directly visualize the distribution of non-specific transient encounter complexes involved in the formation of stereospecific protein-protein complexes2; (c) to determine the structure of a minor species for a multidomain protein (maltose binding protein) where large interdomain motions are associated with ligand binding;3 and (d) to characterize early transient events involved in N-terminal auto-processing of HIV-1 protease.4 The PRE offers unique opportunities to directly probe and explore in structural terms lowly-populated regions of the free energy landscape and promises to yield fundamental new insights into biophysical processes.

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COMP 31

All-atom simulations of coupled folding-binding of unstructured proteins

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It is increasingly recognized that many proteins only assume a specific fold apon binding to their target(s). In many cases, the bound structure consists of one or more helices which are not stable in the absence of a binding partner. Building on recent work to improve the intrinsic treatment of the helix-coil transition in modern protein force-fields, we investigate the binding mechanism of unstructured proteins using all-atom simulations.

COMP 32

Assembly/disassembly mechanisms of multidomain Src kinase revealed by X-ray solution scattering and LRET

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In response to specific cellular stimuli, the Src-family kinases initiate signal transduction in normal or transformed cells by (a) a large-scale intramolecular assembly among its three domains (SH3, SH2 and kinase) and (b) a catalytic activation of the kinase domain. The induced large-scale domain-domain assembly is viewed as a shift of the equilibrium of multiple conformational states adopted by Src in solution. We quantified this equilibrium shift by using a combination of X-ray solution scattering (SAXS) data of the full-length Src from Hck and experimentally-calibrated coarse-grained simulations. By using a newly developed method (Fast-SAXS) for rapid determination of SAXS profiles, we bridged the interpretations of molecular simulations and SAXS data of Src. In particular, we used the Fast-SAXS tool to compute the SAXS profiles from massive simulation data and deconvoluted the population of every visited conformational state from recently collected SAXS data at a variety of conditions. This quantitative characterization is further confirmed by lanthanide resonance energy transfer (LRET) experiments on Hck. We found that Src adopts toward multiple disassembled states (e.g., triggered by SH3-binding ligands) from a self-assembled state, which inhibits the kinase activation. This activation mechanism is subsequently characterized by multi-scale simulations. From atomically-detailed and coarse-grained models, consistent results on conformational transitions of the kinase domain are obtained. Notably, two intermediates are identified from atomic simulations as potential targets of kinase inhibitor designs. I will describe these results with a focus on how the integration between theory and experiment has enabled us to gain critical insights into quantitatively characterizing the energy landscape of the Src multidomain assemblies and qualitatively unifying the assembly mechanism with the activation mechanism of the kinase domain.

COMP 33

Flexible biomolecular recognition and conformational changes

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Combining a single-molecule study of protein binding with a coarse grained molecular dynamics model, we find that biomolecular recognition is determined by

flexibilities in addition to structures. Our single-molecule study shows that binding of CBD (a fragment of

Wiskott-Aldrich syndrome protein) to Cdc42 involves bound and loosely bound states, which can be

quantitatively explained in our model as a result of binding with large conformational changes. Our model

identified certain key residues for binding consistent with mutational experiments. Our study reveals the

role of flexibility and a new scenario of dimeric binding between the monomers: first bind and then fold.

We developed a coarse grained two-well model to study the single molecule protein conformational

dynamics in microscopic detail at the residue level, overcoming the often encountered computational

bottleneck. In particular, we explored the underlying conformational energy landscape of adenylate kinase,

a crucial protein for signal transduction in the cell, and identified two major kinetic pathways for the

conformational switch between open and closed states through either the intermediate state or the transient

state. Based on the parameters fitted to the room-temperature experimental data, we predicted open and

closed kinetic rates at the whole temperature ranges from 10 to 50 °C, which agree well with the experimental

turnover numbers. After uncovering the underlying mechanism for conformational dynamics and exploring

the structural correlations, we found the crucial dynamical interplay between the nucleoside monophosphate

binding domain (NMP) and the ATP-binding domain (LID) in controlling the conformational switch. The key

residues and contacts responsible for the conformational transitions are identified by following the time

evolution of the two-dimensional spatial contact maps and characterizing the transition state as well as

intermediate structure ensembles through -phi value analysis. Our model provides a general framework to

study the conformational dynamics of biomolecules.

COMP 34

Binding cooperativity in R67DHFR

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R67 Dihydrofolate reductase (R67DHFR) is a plasmid-encoded enzyme that exhibits drug resistance. The protein is a homotetramer with D_2 symmetry and forms a ring with the active site in the center. The reduction of dihydrofolate requires the presence of a co-factor (NADPH). Due to its symmetry, the protein uses identical binding sites to bind dihydrofolate (DHF) and NADPH. To ensure that the productive complex (DHF/NADPH) is formed instead of inhibitory complexes (DHF/DHF or NADPH/NADPH), the protein employs binding cooperativity. However, how the enzyme is able to achieve this cooperativity is unclear. Molecular dynamic simulations of different complexes and of Q67H mutants were performed to address this issue. Our simulations were able to predict the structure of the ternary complex (as confirmed by x-ray structure) despite the large differences between it and the docked structure, which was used as the starting geometry. Surprisingly, backbone conformational changes do not appear to contribute to the cooperativity, as the average structure for all complexes and mutants is essentially the same. However, some differences are observed for the side chains of residues 67 and 69. Despite this, the main source of the cooperativity seems to come from ligand-ligand interactions.

COMP 35

Conformational coupling in an effector-GTPase interaction: Differences in the complex formation of the Plexin GTPase binding domain with Rac1 and Rnd1

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Plexins are transmembrane receptors that respond to cell guidance cues. Remarkably, plexins interact directly with small Ras and Rho family GTPases which are involved in cell adhesion and motility. Recently, we have characterized the structure and dynamics of the RhoGTPase binding domain of plexin-B1. The ubiquitin-like fold binds to several Rho GTPases as an effector protein using a novel binding interface. While the conformational changes are limited in the domain itself upon binding, we observe a long range propagation of changes that alter the oligomerization state of the cytoplasmic region of the receptor. Furthermore, conformational dynamics in Rac1 are attenuated upon plexin binding, as shown by solution NMR ps-ns mainchain order parameters whereas the homologous GTPase, Rnd1 does not show such changes. Molecular dynamics simulations suggest that the two GTPases have different modes of interaction with plexin due to differences in the packing of residues in the protein interior.

COMP 36

Deciphering the post-replication DNA-mismatch recognition cycle in prokaryotic MutS and eukaryotic MSH2-MSH6

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Prokaryotic MutS and eukaryotic homolog MSH2-MSH6 recognize base mismatches and base insertion/deletions in post-replication DNA and initiate repair. The DNA mismatch recognition cycle likely involves multiple conformational states and in particular features long-range allostery between DNA-binding domains and ATPase domains of MutS and homologs. Normal mode analyses and submicrosecond MD simulations of the ~1800-residue MutS and MSH2-MSH6 protein-DNA complexes in explicit solvent suggest structural details of the alternate functional states suggested through experiments. In particular, the transitions in MSH2-MSH6 without DNA and with regular DNA vs. mismatched DNA are described based on regular MD simulations and Hamiltonian replica exchange simulations with RMSD-based umbrella sampling. The results provide atomistic details of the allosteric coupling between mismatch

recognition and repair initiation and further clarify the role of DNA deformation in stabilizing the mismatch bound protein-DNA complex during the repair initiation cycle.

COMP 37

Structure activity relationship analysis using PubChem

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PubChem is a free, online public information resource from the National Center for Biotechnology Information (NCBI). The system provides information on the biological properties and activities of chemical substances, linking together results from different sources on the basis of chemical structure and/or chemical structure similarity. With over 500 different targets, 1,400 bioassays, and 45,000,000 activity data points, PubChem is a significant source of publicly available bioactivity data. Unlike many available SAR Knowledgebases, PubChem contains screening data of both actives and inactives. Available tools allow one to dynamically create structure activity relationships based on structure similarity (2D or 3D), target similarity, and target profile. The use and utility of these tools will be discussed.

COMP 38

GOSTAR: GVK BIO online structure activity relationship database: Data and its utility

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GVK BIO is well known for the development of Knowledge databases of chemical entities (~4 million compounds) with structure activity relationships. Information relating chemical structure, biological target, in vitro and in vivo assay for efficacy/pharmacodynamics, clinical as well as Pharmacokinetics and toxicity is well integrated in different databases wherein the source information has been covered from a variety of Journals articles and patents for a variety of target families. Many pharmaceutical companies have been using these databases for different applications and/or modeling studies. Recently, GVKBIO has integrated all its individual databases into one single database, GOSTAR which has a very good web-based UI for different types of online queries. In the process of integration of all individual databases into one data model, all the data has been

standardized and necessary taxonomy and ontology were used to handle the integrated data. Any query will extract the data from all databases whether they feature in discovery, development or marketed drug space. Further, one can analyze the retrieved molecules for any off-target activity as well as other indications. A number of descriptors can be generated using the online available tools and the data can be analyzed for various models. Tools have been developed to study and to visualize the chemical, biological and Therapeutic indication space as well as company related information. Further tools were developed to filter the data based on chemical, pharmacological or toxicity filters and help the research process for better drug discovery. We will be discussing some case studies on the usefulness of the database in the drug discovery.

COMP 39

ChEMBL: Large-scale mapping of medicinal chemistry and pharmacology data to genomes

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Although the majority of effective therapeutics are small molecules, there is relatively little readily accessible public domain data mapping drug to their molecular targets. When one considers clinical trial stage, or discovery stage data, the situation deteriorates further. However, this type of data is essential for Chemical Biology experiments, and is crucial for informed target selection in drug discovery. To address this issue, we have built a series of large scale databases, known as ChEMBL, that map small molecule structures to their target genes and also their functional effects. This data also captures a large ammount of human and model organism pharmacological data, systems often used in pre-clinical validation and safety pharmacology testing. A variety of applications of these databases in the area of target prioritisation, lead discovery, lead optimisation and drug repurposing will be described.

COMP 40

Pharmacoinformatics on very large annotated ligand databases

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Ligand data excerpted, as a repository for past knowledge representation was prioritized. Accordingly, very large annotated ligand databases with more than 2 Million ligands, containing manual annotations on chemical and pharmacological

data from Journals and Patents were used for mining compounds in an effort to identify de-novo candidates in a virtual screen, against selected, previously validated targets. Clustering on controlled datapoints against all major therapeutically relevant target families (GPCR, Ion-channel, Protease, Transporters, Kinase, Nuclear Hormone receptor) was performed and challenging compounds were designed. Designed compounds represented an unique set of chemistry and were synthesized for further validation.

COMP 41

An image-based reaction field method for electrostatic interactions in molecular dynamics simulations of aqueous solutions

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A new solvation model is proposed for simulations of biomolecules in aqueous solutions that combines the strengths of explicit and implicit solvent representations. Solute molecules are placed in spherical cavities filled with explicit water, thus providing microscopic detail where it is needed. Solvent outside of the cavities is replaced with a dielectric continuum whose effect on the solute is modeled through the reaction field corrections. With this explicit/implicit model, the electrostatic potential represents a solute molecule in an infinite bath of solvent, thus avoiding unphysical interactions between periodic images of the solute commonly used in the lattice-sum explicit solvent simulations. For improved computational efficiency, our model employs an accurate and efficient multiple-image method to compute reaction fields together with the fast multipole-expansion technique for the direct Coulomb interactions. To minimize the surface effects, periodic boundary conditions are employed for non-electrostatic interactions. The proposed model is applied to study liquid water. The effect of main geometric parameters of the model, which include the size of the cavity, the number of charge images used to compute reaction field and the thickness of the buffer layer, is investigated in comparison with the particle-mesh Ewald simulations as a reference. An optimal set of parameters is obtained that allows for a faithful representation of many structural, dielectric and dynamic properties of the simulated water, while maintaining manageable a computational cost. With predicable increasing accuracy of the multiple-image charge representation of the reaction field, it is concluded that the proposed model achieves convergence

with only one image charge in the case of pure water. Future applications to pKa calculations, conformational sampling of solvated biomolecules and electrolyte solutions are briefly discussed.

COMP 42

Aromatic oligoamide foldamers: Conformational insights from molecular dynamics simulation using reparameterized molecular mechanics force fields regarding aromatic-amide torsions

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In order to help the design of aromatic oligoamide foldamers, we are developing a computational approach to study and predict foldamer conformational preference. It starts with ab initio calculations of torsional profiles and NMR studies on arylamide model compounds, followed by re-parameterization of important aromatic-amide torsions and molecular dynamics simulations of aromatic oligoamides using the modified force fields. In this presentation, we will focus on the conformational insights gained from molecular dynamics simulation of a series of aromatic oligoamides, having similar sequences with different building blocks. The effects of solvents will also be discussed and comparison with available experimental observations will be made.

COMP 43

Fully-flexible polarizable water model for classical and multiscale molecular dynamics simulations

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Electronic polarization of molecular active sites is crucial in understanding biomolecular reactions and their applications in the reactivity study of proteins and drug designing. Development of a dedicated hardware design has boosted the research on polarizable models, by dramatically reducing CPU time for molecular dynamic simulations. Existing polarizable models, however, rely mostly on mimicking the polarizability with a dipole, which does not necessarily represent the expected charge redistribution, a key factor for stimulating chemical reactions. Aiming to achieve molecular polarizability by self-consistently positioning a fraction of the electronic charge of electronegative atoms and by allowing the charge to be fully seen by all other atoms, we develop a four-site,

fully flexible polarizable water model. Representing the atomic charges by Gaussian, we improve the short-range Coulomb interaction and nullify the real space sum over Coulomb for the EWALD simulation. We compare the results with existing polarizable models.

COMP 44

POLARIS: Software and alanine parameters for fast polarizable calculations

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Our novel POLARIS software package has been used to produce parameters for alanine dipeptide. These parameters will also serve as a general protein backbone model. While our formalism for the fast polarizable calculations has been reported previously, the specific protocol for parameter fitting has been modified and improved, as will be discussed in the presentation. Moreover, performing free energy perturbations with our fast polarizable software and parameters for water, alkanes and methanol has yielded hydration energies within ca. 0.13 kcal/mol of their experimental counterparts. We view these data as a precursor to carrying out accurate calculations of protein-ligand binding free energies to be performed with our fast polarizable force field.

COMP 45

PRIMO: A transferable physics-based coarse-grained model for peptides and proteins

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A new coarse-grained, transferable force field for peptides and proteins, called PRIMO, is presented. PRIMO represents each amino acid with 3 to 7 coarse-grained sites. Interactions consist of bonded and non-bonded terms with an additional empirical hydrogen-bonding term and is combined with implicit solvent. PRIMO is designed to allow one-to-one correspondence between coarse-grained and atomistic levels of detail in order to preserve transferability and accuracy of all-atom force fields while offering a substantial reduction in computational cost. First applications of PRIMO in molecular dynamics simulations of proteins and peptide aggregation studies are presented.

COMP 46

Statistically optimal multidimensional potentials of mean force with large data sets

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The processing of data collected over many different thermodynamics states has become a pressing concern as computational power has dramatically increased and methods for sampling over multiple ensembles have become more popular. Previous papers on our research introduced a minimum variance method to calculate free energies and ensemble averages from multiple equilibrium simulations conducted at different thermodynamic states, based on a multistate generalization of Bennett's acceptance ratio method (hence called MBAR). Unlike the weighted histogram analysis method, this method does not require histograms, eliminating bias due to binning. Previously presented modifications to this method allow the explicit inclusion of only states with significant overlap, making it possible to compute extremely large and high dimensional PMF's with explicit and robust uncertainty estimates with very little loss of precision. We now demonstrate how this method can be used with to compute 3D potentials of mean force over very large data sets, focusing on an example of small molecules in the ribosome exit tunnel generated from microseconds of simulation data, and describe the implementation of the methods in easily configurable python scripts for general use in replica exchange and umbrella sampling simulations.

COMP 47

Simulations of interfaces and nanostructures using first principles based methods

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We will highlight some recent advances in methodology first principles based methods for simulation of interfaces and nanostructures and will illustrate them

with recent applications to problems involving Catalysis, Nanoelectronics, Fuel Cells, materials science, and pharma.

COMP 48

Percolation in networks of nanorods

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Above a certain density threshold, suspensions of rod-like colloidal particles form system-spanning networks. Inspired by experiments on the dielectric properties of suspensions of carbon-nanotubes and surfactant micelles, we performed a computer simulation study of percolation in suspensions of hard rods and spheres. We investigated how the depletion forces caused by the spheres affect these networks in isotropic suspensions of rods. Although the depletion forces are strongly anisotropic and favor alignment of the rods, the percolation threshold of the rods decreases significantly. For light-weight conductive composite materials this implies that the amount of conductive filler material can be increased by addition of a depletant.

COMP 49

The workings of nitrogenase and new developments of the projector augmented wave method

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The mechanism of nitrogen fixation at the FeMo-cofactor of nitrogenase is one of the major challenges of bio-inorganic chemistry. We explored the landscape of the the total energy surface with density functional calculations to determine the most likely pathway. Particular emphasis is placed on the underlying principles that explain the function of the catalytic center. I will use this example to demonstrate some of the more recent developments of the CP-PAW code, the original implementation of the projector augmented wave method.

COMP 50

Molecular dynamics study of the effect of inorganic ions on the aggregation of carbocyanine dyes in aqueous solution

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Carbocyanine dyes are cationic organic chromophores that are known to aggregate in aqueous solution. This aggregation dramatically modifies their optical properties and my give rise to J-band, remarkably narrow peak of high intensity on their absorption spectrum. It was recently suggested to use this aggregation in the design of nonlinear optical materials. Unfortunately, direct experimental evidence on the structure of these aggregates is scarce. In this contribution we use Molecular Dynamics simulations in the explicit solvent in order to obtain an insight into the different modes of self-assembly of carbocyanine dyes. The effect of the molecular structure, sidechains, counterions, dye concentration, and ionic strength of the aqueous solution is studied. The metal cations are found to play an important role in the shape of molecular aggregates.

COMP 51

Conservative algorithm for an adaptive change of resolution in mixed atomistic/coarse-grained multiscale simulations

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Understanding complex materials often requires investigating multiple, tightly coupled time and length scales. Neither atomistic nor coarse-grained simulations are often able to adequately capture all the relevant scales. To combine the efficiency of coarse-grained models with the accuracy of atomistic models for systems that require atomistic resolution only locally, for example at an interface, mixed-resolution models have been developed. These models use a coarse-grained description for the part of the system distant from an active site and atomistic description for the active site and its direct environment. Since the active zone may diffuse during a simulation, the simulation algorithm needs to permit an on-the-fly reclassication of atoms as they transition between the high- and low-resolution regimes. In this paper, we derive a conservative Hamiltonian and present an explicit symplectic integrator for mixed-resolution systems that allows for such a change in resolution of selected groups of atoms during a MD simulation.

COMP 52

Density dependence of azobenzene switching on gold: A mean field/quantum chemistry study

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Azobenzene derivatives exhibit a well-known and well-studied cis-trans photoisomerism. As a result, they have been used in a number of important applications. On a gold surface, scanning tunneling microscopy studies of N-(2-mercaptoethyl)-4-phenylazobenzamide have revealed similar behaviour under the influence of an electric field. The reversible conversion of this adsorbate between a low-current and a high-current state shows promise for possible applications in molecular switches. Some controversy remains as to the nature of the two states, and the relationships between monolayer density, applied electric field and molecular configuration have yet to be rigorously explored. In this presentation, we will discuss the results of our quantum chemical and mean field investigations of the bistable behaviour of mixed N-(2-mercaptoethyl)-4-phenylazobenzamide / n-dodecanethiol monolayers at the Au(111) surface.

COMP 53

Some observations on the quality of 3D QSAR data sets

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Oxazolidinones are a novel class of antibiotics. However, off-target activity has limited the number of agents in this class that have appeared on the market. One such activity is inhibition of monoamine oxidase A (MAO-A). We present a 3D QSAR study MAO-A inhibition by a new set of about a hundred oxazolidinones using the recently introduced Simple Atom-Type Mapping Following Alignment (SAMFA) method. In SAMFA, traditional molecular field-based descriptors are replaced with force-field-like atom types at the atomic centers giving rise to those fields. Although this approach reduces the number of descriptors to the number of atoms for each molecule in a given data set, we show that for nine data sets, including the steroid benchmark, there is no difference between SAMFA and

Comparative Molecular Field Analysis (CoMFA). In fact, in many cases SAMFA descriptors can be further simplified to represent only whether certain atomic positions are occupied among aligned sets of molecules, without significantly affecting q2. We propose that this observation stems from artifacts that arise from incomplete sampling of the biologically relevant chemical space within those data sets. Two diagnostic approaches for characterizing this sort of undersampling will be presented and used to demonstrate that the oxazolidinone data set is less susceptible to artifact.

COMP 54

AutoGrow: A novel algorithm for protein inhibitor design

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Trypanosoma brucei (T. brucei) is an infectious agent for which drug development has been largely neglected. T. brucei is endemic to Africa, where it can infect the central nervous system in humans and cause African sleeping sickness. One potential T. brucei drug target is RNA editing ligase 1 (TbREL1), a critical component of a unique mitochondrial mRNA-editing complex known as the editosome. TbREL1 is an excellent drug target because it is essential for T. brucei survival and has no close human homologues.

AutoGrow, a new program that combines the strengths of fragment-based growing, docking, and evolutionary algorithms, is used to add interacting moieties to NSC16209, a known TbREL1 inhibitor. Careful analysis of the top AutoGrow-generated ligands suggests that they bind TbREL1 in ways similar to ATP, the natural TbREL1 substrate. The compounds presented here may serve as valuable starting points for future drug-design efforts in the fight against Human African Trypanomiasis.

COMP 55

Computational models of the action of protegrin antimicrobial peptides: Transient ion diffusion and osmotic swelling

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Protegrins are a class of highly effective antimicrobial peptides, believed to act primarily by permeabilizing the bacterial cell membrane. We have conducted molecular dynamics simulations of the membrane-embedded pore structure formed by protegrin. We have then used structures extracted from these simulations as input to a continuum electrodiffusion model, in order to quantify the electrical conductance characteristics of such pores, and obtained good agreement with previously published experimental data. Finally, we have modeled the effects of multiple pores on an entire cell, using data obtained from the molecular and continuum electrodiffusion models. We have been able to estimate the number of pores required to reproduce the experimentally measured potassium release rate from an E. Coli cell, as well as quantify the effects of ion exchange processes on osmotic swelling of cells. Combined with experimental data, these models provide a comprehensive picture of the permeabilizing mechanism of protegrin antimicrobial peptides.

COMP 56

Design of new antibacterial drugs: Computational approaches that take advantage of the rapid generation of multiple co-crystal structures

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New classes of antibacterial drugs with novel mechanisms of action are needed to combat bacterial resistance. To meet this challenge, we focus on novel (or underexploited) antibacterial targets and utilize structure-based drug design techniques. We have built a structural biology platform that generates multiple (2-6) structures per week per program. This structural data provides information needed to design compounds with spectrum, selectivity, antibacterial activity and drug properties. This talk will provide a critical overview of the role of computational chemistry in structure-centric antibacterial discovery programs. We will describe our computational chemistry experiences, including:

• Lead Discovery: virtual screening and de novo design

• Lead Optimization: LUDI evolution of leads, ligand docking and scoring, design of compounds with spectrum and selectivity, dealing with enzyme flexibility and design of drug-like properties

COMP 57

Heme oxygenase as antimicrobial target: Results from computer-aided drug design and experiment

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A variety of life-threatening diseases including meningitis, pneumonia, cholera and dysentery are caused by Gram-negative pathogens. They have developed sophisticated mechanisms for iron acquisition, which is important for their proliferation and infectivity. In addition to iron acquisition many of these pathogens can also utilize heme as an iron source. The final step of iron acquisition from heme is oxidative cleavage by a heme oxygenase (HO). We hypothesize that HO may provide a potential target for drug development. In this work, we apply computer-aided drug design (CADD) virtual screening techniques to identify small molecules inhibiting Neisseria meningitidis HO. Several of the compounds were found to have KD values in the micromolar range for Neisseria meningitidis HO and Pseudomonas aeruginosa HO. Moreover, data from simple host-pathogen models indicates that such compounds have antimicrobial activity.

COMP 58

Methodologies for efficient knowledge-based antibody homology modeling

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Antibodies are globular proteins composed of two heterodimers with each set containing a heavy chain (VH) and light chain (VL). The binding to an antigen is in most antibodies facilitated by six loops, three originating from the VL domain, termed L1, L2 and L3, and three from the VH domain, termed H1, H2 and H3. Due to their modular composition and high target specificity antibodies have become increasingly attractive for use as drugs. Antibody Homology Modeling

techniques have often been applied in generating therapeutically more effective antibodies. Here, we demonstrate a collection of procedures as well as an interface to meet the demands of effective antibody homology modeling. The application has flexible components allowing the integration of various work-flows associated with this specific form of modeling. The routines account for the particular structural composition of antibodies when searching for template candidates and building models. A knowledge-based approach is applied with an underlying database of antibody structures originating from the Protein Data Bank (PDB), clustered by class, species, subclass and framework sequence identity. A specially designed loop grafting routine allows for generation of xenogeneic antibody models.

Take-Home Message:

• Fast and efficient generation of antibody models

• Integration of various work-flows associated with antibody homology modeling

• Accounting for the structural composition of antibodies when searching for candidates and model building

• CDR Loop grafting

COMP 59

Prediction of drug resistance using all-atom molecular simulations

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Robust prediction of protein-ligand binding and drug resistance remains a difficult and challenging problem despite great strides made in both rigorous and more approximate free energy calculation methods. In this talk, we present our experiences using all-atom molecular dynamics followed by post-processing methods for estimation of binding free energies with application to the drug targets neuraminidase and epidermal growth factor receptor. Results of our optimization efforts, to improve virtual screening procedures using the program DOCK, will also be presented which focus on development of efficient protocols for reproduction of crystallographically observed binding poses using rigid, fixed anchor, and flexible ligand docking for a wide variety of targets.

COMP 60

Unveiling conformational changes of biological molecules using multiscale modeling and multiresolution experiments

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Multipronged approaches have recently gained interest for tackling structural problems related to large biological complexes. Structural dynamical information is often obtained by low-resolution experimental techniques, such as Cryo Electron Microscopy (cryo-EM), Small Angle X-ray Scattering (SAXS) and Fluorescence Resonance Energy Transfer (FRET). Each of these techniques offers different advantages and meet with different pitfalls, artifacts and limitations. Therefore a more accurate description could be obtained if all pieces of experimental data were taken together to annotate conformational states.

To achieve this goal we will present our current developments of multi-resolution/multi-scale computational tools to interpret conformational changes of biological molecules based on cryo-EM, SAXS or distance constraints. Normal Mode Analysis or Molecular Dynamics simulations are used to deform, in a physical manner, X-ray structures to fit low-resolution data. Using simulated data, we will show that such approaches are successful to predict structures in the range of 2~3 Å resolution.

COMP 61

Examining protein dynamics and function using multiscale methods

***Bernard R. Brooks**, brb@nih.gov, NHLBI, National Institutes of Health, Laboratory of Computational Biology, 5635 Fishers Ln, Bethesda, MD 20892-9314*

This presentation focuses on our recent efforts to develop multi-scale macromolecular modeling methods and to apply them to problems of examining protein dynamics and function. One objective in developing multi-scale modeling techniques is to be able to include multiple scale representations within a single study. By combining scales, one can examine properties that would be difficult or too costly to examine with a single model. Examples are presented from the following models:

(1) Grid based map objects (EMAP), (2) Coarse-grained models using elastic network models (ENM) and Langevin network models (LNM), (3) Coarse-grained models using Hydrophibic/Hydrophibic/Neutral models (BLN), (4) Atomic models using a classical force field (CHARMM, Amber,…), and (5) Models employing a quantum mechanical subsystem (CHARMM/Q-Chem,…)

Examples of methods employing these models include:

(1) Protein-protein docking with grid based methods, (2) Vibrational free energy partitioning and subsystem analysis, (3) Examining protein folding in confinement, and (4) Rapid exploration of local conformational space using self guided Langevin dynamics and replica exchange

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COMP 62

Extracting multiscale information from time series characterizing proteins under the influence of time dependent external forces

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Single-molecule experiments and computer simulations have generated data sets containing useful information about protein dynamics. However the many degrees of freedom present, time dependent external forces, and multiple time-scales complicate the task of summarizing the interesting information in these dynamical systems. I demonstrate how a collection of surrogate processes, estimated from a relatively small number non-equilibrium time series, can assist some PMF and diffusion coefficient computations. The methods are also useful when a good set of reaction coordinates is unknown, e.g. a collection of surrogate models can also be used to infer information about slowly evolving

degrees of freedom not directly monitored. Illustrative results obtained using various MD protein simulations [1-2] and AFM experiments are presented [3-4].

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COMP 63

Mixing structure-based and physics-based coarse-grained models: Application to membrane proteins

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We will present our recent development of new molecular models in which structure-based and physics-based coarse-graining (CG) approaches are combined. Physics-based concepts: while conserving the physicochemical properties of the different components in a system the MARTINI CG force field allows reducing the complexity of the description of a system down to chemical entities (3 to 6 heavy atoms). Structure-based concepts: elastic networks (ElNeDyn) are used to control the conformational space accessible to a protein. The results obtained from self-assembly simulations, potentials of mean force (PMF), and 3D pressure profiles of visual pigment rhodopsin in model membranes will be presented. The data show that the protein binding energies are strongly correlated to the interfaces involved and that the membrane bilayer has a significant contribution to the energy barriers encountered during association. This work brings new insights to our understanding of the forces driving protein self-organization in membrane bilayers.

COMP 64

Modeling of transmembrane proteins and peptides: All-atom and coarse grain molecular dynamics simulations of helical bundles in palmitoyloleoylphosphatidylcholine (POPC) lipid bilayer

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All-atom and coarse grain (CG) molecular dynamics (MD) simulations are carried out on systems containing a single helix, and four-, five- and six- helical bundles of three different proteins in a POPC lipid bilayer immersed in water. The AMBER99 force fields are used for the all-atom MD simulations. The new CG model utilized involves a new mapping method, non-bonded parameters recently developed, as well as internal parameters (bond, bend and torsion) fitted from all-atom simulations of 400 tetrapeptides in water and transmembrane protein systems. Through the comparison between all-atom MD, available experimental data and CG results, the accuracy of the new CG model is assessed and CG protein parameters are being improved. Insights gained on the relative stabilities of the different sizes of helical bundles will also be discussed.

COMP 65

Systematic coarse-graining of biomolecules

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The derivation of reliable and accurate coarse-grained (CG) force fields for biomolecular simulations is a significant challenge. This is particularly true for systems where different length and time scales must be bridged together. Multiscale coarse-graining based on statistical mechanical force matching is a systematic method based on a sound theoretical foundation, allowing the it to be used for both the development and testing of CG force fields. In this work the aggregation of a polyalanine peptide will be used as a test case because of its simplicity. The analysis performed on this system reveals some general aspects of coarse graining which can be directly applied to other systems.

COMP 66

Conserved networks underlying protein structure, folding, and dynamics

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Understanding the transition of one-dimensional information into three-dimensional information is the key to resolving the protein folding problem. Novel programs written in C++ were designed to identify conserved long-range interactions, which we propose govern protein topology, within our model system. This system consists of twenty-seven proteins belonging to three superfamilies: the all beta-sheet immunoglobulins, the mixed alpha/beta-plaits and the all alpha-helical death domains. Despite differences in sequence, function and secondary structure composition these three groups share a common sequence length and Greek-key topology. The results of exhaustive computational studies revealed a conserved network within each superfamily as well as a subset of conserved interactions shared between the superfamilies. Molecular dynamics simulations at high temperature clearly show that the conserved interactions are the most stable in comparison to the nonconserved interactions. Simulated annealing studies support their proposed role in dictating the Greek-key topology during folding. These novel results will be presented.

COMP 67

Linking genomic knowledge to natural products and drugs

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The large-scale datasets generated by genome sequencing and other high-throughput experimental technologies are the basis for understanding life as a molecular system and for developing medical, pharmaceutical, and other practical applications. The key to linking such large-scale datasets to practical values lies in bioinformatics technologies, not only in terms of computational methods, but also in terms of knowledge bases. In the KEGG database resource (http://www.genome.jp/kegg/) we organize our knowledge on higher-level systemic functions in computable forms, such as metabolism in KEGG pathway maps and therapeutic category of drugs in BRITE functional hierarchies. This enables bioinformatics analysis of genomic and molecular-level data to infer

higher-level functions through the process of pathway mapping and BRITE mapping. A variant of this approach is to infer chemical structures of endogenous molecules that can be synthesized in a given organism, knowing the enzyme repertoire in the genome and the biosynthetic pathways, together with possible biological activities. I will report on our strategy to analyze the chemical architecture of natural products derived from enzymatic reactions (and enzyme genes) and the chemical architecture of marketed drugs derived from human made organic reactions in the history of drug development.

COMP 68

Metabolic liability and SAR analyses derived from bioactivity databases

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SAR analyses conducted on libraries taken from bioactivity databases can yield insight into the dependence of therapeutic activity (and/or adverse side effects) on variations in chemical structure. Often such studies make the assumption that administered compounds are, in fact, the active chemical agents. Metabolic transformations following administration but prior to key biochemical processes involved in observed activity can produce significant structural modifications in the actual bioactive entities. Ideally, then, SAR analyses should include examination of known metabolic outcomes for compounds under investigation. Mining this information from available electronic collections of known biotransformations and correlating it to SAR data will be discussed.

COMP 69

Discovery and data mining using the NCBI BioSystems database, a centralized repository linking small molecules to their biological function

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The NCBI BioSystems database contains biological relationships between the small molecule records found in PubChem and the gene and protein records found in Genbank. These relationships directly link the structure of small molecules to their biological function. By centralizing and standardizing these records and then linking them to multiple NCBI databases like PubMed and PubChem BioAssay, the BioSystems database is intended to be a convenient and extensive resource for fundamental structure-function information and associated annotations.

COMP 70

SAR studies using ChemBiobase, a knowledgebase on Target centric small molecules

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Scientists involved in drug discovery process require broad range of information to assist their decision making process. To help in this task, they have access to large databases built in-house as well as provided by various vendors. In addition, they refer to vast amount of scattered information available as Patent and Journal literature. They further look for solutions which help to manage the data deluge. Given this, Jubilant has developed comprehensive set of target centric ligand databases i.e. ChemBioBase which provide useful and important complimentary information on small molecules that exhibit activity against targets in a particular family. These databases cover wide range of druggable targets including Kinases, Proteases, GPCR's, Ion channels and Nuclear Hormone receptors. Such thematic databases would help the researchers to know everything in the given field and carry out several virtual screening tasks. ChemBioBase would allow the researchers to perform structure-activity relationship (SAR) studies for molecules tested for a particular target at a given assay condition across the publications. Manually drawn chemical structures from ChemBioBase are used for clustering of molecules. This is done with respect to defined scaffold or activity and to create chemical libraries. Utility of these databases towards SAR along with content and coverage in terms of chemistry/biology spaces will be discussed.

COMP 71

Ab initio transition state optimizations of the peptidyl transfer reaction in the ribosome

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There are still open questions regarding the mechanism of peptide bond synthesis in the ribosome. To remedy this, unconstrained minimal models that include the first shell of solvation have been derived from previous quantitative

EVB calculations. Not only are the resulting energies close to the experimental enthalpy of activation, density functional theory insists on a conformation in close agreement with the crystal structure of the RAP transition state (TS) analog (1VQP). Furthermore, the 2'OH-C2063 bound water molecule, whose presence is acknowledged but not fully understood, is predicted to be a hydrogen transfer intermediary in an eight membered TS. In its absence the reaction is seen to progress through a six membered TS. Also, the experimentally observed water molecule bound to the oxyanion of the tetrahedral intermediate is seen to be crucial for its stabilization making it one of the most important catalytic groups in this reaction.

COMP 72

Artificial reaction coordinate “tunneling” in free energy calculations: The catalytic reaction of RNase H

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We describe a method for the systematic improvement of reaction coordinates in quantum mechanical / molecular mechanical (QM/MM) calculations of reaction free energy profiles. In umbrella-sampling free energy calculations, a biasing potential acting on a chosen reaction coordinate is used to sample the system in reactant, product, and transition states. Sharp, nearly discontinuous changes along the resulting reaction path are used to identify coordinates that are relevant for the reaction but not properly sampled. These degrees of freedom are then included in an extended reaction coordinate. The general formalism is illustrated for the catalytic cleavage of the RNA backbone of an RNA/DNA hybrid by the RNase H enzyme of bacillus halodurans. We find that in the initial attack of the phosphate diester by water, the oxygen-phosphorus distances alone are not sufficient as reaction coordinates, resulting in substantial hysteresis in the proton degrees of freedom and a barrier that is too low. If the proton degrees of freedom are included in an extended reaction coordinate, we obtain a barrier consistent with the experimental rates. The method used to identify important degrees of freedom, and the procedure to optimize the reaction coordinate are general and should be useful both in classical and in QM/MM free energy calculations.

COMP 73

Improvements of a fragment-based quantum chemical approach: The border region problem

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For the accurate description of reactions in biochemical systems, QM/MM calculations became more and more important in the last few years. In these calculations, the system is divided into a small part, in which the reaction is taking place, calculated with an ab initio or semi-empirical approach, and the rest, treated by means of a molecular force field. Another possibility to calculate large molecular systems on a fully quantum chemical basis are fragment-based approaches, in which a macromolecule is segmented into many fragments, for which conventional quantum chemical calculations are performed. In one of these approaches, the Field-Adapted Adjustable Density Matrix Assembler (FA-ADMA [1, 2]), fragment electron density matrices are combined to form the total density matrix of the complete system, from which partial charges, electrostatic potentials but especially also energies and gradients can be calculated for fully quantum chemical optimizations.

To divide a macromolecular system for the just mentioned approaches, bonds in the border region between the QM and the remaining part must be broken. For the QM calculations these dangling valences must be saturated. Many methods to tackle this border region problem have been proposed. Especially the use of hybrid orbitals or highly parameterized capping atoms seems to be promising to improve the accuracy. We will use FA-ADMA to quantitatively evaluate and compare three different border region treatments: capping hydrogen atoms, pseudobonds [3], and generalized hybrid orbitals [4, 5].

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COMP 74

QM/MM Studies of interaction mode of B12-independent dehydratase with glycerol

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QM/MM simulations and high-level quantum mechanics analysis of glycerol B12-independent glycerol dehydratase were performed based on the high-resolution model at 1.8 Å in the Protein Data Bank (PDB code: 1r9d). Our QM/MM studies show that four hydrogen bonds formed between glycerol and H164, S282, E435, and D447 anchor glycerol for hydrogen abstraction by thiyl radical on C433, which agrees with the solved structure. In addition, our analyses indicate that the distance between the hydrogen on C3 and the thiyl group is slightly shorter than that of hydrogen on C1 and the strongest H-bond occurs between S282 and hydroxyl group on C1 of glycerol. This strongest H-bond leads to more deficient electron density on the hydrogen of the H-C bond on C1 than that on C3. Based on the distance between the thiyl group and C1/C3 hydrogens, and the electron density of the hydrogens on C1 and C3, the hydrogen abstraction can occur both on C1 and C3, probably more favorable on C3. Furthermore, the interaction energies between glycerol and its two radical form and two Tyr residues suggest that the presence of Y339 and Y640 mainly provides an inert environment that stabilizes the free radical intermediates during the catalytic reaction. This study advances understanding of binding mode of the B12-independent glycerol dehydratases and aids in rational design of glycerol dehydratase by an enzyme engineering approach.

Keywords: QM/MM, Glycerol, B12-independent dehydratase, Hydrogen abstraction

COMP 75

Using semiempirical methods to predict Young's moduli of elastomeric proteins

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Structural proteins are obviously of great importance in biology. One of their more interesting mechanical properties, elastic modulus, has now been modeled using the newly developed PM6 semiempirical method. The computational issues involved will be discussed, and illustrations of the application of the resulting method to the simulated stretching of two fibrous proteins, collagen and silk, in regions where Hooke's law is applicable, will be given. A curious and as

yet unresolved distortion that occurred during the stretching of the crystalline domain of silk from bombyx mori will be described.

COMP 76

What happens to amino acids' hydrogen bonding in variable pH?

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In this study we calculate different conformations of asparagine (Asn), aspartic acid (Asp), cysteine (Cys), and histidine (His) using density functional (DFT) methods. Amino acids intra- and intermolecular interactions are significantly influenced by surrounding residues and the pH of their environments. Hydrogen bonds, in particular, control folding in secondary and tertiary structures in proteins and significantly affect enzymatic activity. By employing the B3LYP/6-31+G(d,p) method we determine the major conformers of Asp, Asn, Cys, and His in their neutral (no charges), zwitterionic, acidic (protonated), and basic (deprotonated) forms, in gaseous and aqueous media. We find that changes in acidity critically influence and limit hydrogen bonding patterns, and thus the stability of the resulting conformers. We compare these findings with our previous results on serine (Ser) and threonine (Thr) conformers.

COMP 77

Dynamic contributions to enzyme catalysis as illustrated by orotidine monophosphate decarboxylase

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Orotidine 5'-monophosphate decarboxylase (OMPDC) catalyzes the exchange of CO_2 for a proton at the C_6 position to form uridine 5'-monophosphate (UMP), providing a rate acceleration with respect the uncatalyzed reaction of 17 orders of magnitude. The remarkable catalytic proficiency of this enzyme has given raise to a number of different reaction mechanism proposals. In this work, by mean of combined QM/MM simulations, we analyze the contributions to the lowering of the free energy barrier from transition state stabilization, evolution of protein conformations along the reaction path, and reaction dynamics. Both computation and experiments show that there is an upper limit that the transition state can be stabilized in OMPDC catalyzed reaction, whereas the remaining

effects are elucidated from structural and dynamics investigations. This paper summarizes the findings from our theoretical study to account for the origin of this remarkable enzyme.

COMP 78

Integrating electronic-embedding QM/MM approaches with a conductor-like screening model

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An open problem in modeling chemical events in QM/MM methods is how to incorporate solvent effects via implicit electrostatic models. Implicit solvent models have today wide use in electronic structure calculations of small molecules. One of these models is based on the COSMO method which assumes that the surface of the molecule acts as a conductor. Image charges are added on the molecular surface to satisfy the appropriate boundary conditions in the presence of solute charges. We have developed a self-consistent domain fragmentation of conductor-like screening charges (FCOSMO). The approach is based on a fragmentation of the macromolecular surface into small density domains, which are iteratively and self-consistently derived by solving classical electrostatic boundary conditions, allowing for analytical solutions of each charge domain, largely improving scalability. Furthermore, iteration on density domains is then coupled with iterations on QM spatial domains in QM/MM calculation.

COMP 79

Intramolecular hydrogen bonding of ortho-substituted arylamide oligomers: Model compound study

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Foldamers, synthetic oligomers that fold into well-defined secondary structures, are designed to mimic important biological motifs. Hydrogen bonding is one of physico-chemical interactions that influences the overall conformation of a

foldamer. In this study, we performed a systematic study to assess the structural features of arylamide foldamer building blocks that affect hydrogen bonding. We employed a combination of quantum mechanics, molecular dynamics simulations and NMR experiments to investigate hydrogen bonding and its effect on the conformational distributions. The effect of varied solvent polarities was also investigated. This work is aimed at understanding the principles that control the shape of aromatic foldamers and ultimately their function.

COMP 80

Quantum chemistry for protein structure and dynamics

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Efficient fragment-based quantum mechanical method for accurate calculation of protein in

solution is developed and applied to study protein structure and dynamics. The quantum calculation of

protein is further employed to generate new force field that features polarized protein-specific charges

(PPC). The PPC provides a realistic description of the polarized electrostatic state of the protein than the

widely used mean field charges such as AMBER and CHARMM. Extensive MD simulations have been

performed to study the efficacy of PPC through direct comparisons between results obtained from PPC,

the standard AMBER charges and experimental results. The impact of PPC on protein electrostatic

interaction, stability of hydrogen bonds, protein-ligand binding and protein dynamics are presented in

this talk. The results clearly demonstrate that the correct description of the electronic polarization of

protein is crucial and PPC shall have important applications for MD simulation studies of protein

structure and dynamics.

COMP 81

Post density functional theory approaches for elucidating metalloenzyme function and reactivity

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Open shell transition metal ions play a crucial role in the function and reactivity of metal-containing enzymes. For example, mononuclear and binuclear iron centers are present in the active sites of many heme and non-heme proteins. We have developed a variety of computational methodologies based on "post" spin density functional theory calculations to accurately predict physico-chemical parameters of iron sites in proteins. In particular, we have implemented a rigorous method based on sum-over-states perturbation theory to account for spin-orbit coupling effects which are not included in non relativistic Kohn-Sham calculations. We have applied these methodologies to study the electronic structure, magnetic properties, and reactivities of heme and non-heme iron proteins and related model compounds. We predict, with a high degree of accuracy, and also interpret spectroscopic (e.g., Mossbauer) parameters of iron proteins and establish new relationships between their electronic structures, geometric structures, and spectroscopy.

Supported, in part, by NSF CAREER award CHE-0349189 (JHR)

COMP 82

The snake that fits your brain: Python for computational chemists

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Because of its easy to understand structure and syntax, extensive standard library, supportive community, and the easy of connecting to external components, Python has attracted a fair amount of attention in the chemistry community. In addition to a large number of open-source projects, multiple vendors of computational chemistry tools have provided Python support for their tools. After a brief overview of the language's history and features, I will present a series of case studies of the use of Python to automate day-to-day tasks and generally make one's life easier. Following this, I will describe a model for using Python to interact with legacy code in a straightforward manner. I will close with a

few words about the future directions of the Python language. Since no talk about programming languages and computational chemistry is complete without an example of handling legacy Fortran code, this talk will be incomplete; and we can all be happy for that.

COMP 83

The Cactvs Chemoinformatics Toolkit: Universal chemical information processing with Tcl scripts

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At its core, the Cactvs Toolkit is an universal chemical information processing interpreter with specific strengths in the areas of custom batch processing of large datasets and for implementing chemistry-oriented cgi/fcgi-based Web applications. Its standard scripting language interface is industry-standard Tcl (optionally also Tk for graphical user interfaces) enhanced with a rich orthogonal set of chemistry-specific command additions and object classes. Nearly unlimited extensibility, automatic lookup and invocation of computation sequences for user-definable property sets as well as intelligent maintenance of object data validity are unique features of this tool. Support for multi-threading on the script level, object transfer via network connections for distributed processing in combination with a very high-level scripting language interface enable the rapid implementation of concise yet scalable solutions for chemistry data processing tasks.

COMP 84

Vision: A software tool for visual programming and scientific workflows

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Visual programming has been around for several decades and has been popularized by tools such as AVS and AVS Express, Data Explorer and Open DX. These software tools pioneered the concept of software extensibility by users without requiring them to learn the syntax of a programming language or the intricacies of the data structures used to represent complex data in memory. We have used AVS with great success for over a decade for the visualization and analysis of structural data in biology. However, constraining data types and data models, the lack of scripting ability, and some of the architectural choices made in the design of AVS presented substantial hurdles in using AVS. Over the

past 7 years we have developed a Python-based software component Vision that supports the paradigm of visual programming.

We will shortly demonstrate Vision and emphasis its main architectural and design differences with other visual programming tools including: its design as a component to be integrated in other software applications, its flexibility in defining new computational node and data types, and its scripting capabilities. We will also demonstrate Vision's use for tasks as varied as extending molecular visualization and analysis tools with new functionality, creating end-user applications abstracting a complex computational workflow, and building scientific workflows that can be executed as standalone programs.

COMP 85

Crunching molecules and numbers in R

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R is a well established environment for statistical and numerical modeling. Many areas of chemistry involve statistical analysis and R is well suited for these applications. On its own R is ignorant of chemical information, and provides purely statistical functionality. In this talk I will provide a high level overview of the capabilities of R, briefly describing the environment and language, as well as linking R to pre-existing code. I will then discuss how R can be converted from a chemistry agnostic system to one that is capable of manipulating and analyzing chemical structures. I will also highlight applications in various areas of chemistry covering topics such as the analysis of molecular dynamics runs, QSAR modeling, chemometrics and accessing public chemistry databases. I will finally touch upon some issues related to the use of R in HPC scenarios, focusing on parallelization and large datasets.

COMP 86

Optical structure recognition application

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We present recent developments in the Optical Structure Recognition Application (OSRA) project. OSRA is open source software that allows recognition and

extraction of chemical structure information from sources such as journal articles, patent documents, and web-based images of small molecules. The new version of OSRA features an advanced page segmentation algorithm for separation of chemical images from the surrounding text, better recognition of structural elements such as wedge bonds, double and triple bonds etc., structure definition (SD) file format output, and better integration with third-party chemical editors and chemoinformatics software.

COMP 87

Free energies and mechanisms of chemical reactions in enzymes and in solution with QMMM minimum free energy path

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Combined QM/MM methods provide an accurate and efficient energetic description of complex chemical and biological systems, leading to significant advances in the understanding of chemical reactions in solution and in enzymes. Ab initio QM/MM methods capitalize on the accuracy and reliability of the associated quantum mechanical approaches, however at a much higher computational cost compared with semiempirical quantum mechanical approaches. Thus reaction path and activation free energy calculations encounter unique challenges in simulation timescales and phase space sampling. Recent developments of the QM/MM minimum free energy path method overcome these challenges and enable accurate free energy determination for reaction processes in solution and enzymes. Applications to several enzymes will be featured. (H. Hu and W. Yang, “Free energies of chemical reactions in solution and in enzymes with ab initio QM/MM methods,” Ann Rev of Phys Chem, 59:573, 2008.)

COMP 88

Dynamical effects are important in ultrafast reactions but not in enzyme catalysis: Advances in modeling long time enzyme dynamics

***Arieh Warshel**, warshel@usc.edu, Chemistry, University of Southern California, los Angeles, CA 90089*

Dynamical effects play important role in ultrafast photobiological reactions. However the role of such effects in enzymatic reactions is far less clear. That is, although recent works have focused on the idea that the motions associate with the folding coordinate (or related conformational transitions) provides major

contribution to enzyme catalysis, the available experimental studies could not confirm this idea

Simulation techniques have been used to examine the magnitude of the dynamical effects and their functional role. Overall it was found that these effects do not contribute to catalysis, regardless of the definition used. Unfortunately computational studies were unable to explore this problem in a direct way due to the enormous computer time needed for simulation of millisecond processes .

Recently we have developed a multiscale approach that allowed us to explore the dynamics of the conformational and chemical motions in enzyme catalysis in the ms time scale. Our preliminary study shows that the thermal energy of the conformational motion is dissipated completely during opening and closing of the active site and cannot not affect the time of the chemical process as long as the chemical barrier is higher than the binding barrier (kcat < kon) .

COMP 89

Computational delineation of the influence of slow modes on the catalytic step in DNA replication in a high fidelity polymerase

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The Bacillus fragment enzyme belongs to a class of high fidelity polymerases which are essential for DNA replication/repair. The enzyme is highly processive, capable of adding the correct nucleotides (Adenine opposite thymine, etc.) at high rates of 115 bases per nucleotide binding event with exceptionally high accuracy (1 error in 1000 incorporations). We present an analysis of the energetics and structural rearrangements just prior to and during the chemical step through free energy (umbrella sampling) studies using a combination of classical molecular dynamics, mixed quantum mechanics molecular mechanics simulations. Our results provide molecular-level insight on several new aspects of the catalytic machinery employed by this enzyme. Specifically, we suggest that an intriguing coupling between local structural arrangements at the active site and more global DNA-polymerase modes further lower the barrier for catalysis and contribute to the efficiency of the enzyme. We also find that the different stages of the reaction show different frequent spectra; specifically, we liken the flattening of the spectrum to the engagement of a molecular clutch for efficient energy transfer across different modes. We discuss the consequence of these results to polymerase fidelity (mismatch and non-native incorporations) and the relevance to single molecule experiments.

COMP 90

Engineering enzyme:substrate specificity: From free energy simulations to computational protein design

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Specific interactions between aminoacyl-tRNA synthetases (aaRSs) and their amino acid substrates are crucial for maintaining the integrity of the genetic code; conversely, engineering these interactions can lead to a modified genetic code. We report the “in silico” engineering of several aaRSs, using computer simulation methods, in an effort to understand and rationally modify their amino acid substrate specificity. Two main approaches are employed. Molecular dynamics free energy simulations are used to perform rational, site-directed mutagenesis. Free energy simulations have matured into a predictive tool, which can probe effects that are difficult to study experimentally. We have applied this approach extensively to study electrostatic interactions in the active site of aspartyl-tRNA synthetase, revealing for example substrate-assisted specificity and electrostatic induced fit. A second main approach is a recent directed evolution method, where selected positions in the protein are mutated combinatorially to increase the binding of a cognate or non-cognate ligand. This approach has been implemented, tested, and applied to class I and class II aaRSs; the results compare favorably with both site-directed mutagenesis and directed evolution experiments.

COMP 91

Proton transfer reactions in ketosteroid isomerase.

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Ketosteroid isomerase (KSI) catalyzes the isomerization reaction of steroids to their conjugate isomers by a two-step proton transfer mechanism. The overall reaction involves the formation of a dienolate intermediate stabilized by hydrogen bonds. The mechanism of these proton transfer reactions was investigated using a hybrid quantum/classical molecular dynamics approach. Free energy profiles for both proton transfer steps were calculated along a collective reaction coordinate. The nuclear quantum corrections to these energy barriers were

determined using path integral methods. The transmission coefficients for both reactions were calculated to account for barrier recrossings. Average structures were calculated along the collective reaction coordinate to identify the conformational changes that facilitate the proton transfer reactions. Analysis of thermally averaged distances between the substrate and key residues provides new insight into the formation of catalytically critical hydrogen bonds in KSI. This study demonstrates the impact of enzyme motion and hydrogen bonding interactions in enzyme catalysis.

COMP 92

Linking enzyme structure, dynamics, and catalysis

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Enzymes are dynamic molecules. In the past, enzymes have been viewed as static entities and their high catalytic power has been explained on the basis of direct structural interactions between the enzyme and the substrate. Recent evidence has linked protein dynamics to catalytic efficiency of enzymes. Further, motions in hydration-shell/bulk solvent have been shown to impact protein motions, therefore, function.

Theoretical and computational studies of protein dynamics linked to enzyme catalysis will be discussed. Investigations of cyclophilin A and dihydrofolate reductase have lead to the discovery of networks of protein vibrations promoting catalysis. Results indicate that the reaction promoting dynamics in these enzymes is conserved across several species. Moreover, we have characterized the protein dynamics of a diverse super-family of dinucleotide binding enzymes. These enzymes share very low sequence similarity and have different structural features. The results show that the reaction promoting dynamics is remarkably similar in this enzyme super-family.

COMP 93

Protein flexibility and energy flow during enzyme catalysis

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Enzymes are dynamic molecules. Although in the past enzymes have been viewed as static entities, recent evidence from experimental, theoretical and computational work indicates that protein dynamics play a significant role in enhancing catalytic activity. Investigations of the biophysical mechanisms for several enzymes such as cyclophilin A and dihydrofolate reductase have revealed a network of protein motions that promote catalytic activity. Further characterization also indicates that the reaction-promoting motions are conserved as part of the enzyme fold across several species, even though they have low sequence similarity. Extending this study to a superfamily of enzymes, namely the dinucleotide binding Rossmann Fold proteins (DBRP), shows that in spite of having very low sequence homology and different structural features, the overall intrinsic dynamical flexibility of the superfamily is remarkably well preserved with respect to the catalytic step.

The dynamical coupling observed between exterior surface regions with the active site entails energetic coupling between them. To characterize this energetic coupling, we use an integrated approach to analyze residues that constitute pathways through which energy propagates from the flexible exterior surface regions to the active site of the protein. Our results reveal that the network residues identified previously are effective receivers of energy to the active site. This is particularly observed in the context of looking at shortest paths that lead into the active site, where by the network residues act as junctions to receive energy from various sources surrounding them. The dynamics of these residues immediately affect that of the substrate/ co-factor and hence affect the catalytic step. The identification of such networks may have significant impact in understanding the nature of allosteric controls these proteins may exhibit.

COMP 94

Binding free energy prediction by molecular dynamics based docking and volunteer computing

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The distributed volunteer computing paradigm has been employed by the Docking@Home project to perform protein-ligand docking calculations. Using this computing paradigm our aim is to develop a dynamically adaptive and multi-scale docking protocol which will provide fast and accurate predictions for protein-ligand binding geometries and binding free energies. We have augmented a force-field based docking method with an empirical scoring scheme based on the categorization of interacting protein-ligand atom pairs. The proposed scoring function is simple and applicable to any protein-ligand complexes. The performance of this novel scoring function was compared to the performance of a significantly more computationally expensive linear interaction energy approach based on short molecular dynamics simulations of docking poses. The novel scoring function demonstrated improved performance in comparison to binding free energies for native ligand conformations. The novel scoring function also significantly improved enrichment of active compounds in virtual screening against a large number of decoys.

COMP 95

A fresh look on 3D database searching: Toward a unified description of pharmacophoric features and shape

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Structure- and ligand-based virtual screening are very much in the heart of lead discovery efforts at early stages. Since three-dimensional molecular properties like the arrangement of pharmacophore features and the shape determine a molecule's ability to bind to a protein target of interest, the question arise, how molecules should be represented in screening databases.

In this talk, we introduce a novel molecular descriptor representing potential pharmacophoric points and shape such that they are suited for indexed database access. The descriptor can be combined with recently developed compressed bitmap indices to allow a highly efficient access to compounds based on structural features. The realization within structure-based and ligand-based virtual screening tools together with example applications will be presented.

COMP 96

A gradient-directed Monte Carlo approach to molecular design

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The recently developed linear combination of atomic potentials (LCAP) approach allows continuous optimization in a discrete chemical space, and thus is useful in the design of molecules for targeted properties. To address further challenges arising from the rugged, continuous property surfaces in the LCAP approach, we developed a gradient-directed Monte Carlo (GDMC) strategy as an augmentation to the original LCAP optimization method. The GDMC method retains the power of exploring molecular space by utilizing local gradient information computed from the LCAP approach to jump between discrete molecular structures. It also allows random MC moves to overcome barriers between local optima on property surfaces. First, the combined GDMC-LCAP approach is demonstrated for optimizing nonlinear optical properties in a class of donor-acceptor substituted benzene and porphyrin frameworks at the quantum mechanical level. Second, GDMC is applied to protein sequence design and protein folding using the HP lattice model and RosettaDesign. The GDMC algorithm proves to be particularly efficient and significantly improves the sampling of the sequence and conformation spaces. In summary, the GDMC approach is general and robust for discrete global optimization problems as long as the gradients can be constructed from a continuous treatment of the discrete molecular space.

COMP 97

Validating conformer generators using experimental structures: Promise and problems

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The problem of validating conformer generators has been of longstanding interest to the modeling community. A popular approach has been to assess the ability of a conformer generator to reproduce experimental solid state structures from databases such as the PDB and the CSD. These investigations provide great promise and hold significant problems. The promise is that these experiments will allow an estimation of the ability of a conformer generator to sample conformational space close to the experimental structure. Identifying this structure or one close to it is of considerable interest in the areas of docking, binding mode perception and detection of common binding elements among different compound classes. The problems fall into two classes: identifying suitable structures to try to reproduce and selecting the correct metrics to compare the computed conformers to the experimental.

This presentation will present datasets of structures suitable for this sort of comparison and introduce some new metrics for the comparison of experimental

and computed conformations that overcome the inherent problems with metrics such as RMSD. Particular attention will be paid to appropriate handling of experimental error in PDB structures and to matching conformers to the experimental data (electron density) and not the atomic models for this data.

COMP 98

Binding of ruthenium-based organometalic protein kinase inhibitors to PIM1, GSK-3, and CDK2 protein kinases evaluated through ensemble molecular docking simulations

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Vast majority of enzyme inhibitors are small organic molecules that gain their specificity by a combination of weak interactions, including hydrogen bonding, electrostatic contacts, and hydrophobic interactions. We investigate a class of inhibitor coupounds derived from staurosporine and built around a Ru-based organnometalic scaffold. We employ a combination of molecular docking and molecular dynamics simulations on a highly scalable parallel computing platform to study the interactions of these compounds with three kinases, namely PIM1, GSK-3 and CDK2. As both the structural and sequence alignment of these kinases showed high conservation in the ATP binding pocket, we focussed our studies on the understanding the molecular features of interaction the inhibitors with the kinases to predictively model the structure of the inhibitor-protein complex as well as to provide insights on the selectivity of these inhibitors toward each kinase. Our results provide molecular-level insight into the role of protein flexibility in molecular recognition and the importance of accounting for such flexibility in predictive modeling of kinase-inhibitor complexes.

COMP 99

CNS library design using multiple parameter optimization

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Multi-parameter Optimization (MPO) techniques have been used to design a series of libraries around pyrazolopyrimidine core for the Casein Kinaseδ/ε (CK1δ/ε) project. These MPO models are generated via the summation of the following series specific models: cell-free and whole-cell potency, rat and human clearance, in vitro permeability (MDCK); as well as the following physical properties: molecular weight, lipophilicity: clogP, cElogD, and polar surface area (PSA). The calculated MPO scores show a strong correlation with the MPO scores calculated from the summation of the experimentally determined properties themselves. Finally, we show how the MPO tool has affected the overall physical property profile of the synthesized libraries.

COMP 100

Lead optimization of progesterone receptor partial-agonists by structure-based design and QSAR approaches in tandem

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Endometriosis is an estrogen-dependent disease in which endometrial tissue proliferates at extra-uterine sites. This condition is associated with pain and infertility and it afflicts 10-15% of women of child-bearing age. Progestins (full progesterone receptor agonists) are effective in treating endometriosis by opposing the action of estrogen in ectopic endometrial tissue but have numerous side effects associated with their full agonist activity and poor steroid receptor selectivity.

The goal of this program was to identify selective progesterone receptor partial-agonists that can provide antiproliferative effects while minimizing side effects associated with progestins. The initial “amide” lead was optimized to a pyrrolidine template, which was further optimized to build in the desired potency, agonism, selectivity and P450 profiles using structure-based design and QSAR modeling approaches.

This presentation will discuss the utilization of modeling approaches to optimize the pyrrolidine template to the pyrrolidine amide and carbamate templates.

COMP 101

Prediction of environmental impact of energetic materials with atomistic computer simulation

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There has been considerable interest in the development of new Insensitive Munitions (IM) compounds due to their thermal stability and low shock sensitivity over traditionally used explosive compounds. Six such compounds are 2,4-dinitroanisole (DNAN), N-methyl-p-nitroaniline (MNA), Dinitropyrazole (DNP), Nitrotriazolone (NTO), 1-methyl-2,4,5-trinitroimidazole (MTNI) and 1,3,5-triamino-2,4,6-trinitrobenzene (TATB). Due to the increased environmental and safety concerns, it is necessary to determine how these compounds behave in the environment in terms of bioaccumulation potential and aqueous solubility. A pre-biological screen based on the knowledge of octanol-water partition coefficients and Henry's law constants is useful in this aspect. In this work, we develop force fields for the explosives to predict their octanol-water partition coefficients, Henry's law constants and also vapor-liquid equilibria, vapor pressure and critical points. NPT molecular dynamics simulation coupled with free energy perturbation technique is used to compute the physicochemical properties and Gibbs-Duhem integration is used to determine the vapor-liquid equilibria, vapor pressure and critical parameters.

COMP 102

Investigating intramolecular hydrogen bonding in aromatic oligoamide foldamers

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We investigate aromatic oligoamide foldamers, which can be designed to have medical functions. As the shape of a foldamer strongly influences its function, an atom-level understanding of interactions that govern the foldamer shapes and stabilities is necessary for rational design. Hydrogen-bonding (H-bonding) plays a critical role in the conformation of an oligomer along with its related function. The formation of a stable, intramolecularly H-bonded system is associated with solvent effects and intricate arrangements of the proton donor/acceptor units, which can be oriented to enhance stability.

A comprehensive ab initio study followed by molecular dynamic calculations has been performed on diarylamide model compounds containing various intramolecular H-bond patterns, with an aim of studying the influence that the presence of one H-bond has on the strength of another, shared one. Our results demonstrate to what extent the cooperativity between shared H-bonds exists in this type of foldamer monomer unit.

COMP 103

Modeling the reactivity of acid amplifiers

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Simultaneously improving resolution, line-edge roughness (LER), and sensitivity of extreme ultraviolet (EUV) chemically amplified photoresists is essential to the continued success of microlithography. We have proposed that the best way to meet this goal is to create more acid using compounds known as acid amplifiers. These compounds decompose autocatalytically in the presence of acid to generate additional acid. We present the thermal stability properties of fifteen new acid amplifiers and present detailed kinetics of five new compounds using

19F NMR in the absence and presence of base allowing for the study of autocatalytic and non-catalytic reaction pathways, respectively. Compounds with the largest distinction between catalyzed and uncatalyzed rates should give the best lithographic performance. Thermodynamic and kinetic models are used to study these new acid amplifiers. This approach allows us to predict the reactivity of these compounds and provides insight into some of the unexpected chemistry.

COMP 104

Thermodynamically dominant hydration structures of aqueous ions

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A statistical mechanical framework to parse the hydration free energy of an ion into chemical, packing, and long-range interaction contributions is developed. The local chemical term is recast as a sum over coordination states, with each step-wise increment in the coordination number more fully accounting for the chemical contribution. This approach is used to interrogate the thermodynamic importance of various hydration structures $X[H_2O]_n$ of X(aq) ($X= Na^+, K^+, F^-$) within a classical molecular mechanics framework. States with $n \leq n'$ (n' is the most probable coordination state) account for all of the chemical term. For states with $n > n'$, the influence of the ion is tempered and changes in coordination states due to density fluctuations in water appears important. The influence of the ion on the solvent matrix is local and only a subset of water molecules ($n \leq n'$) contribute dominantly to the hydration thermodynamics. The importance of our work to ion-specific interactions is discussed.

COMP 105

Solvent-dependent mechanisms for triazolinedione and singlet oxygen ene reactions from QM/MM simulations

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Combined quantum and molecular mechanics (QM/MM) simulations have been used to study condensed-phase ene reaction mechanisms. Speed and accuracy demands have led to the development of enhanced algorithms and a novel 3–D potentials of mean force (PMF based on three reaction coordinates) method for

analytically reproducing free–energy profiles and surfaces with full sampling of solute and solvent coordinates. The presentation will focus on the two ene reactions between tetramethylethylene with singlet oxygen ($^1O_2$) and 4–phenyl–1,2,4–triazoline–3,5–dione (PTAD) in multiple solvents. The calculations find both reaction mechanisms to be highly dependent on the reaction medium with different intermediates proceeding to products in the PTAD system and a conversion from a concerted to stepwise mechanism when proceeding from gas to solution for the $^1O_2$ system. (*J. Am. Chem. Soc.* **2009**, *131*, 2530–2540.; *J. Org. Chem.* **2008**, *73*, 912–922.)

COMP 106

Reactive force field modeling of Cu2+ and CuCl+ in aqueous solutions

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Non-polarizable and non reactive force fields perform poorly at realistic modeling of Cu2+ in water due to the strong polarization effect, charge transfer and quantum phenomenon like Jahn Teller Distrortion. We have parameterized ReaxFF, a polarizable and reactive force field, to simulate Cu2+ and CuCl+ in water with high accuracy. We have employed a multistage fitting of the force field parameters against a training set including several ab initio derived copper-copper, copper-oxide and copper-chloride condensed phases as well as classically derived configurations of several Cu2+-water, Cl--water and CuCl+-water clusters generated iteratively by the model potential. MD simulations using the trained force field successfully reproduced the experimentally observed Jahn-Teller distorted octahedral geometries of aqueous Cu2+ and CuCl+. The effect of pH on the configurations of copper chloride in water has been studied. The force-field is under development to extend it to model copper-glycine binding and eventually copper-peptide binding.

COMP 107

Simulating macromolecules by structure based coarse graining and adaptive resolution methods

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The relation between atomistic structure, architecture, molecular weight and material properties is a basic concern of modern soft material science. The longstanding aim by now goes far beyond standard properties of bulk materials. A typical additional focus is on surface interface aspects or the relation between structure and function in nanoscopic molecular assemblies. This all implies a thorough understanding on many length and correspondingly time scales ranging from (sub)-atomic to macroscopic. Traditionally computer simulations have been separated in two main groups, namely simplified models to deal with generic or universal aspects, i.e. critical exponents, of polymers and those employing classical force field simulations with (almost) all atomistic detail, i.e. for the diffusion of small additives in small “sample”. To progress further adaptive schemes have to be developed, which allow for a free exchange of particles (atoms, molecules) between the different levels of resolution. First attempts towards this direction will be presented in this lecture. We study model systems, which display a spatially variable resolution with a free exchange of particles between the different regimes. The new scheme can be understood within a (limited analogy) to a geometry induced phase transition, where in the transition regime degrees of freedom are switched on or off. Theoretically one can formulate this in terms of fractional degrees of freedom. This methodology has been tested for methane like tetrahedral liquids, polymers in solution as liquid water.

COMP 108

Designing self-propelled trains of microcapsules

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Using simulation and theory, we demonstrate how nanoparticles can be harnessed to regulate the interaction between multiple initially stationary microcapsules on a surface and promote the self-propelled motion of these capsules along the substrate. The first microcapsule, the “signaling” capsule, encases nanoparticles, which diffuse from the interior of this carrier and into the surrounding solution; the remaining capsules are the “target” capsules, which are initially devoid of particles. Nanoparticles released from the signaling capsule modify the underlying substrate, and thereby initiate the motion of the target capsules. The latter motion activates hydrodynamic interactions, which trigger the signaling capsule to follow the targets. The continued release of the nanoparticles sustains the motion of all the capsules. In effect, the system constitutes a synthetic analogue of biological cell signaling and our findings can shed light on fundamental physical forces that control interactions between cells. Our findings can also yield guidelines for manipulating the interactions of synthetic microcapsules in microfluidic devices.

COMP 109

Single-chain dynamics in a homogeneous melt and a lamellar microphase: A comparison between Smart-Monte-Carlo dynamics, slithering-snake dynamics, and slip-link dynamics

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We investigate the ability of Monte-Carlo algorithms to describe the single-chain dynamics in a dense homogeneous melt and a lamellar phase of a symmetric diblock copolymer. A minimal, coarse-grained model is employed that describes connectivity of effective segments by harmonic springs and where segments interact via soft potentials, which do not enforce non-crossability of the chain molecules. Studying the mean-square displacements, the dynamic structure factor and the stress relaxation, we show that local, unconstraint displacements of segments via a Smart-Monte-Carlo algorithm give rise to Rouse dynamics for all but the first Monte-Carlo steps. Using the slithering-snake algorithm, we observe a dynamics that is compatible with the predictions of the tube model of entangled melts for long times, but the dynamics inside the tube cannot be resolved. Using a slip-link model, we can describe the effect of entanglements and follow the different regimes of the single-chain dynamics over seven decades in time. Applications of this simulation scheme to spatially inhomogeneous systems are illustrated by studying the lamellar phase of a symmetric diblock copolymer. For the local, unconstraint dynamics, the single-chain motion parallel and perpendicular to the interfaces decouples; the perpendicular dynamics is slowed down but the parallel dynamics is identical to that in a homogeneous melt. Both, the slithering-snake dynamics and the slip-link dynamics, give rise to a coupling of parallel and perpendicular directions and a significant slowing-down of the dynamics in the lamellar phase.

COMP 110

Simulation of organic-inorganic interfaces: The case of self-assembled monolayers on metal oxides in organic opto-electronic devices

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Over the past two decades, the science and engineering of organic semiconducting materials have advanced very rapidly, leading to the demonstration and optimization of a range of organics-based solid-state devices, including organic light-emitting diodes, field-effect transistors, photodiodes, and photovoltaic cells. The flexibility of plastics combined with the ability to tune the physical properties of organic (macro)molecules by fine tuning their chemical structure, is one of the main drivers boosting research and industrial interest in organic electrically- and optically-active materials. Critical to the operation of organic light-emitting diodes or solar cells are the interfaces between the electrodes made of metal oxides and the organic layers. This presentation will focus on the computational characterization and optimization of the interfacial properties between metal oxides, self-assembled monolayers, and organic transport layers.

COMP 111

Self-organized dispersion in a multicomponent nanoclay composite by a coarse-grained Monte Carlo simulation

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Designing a nano-clay composite consists of mobile solvent, dynamic polymer matrix, and stacks of clay platelets. The physical properties of the composite depend on the distributions of these constituents. Thus, how the constituents move and organize in appropriate time scales for a set of parameters, e.g., concentration, interaction, molecular weight, and temperature is the focus of this study. Particularly, how to exfoliate a stack of clay platelets in such a complex system is one of the major issues. While the dynamics of solvent and polymer chains in a range of mono-disperse systems are relatively well understood, their mixture in presence of platelet layers remains a challenging issue due to interplay between their cooperative and competitive effects enhanced further by steric constraints and relaxation times. In this talk, attempts will be made to identify conditions and parameters for the clay platelets to exfoliate and disperse using coarse-grained computer simulations.

COMP 112

Modeling of polymer-attached metal complexes for energy-dissipative materials

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Recently interest has increased in modifying polymer properties by integrating functional metals. Such metallo-supramolecular polymers potentially offer the functionality of the metal ion along with the processibility of a polymer. Properties of particular interest are elasticity and energy dissipation. We present calculations on polymer-linked metal complexes for the evaluation of energy dissipation. To this end, we investigate the energy profiles of stretching, bending and shearing the complexes according to external forces exerted on each complex via the attached polymer strands. Zn, Co and Cu in conjunction with 2,6-bisbenzimidazolyl-pyridine derivatives were considered in a poly-ethyleneglycol environment with various counterions. We have used a multiscale simulation approach consisting of quantum-mechanical (Semi-empirical and density-functional) methods and molecular dynamics simulations to predict various deformation modes in a realistic polymer environment. At the semi-empirical level, we have also employed a recently developed inverse design method to discover optimal combinations of metals and pyridine substituents that strengthen the stretching mode of the complex.

COMP 113

Combined ab initio/continuum mechanics approach for calculation of mechanical properties of polystyrene grafted nanotubes

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Exceptional strength and stiffness of chemically functionalized, doped and grafted carbon nanotubes (CNT) draw considerable attention last years. In particular, mechanical properties of CNT have been investigated using various ab initio and continuum mechanics approaches. However, due to extremely large size of the system the nanotube composites require enormous computational resources to be investigated by full-electron ab initio methods. We developed computationally effective combined ab initio/continuum mechanics approach to

estimate mechanical properties of CNT composites. The Young's moduli of pure, N-doped and polystyrene grafted single wall CNTs have been estimated.

COMP 114

Self-adaptive surface: Atomistic modeling approach to structural reorganization of self-assembled monolayer on H-Si (111) surface

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In this talk, we present our study on amphiphilic self-assembled monolayers (SAM) on Si (111) surface which has the capability of adapting its configuration to minimize the interfacial tension for both hydrophilic and hydrophobic solvent. To simulate such amphiphilicity of SAM, we attached Y-shaped amphiphilic molecules on Si (111) surface through covalent bonds and then equilibrated the systems in the presence or absence of solvent molecules using molecular dynamics simulations. From these simulations, we found that indeed, the amphiphilic molecules attached on the Si (111) surface reorganize themselves depending on the solvent condition. This structural reorganization was also confirmed from the corresponding change of interfacial tension calculated by Kirkwood-Buff theory. We believe the importance of this study is not only because of its promising potential for various technological applications but also because of fundamental knowledge on molecular interface regarding to how it reorganizes its configuration as a function of hydrophobicity/hydrophilicity of solvent.

COMP 115

Implementation of coarse-grained models for molecular simulation on GPU architecture

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We describe an implementation of the Kim-Hummer[1] coarse-grained model on a graphics processing unit (GPU). The combination of coarse-grained models with the highly parallel GPU hardware vastly increases the size- and time scales accessible to molecular simulation. We provide details of the parallelization strategy, which is specific to the requirements of the GPU hardware. We evaluate

the algorithms' performance with replica exchange Monte Carlo simulations of large molecular assemblies.

[1] Y. Kim and G. Hummer, J. Mol. Biol. (2008) 375, 1416–1433

COMP 116

A catchment basin self-avoiding simulated annealing algorithm

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We develop a generic global minimization algorithm which can escape from catchment basins on full potential energy surfaces. The essential idea is to combine the simulated annealing with our recently developed history-penalized basin filling algorithm. Using this method, we have successfully identified the most energetically favorable configurations of all Lennard-Jones (LJ) clusters up to 60 atoms, including the most challenging 38-atom cluster which the conventional simulated annealing algorithm failed. In addition, we report for the first time the most energetically favorable configurations for the polymer chains consisting of up to 60 LJ monomers.

COMP 117

Just add water: The prediction of the water content of binding sites

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Water molecules play an important role in mediating host-guest interactions in binding sites. Information about the location and strength of interaction of water molecules in a protein-ligand complex is not always available from experiment, yet can prove useful to understand protein-ligand interactions.

We present JAWS, a novel molecular simulation methodology to determine the water content of biomolecules efficiently and accurately. The method is based on free energy simulations and considers fully the entropy of binding of water molecules. Key approximations render the approach orders of magnitude more efficient than a conventional free energy simulation.

We will discuss the application of the methodology to a variety of problems ranging from docking, lead optimization, and characterization of water network structures. JAWS is expected to prove useful in many applications of biomolecular simulations.

COMP 118

Role of the active-site solvent in assessing feasibility of small-molecule lead discovery programs

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Lead discovery remains a major hurdle in small-molecule drug discovery. It would be valuable to be able to predict a priori how tractable a novel target is for lead discovery and the feasibility of this target to structure-based or fragment-based expansion efforts. Towards this end, we characterize a target binding site based on protein solvation and quantitatively estimate the thermodynamic properties of active-site water molecules using Schrodinger's WaterMap program. Insights gained from this analysis and their utility in assessing feasibility of a small-molecule lead discovery program will be presented.

COMP 119

Simultaneous discrete optimization of color and electronic hyperpolarizabilities in a chemical subspace

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Due to their importance in telecommunications applications, new scaffolds for electro-optical materials appear regularly. But systematic exploration of all candidate molecules remains difficult because of the astronomical number of possible structures. We have formulated an efficient method related to branch-

and-bound/tree-search methods for constrained searching of chemical spaces based on an interpolation of property values on a hypercube. This algorithm was applied to the optimization of hyperpolarizabilities under the constraint of transparency in the visible spectrum of various libraries of substituted tolanes. The search includes configurational and conformational information. Geometries were optimized using AM1, and hyperpolarizabilities were computed using INDO/S. The transparency constraint has no impact on the overall performance of the algorithm. Even for small libraries, a significant improvement of the hyperpolarizability, up to a factor of ca. 4, was achieved. For larger libraries, the improvement was accomplished by performing electronic structure calculations on less than 0.01% of the compounds in the larger libraries. Alternation of electron donating and accepting groups in the tolane scaffold was found to produce the best candidates consistently.

COMP 120

Quantum-mechanical simulation of biological macromolecules and its application in structure-based drug design

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We developed variational finite LMO approximation and linear scaling semiempirical method LocalSCF and expanded the size limit of biological systems treated on a desktop computer at QM level to million atoms protein multimers. The quality of the semiempirical electrostatic model is in good agreement with “ab initio” data. We performed molecular dynamics on proteins at QM level and computed protein-ligand binding free energy from first principles utilizing QM MD. We developed two-layer QM/QM method for the purpose of entirely quantum-mechanical high throughput docking of million-compound libraries. The immense size of such libraries makes difficult to ascertain quality of the stored compounds. We performed structure validation of 10,962,930-compound ZINC database using LocalSCF. This calculation took 1 day on 1 CPU and identified 37848 compounds having various structural problems. The wide range of applications announces the begin of entirely quantum-mechanical simulation of biological macromolecules and structure based drug design.

COMP 121

Combining self-guided Langevin dynamics with temperature-based replica exchange enhances thermodynamic sampling of protein folding

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In the last decade, several algorithms have been developed to enhance thermodynamic sampling in protein folding simulations. One notable example is self-guided Langevin dynamics (SGLD), where sampling of the energy landscape is expedited by accelerating low-frequency/large-scale conformational motions. Another commonly used method, temperature-based replica-exchange (ReX), improves sampling via an automated heating and cooling of protein conformations based on a rigorous Metropolis exchange criterion. We have combined the two methods to assess whether further sampling enhancements can be achieved compared to ReX alone. Using CHARMM, we performed folding simulations of the Trp-cage mini-protein with the PARAM22 all-atom force field and the generalized Born molecular volume implicit solvent model. Starting from the unfolded trans state, the SGLD-ReX simulation folded the protein to the native basin approximately twice as fast as LD-ReX. It appears that SGLD achieved this speedup by smoothing the free energy landscape, thereby reducing the barriers between intermediate collapsed states. A structural assessment of the resultant low-energy models suggests that the self-guided formalism did not degrade the accuracy of near-native conformations, in contrast to the known effects of other smoothing approaches, such as coarse-grained lattice models. Finally, due to improved convergence after 40 ns of simulation time per ReX thermal window, SGLD-ReX, unlike LD-ReX, predicts a melting temperature, heat capacity curve, and folding free energy in remarkably good agreement with the experimentally observed values.

COMP 122

Leaving the nest: Life after post-doc'ing

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For many post-docs and graduate students, the first time they think about an academic or industrial position is when they are getting ready to graduate and start looking for a job. However, a little bit of thought beforehand can provide a much smoother transition into the work world. This session will provide you with the knowledge and tools you need to make your next career move in the right direction. This brief introductory session will cover:

The different types of employers - academic, industrial and government, their subtypes and expectations

How to find employment in each field

Resumes, curriculum vitae (CV), and the other documents that should make up your employment portfolio.

Nontechnical skills and knowledge that are crucial for continual career development

Career ladders and nontraditional career fields

COMP 123

An emerging perspective in free energy simulation of protein interactions

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Recently, novel free energy simulation methods, such as the orthogonal space random walk algorithm and its further derivatives, are developed. Their demonstrated efficiency convinces us that we may have or be about to break the sampling bottleneck in free energy simulations. These methods allow reliable and efficient predictions of free energy changes associated with large-scale conformational transitions and non-trival protein interior water movements within 100ps - 1ns simulation length. The theoretical foundation and biological application will be presented.

COMP 124

Simulation of pH-dependent conformational changes in biomolecules

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Biology presents many cases where protonation states of its building blocks are strongly coupled to the conformations the molecules explore.

We will show some of our recent work on pKa prediction using a discrete protonation state model, as well as some recent results on simulating very large conformational changes that depend on pH.

We will show that experimental assignment of pKas, when large conformational changes are observed, might be proving the configurations sampled and not the protonation state of the system

COMP 125

Molecular dynamics studies on the interactions between cell-penetrating peptides and lipid bilayers

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Although numerous membrane penetration mechanisms have been proposed for antimicrobial and cell-penetrating peptides, no apparent peptide sequence has been found responsible for specific peptide functions. Recently, based on kinetics studies on two amphipathic peptides, tp10 and δ-lysin, a different membrane translocation mechanism, “sinking raft” model, was suggested, which does not require the formation of a permanent pore. The details of translocation patterns are, however, different between two peptides. Tp10 is believed to act alone, whereas δ-lysin translocates as a small aggregate, possibly a trimer.

To investigate the validity of proposed model and the effect of peptide sequence on the nature of peptide-lipid interactions, molecular dynamics simulations are performed for POPC bilayers interacting with tp10 and δ-lysin. Multiple trajectories starting from different numbers of peptides and peptide orientations are obtained to improve the statistics. The details of peptide structure on the lipid bilayer surface and possible translocation mechanisms are discussed.

COMP 126

New method for enhanced sampling

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We present an efficient sampling method for computing a partition function and accelerating configuration sampling. The method performs a random walk in the λ space, with λ being any thermodynamic variable that characterizes a canonical ensemble such as the reciprocal temperature ß or any variable that the Hamiltonian explicitly depends on. The partition function is determined by minimizing the difference of the thermal conjugates of λ (the energy in the case of λ=ß), defined as the difference between the value from the dynamically updated derivatives of the partition function and the value directly measured from simulation. Higher-order derivatives of the partition function are included to enhance the Brownian motion in the λ space. The method is much less sensitive to the system size, and the size of λ window than other tempering methods. It is shown that the method asymptotically converges the partition function, and the error of the logarithm of the partition function is much smaller than the algorithm using the Wang-Landau recursive scheme.

COMP 127

Characterization of intrinsically unstructured p53 peptide conformations using simulations and experiment

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We have characterized, in atomistic detail, the conformational preferences of intrinsically unstructured peptide fragments of tumor suppressor p53 using atomically detailed, converged molecular dynamics simulations in explicit water. P53, a key multi-domain tumor suppressor, is of great biomedical interest because more than half of human cancers are associated with loss or mutation of p53. Characterizing the conformational preferences of p53 peptides enables us to test the hypothesis that the unbound ensemble of peptide conformations contains preformed local structural elements that may act as nuclei for binding other “partner” proteins. Results are validated using Psi-angle distributions from UV Raman spectroscopy and J-coupling constants from NMR spectroscopy.

COMP 128

Energy landscapes analysis of disordered proteins: A case study of histone tail dynamics

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Histone tails mediate and maintain nucleosomal packaging in chromosome and, thus, significantly contribute to chromosomal remodeling and gene activation processes. Despite their key importance in chromatin regulation, the structural mechanism of their action has remained elusive. Some of the difficulties stem from histone tails being highly disordered, thus, challenging the classical paradigm of structural molecular biology, that biological function strictly follows from well defined three-dimensional structure. In our work, we have carried out several microsecond long explicit solvent molecular dynamics simulations of all three histone tails to gain fundamental understanding of physics of natively disordered proteins and link our understanding of histone tail dynamics to chromosomal organization. Subsequently, we constructed two-dimensional free energy landscapes of various histone tails, as a function of physically motivated order parameters, such as the number of hydrogen bonds and the radius of gyration. This approach, combined with principal component analysis, revealed a co-existance of ordered and disordered structural basins, that, in turn, shed light on the multitude of functional roles performed by histone tails. We carried out additional analysis, borrowing some ideas from disordered magnetic systems, to classify dominant structural forms for all three histone tails.

COMP 129

Toward a biophysical characterization of enzyme evolution

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Enzymes evolve to optimize their catalytic efficiency in the context of a biochemical reaction network in part by stabilizing the transition state of a specific reaction with respect to the ground state. However, the molecular basis of enzyme evolution is not very well understood and the factors responsible for the optimization of catalytic efficiency during evolution have not been well quantified. Through an application of the MMPB/SA approach for estimating free energy differences, the impact of many single amino acid mutations on the affinity between the HIV protease and both the MA/CA substrate and a model of the corresponding transition state intermediate has been characterized. In the context of transition state theory, the free energy differences are used to estimate

the impact of mutations on the activity of the enzyme and are compared to recently determined experimental results. A more detailed examination of the calculated binding energies suggests ground-state destabilization as a viable physical mechanism underlying the evolutionary optimization of this enzyme. An application of the Michealis-Menten rate laws in the context of the biological environment associated with the activity of this enzyme also supports the mechanism of ground-state destabilization. Large-scale applications of free energy methods applied to classical molecular models can yield results that are predictive of changes in enzyme activity through mutation, and can also provide insight into the molecular and physical origins of enzyme evolution.

COMP 130

Computational analysis on NMR screenings of the Pfizer Fragment Initiative collection

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Fragment-based Drug Discovery (FBDD) is an emerging technology utilized by increasing number of biotech and pharmaceutical companies as a promising approach for lead finding and optimization. In addition to the high efficiency nature of the leads identified, the approach offers the following benefits: 1) relatively small number of compounds (compared to HTS) needs to be screened; 2) novel chemical matter for differentiation and 3) wider coverage of chemical space.

Pfizer's proprietary fragment screening collection was assembled by the Global Fragment Initiative (GFI) approximately a year ago. Since its creation approximately 25 screens have been completed globally for multiple projects in different stages across various therapeutic areas. Screening methods include NMR techniques, high concentration bioassay, SPR and X-ray crystallography. The availability of these screening results allows a computational analysis of pooled data to look for patterns. Such an analysis could be useful in how future screen results are handled and contribute to optimization or expansion of the GFI collection.

In this talk we present the analysis of results from 13 fragment screens using NMR STD (Saturation Transfer Differentiation) techniques conducted at two sites. We look at the overlap in the identity of fragment hits across screens, the profiles of hits in terms of size, lipophilicity, shape characteristics and other computed properties. Based on our analysis, we provide some key conclusions about the specificity, selectivity, and property distribution of fragment hits across the screened targets.

Key questions:

• Is there significant overlap of fragment hits across different screens?

• Can fragment-sized molecule exhibits specificity/selectivity despite their small size?

• How specific are the hits across diverse protein families?

Physical properties

3D Shape

COMP 131

Computational and lipophilicity based studies drive optimization of γ-carbolines as CB1 agonists for analgesic activity

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Interesting optimization challenges were faced during a drug-discovery LI phase analgesia project, where a novel chemical series (γ-Carbolines) was being progressed as peripherally restrictive and orally available CB1 agonist compounds with chronic nociceptive and/or neuropathic pain as the major therapeutic endpoint. The main issues encountered were Potency optimization, Solubility enhancement, hERG reduction and minimization of CNS penetration. All these properties were influenced by Lipophilicity considerations but not in the same direction. While CB1 receptor recognition, Permeability and CNS penetration is favored by higher lipophilicity; the opposite consideration drives good hERG and good Solubility. Consequently, our strategy devised clever ways to not only control a fine balance of Lipophilicity amongst these contrasting properties but also employ modeling to compliment physical property driven optimization of γ-Carbolines as CB1 agonists.

COMP 132

Computational evaluation and development of novel antiarrhythmic agents targeting human ether go-go potassium ion channel

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Human ether go-go potassium ion (hERG) channel is a key to the number of life threatening conditions such as arrhythmias, LQT syndrome and sudden death syndrome. Traditional strategy of blocking hERG at the selectivity filter and thus knocking out troublemaker was adapted up to date. Recently, new approach of hERG ion channel openers/activators arrived. Those drugs are predicted to target exclusively voltage-sensing domain or external linkers presumably involved in inactivation mechanism rather than pore domain. Dozens of opener's structures hit the research scene up to date and 2-[3-(trifluoromethyl)anilino]pyridine-3-carboxylic acid (niflumic acid) is among them. Nicotine amide sharing some similarity in chemical structure is also in spot of interest.

Here we present the scope of results on the establishment of binding sites and structural basis for such unique targeting. Initially the complete structure of hERG consisting of S1-S6 transmembrane domains and including all extracellular

linkers were delivered through the scope of techniques (homology modeling, ROSETTA, MD/implicate membrane). The spatial arrangement of elongated S5-pore domain linker was established to have two helices. Obtained model of protein is believed to be in closed state. It is an excellent accord with previously reported experimental structural details. Unknown novel elements were proved by electrophysiological experiments on single and double mutants. The training set of openers was parameterized to proceed through CHARMM environment (geometry, charges). To evaluate the binding sites/ pharmacophores the extensive docking protocol build on initial guessing with Autodock techniques and final refinement based on free energy calculations through MD techniques (MM-PBSA, FEP) were adapted. Side mutagenesis provided experimental evidences for theoretical predicted binding sites. It was predicted by computational study that nicotine amide may block hERG at the level of selectivity filter as well as via targeting of voltage sensing domain (S1-S4 TMDs).

COMP 133

Computer aided design of novel inhibitors of the p53-hDM2(X) interactions

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A broad range of computational methodologies are being used to assist the structure based design of novel inhibitors of the p53-hDM2 and p53-hDMX interactions. These two protein-protein interactions are currently considered important targets for novel anticancer therapies.

New classes of small molecule inhibitors and improved β-peptide ligands were discovered by molecular docking and de-novo design using the software Glide and BOMB. Optimization of the potency, selectivity and drug-like properties of the hits is conducted by Monte Carlo/free-energy perturbation calculations using the software MCPRO and ADME predictions with the software QikProp.

The most promising designs arising from the computational work are subjected to synthesis and assaying, thus allowing a critical assessment of the ability of the computations to efficiently guide the design of novel inhibitors of protein-protein interactions.

COMP 134

Design of CETP inhibitors: A comparison of structure-based and knowledge-based library design methods

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CETP is a highly hydrophobic target that acts in plasma. It facilitates the transfer of cholesteryl ester (CE) from high-density lipoprotein (HDL) to very low density lipoprotein (VLDL) and low-density lipoprotein (LDL) with a balanced exchange of triglyceride (TG). Inhibition of CETP activity will help to elevate HDL level in plasma. The inverse relationship between HDL-C levels and coronary heart disease (CHD) has stimulated tremendous interest in finding a drug inhibiting CETP. One of the clinical candidates was Torcetrapib which was withdrawn from development by Pfizer in December 2006.

Torcetrapib was successfully co-crystallized with CETP providing details of the key binding interactions in addition to insights as to how the protein functions (Qiu, etc. Nature structural & molecular biology 2007, 14, 106-13). In an effort to modulate the physicochemical properties of Torcetrapib, we designed libraries to scope the SAR in the 'northern' region based on the following reaction scheme.

Two design methods were applied in parallel. One was based on the docking and scoring of the virtual compounds in the target, and the other was based on

diversity and hand picked by project team medicinal chemists. 302 compounds were made and screened. We will present the results of this library, and discuss the pros and cons of each design method.

COMP 135

Development of a CNS multiparameter optimization (MPO) design tool to increase the probability of a compound survival by aligning metabolism, permeability, and safety properties in one molecule

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As the cost to develop pharmaceutical drugs increases and the regulatory environment for the industry becomes more conservative it is imperative that clinical candidates are designed with an improved probability of success. CNS MPO provides a prospective holistic assessment of a compound's attributes with respect to metabolism, permeability, safety, and drug-likeness. The CNS MPO algorithm was designed by incorporating knowledge from CNS drug space, general medicinal chemistry expertise, and safety and ADME analyses. Six physicochemical properties were selected to be the foundation of the CNS MPO algorithm. Looking at the in-vitro metabolism, permeability, and efflux, data from thousands of compounds and in-vivo safety data from CNS candidates, the CNS MPO has improved the probability of aligning and optimizing these parameters in one molecule. The overall MPO score defines the CNS drug space and correlates with Pfizer CNS clinical candidate survival. The power of this MPO is that it is prospective, expands drug design space versus hard property cut-offs, and can predict probability of outcomes prior to compound synthesis.

COMP 136

Electronic structure of 3D-M(smif)$_2$: A case study for computational investigations of transition metal complexes and their spectroscopic characterization

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Recently, 3d-metal complexes with the 'smif'-ligand (1,3-di(2-pyridyl)-2-azapropenide) from vanadium to nickel were synthesized by Wolczanski *et al.*. Most of the M(smif)$_2$ complexes are paramagnetic open-shell systems with small

spin gaps. Spectroscopic data of these complexes and their ions indicate a number of unusual electronic properties including unusual oxidation states, low-temperature spin crossovers, and non-innocent ligand behaviour.

We approached these issues in the present theoretical investigation employing a range of *ab initio* methods from single-reference density functional theory to multi-reference wavefunction based theory. Single-metal coordination complexes are often considered complicated but tractable systems for modern electronic structure methods. However standard black-box techniques still need to be applied with care to obtain meaningful and robust results for these problems. Using the $M(smif)_2$ complexes as a showcase, we highlight some of the technical and methodological pitfalls that can arise in these calculations and the interpretation of their results. We also discuss the limitations and reliability of results at various levels of theory within the context of the experimental evidence.

COMP 137

First principles computational study of chemical degradation of polymer materials

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Chemical stability of polymers in carbon composite materials used in airplane parts is an important issue for aviation safety. This study involves modeling chemical characteristics and reactions of select regions in amine-epoxy polymers, with goals to understand mechanisms and risks of their degradation, and to elucidate how the local chemical structure affects polymer reactivity. Our investigation method is the ab initio quantum-mechanical calculations. These calculations focus on mapping out the energy profile of the reactions of ethanolamine molecule and its derivatives that represent the degradation-susceptible regions in amine-epoxy polymers. We will present comparative thermodynamic results for a range of degradation channels.

COMP 138

Molten n-pyrrole systems: An adaptive tempering Monte Carlo study

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A classical potential model for n-Py oligomers is developed to simulate condensed polymeric systems. The parameters of the new model potential are fitted on previous density functional theory results [1]. The Adaptive Temperature Monte Carlo Method [2] is used to drive two systems containing 192 chains of 4-Py (6528 atoms) and 64 chains of 12-Py (6272 atoms) from high temperature to the most ordered state at low temperature. At T=300 K and at high density (ñ>0.8 for 4-Py and ñ>0.66 for 12-Py), the molecular systems present regions of stacked chains; at lower density (ñ<1.1 for 4-Py and ñ<0.50 for 12-Py), the systems behave as a liquid. Density dependence of the energy, radius of gyration, end-to-end distance and pair correlation functions are calculated. (Partially supported by the National Institute of Standards and Technology, grant 70NANB5H1110. Teragrid grant PHY050023T is acknowledged.)

COMP 139

Recent developments in ab initio composite methodologies

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The correlation consistent Composite Approach (ccCA) has been an effective approach for producing energetic properties of a quality produced by CCSD(T) all-electron calculations at the complete basis set (CBS) limit, but at substantially reduced cost. In this presentation, we highlight a number of recent developments in ccCA which enable larger molecules to be addressed, via the development of a resolution-of-the-identity based approach and enable species with substantial multi-reference character to be addressed, via a multi-reference form of ccCA (MR-ccCA). We also describe the tremendous utility of ccCA approaches upon transition metal species.

COMP 140

Time evolution of electronic populations from a combined ab initio structure/reduced density matrix description: Excited metal nanoclusters on silicon

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We present a theoretical treatment of the dynamics of photoinduced charge redistribution in many-atom systems that combines ab initio electronic structure calculations and a reduced density matrix description. Time-evolving electronic densities are calculated from numerical solutions of equations of motion (EOM) for the reduced density matrix (RDM). The relaxation and dephasing rates are obtained from the Fermi golden rule and calculated with ab initio data about vibrational density of states and electronic state couplings induced by fluctuations of local polarization. These properties of electronically excited states are obtained using density functional theory in a basis set of plane waves to generate matrix elements of the Hamiltonian and dipole coupling to an electric field. Results are presented in terms of the evolution of the electronic population density in energy and in space versus time. Applications have been done to models of silicon surfaces with and without adsorbed clusters of silver atoms. [DSK and DAM, J. Phys. Chem. C, 2009, 113, 3530] We predict that silver clusters adsorbed on the (111) surface add surface-localized states that enhance electron transfer to the Ag-cluster as shown by the time evolution of electron-hole excitations. [Work partly supported by the National Science Foundation, of the USA]

COMP 141

Hydrogen-catalysis phenomenon as an option in biological fixation of N2: A theoretical view

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Chemical activation study of hydrazine formation from NH2+NH2 at CCSD(T)/6-311+G(2df,2p) and CBS-QB3 theoretical levels reveals a new stereoselective reaction relevant to the fixation of molecular nitrogen: N2H2-cis+H2=N2+H2+H2.

The reverse, activation reaction encounters a barrier of only 75 kcal/mol, which is significantly lower than the best available value for N2+H2 bimolecular reaction (125 kcal/mol). This novel “dihydrogen catalysis” is shown to have heterogeneous, transition-metal complex analogues with lower barriers passing through the same transition state modes. This mechanism may explain evolution of hydrogen observed experimentally in turnover cycle of nitrogenase.

We have examined several Fe-S(C)-N-H models and biomimetics of nitrogenase (various electronic and spin states) and discovered additional concerted H-transfer reactions between Fe-H/S-H and Fe-NHx-NHy adsorption centers mediated by a gas-phase hydrogen molecule, a catalyst of heterogeneous hydrogenation reaction. For Fe-clusters we employ B3LYP hybrid-DFT method with different basis sets and Los-Alamos/Stuttgart-Dresden pseudopotential for Fe as implemented in Gaussian-03 suit program.

COMP 142

The role of QM/MM studies in mechanistic analysis of biomolecular motors and ion pumps

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In this talk, I'll discuss several examples where QM/MM studies have made useful contributions to the understanding of key mechanistic issues in biomolecular motors and ion pumps. The specific questions concern (1) the catalytic pathway and regulation of ATP hydrolysis in the prototypical molecular motor myosin and (2) characterization of the molecular identity of the proton release group in bacteriorhodopsin. Necessary improvements in the QM/MM methodology motivated by those mechanistic studies will also be briefly discussed, which include further developments in QM/MM methods with an approximate density functional theory (SCC-DFTB) as the QM method and improving the efficiency of conformational sampling in microscopic pKa calculations.

COMP 143

Quantum mechanical scoring for protein docking

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While the pose generation problem for protein docking to a large extent is solved with numerous search algorithms having been successfully applied in many programs, universally reliable scoring function for accurate prediction of ligand binding poses and energies has been elusive. Most of scoring functions developed up to date are based on physical/chemical energy functions, and incorporate some empirical/experimental parameters, which are often fine-tuned with “training sets”. Though quantum chemical calculations are widely used in computational chemistry, for docking it is considered too costly and its effectiveness is still in question. In this talk, we will follow up on the previous discussion about development of a protocol which utilizes quantum mechanical energy as scoring for docking and discuss the result of an extensive test of the idea on a much larger set of examples. We found that, in overall, the new method gives better or equal docking pose predictions than force field based methods. In particular, it seems that π-π stacking motifs in hydrophobic binding sites can be well accounted for in QM scoring scheme, which is an aspect previous docking methods could not afford.

COMP 144

Large-scale ab initio calculations of DNA oligomers

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We present the results of a set of systematic benchmark calculations that elucidate the technical challenges unique to electronic structure calculations of nucleic acid systems. Using density function theory, we have calculated results for DNA oligomers of up to 14 base pairs (960 atoms). The role of basis set effects and comparison to linear-scaling semi-empirical results will be discussed as well as some novel insights into the electronic structure of these small biopolymers.

COMP 145

QC in Med Chem

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Abstract text not available.

COMP 146

Visualization of cyclic and multibranched molecules with VMD

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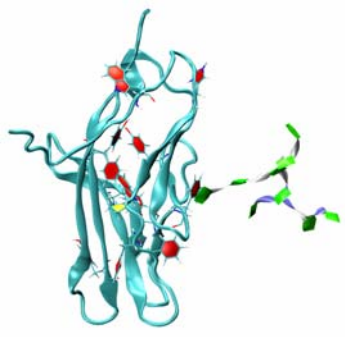
We have added two new visualization algorithms, termed *PaperChain* and *Twister*, to the Visual Molecular Dynamics (VMD) package. These algorithms produce visualizations of complex cyclic and multi-branched molecular structures. *PaperChain* highlights each ring in a molecular structure with a polygon, which is coloured according to the ring pucker. *Twister* traces the glycosidic backbone with a ribbon that twists according to the relative orientation of successive sugar residues. Combination of these novel algorithms with the large set of visualizations already available in VMD allows for unprecedented flexibility in the level of detail displayed for glycoproteins, as well as other cyclic structures. We highlight the efficacy of these algorithms with selected illustrative examples, clearly demonstrating the value of the new visualizations, not only for structure validation, but for facilitating insights into molecular structure and mechanism.



COMP 147

PoseView: 2D Visualization of protein-ligand complexes

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Although computer-aided molecular design and virtual screening software tools improve continuously, manual investigation of the resulting complexes a control task in modelling. In contrast to 3D visualization, information contained in 2D plots can be identified by a short glance and are therefore more appropriate for scanning through large datasets.

We present a new version of PoseView,[1,2] a computational method for the automatic generation of two-dimensional protein-ligand complex diagrams. The layout is computed considering hydrophilic, hydrophobic and metal contacts between ligand and receptor. While the ligand and protein residues forming hydrophilic interactions to the ligand are drawn according to chemical structure diagram conventions, the hydrophobic contacts are visualized by means of splines around the ligand and the appropriate residue labels. PoseView is based on a combinatorial layout optimization strategy which solves parts of the problem non-heuristically. The computation is performed in a sequential manner: An initial ligand structure diagram is created and subsequently modified in order to find a non-intersecting arrangement of interaction lines. In the following the initial placement of each hydrophilic interacting amino acid is computed. During the placement collisions are resolved by a branch & bound algorithm selecting an optimal relative arrangement of all amino acids and the ligand. Finally, the remaining components of the complex diagram are placed based on an underlying arrangement grid.

For validation, PoseView was applied to the protein-ligand complexes contained in the Brookhaven PDB database. Advantages and limitations of the approach will be discussed by means of representative test cases.

For examples see www.zbh.uni-hamburg.de/poseview

Literature:

1.Stierand, K., Maaß, P., Rarey, M. (2006) Molecular Complexes at a Glance: Automated Generation of two-dimensional Complex Diagrams. Bioinformatics, 22, 1710-1716.

2.Stierand, K., Rarey, M. (2007). From Modeling to Medicinal Chemistry: Automatic Generation of Two-Dimensional Complex Diagrams. ChemMedChem 2, 6, 853-860.

COMP 148

A general interface to quantum chemistry simulations in VMD

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We describe our efforts in supporting quantum chemistry data in the VMD software package. VMD has long been used for visualization and analysis of classical molecular dynamics simulations, but representation of results from quantum chemistry software was limited to coordinates or precomputed orbital grids (e.g. cube files). Recent advances in the use of multi-core processors and massively parallel graphics processor provided an opportunity for truly interactive dynamic trajectory visualization of orbitals, the molecular electrostatic potential, etc. In combination with VMD's other powerful graphics capabilities this lays a foundation for new visualization paradigms for quantum chemistry data appealing to the chemist's intuition. Further, arbitrary postprocessing and analysis steps can be applied interactively or through scripting. New extensions to the VMD plugin interfaces allow the easy import of various data from a wide variety of quantum chemistry packages into VMD. Additional plugins assist in generating input for quantum chemical calculations.

COMP 149

Boltzmann 3D simulations for visualizing molecular motion in the classroom and laboratory

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In addition to visualization of chemical structures, computers can also help in visualizing molecular motion. In particular, the distribution of molecular velocities is an essential concept in understanding gas laws, rates of diffusion and effusion, rates of evaporation, rates of chemical reaction, and the nature of equilibrium. Boltzmann 3D is a free Java application available at http://people.chem.byu.edu/rbshirts/research/boltzmann_3d that performs real-time simulation of hard spheres for classroom demonstrations or hands-on interactive laboratories from high school chemistry to graduate statistical mechanics. I will demonstrate the capabilities of this freeware including new

modules for doing isothermal or adiabatic expansions/compressions and for kinetics and equilibrium.

COMP 150

Visualization of molecular orbitals and the related electron densities

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When plotting different molecular orbitals and the related electron densities with consistent contour values, one can create illusions about the relative extension of charge distributions. We have recently suggested that the comparison is not biased when plots reproduce the same fraction of the total charge. We developed an algorithm and software that facilitate this type of visualization. This presentation will illustrate the application of our tools in the analysis of molecular orbitals, the related electron densities, and the total electron densities of molecules. In addition, we will present approaches that can be useful in the analysis of the electron density fields but they have not yet been implemented in the mainstream visualization packages. An example of such approaches is the field topology analysis using contour trees representations.

This work is supported by the U.S. Department of Energy under Contract No. DE-AC02-05CH11231.

COMP 151

Molekel: A program for the visualization of quantum chemistry data

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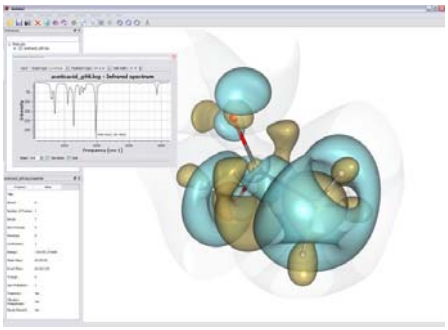
Molekel is a multi-platform open-source molecular visualization program that can display 3-D models of chemical structures as well as the results of quantum chemistry computations. The presentation gives an overview of the main program features with a focus on the visualization and analysis of data read from the output of popular quantum chemistry packages such as ADF, Gaussian and GAMESS. The final part of the presentation covers the new hardware-accelerated visualization techniques available in future versions of Molekel which

are used to enhance depth perception of 3-D structures and achieve very fast and high-quality display of electron density and molecular orbitals.



COMP 152

WebMO: Web-based, state-of-the-art, and cost effective computational chemistry

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WebMO is a web-based interface to modern computational chemistry programs (GAMESS, Gaussian, Molpro, MOPAC, NWChem, PQS, Q-Chem). Using just a web-browser, users can draw 3-D structures, run calculations, and visualize results. WebMO is simple enough for novice users (reasonable defaults are provided; result are presented graphically) but flexible enough for experts (full access to input and output files is provided; templates allow customization of calculation types). WebMO is ideal for teaching at the undergraduate and graduate levels, for research students learning and using computational chemistry, and for creating input files and visualizing computed results.

COMP 153

X-Pol potential: An explicit quantal force field for protein dynamics and function

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At the heart of dynamics simulation of proteins is the potential energy function that describes intermolecular interactions in the system, and often it is the accuracy of the potential energy surface that determines the reliability of simulation results. The current generation of force fields was established in the

1960s. While the accuracy has been improved tremendously by systematic parameterization, little has changed in the formalism and the representation of molecules. The explicit polarization (X-Pol) potential is an electronic structure-based force field, designed for molecular dynamics simulations and modeling of biopolymers. In this approach, the macromolecular system is represented by explicit electronic structure theory, and the wave function of the entire system is variationally optimized. We illustrate the possibility of parametrizing the X-Pol potential, and demonstrate the feasibility of carrying out molecular dynamics (MD) simulation of solvated proteins. We use a system consisting of 14281 atoms and about 30,000 basis functions, including the protein bovine pancreatic trypsin inhibitor (BPTI) in water with periodic boundary conditions, to show the efficiency of an electronic structure-based force field in atomistic simulations. The electronic wave function for the entire system is variationally optimized to yield the minimum Born-Oppenheimer energy at every MD step. This new-generation quantal force field permits the inclusion of time-dependent electronic polarization and charge transfer effects in much larger systems than was previously possible.

COMP 154

Anton: A specialized machine for millisecond-scale molecular dynamics simulations of proteins

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The ability to perform long, accurate, atomic-level molecular dynamics simulations could in principle provide insights into the structural, dynamic, and functional characteristics of proteins. A wide range of biologically significant phenomena, however, occur over timescales extending orders of magnitude beyond the previous state of the art. We have constructed a specialized, massively parallel machine, called Anton, that is capable of executing MD simulations of explicitly solvated proteins over periods of up to a millisecond. Using novel algorithms developed within our lab, the machine has been used to simulate the behavior of a number of proteins over periods far longer than the longest previous MD simulations. Although it is too early to fully assess the utility and limitations of very long simulations using current force fields, we are hopeful that Anton will allow the observation of structural changes underlying various biological phenomena not previously accessible to either computational or experimental study.

COMP 155

Testing and validation of the newly developed drude polarizable force field for CHARMM

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Results are presented on extensive testing and validation of a polarizable CHARMM force field for proteins based on the classical Drude oscillator model. The Drude polarizable CHARMM force field has been developed focusing on the determination of bonded and non-bonded parameters of small molecules building blocks of the larger biomolecules. The newly developed force field is now extended and applied to the simulation of peptides and small proteins in both aqueous solution and crystal envirionments. Structural and dynamical properties are compared with available experimental data and results from the additive CHARMM force field. Extensive discussion of the parameterization strategy will be presented.

COMP 156

Protein dynamics from atomistic and coarse-grained simulations

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The role of combined atomistic and coarse-grained simulations in analyzing the dynamics and function of several protein systems will be discussed. This includes (i). the analysis of mechanical properties of protein/membrane interface in the context of mechanosensation by mechanosensitive channels, (ii). exploration of mechanistic details of structural transitions of adenylate kinases from different organisms. If time permits, the importance of properly describing electrostatics in coarse-grained models will also be discussed in the context of peptide/membrane interactions.

COMP 157

Reorganization free energies for electron transfer systems with different protein folds: Comparing cytochrome c, cytochrome b5, and a 4-helix bundle

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In the Marcus picture of electron transfer (ET) the rate is determined by three parameter:

electronic coupling, reorganization free energy and driving force. Given their importance

in tuning biological ET rates, it is desirable to

establish techniques, experimental and computational, that allow one to measure or predict these

properties quantitatively. It turns out that the determination of reorganization free energy is

particularly difficult experimentally. In recent work we have devised a computational

approach based on ab-initio calculations and molecular dynamics simulation that aims

at quantitative estimation of reorganization free energy. In this contribution we present

applications to ET between the heme cofactor of cytochrome c and a chromophore

(Ru(NH3)5 and Ru(bpy)2(im) (bpy=bipyridine, im=imidazole)) docked to a histidine residue at the

surface of cyt c. This is one of the very few systems for which experimental data are

available allowing us to benchmark our computational scheme. We find that

it is particularly important to use a polarizable model for solvent and protein. Nonpolarizable

models greatly overestimate reorganization free energy, which is a consequence of the too low optical

dielectricity constant of these models. We then present results for reorganization free energy

for ET systems with different protein folds, by comparing ET in cytochrome c, cytochrome b5 and a

designed 4-helix bundle protein. Contributions of the redox active cofactor, protein residues and

the solvent to reorganization free energy are analyzed and discussed. We expect that such atomistic

information obtained from simulation will prove helpful in establishing guidelines for the

rational design of electron transfer proteins.

COMP 158

Theoretical studies of the role of water in interprotein ET between cytochrome b5 and myoglobin

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We report here the theoretical study of the role of the water environment in interprotein ET complex between cytochrome b5 (cyt b5) and its physiological partner, myoglobin (Mb). Experimental studies showed that this complex obey the dynamic docking (DD) paradigm: a large ensemble of weakly bound protein-protein configurations contribute to binding in the rapid-exchange limit, but only a few are ET-active. Molecular dynamics simulations coupled to ET calculations, with both the empirical pathways model as well as Greens function calculations parameterized by quantum chemistry calculations, are performed on a fully solvated cyt b5–Mb complex. Specifically, we are interested in understanding the role of water in lowering the entropic penalty of bringing the two negatively charged heme carboxylates (one on each protein) into close proximity, and how this role is changed by specific protein mutations. We compare here the wild type protein to a triple mutant, where the interprotein complex is more stable, the ET rates are faster than for the wild type protein, and the DD paradigm no longer applies.

COMP 159

Protein heat capacity calculated from replica-exchange molecular dynamics simulations with different implicit solvent models

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Calculation of protein heat capacity by atomistic simulation methods remains a significant challenge due to the complex and dynamic nature of protein structures and their solvent environment. To better understand these factors on calculating a protein heat capacity, we provide a comparative analysis of simulation models that differ in their implicit solvent description and force-field resolution. We report a series of 10 ns replica-exchange molecular dynamics simulations on the src Homology 3 domain of α-spectrin, starting from the native structure. We apply different generalized Born (GB) solvent models with the all-atom CHARMM22 and the united-atom CHARMM19 force fields. We observed that, for CHARMM22, the unfolding transition and energy probability density were quite sensitive to the implicit solvent description. For the lower-resolution CHARMM19/GB model, the simulations failed to yield a bimodal energy distribution, yet the melting temperature was observed to be a good estimate of higher-resolution simulation models.

COMP 160

Computation of 3D queries for ROCS based virtual screens

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ROCS (Rapid Overlay of Chemical Structures) is a method that aligns molecules based on shape and/or chemical similarity. It is often used in 3D ligand-based virtual screening. ROCS can generate highly enriched hit lists when the query is a single conformation of a single active molecule. Typically the chosen query conformation is a minimum energy structure.

The question we asked is: Can we obtain better enrichment using conformations other than the minimum energy structure? To answer this question we developed a methodology called CORAL. For a given set of molecule conformations it computes optimized geometries for ROCS screening. It does so by clustering all the conformations of all known actives using their pairwise ROCS combo scores. The best representative conformation from each cluster is that which has the highest average overlap with the rest of the conformations in the cluster.

CORAL was tested by performing virtual screening experiments with the 40 DUD data sets. Both CORAL and minimum energy queries were used. The early recognition capability of each query was quantified as the area under the enrichment curve out to 1% (AUC-1) of the database sampled. Results show that the CORAL AUC-1 values are consistently larger than the minimum energy AUC-1 values. This demonstrates that one can indeed obtain better ROCS enrichments with conformations other than the minimum energy structure. As a result, CORAL analysis can be a valuable first step in virtual screening workflows using ROCS.

COMP 161

Driving the discovery of novel GlyT1 inhibitors by in silico ADME modeling

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The type 1 glycine transporter (GlyT1) is believed to be an important target for symptoms of schizophrenia, and GlyT1 inhibitors have been proposed as novel antipsychotic agents. In this talk, we will describe an unprecedented utilization of in silico ADME modeling to drive the design and screening of a discovery project. The in silico ADME strategy reduced project design and screening cycle time and saved in vivo screening resources. The analyses of the in silico model performance and life cycle (“freshness period”) will be discussed.

COMP 162

FOG: Fragment Optimized Growth algorithm for the de novo generation of molecules occupying drug-like chemical space

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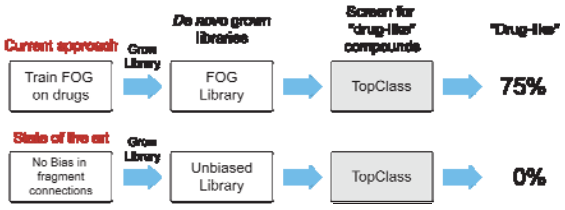
An essential feature of all practical de novo molecule generating programs is the ability to focus the potential combinatorial explosion of grown molecules on a desired chemical space. It is a daunting task to balance the generation of new molecules with limitations on growth that produce desired features such as stability in water, synthetic accessibility, or drug-likeness. We have developed an algorithm, Fragment Optimized Growth (FOG), which statistically biases the growth of molecules with desired features. At the heart of the algorithm is a Markov Chain which adds fragments to the nascent molecule in a biased manner, depending on the frequency of specific fragment-fragment connections in the database of chemicals it was trained on. We demonstrate that FOG can be trained to grow synthetically feasible drug-like molecules that possess characteristic features of drugs that distinguish them from non-drugs.



COMP 163

Identification of good and bad chemical structural features for microsomal stability

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High throughput microsomal stability assays have been widely implemented in drug discovery and many companies have generated large data sets with thousands of compounds. Such data sets have been used to develop in silico models to predict metabolic stability and select promising candidates for synthesis. However, these models are usually not interpretable and therefore

cannot be used directly to generate ideas for further synthetic efforts. In this presentation, we will discuss the development and validation of classification models of rat, mouse and human liver microsomal stability using in-house data. These models were built with FCFP_6 fingerprints using a Naïve Bayesian classifier in Pipeline Pilot. Using the resulting models, we developed a data mining strategy to identify structural features associated with good and bad microsomal stability. We also examined whether this approach could be used to identify structural features which are good for one species but bad for another. We will discuss how these features can be incorporated in the design of new compounds with improved metabolic stability.

COMP 164

Induced-fit docking studies of protein tyrosine kinase ihibitors

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Inhibition of tyrosine kinases is a topic under extensive research. The identification of binding interactions between protein kinases and ligands can facilitate the structure-based molecule design. We carried out induced-fit docking (IFD) studies of eighteen structurally diverse kinase inhibitors against the EGFR, the active and inactive states of the ABL protein. Our docking data show that the IFD protocol can successfully reproduce the native poses of ligands from different sources. Our results indicate that imatinib is a weak binder to the active state of ABL but a strong binder to EGFR. The increased sensitivity of erlotinib to EGFR might be attributed to the H-bond interaction between erlotinib and Cys797 of EGFR. Other important residues for drug design include Thr790, Met793, Lys745 and Asp855 of EGFR; and Thr315, Met318, Asp381 and Glu286 of the ABL. This paper also explains the basis for the effectiveness of nilotinib against most imatinib resistant mutants.

COMP 165

Large scale evaluation of logP predictors: Local corrections may compensate insufficient accuracy and need of experimentally testing every other compound

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A large variety of logP calculation methods failed to produce sufficient accuracy in log P prediction for two in house datasets of more than 96,000 compounds contrary to their significantly better performances on public datasets. The minimum Root Mean Squared Error (RMSE) of 1.02 and 0.65 were calculated for the Pfizer and Nycomed datasets (see also our poster at MEDI). Importantly, the use of local corrections implemented in ALOGPS (http://www.vcclab.org) based on experimental logP data significantly reduced the RMSE to 0.59 and 0.48 for the Pfizer and Nycomed datasets without retraining. The use of the predicted logP values with high confidence may eliminate the need of experimentally testing every other compound. This strategy could reduce the cost of measurements for pharmaceutical companies by a factor of 2, increase the confidence in prediction at the analog design stage of drug discovery programs and could be extended to other biological and ADMET properties.

COMP 166

Lead finding using 2D similarity and QSAR methods: Assessment of method/descriptor combinations

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Using a set of 47 protein targets from the MDDR, we assess the performance of 2D similarity and QSAR methods at identifying active compounds for each target when starting with some number (1, 5, 10, 20, or 40) of actives. Two 2D similarity methods are tested - Toposim, which uses Dice similarity, and Lassi, which uses latent semantic structural indexing. Three QSAR methods are included - random forest, trendvector, and support vector machine (SVM). Each 2D similarity and QSAR method is used in combination with different descriptor sets, including atom pairs (AP), topological torsions (TT), binding property torsions (DT), extended connectivity fingerprints (ECFP4), and MACCS. We assess retrieval rates for single compounds as well as clusters. Among the descriptor sets, ECFP4 performed consistently the best. Although Toposim and Lassi found

different hits, their retrieval rates for individual compounds were surprisingly similar. Among the QSAR methods, random forest and trendvector outperformed SVM. Combinations of methods are also explored to maximize both lead hopping and retrieval of close neighbors.

COMP 167

Atomistic simulations of lipid bilayer interactions with a carbon nanotube

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Carbon nanotubes (CNT) are currently being studied for applications in a variety of biological and biomedical devices. These include Nanocapsules, Nanosyringes and Atomic Force Microscopic (AFM) tips. Nanocapsules and Nanosyringes are devices that could be used to transport therapeutic molecules or genetic information across the cell membrane. Existing technologies such as microinjection, that use glass micropipettes, can cause membrane rupture and damage crucial cell organelles. Carbon Nanotubes with diameters as small as 0.4 nm and high aspect ratio can deliver a large volume of therapeutic molecules while being minimally invasive. These properties of CNTs are particularly essential during gene therapy where cell viability is important.

Precise definition of CNTs can also be used to measure sharp recess samples and obtain high definition images in Force Spectroscopy using AFMs. Carbon Nanotubes also have a very high tensile strengths and young's modulus. Therefore they are stiff when touching the surface and bend when the buckling force is reached. Their flexibility above the Buckling force prevents the nanotube from breaking and possible tip crash and therefore has a longer life than conventional probe tips. In our group, we study the interactions of CNTs with lipid bilayer membranes using Atomistic Simulations. Understanding these interactions is vital in the design and development of nanovectors and imaging devices using nanotubes.

The objectives of the research are, 1) to understand the mechanism of carbon nanotube internalization in to lipid bilayer and 2) to establish using carbon nanotubes as atomic microscopic tips to produce high resolution images of complex biological molecule such as the lipid membranes in simulations. Preliminary force-distance curves provided insight in to the forces experienced by the nanotube as it traverses across the lipid bilayer and suggested a two phase internalization mechanism that involves diffusion of the nanotube and an energy dependent process.

COMP 168

Coarse grain molecular dynamics simulations of membrane proteins

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Integral membrane proteins mediate a number of cell processes such as signal transduction, ion transport, membrane budding, and fusion. Coarse grain (CG) molecular dynamics simulations provide a valuable approach to study structure, function and dynamics of membrane proteins. In this work, we employed our novel coarse grain molecular dynamics method to examine important membrane proteins such as the human beta2-adrenergic receptor and the bacterial chemotaxis system. We examine the structural changes of the protein in a membrane bilayer environment, for example, the conformational changes of the binding pocket and neighboring helices upon ligand binding. We will also compare the results with available experimental and modeling results from literature.

COMP 169

Coarse grain paramaterization of drugs, proteins, and lipids for use in molecular dynamics simulations

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The study of drug interaction with lipid bilayer is essentially for drug design, efficacy, and toxicology. For a detail molecular understanding, we have conducted investigations into the mechanism of drug binding to the lipid bilayer using molecular dynamics (MD) simulations. Specifically, we investigate the interaction of the drug Dibucaine with that of the lipid bilayer POPC ((1-palmitoyl-2-oleoyl-sn-glycero-3-phosphatidylcholine), using a novel CG parameterization of lipids and proteins. These CGMD simulations are used to understand the

molecular contribution of the binding energy, enthalpy, and entropy of mixed drug, protein, and lipid bilayer systems. Preliminary data suggest that the increased entropy comes mainly from the tails of the lipids, while the enthalpy term is dominated by the head group-drug interaction. These investigations could leads to the rational drug design to improve efficacy, efficiency, and reduced toxicity of therapeutic agents

COMP 170

Membrane attachment, allostery, and population-shift in Ras GTPases

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Ras GTPases are membrane anchored signaling mediators that control cell division and development. Despite their prominent role in many forms of cancer, the mechanism and thermodynamics of membrane insertion, the structure of the membrane bound Ras, and the allosteric modulation of lateral segregation by the catalytic domain remained elusive. Elucidating the structural and dynamic link between the conserved active site switch regions and the membrane interacting C-terminal hypervariable region is vital for addressing these issues. We employed a variety of computational techniques, including classical and accelerated molecular dynamics simulations, structural bioinformatics, and potential of mean force and configuration entropy calculations to characterize the Ras switch both in solution and in membrane. Here, after briefly summarizing the main findings of these efforts, we will discuss recent results regarding novel conformations found to be intermediate between the main GTP-bound active and GDP-bound inactive conformations of Ras. In addition, several spatially distant structural regions were found to undergo correlated motions during conformational transitions. These correlated motions, which are intrinsic to the structure, provide evidence for a dynamic linkage between the nucleotide binding site and the membrane interacting C-terminus. Based on these results and evidence from in-silico and experimental mutagenesis, we propose that a population–shift mechanism underlies the nucleotide-dependent structural properties of Ras proteins, with GDP, GTP and mutations selecting and stabilizing pre-existing conformations.

COMP 171

Reactivity of DFP in water saturated polymer membrane

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A copolymer of poly(vinyl alcohol-co-vinyl amine) (PVA-Am) has been demonstrated to be an effective self-decontaminating material for phosphonate nerve agents. The hydrolysis of the nerve agent analogue, diisopropyl fluorophosphate (DFP), shows a significant activity but only at a high moisture contents in the copolymer. In this work, we investigated the structural and dynamical properties of DFP in a hydrated PVA-Am membrane. The interaction of polymer hydroxyl and amine groups with the water and DFP was investigated by using the Molecular Dynamics (MD) and Quantum Mechanics (QM) approaches. We have also studied properties of the PVA-Am blends with polyethyleneimine (PEI) and beta-cyclodextrin functionalized PEI. We found a higher water concentration around the amino groups, as compared to the hydroxyl groups of the PVA-Am polymer. The DFP agent replaces some of the water molecules close to the amino groups. We propose a concerted mechanism of the DFP hydrolysis reaction involving water molecules.

COMP 172

Understanding how flavonoids provide protection to skin cells: A molecular modeling study

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Collagen is one of the most abundant proteins present in humans and it accounts for more than 30% of protein content in our body. It is also the commonly used molecule in a wide range of biomaterial applications such as health care, drug delivery, dentistry and cosmetics. It is now well-known that polyphenolic natural substances such as protanthocyanidins play a critical role in controlling several biological processes such as inflammation and allergy. Recent studies have shown that proanthocyanidins can also bind to collagen and provide a protective layer and strengthen our skin. This has renewed the interest of using these products as health care supplements but a molecular level understanding of this phenomenon is not complete. In this study I have carried out molecular modeling simulations to understand the binding of proanthocyanidins to collagen. The results from this study agree with the existing experimental observations and provide an atomistic description of the interaction of proanthocyanidins to collagen. The results from this study were further used as a basis for searching novel compounds with improved binding affinity.

COMP 173

Biological-nanomaterial interactions

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Nanomaterials exhibit unique optical, electronic and catalytic properties due to their quantum size confinement. Several strategies are employed in the synthesis and assembly of nanomaterials. One of the key approaches has been exploiting the ability of biological systems to synthesize and assemble nanostructures. The highly specific molecular recognition and self-assembly properties of biomolecules, along with their design flexibility, make them attractive as building blocks for fabricating and assembling nanostructures. Our research highlights the utility of biomolecules to control nucleation, growth and stabilization of nanoparticles, as well as in the assembly of hybrid materials. Several groups have demonstrated the use of biological templates to direct the synthesis and/or assembly of nanomaterials, but underlying mechanism of interaction between biomolecules and nanomaterials is not well understood. In my talk I will describe experimental and modeling results that are aimed at developing a better understanding of bio-nano interactions.

COMP 174

Controlling crystal growth using organic molecules, biomolecules, and arrays

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Nucleation and growth of biominerals can be controlled by the presence of large organic molecules or arrays of molecules. An array of organic molecules can act as a template for the initial crystal growth. Individual biomolecules can control the growth of crystal surfaces by blocking the growth of steps and kinks. Biomolecules can control the shape and phase of nanoparticles in solution. We shall show how simulation can help experimentalists to understand the interface between organic arrays, large molecules and minerals and so gain insight into biomineralisation. In particular, simulations strongly support models involving an amorphous mineral precursor. We will also show the importance of solution

composition and the local structure of water in determining the interactions between molecules and mineral surfaces. Finally, we will present calculations of the free energy of adsorption of molecules on calcium carbonate to show the relative importance of enthalpy and entropy effects.

COMP 175

Generalized-ensemble simulations of bionanostructures

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Conventional simulations of bio-nanostructures are greatly hampered by the multiple-minimaproblem, where the simulations tend to get trapped in some of astronomically large number of local-minimum energy states. In order to overcome this difficulty, we have been advocating the uses of generalized-ensemble algorithms which are based on non-Boltzmann weight factors (for a review, see, e.g., A. Mitsutake, Y. Sugita, and Y. Okamoto, Biopolymers 60, 96-123 (2001)). With these algorithms we can explore a wide range of the conformational space. The advantage of generalized-ensemble algorithms such as multicanonical algorithm and replica-exchange method lies in the fact that from only one simulation run, one can obtain various thermodynamic quantities as functions of temperature. In this talk, I will present our latest results of various applications of generalized-ensemble simulations to bio-nanostructure systems.

COMP 176

Multiscale modeling of bioinorganic interfaces

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Computational modelling of interfaces in bio-inorganic systems encompasses a wide range of phenomena, from the nucleation and aggregation of biomineral nanoparticles to the adsorption of organic macromolecules on the planar or curved surfaces of the resulting assembly. This poses extreme challenges to conventional simulation techniques due to the large range of length and time scales that must be bridged in order to obtain a complete description of the system. We present a multiscale simulation study of a polymer-nanoparticle system; starting from an investigation of the stability of calcium carbonate

nanoparticles as function of size and environment by molecular dynamics, to Wang-Landau lattice Monte Carlo simulations of polymer adsorption to a free suspension of particles. We also describe methods for reverse-mapping lattice simulations onto atomistic models to generate relaxed nanocomposite structures.

COMP 177

Nature of molecular interactions of peptides with gold, palladium, and Pd-Au bimetal surfaces in aqueous solution

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The nature of molecular interactions involved in the binding of short peptides (8-12 aa) to metal surfaces in aqueous solution has been identified as a soft epitaxial process on the basis of molecular dynamics simulation with advanced analysis techniques and experimental data. Peptides preferably interact with vacant sites of the fcc lattice above the metal surface, whereby a hexagonal spacing of ~1.6 Å between available lattice sites on {111} surfaces accounts for the characteristic adsorption of aromatic side groups and various other residues (including Tyr, Phe, Asp, His, Arg, Asn, Ser), and a quadratic spacing of ~2.8 Å between available lattice sites on {100} surfaces accounts for a significantly lower affinity to all peptides in favor of mobile water molecules. Adsorption energies (0 to -100 kcal/(mol peptide)) further scale with the surface energy of the metal, the affinity of individual residues versus water, conformation aspects, polarization and charge transfer at the metal interface.

COMP 178

Theoretical insights into the interaction mechanism between protein and SWCNT

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Adsorptions of nine tripetides GXG (X= D, K, G, N, S, V, F, W, and Y), which range from negatively (D) and positively (K) charged, to hydrophilic (G, N and S), and to hydrophobic (V, F, W, and Y) residues, on the (10,0) SWCNT models are systemically investigated with MPWB1K and MP2 methods. The objective is to provide novel insights into the interaction mechanism between proteins and SWCNT. The solvent effects are taken into account with implicit CPCM method as well as explicit water molecules. Charge effects, and electron effects are also systematically discussed. In aqueous solution, because of considerable solvent effects the adsorptions of charged (D and K) and hydroplic (G, N and S) amino acids on the surface of SWCNT are rather weak and can be negligible. Although adsorptions of hydrophobic tripeptides on SWCNT are also weakened by solvent effects, they are still quite significant, especially the tripeptides (GFG, GYG, GWG) with aromatic rings. The results imply that for adsorptions of protein on naked SWCNT it is most likely that hydrophobic interaction and van der Waals are the dominant driving forces.

COMP 179

Quantum mechanics-coupled AMBER ff99 compatible heme parameters for the P450 catalytic cycle

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The lack of a consistent set of atomic parameters for the key heme species during the P450 catalytic cycle has limited the accuracy of computational methods for predicting drug metabolism. Our research focuses on elucidating the contribution of electronic, conformational and thermodynamic factors to competing P450-catalyzed reaction mechanisms during the metabolism of tamoxifen - the current drug of choice for the treatment of breast cancer. We present the results of our quantum mechanics calculations for key heme species during the P450 catalytic cycle at the UB3LYP/LACVP level. These results have been further used to develop a consistent set of AMBER ff99-compatible parameters for the P450 catalytic cycle. We will discuss the contribution of these parameters towards the improved accuracy of our combined empirical and computational approach which uses coupled QM-based force field development,

flexible docking, and extensive MD in explicit solvent to study the biophysical factors involved in P450-mediated drug metabolism.

COMP 180

Binary QSAR study for identifying selective LPA_3 antagonists

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A binary QSAR model has been developed to predict antagonists for the LPA_3 receptor using a set of 121 compounds. A binary QSAR model with a threshold at Imax > 30% at 30μM was generated using 2D descriptors. Two-dimensional descriptors were used because of their relative ease to calculate and independence from choice of conformation and molecular orientation in the coordinate system. The model was validated both internally and externally. Interval validation of model gave an overall accuracy of 82%. The model's accuracy on the actives and inactives in the training set was 53% and 93, respectively. External validation gave an accuracy of 71% overall. The model performed nearly as well on the test set as it did on the training set. The accuracies on active and inactive compounds in the test set were 50% and 88%, respectively. This model is expected to be useful in identifying selective LPA3 anatagonists. We will use this binary QSAR model in conjunction with our previously designed pharmacophore to rapidly identify and prioritize compounds for experimental characterization.

COMP 181

Drug pressure induced mutations in HIV-1 protease alter flap conformations

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The introduction of multidrug treatment has dramatically prolonged the progression and survival of AIDS patients. However, the success of long-term treatment has been hindered by strains of HIV that are increasingly resistant to inhibitors of targets such as HIV protease (HIV PR). Therefore, the need for a thorough understanding of the structure and dynamics of HIV PR and how these are altered in resistant mutants is crucial for the design of more effective

treatments. In this present work, we linked pulsed electron paramagnetic resonance (EPR) experiments with MD simulations, and established the relationships between the EPR distances and structural and dynamic features of the flaps in the WT apo protease, LAI' sequence, and two mutants, V6' and MRD769' sequence. The combined analysis of EPR and MD simulations provide valuable insight into the coupling of drug resistance and protein backbone conformational flexibility. It is likely that mutations have dramatic effects upon flap conformations in HIV-1PR, and thus affecting the flap dynamics which is associated with its enzymatic activity.

COMP 182

Dynamics of 1,3-dipolar cycloadditions of diazonium betaines to acetylene and ethylene: Bending vibrations facilitate reaction

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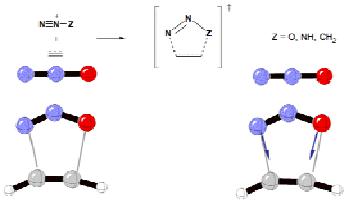
The dynamics of 1,3-dipolar cycloaddition reactions has been explored by decomposing the transition vector by quasiclassical trajectories and by single trajectories. Dipole bending makes the largest contribution to the TS distortion energy and constitutes the major vibrational mode that must be excited in the favored concerted pathway. The consequences for understanding reactivities of different 1,3-dipoles will be discussed.



COMP 183

Pair-wise property-encoded shape distribution descriptors applied to prediction of protein-ligand binding affinities

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Creating tools capable of making accurate predictions of ligand binding affinities with target proteins has been an elusive goal, but if perfected, would also greatly increase the value of virtual screening and facilitate structure based drug-discovery efforts. Pair-wise property encoded shape distribution (PESD) descriptors have been recently developed in our group that capture shape and surface mapped property distributions of interaction regions in a protein-ligand complex. Binding affinities for a total of 1446 protein-ligand complexes from the PDBbind database [1] were predicted from their respective crystal structures by partial-least squares (PLS) models built from only PESD descriptors. No feature selection was employed, but the optimum number of latent variables for each model was determined automatically by cross-validation. With just two property mapped surfaces encoded with electrostatic potential, hydrogen bonding, polar and hydrophobic regions, PLS models derived from PESD descriptors displayed prediction accuracies comparable to other well known scoring functions [2]. Moderate to good correlations with experimental binding affinities were obtained. The mean errors of prediction were less than 1.5 pKd/pKi units.

[1] Wang et al. J. Med. Chem. 2005, 48, 4111-4119.

[2] Wang et al. J. Chem. Inf. Comput. Sci. 2004, 44, 2114-2125

COMP 184

Accelerated molecular dynamics in studying long-timescale biomolecular events

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Computational modeling of biomolecules presents a two-fold challenge: the large size of the system and the long timescale of the phenomenon. The advancement in computational chemistry has led to the development of an incredible amount of methodologies to circumvent these problems. These computational methodologies are fast becoming indispensible in the field as a whole. We present an accelerated MD method to study the mechanism of cis-trans isomerization of the peptide prolyl bond. We have provided detailed description of cis-trans isomerization of the free substrate and the enzyme-assisted process. We have extensively studied the reweighting step of the accelerated MD method and have provided a priori guidance for improving the accuracy and sampling of reweighting-based simulations. We also present an approach to extract the

kinetics from the accelerated MD by establishing the relationship between the local energetic roughness of the energy landscape and the effective diffusion coefficient.

COMP 185

Computational predictions of binding affinities

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My work focuses on improving methods for computational prediction of thermodynamic properties such as protein-ligand binding affinities and small molecule solubilities and solvation free energies. I will discuss my recent work improving methods for estimating binding free energies, and some recent prospective tests of these methods. I focus partly on insights gained from these studies and methodological innovations already made, and point towards where new innovations are still needed. A particular focus is on predicting absolute binding free energies in lysozyme model cavities and subsequent experimental tests, as well as similar predictions and tests of relative binding free energies. Insights resulting from this work can guide further algorithmic enhancements making these methods more practical to apply in a drug discovery context.

COMP 186

Integrating electronic-embedding QM/MM approaches with implicit electrostatic solvent models

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An open problem in modeling chemical events in QM/MM methods is how to incorporate solvent effects via continuum dielectric models. Implicit solvent models have today wide use in electronic structure calculations of small molecules. One of these models is based on the COSMO method which assumes that the surface of the molecule acts as a conductor. Image charges are added on the molecular surface to satisfy the appropriate boundary conditions in the presence of solute charges. We have developed a self-consistent domain fragmentation of conductor-like screening charges (FCOSMO). The approach is based on a fragmentation of the macromolecular surface into small density domains, which are iteratively and self-consistently derived by solving classical electrostatic boundary conditions, allowing for analytical solutions of each charge domain, largely improving scalability.

Furthermore, iteration on density domains is then coupled with iterations on QM spatial domains in QM/MM calculation.

COMP 187

Multiscale simulation methods for protein dynamics and synergistic regulation of enzyme complexes

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It has long been of interest to know which mechanisms and rules that proteins utilize for allosteric and synergetic regulations. We develop and apply computational tools to elucidate the role of conformation, dynamics and allosteric regulation in the enzymatic function of multi-enzyme complexes. This study uses the tryptophan synthase complex as a model system, which has been studied as a model for allosteric regulation and substrate channeling within protein complexes for decades. The enzyme is a bienzyme nanomachine. Its catalytic activity is intimately related to allosteric signaling and metabolite transfer between its alpha- and beta-subunits that are connected by a 25 Å-long channel. Molecular dynamics simulations are carried out to study the allosteric regulation. Moreover, the Brownian dynamics algorithm, together with a coarse-grained model are used to study the travel of the substrate (channeling) within the protein. A new program for analysis of simulations based on Bond-Angle-Torsion coordinates will also be introduced.

COMP 188

Sequence effects on the charge transfer in DNA

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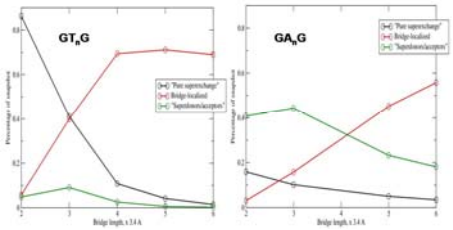
The effect of DNA sequence on charge transfer (CT) properties is studied for the DNA sequences GTnG (Giese et al., 2001) and GAnG. In singly oxidized DNA, the terminal Gs serve as a hole donor and acceptor separated by a bridge of n=1-5 AT base pairs. The energy and localization of the hole are calculated for ensembles of DNA structures obtained for each sequence by molecular dynamics. The hole delocalization between a G and its neighboring A is found to be significant in the GAnG sequences, resulting in the formation of GA "superdonors/superacceptors". Consequently, the hole is less likely to be

localized solely on a G or on the bridge than in the GTnG sequences. We therefore predict that the transition between the superexchange and hopping CT regimes occurs at a longer bridge length in the GAnG sequence than at n=3 measured by Giese et al. for the GTnG sequence.



COMP 189

3D-QSAR of cell-based biological activities: Integration of disposition function with multispecies, multimode CoMFA

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Cell-based assays are used in primary screening in drug development when the receptors are not known, isolable, or functional upon isolation. Transport, elimination, and binding to non-receptor cell constituents, affecting the concentration in the receptor surroundings, can be accounted for by the disposition function (DF). The DF describes the relationship between the dose and the ligand concentration in the receptor surroundings as a model-based, nonlinear function of ligand's lipophilicity, acidity, and other properties. We conceptually integrated the DF into CoMFA approach that we previously extended for multiple-species (MS), multiple-mode (MM) binding, using C and Sybyl Programming languages. This approach was applied to the Selwood data set on filaricidal activities of antimycin analogs. The result demonstrates that each component of the model (DF, MS, and MM) significantly improves the calibration and predictability. Thus, the DF-MSMM CoMFA method is a promising tool for the ligand-based prediction of biological activities using cell-level data.

COMP 190

Comparative analysis of the packing topology of structurally important residues in helical membrane and soluble proteins

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Elucidating the distinct topology of residue packing in transmembrane proteins is essential for developing high quality computational tools for their structure prediction. Network approaches transforming a protein's three dimensional structure into a network have proven useful in analyzing various aspects of protein structures. Residues with high degree of connectivity as identified through network analysis are considered to be important for the stability of a protein's folded structure. It is thus of interest to study the packing topology of these structurally important residues in membrane proteins. In this work, we systematically characterized the importance and the spatial topology of these highly connected residues in helical membrane and helical soluble proteins from several aspects. A representative helical membrane protein and two helical soluble protein structure data sets were compiled and analyzed. Results of analyses indicate that the highly connected amino acid residues in membrane proteins are more scattered peripherally and more exposed to the membrane than in soluble proteins. Accordingly, they are less densely connected with each other in membrane proteins than in soluble proteins. Together with the knowledge of a centralized function site for many membrane proteins, these findings suggest a structure–function model that is distinguishable from soluble proteins.

COMP 191

Designing specific or promiscuous drug molecules: Theory, methods development, and application to the HIV-1 system

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A designed drug molecule should not only recognize its intended target, but it should also avoid off-target binding and perhaps recognize potential mutant variants of its target to prevent drug resistance. The particular system of which the drug will be a part therefore dictates whether a highly specific or a somewhat promiscuous drug molecule is required. This work combines theoretical analysis, methods development, and application to further the computational treatment of considering multiple target molecules in the drug design process. First, we describe and computationally validate a theoretical framework to understand and predict how structural properties of a biological molecule (size, charge distribution, flexibility, etc.) affect binding promiscuity. Secondly, methods are developed that either select or combinatorially design members of optimally small drug cocktails to collectively recognize multiple target variants. Finally, these methods are applied to design drug cocktails that are predicted to collectively recognize multiple drug-resistant HIV-1 protease mutants.

COMP 192

Modeling the sorption dynamics of aluminum hydride using a reactive force field

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We have parameterized a reactive force field, ReaxFF, for aluminum hydride with the objective of describing hydrogen desorption process in aluminum hydride. We aim to shed more light on the long range transport mechanisms of Al atoms during (de)sorption process and the dynamics governing hydrogen desorption process in NaAlH4. ReaxFF has already been shown to be able to accurately predict the dynamical and reactive processes in MgH2[1] and NaH[2]. In this presentation the details of the parameterizations of ReaxFF, the diffusion mechanism of hydrogen atoms and hydrogen molecules in AlH3 and abstraction process of molecular hydrogen in AlH3 clusters will be discussed.

Parameterizations of the ReaxFF's energy expressions was done by fitting to a training set containing the ab initio derived equations of state (EoS) of pure Al and AlH3 condensed phases, reaction energies and bond dissociation profiles on small finite clusters. The parameterized force field, ReaxFFAlH3, is used to study the dynamics governing hydrogen desorption in AlH3. During the abstraction process of surface molecular hydrogen in AlH3 charge transfer is found to be well described by the parameterized force field. A molecular dynamics run is done, which shows that a clear signature of hydrogen desorption is the fall in potential energy surface during heating. Using the force field we have also unambiguously identified a molecular hydrogen trapped in the channels of a cluster of AlH3[3].

[1] Sam Cheung, Wei-Qiao Deng, A. C. T. van Duin, and W. Goddard III. J. Phys. Chem. A, 109 (2005) 851–859

[2] Ojwang et al., J. Chem. Phys. 128 (2008) 164714

[3] L. Senadheera et al., J. Alloys and Compd. 463 (2008)1

COMP 193

pH-Dependent conformational states of AcrA protein: Implications for the assembly of AcrAB-TolC multidrug efflux pump

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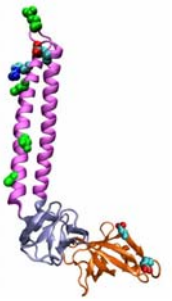
In gram-negative bacteria much of the drug resistance is acquired by increased expression of multidrug efflux pumps. The most common multidrug efflux system is the resistance-nodulation cell division type such as the AcrAB-TolC system of Escherichia coli. AcrA has been shown experimentally to undergo a reversible pH induced conformational change that regulates the AcrA-TolC binding affinity. We have conducted constant pH molecular dynamics studies on AcrA and have identified residues that may be the source of the pH dependent behavior. These results support the suggestion that periplasmic pH may help regulate the assembly of the complex and possibly aid in substrate extrusion. Our hypothesis regarding the role of the specific residues in TolC binding is currently being tested by our collaborators. The identification of the origin of the pH dependent conformational states of AcrA may provide the ground work for the design of strategies to disable the efflux system.



COMP 194

Preferences across phases: Structural preferences in Group 2 dihalide and dihydride monomers, dimers, trimers, and solids

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Links between the bending in the group 2 dihalides and the structural preference in the dimers, trimers, and solids are examined theoretically. Structural preferences in the dihalide dimers are determined by structural preferences in the monomers: the bent monomers prefer the triply bridges C3v geometry; the

linear molecules prefer the D2h doubly-bridged structure. In fact, for the most bent dihalides, like BaF2, the D2h isomer is not even a local minimum. For the solids, the bent monomers condense to form the high coordination number CaF2 and PbCl2 structure types. The rigid linear monomers prefer lower metal coordination. Connections the structural preferences in the group 2 dihalides and dihydride molecules, dimers, trimers and extended solids are assessed. Understanding connections between structural preferences in extended solids and their oligomeric building blocks may help us rationalize relative stabilities of extended solid polymorphs. Reasons for the correlations we observe in the dihaldies are discussed.

COMP 195

3D-QSAR model for inhibition requirements for hASBT using glutamyl-chenodeoxycholate (glu-CDCA) conjugates of aniline

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Inhibition of human apical sodium-dependent bile acid transporter (hASBT) was evaluated using substituted aniline conjugates of glu-CDCA. Compound inhibitory values, K_i, were measured by testing compounds at various concentrations, using taurocholate as a substrate and stably transfected hASBT-MDCK monolayers. The *in silico* models of compounds were built using all-atom CHARMM General Force Field. A 3D-QSAR model for hASBT inhibition using conformationally sampled pharmacophore method (CSP-SAR) was built using the 1-D and 2-D probability distributions of various structural descriptors obtained from MD simulations. CSP-SAR models were selected based on multivariable regression and Akaike Information Criterion (AIC) analysis. Models were evaluated by the leave-one-out cross validation method. Interestingly, 2 and 3-amino benzoic acid glu-CDCA allow intramolecular hydrogen bonding, promoting compound potency; while 4-amino benzoic acid lacked intramolecular hydrogen bond resulting in poor binding affinity. Aniline conjugates of glutamyl-CDCAs were potent inhibitors of hASBT. A highly predictive and robust hASBT-inhibition CSP-SAR model was developed and considers compound hydrophilicity and intramolecular hydrogen bonding on compound activity.

COMP 196

A Kirkwood-Buff force field for thiols, sulfides, and disulfides

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A force field for thiols, sulfides and disulfides has been developed based on the Kirkwood-Buff theory of solutions. Experimental activity coefficients for solutions of methanethiol/methanol, dimethyl sulfide/methanol, and dimethyl disulfide/methanol have been accurately reproduced. and the solubility of dimethyl sulfide in water has been calculated.

COMP 197

A tight-binding study of ionic hydrogen-bond networks in ion solvation

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Water hydrogen-bond networks reorganize surrounding ions, requiring accurate but affordable ab initio computation. For this purpose we are combining molecular dynamic simulation with a computationally efficient density-functional-based tight-binding (DFTB+) method. The approach was tested for the stepwise hydration energies of the ammonium ion in NH4+-nH2O water clusters (n = 1 – 8), for which experimental data are available. The Monte Carlo/DFTB+ search identifies the lowest energy structure, giving the binding energies in the accuracy similar to the experimental measurement and highly correlated, but significantly more computationally intensive, ab initio quantum chemical methods. Upon triumph of the assessment, we computed 3-dimensional density distributions of ion-centered water clusters with 100-500 molecules of H2O.

COMP 198

Ab initio studies of ether-carbene ylides

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Oxonium ylides are formed from the interaction of a singlet carbene with an oxygen-containing molecule. The simplest oxonium ylide, H_2O-CH_2, has previously been characterized as a weakly bound complex with a long C-O bond distance of about 1.8 Å and a binding energy of around 6 kcal/mol. In this work, the structure and bonding of oxonium ylides formed by the interaction of ethers with the singlet carbenes methylene and carbomethoxycarbene have been investigated using ab initio methods at the MP2 level of theory. The ether-methylene ylides are characterized by C-O bond distances that are longer than typical single bonds, relatively low charge transfer, and low binding energies. The ether-carbomethoxycarbene ylides, on the other hand, are characterized by C-O bond distances that are comparable to typical single bonds, higher charge transfer, and larger binding energies. The character of the bonding for the ether-methylene and ether-carbomethoxycarbene ylides has been analyzed using Natural Bond Orbital and Natural Resonance Theory methods, and differences in bonding have been attributed in part to the ability of singlet carbomethoxycarbene to better delocalize the charge transferred from the ether to the carbene.

COMP 199

Accelerating DFT calculations with GPU: A hybrid computing approach

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Hybrid computing systems which incorporate hardware acceleration components (GPU,Cell, FPGAs) has become an emerging trend in HPC solutions. In this presentation we described our Fock XC matrix implementation accelerated by GPU using CUDA toolkit. A BLAS3 kernel based algorithm has been developed to achieve high performance on both CPU and GPUs. The benchmark calculation of Taxol employing aug-cc-pVTZ basis set (4025 basis functions) was speedup by more than 30 times using CPU (Quadcore Phenom) and GPU (C1060) together compared with original code running on single Phenom core.

COMP 200

Adaptively biased dynamics study of the excited states of TIM

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Conformational changes of proteins are closely related to a wide range of protein functions. The "conformation selection" theory suggests that these conformational changes can be facilitated by the coexistence of lowly-populated conformational states with the ground state. In this study, we sought to find and characterize the minor conformational states of triosephosphate isomerase (TIM), which exhibits localized loop motion with catalytic significance. Furthermore, the existing force field and methods of free energy calculation were evaluated. We studied TIM using adaptively biased molecular dynamics (ABMD) simulations. Starting from an “open” loop conformation, a metastable state with “closed” loop conformation was predicted in absence of the ligand. However, comparisons with experimental data suggest that either the force field or procedure for generating the potential of mean force may have systematically underestimated barriers for us-ms transitions in proteins. In addition, comparisons will be made to analogous conformational transitions in other proteins.

COMP 201

A docking model for convulxin and convulxin-like proteins with human glycoprotein VI

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Convulxin, one of C-type lectin-like proteins, was extracted from the South American rattlesnake and has been use as platelet agonist. However, the fragments of convulxin displayed antagonist properties. There is no developed binding model to explore the mechanism of convulxin. Herein, we used the human glycoprotein VI receptor and convulxin structures from PDB (2GI7, 1UMR) to predict the binding model with Genetic Algorithm which build in the AUTODOCK. We also present a new type of C-type lectin-like protein with homology modeling structure that can be used to predict and explain the previous experimental binding activities. Convulxin and this new convulxin like protein share similar binding site and activity pattern but different from the collagen binding site at glycoprotein VI which proposed in the previous literature. Our model suggest that these two protein shares similar binding model and both protein fragment have the potential as potent platelet antagonist.

COMP 202

Modeling macromolecular structure, dynamics, and energetics

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My primary research interests are focused on 1) the development of novel computational methods for modeling macromolecular structure and dynamics in biological systems and 2) structure-based discovery and lead optimization of small molecule therapeutics. In working with interdisciplinary teams to incorporate their experimental data into effective scoring functions, I have developed computational methods for constructing three-dimensional models for large transcription complexes using FRET data and for generating structurally-diverse models using X-ray data. While focusing on drug optimization strategies, I have performed QSAR for optimizing carbamate anticonvulsants and am developing the λ-dynamics free energy method for efficiently computing ligand binding free energies. As an instructor in outreach programs to high-school students and as a mentor to undergraduates and graduate students, I am committed to encouraging others in their exposure to science and in their ability to carry out high-quality scientific research.

COMP 203

Solving problems of biomedical relevance through multiscale computational methods and high performance computing

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My research is aimed at making significant contributions toward the emerging understanding of the relationship between the structure and function of biomolecules using state-of-the-art computational and theoretical methods. My future research plan is the following: (a) apply multi-scale modeling and simulations to study dynamics of biomolecular systems. In particular, I plan to investigate the mechanism of chemo-mechanical coupling in motor proteins and investigate their potential use in the drug delivery applications; (b) apply simulations to study recognition of DNA damage and repair and use the acquired dynamic and quantitative information for the rational design of anti-cancer drugs.

I look forward to developing an extramurally funded research program at the research university and dedicate myself to training students and post-doctoral fellows.

COMP 204

Algorithmic improvements in DOCK6 for enhanced conformational sampling

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In an effort to optimize docking and virtual screening protocols for the DOCK6 program we have performed a critical analysis of three core docking experiments. Results will be presented from experiments which aim to recover the native bound structure of ligands using rigid (RGD), fixed anchor (FAD), and flexible (FLX) docking. Success rates for individual protein families and specific considerations such as average ligand flexibility, presence of ions etc. will be examined. Growth trees were implemented to visualize partially grown ligand conformations and trace the behavior of the core DOCK anchor-and-grow algorithm, which in turn facilitated debugging and optimization of input parameters. Aggressive pruning of unfavorable ligand geometries, using the repulsive term from the ligand intramolecular van der Waals energy, yielded faster run times and enhanced sampling over baseline DOCK protocols.

COMP 205

WITHDRAWN

COMP 206

Large-scale QM/MM calculations of protein-ligand interaction in Thrombin S1 pocket

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Thrombin is a human protein converting fibrinogen into fibrin, which can lead to stocks and heart attacks. It has been discovered that a meta-chloro benzyl side chain of a protein inhibitor (ligand), is responsible for high binding affinity in the thrombin S1 pocket. We have calculated the interaction energy between the ligand and the protein for a series of the most reported potent thrombin inhibitors, which consisted of a meta halogen (X), as well as a second halogen at the ortho position (Y). The calculations have been performed using a large-scale quantum-mechanical molecular-mechanical (QM/MM) approach, which is based on a long molecular dynamics (MD) followed by a series of individual QM/MM calculations, randomly selected from a MD trajectory [submitted to JACS]. The MD simulations have been performed for the protein with the ligand in a TIP3P water sphere of a radius 50A, for 10ns at constant temperature and volume using AMBER program. The similar MD has been performed for the ligand alone in TIP3P water solution for 5ns. After MD, 600 protein structures have been randomly selected and for each protein snapshot, geometry of the ligand has been QM optimized in the fixed MM protein matrix using Q-Chem program. The similar QM/MM calculations have been performed for the ligand alone in water solution. The interaction energy was calculated as an energy difference between an average energy of the ligand in the protein and an average energy of the ligand in water. The overall correlation was observed in our study between the calculated interaction energy and the measured ITC enthalpy of binding for the selected thrombin inhibitors. The unusual binding affinity of the meta-chloro ligand is explained in our study by its small desolvation energy.

COMP 207

Support vector machine classification model of Pubchem hERG bioassay data with 4D-fingerprint and MOE descriptors

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The human Ether-a-go-go Related Gene (hERG) potassium ion channel plays a key role in cardiotoxicity, and it has become a popular issue to access to binding activity. We tried to develop a support vector machine classification model of

largest public high throughput screening data we can find from PubChem hERG Bioassay including 1720 structure diverse compounds from the PDSP. We include a set of similarity/diversity generated by 4D fingerprints, and 204 traditional 2D descriptors, and 76 3D VolSurf descriptors from MOE2008. We estimated different combinations of these descriptors to build a binary classification model with support vector machine for evaluating hERG blockers and nonblockers. We also randomly select 1200 compounds as training data set. Our models show that the range accuracy is between 87%~89% with 10-fold cross validation and 87% of the other 520 compounds were correctly predicted (F-measure of 0.16 for blockers and 0.93 for nonblocker). Moreover we also have collected other 250 literature compounds as our external testing set. The results verified our model which based solely on public PubChem data is comparable to other published in-silico models. Since our training set includes much more structure diverse compounds then from the literature available collection set, this work leads to a more general model.

COMP 208

In silico binary QSAR model based on 4D-fingerprints and MOE descriptors for hERG blockage evaluation

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Blockage of the human Ether-a-go-go Related Gene (hERG) potassium ion channel is one of the major factors related to the cardiotoxicity, and it has become a popular issue to assess the binding activity. Herein, we have collected all available diverse structurally compounds from the literature thus far, total of 250 as our training sets to construct a Partial Least Squares (PLS) QSAR model. Descriptors include the 4D fingerprints generated by the thermodynamic distribution of conformer states available to a molecule in constructing a set of similarity/diversity descriptors and 204 traditional 2D descriptors and 76 3D volSurf descriptors from MOE. We constructed and converted the final model into binary data. The model achieves 90% accuracy even with large collection of diverse structures. Other published in-silico models achieves 87~90% accuracy with much less number of collection. Moreover, we collected our external test set from PubChem bioassay database containing 1753 compounds to verify our model. The proposed binary 4D fingerprint model combining 1D to 4D structure

features can be used to assess the potential hERG blockage and otherwise, it takes advantages with interpretable information for the generated QSAR models and achieves high accuracy.

COMP 209

2D- and 3D-Similarity based classification systems for substrate prediction of ABCB1

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As part of the ATP-binding cassette transporter superfamily ABCB1 (P-gp) exports a multitude of xenobiotics and is strongly connected to multi-drug resistance (MDR). A valid crystal structure of this protein is still missing and ligand based approaches are the methods of choice. Its high promiscuity and implications in drug/drug interactions and brain permeation of drugs renders prediction of possible substrates highly demanding. Recently we could demonstrate that Similarity Based Descriptors (SIBAR) are a useful tool to establish predictive in silico models for drug/ABCB1 interaction. Based on a reference set representing satellite structures in the chemical space we compared a 3D-shape based comparison (ROCS) with SIBAR based on VSA and Volsurf descriptors. Our results validated on an external test set showed an overall prediction accuracy of 74 % with the VolSurf Descriptors achieving the best overall classification performance.

Financial support provided by the Austrian Science fund (L344-N17 and F3502).

COMP 210

Analyzing the robustness of the MM/PBSA free energy calculation method: Application to DNA conformational transitions

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The ability to predict conformational equilibria of biomolecules is vital to understanding many important biological processes. The aim of this study is to examine the robustness of the end-point free energy method termed the

molecular mechanics Poisson-Boltzmann solvent accessible surface area (MM/PBSA) method. Specifically, applications of MM/PBSA to nucleic acid (NA) systems are explored. MM/PBSA calculations of the free energy difference between A-form and B-form DNA are shown to be in very close agreement with the PMF result determined using an umbrella sampling approach. Further, it is found that the MM/PBSA conformational free energy differences were sensitive to a change from the CHARMM to AMBER force field, however the influence of ionic strength on conformational stability was reproduced very accurately. Finally, a comparison of free energy differences obtained using explicit and implicit solvent models during conformational sampling demonstrates significant differences.

COMP 211

Annelated derivatives of cyclooctatetrane in which σ→π* electron transfer is energetically favorable

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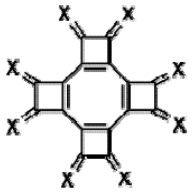
UB3LYP, CASSCF and CASPT2 calculations have been performed on tetrakis-annelated cyclooctatetraenes 1 – 3, in order to predict the relative energies of open- and closed-shell states in which one or two electrons are π LUMO. We have transferred from a high-lying filled σ MO into the non-bonding found that replacement of the oxygens in 1 by the sulfur or selenium atoms in, respectively, 2 and 3 gives molecules that are calculated to have singlet ground states, with 10 π electrons in the π orbitals of the eight-membered rings and a pair of electrons in two nearly degenerate σ MOs.



1, X = O
2, X = S
3, X = Se

COMP 212

Application of flexible volumetric alignment in ligand based virtual screening

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Conformational sampling is used in various chemical computations ranging from pharmacophore elucidation to virtual screening. Sampling alleviates the task of dealing with flexible three dimensional molecules by representing them with a set of rigid conformers. Though computationally tractable, yet this approach has some drawbacks. Most importantly, it is prone to miss biologically relevant conformations. Representing flexible molecules on a continuous scale without the need of discrete sampling provides much higher degree of reliability and accuracy .

Based on an analytical representation we have developed a molecular alignment method that can work with an arbitrary number of flexible molecules and it is also capable of maximizing the overlap of their molecular volumes while maintaining their full flexibility.

This method enables high throughput virtual screening for query structures with unknown bioactive conformation relying merely on a single 3D conformation.

The presentation overviews the corresponding mathematical apparatus, the implemented methods and reviews results.

COMP 213

Automatic and systematic search for routes of chemical reactions in large flexible systems with a given reaction center by the microiteration technique and the GRRM method

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Geometry optimizations of transition state structures for very large systems have become possible by the ONIOM method and the microiteration technique. The microiteration divides variables of potential energy surfaces (PES) into reaction-center variables and the others, and this enables an optimizer to find out a desired reaction coordinate from huge numbers of flexible coordinates. However, results of geometry optimizations strongly depend upon choices of initial guesses. There has been no approach which can search for bond-rearranging pathways in flexible systems systematically. The GRRM (global reaction route mapping) method can automatically search for all reaction pathways by following anharmonic downward distortions on PESs, although applications of it have been

limited to small systems because of the numbers of variables in large systems. In this paper, we demonstrate that automatic and systematic search for reaction pathways in large flexible systems can be performed by combining the microiteration technique with the GRRM method.

COMP 214

Biophysical resolution: How tolerant are binding free energy calculations to errors in protein structure?

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Homology modeled protein structures are often used as the basis for further biophysical calculations including small-molecule docking and binding free energy calculations. While homology-modeling methods continue to improve in their ability to reliably predict protein structures based on weaker and weaker sequence homology, some errors in the predicted structures are unavoidable. How much error in the protein structure is tolerated by biophysical calculations? This question is addressed through a large-scale study involving the systematic structural perturbation of protein/small-molecule complexes followed by binding free energy calculations. The results of these calculations are analyzed in order to determine the robustness of binding free energy calculations with respect to the accuracy of the protein structure. When combined with information from previous studies, a set of rules is constructed to inform the modeler of the expected statistical error in calculated binding free energy as a function of protein sequence homology.

COMP 215

Calculations of the relative energies of the low-lying electronic states of 2-methylenedihydrophenalene-1,3-diyl: Effects of a 1,8-naphtho bridging group on trimethylenemethane and of a vinylidene bridging group on 1,8-naphthoquinodimethane

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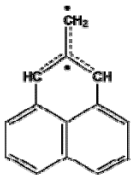
CASSCF and CASPT2/6-31G* calculations have been performed on the low-lying electronic states of three, non-Kekulé, hydrocarbon diradicals – 2-methylene-dihydrophenalene-1,3-diyl (1), trimethylenemethane (2), and 1,8-naphthoquinodimethane (3). Addition of ferromagnetic coupling groups – 1,8-naphtho to 2 and vinylidene to 3 – is found to modulate the energy differences between the two lowest singlet states and the triplet ground states of 1 – 3. The most dramatic effect is the 30.4 kcal/mol change in the relative energies of the 1A1 and 1B2 states on addition of a vinylidene bridging group to 3 to form 1. The relative energies of the electronic states of 1 – 3 are discussed in terms of the topologies of the pair of non-bonding MOs for each state of each diradical. A strategy for making 1A1 the ground state of a nitrogen analogue of 3 is proposed.



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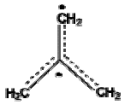

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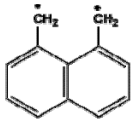

3

COMP 216

CHARMM additive all-atom force field for aldopentofuranoside carbohydrates and fructofuranoside

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We present the parametrization of monosaccharide furanoses for the CHARMM force field. Furanoside carbohydrates are contained in many biological and natural products, including Mycobacterium Tuberculosis cell wall. Initially, parameters are transferred from hexopyranoses and cyclic ethers. The non-bonded parameters are optimized to reproduce monosaccharide-water pair interactions. The bonded parameters are optimized to reproduce crystallographic data and gas-phase quantum mechanical conformational energies at the MP2/cc-pVTZ//MP2/6-31g(d) level. Torsional parameters are optimized using a Monte-Carlo simulated annealing procedure. Optimized parameters are validated by comparing crystal simulations and aqueous-phase simulations data to experimental crystal lattice parameters, molecular densities, diffusion coefficients and NMR data. Moreover, we investigate the pseudorotation angle, characterized by the five-member ring pucker, as well as the exocyclic rotamer populations.

The carbohydrate force field will be applied to bacteria cell walls, glycoproteins, glycolipids and lectins.

COMP 217

Comparison of biomolecular force fields for the peptide group and ionic sidechains

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A Kirkwood-Buff (KB) derived force field (KBFF) for the computer simulation of aqueous solutions of amides is presented in a recent paper. Here, the KBFF is compared with results from existing force fields for the aqueous solutions of N-methylacetamide (NMA) and the glycine zwitterionic system. NMA represents a model for a peptide group. Glycine, the simplest amino acid, is selected as an example for ionic interactions. Experimental properties such as density, partial molar volume, and heat of mixing, as well as the KB integrals, are compared for a variety of common biomolecular force fields. No one force field, with the exception of KBFF, accurately reproduces the properties of both solutes.

COMP 218

Computational analysis of crystal shapes as modified by surrounding microstructure and effect on crystal size distribution

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Recent advances in crystallization theory have linked the crystal size distribution (CSD) to the formative crystallization kinetics opening up new possibilities for studying crystallization of ancient igneous rocks. However, the constraints of microstructure on crystal shapes, sizes and CSD need to be more fully explored with computer simulated crystallization, presently the only method possible. Thus we simulated the nucleation and growth of crystals with shape ratios of 1:3:5 using simple kinetic expressions that predicted the number of unit cells added to each crystal in each time step as space permitted, forming a microstructure consisting of several thousand interlocking crystals. Computer rendering of individual grains revealed shape irregularities caused by the microstructure such as embayments due to impingement of adjacent grains and host growth offshoots into adjacent grain boundaries. CSDs based on longest dimensions of crystals compared poorly with CSDs predicted from the kinetic models indicating that such lengths are poor indicators of crystal size. The direct measurement of

3-D grain sizes, in contrast to widely used 2-D measurements, is important for developing CSD work on real rocks using high resolution X-ray tomography. Work in progress is focused on image processing of computer generated 3-D shapes and determining their best fit ellipsoids as indicators of grain sizes.

COMP 219

Computational analysis of HIVgp41 mutants in complex with peptide based fusion inhibitors

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The viral protein gp41 mediates fusion of the viral envelope with the host cell membrane during infection by HIV. The potential to halt the fusion event, thus interrupting the viral life cycle, has made gp41 an attractive drug target. Currently, there are two entry inhibitors approved by the FDA including the peptide-based inhibitor T20 (Fuzeon) which targets gp41. Despite T20's importance as the first entry inhibitor of this class, experimentally determined s-tructural information on binding has not yet been reported. Thus, the origins of drug resistance which arise from use of T20 are unknown. In this study, structural models of gp41 in complex with T20 have been constructed, which are embedded into an explicit lipid bilayer, and all-atom molecular dynamics simulations were used in an effort to characterize binding in this system. The goal is to deduce the origins of resistance to clinically relevant gp41 mutants.

COMP 220

Computational approaches to understand the interaction of HIV-1 integrase and its inhibitors from natural sources

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An essential step in the life cycle of human immunodeficiency virus type 1 (HIV-1) is integration of the double-stranded retroviral DNA into the genome of the host cell. HIV-1 integrase, the enzyme that inserts the vital DNA into the host chromosome, is an attractive and rational target for anti-AIDS drug design because it is essential for HIV replication and there are no known counterparts in the host cell. Inhibitors of this enzyme have the great potential to complement the therapeutic use of HIV protease and reverse transcriptase inhibitors. Natural products have provided a source of new drug candidates for anti-AIDS therapy. The number of compounds exhibiting anti-HIV activity and isolated from natural sources has increase steadily. Baicalein and baicalin, identified components of a Chinese herbal medicine Scutellaria baicalensis Georgi, have been shown to inhibit infectivity and replication of HIV. They are therefore promising lead compounds for developing new anti-AIDS drugs.

To understand how the inhibitors work and therefore design more potent and specific inhibitors, we have used molecular modeling techniques to investigate the binding modes of these inhibitors. The three-dimensional structures of these inhibitors were first built. Then, computational binding studies of these inhibitors, based on the crystal structure of the HIV-1 integrase catalytic domain, were performed to study the complex structure.

The preliminary results of our computational modeling study demonstrated that Baicalein binds to the active site region of the HIV-1 integrase. Our study will be of help to identify the pharmacophores of these inhibitors binding to HIV-1 integrase and design new pharmaceuticals for the treatment of AIDS.

COMP 221

Computational studies on carboxyphosphate

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Carboxyphosphate is a highly unstable compound which has been postulated to be an intermediate in a number of carboxylating enzymes. This intermediate is believed to be formed by reaction of bicarbonate with ATP, but direct observation and study of this intermediate has not been observed due to its remarkably short half life (~70ms). This instability, coupled with its importance in mechanistic enzymology, has prompted us to investigate the structural and energetic

properties of carboxyphosphate using ab initio and density functional theory. Our results suggest that after bicarbonate attacks ATP, there is a proton transfer from the carboxylic acid group to the phosphorus group and that this transfer takes place through a pseudo-chair conformation. Such a result has important mechanistic implications for carboxylating enzymes.

COMP 222

Computational study of intramolecular hydrogen bonding in arylamide compounds: Delocalization effect

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Foldamers are oligomers that assume stable secondary structures in solution, and quite a few of them have been synthesized to have biological applications. This poster presents our computational analysis of important structural and electronic features of foldamer building blocks used in a number of artificial duplexes. We focus on how the electronic delocalization affects the $C_{aromatic}$-$C_{peptide}$ torsional barrier and charge distribution in a series of model compunds and its subsequent effect on foldamer shape. The series comprises a set of arylamide model compounds with systematically varied structural features. For the analysis, we use a combination of *ab initio* methods, including natural bond orbital analysis.

COMP 223

Computational study of the conformational properties of the amino acid side chains

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Amino acid side chain flexibility is an important property that influences the stability of the folded state of proteins. In molecular mechanics, the conformational properties of sidechains is largely dictated by torsional parameters. In this study, we analyze the conformational properties of sidechains via quantum mechanical calculations. One and two- dimensional chi energy

surfaces were performed on dipeptides representative of the amino acids. Analysis was performed for relevant peptide backbone conformations corresponding to the alpha helical (alpha R), beta stranded (extended) and alpha L conformations. QM optimizations were performed at the MP2/6-31G(d) or MP2/6-31+G(d) levels followed by single point calculations at the RIMP2/cc-pVTZ. The resulting energy surfaces are indicative of the conformational properties of the different amino acid sidechains and the data is of utility as target data for force field optimization.

COMP 224

Continuum electrostatic and free energy perturbation calculations on leucine transporter complexed with tricyclic antidepressants

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Leucine transporter (LeuT) is a transmembrane protein belonging to neurotransmitter sodium symporter (NSS) family. Crystal structures of LeuT with tricyclic antidepressants, e.g. clomipramine, desipramine, and imipramine, have been recently reported. Free energy changes involved in the binding of these tricyclic antidepressants with the LeuT have been calculated using the continuum electrostatic method, and the relative free energy of binding for clomipramine to imipramine, imipramine to desipramine, and clomipramine to desipramine complexed with LeuT has been calculated using the free energy perturbation method (FEP). The continuum electrostatic and FEP results are in agreement with the experimental values.

COMP 225

Correlation between quantum mechanical/molecular mechanical (QM/MM) docking performance and binding site classification

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Molecular docking is used for hit identification and lead optimization in pharmaceutical industry and has been gaining more importance over the years. In recent years, QM/MM docking, in which combined quantum mechanical/molecular mechanical (QM/MM) method is used to reflect the quantum chemical effect in prediction of binding mode, has attracted considerable attention. It has been found that the implementation of QM/MM method for docking significantly improves the accuracy of binding pose prediction compared with classical force field based method. Since in QM/MM docking, partial charges of ligands altered by their environment are used, it could describe more precisely protein-ligand interactions including Coulombic, van der Waals, and hydrogen bond, all of which have their origin in electric charge. It was speculated that this new docking method with quantum mechanically modified charges is more suitable for description of binding sites for which polarization is more pronounced. In the present study, we examine the relations between the performance of QM/MM docking and polarization property of binding sites of target proteins. More than 460 protein-ligand complexes, for which high-resolution X-ray crystallographic structures are known, were separated into three groups according to analysis of their binding sites: hydrophilic, hydrophobic, and metal-contained. The results of redocking experiment with QM/MM docking on these complexes were examined with relation to this grouping. The examination reveals that the QM/MM docking performs better for complexes with hydrophilic binding sites than the ones with hydrophobic binding sites; and that the metal-containing complexes must be treated with a different method. The finding is consistent with our initial prediction and we provide possible solution for the exceptional metal-containing complex docking.

COMP 226

Coupling accelerated molecular dynamics methods with thermodynamic integration simulations

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In this work we propose a straightforward and efficient approach to improve accuracy and convergence of free energy simulations in condensed-phase systems. We also introduce a new accelerated Molecular Dynamics (MD) approach in which molecular conformational transitions are accelerated by

lowering the energy barriers while the potential surfaces near the minima are left unchanged. All free energy calculations were performed on the propane-to-propane model system. The accuracy of free energy simulations was significantly improved when sampling of internal degrees of freedom of solute was enhanced. However, accurate and converged results were only achieved when the solvent interactions were taken into account in the accelerated MD approaches. The analysis of the distribution of boost potential along the free energy simulations showed that the new accelerated MD approach samples efficiently both low and high-energy regions of the potential surface. Since this approach also maintains substantial populations in regions near the minima, the statistics are not compromised in the thermodynamic integration calculations, and as a result, the ensemble average can be recovered.

COMP 227

Density functional theoretical study on redox-dependent hydrogen bonding between amide and arylurea

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Changes in the strength of hydrogen bonding by oxidation/reduction have attracted much attention because they provide a means of externally controlling synthetic supramolecular systems, such as, those used in sensors, molecular electronics, and molecular machines. We performed density functional theoretical calculations on arylurea–amide hydrogen bonding and its dependence on the oxidation/reduction. We calculated the binding energy in the reduced and oxidized states and compared the results with the experimental data. A weak interaction was found between these species in the neutral state. Urea dimer formation energy is also comparable to that of the amide/urea complex. However, the oxidation of the urea into its radical cation induces a strong hydrogen bonding interaction with the amide guest.

COMP 228

Density functional theoretical study on the pKa values of bipyridines

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Polypyridines and their derivatives have widely been used as ligands for transition metal complexes. One of the properties that defines the characteristics of a ligand is its acid dissociation constant (or pKa). This value can be regarded as a solution phase property that is essential for novel photosensitizer designs and for other applications. The pKa values of bipyridines in aqueous solution were calculated using a density functional theoretical method in combination with the Poisson-Boltzmann continuum solvation model. Calculated pKa values correlates well with experimental results.

COMP 229

Development of serotonin and norepinephrine transporter inhibitor pharmacophore models: Design of selective ligands

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Mononamine transporters, including the 5-hydroxytryptamine (5-HT; serotonin) transporter (SERT) and the noradrenaline (norepinephrine) transporter (NET), play an important role in maintaining the concentration of biogenic amine neurotransmitters in the central nervous system (CNS). Along with the dopamine transporter (DAT), SERT and NET have been implicated in the pathology of various psychological and neurological disorders but despite their clinical significance, the understanding of the structural aspects of SERT and NET and the relation to function and antagonist recognition is limited. With no reported 3D molecular structures for these transporters, there have been attempts to develop 3D structures of SERT and NET based on homology to available crystal structures of genetically- and functionally-related transporter proteins. While such models have provided insights as to the molecular mechanism of action, detailed results have been hampered by the approximations used in the homology modeling process. Conversely, the availability of a plethora of ligands has allowed the development of pharmacophore models specific to serotonin and norepinephrine reuptake inhibitors. In this study, we describe the derivation of 3D pharmacophore models rationalizing the affinity of multiple chemical series for the serotonin and norepinephrine transporters. We present their major

characteristics and differences, and their use in the design of ligands targeting SERT and NET as well as design of ligands with mixed activity profiles.

COMP 230

DFT calculations on the stability of 2D covalent organic frameworks

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Covalent organic frameworks (COFs) have been studied with density functional theory (DFT) calculations. We investigated the stacking preference for the COF-1, -5, -6 and -10 by comparing the features of the optimized structures of possible arrangement. After the validation of the suitable functional, staggered and eclipsed stacking structures were modeled based on the experimental data, and were compared in terms of relative energy. In the case of staggered stacking of COF-1, the interaction between B and O atom is possible, and the π–π stacking of aromatic rings is observed for the eclipsed arrangement of both COF-1 and -6. Electrostatic interaction in the staggered form of COF-1 makes the charge separation between the boron atom and oxygen atom in the neighboring layers supported by the partial density of states (PDOS) analysis.

COMP 231

DFT study of the effect of Al2O3 support on Pt catalytic activity

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Alumina supported catalytic Pt-nanoclusters have been used to promote a variety of reactions including the steam reforming of methane and Fischer-Tropsch

synthesis. Understanding the influence of the Pt/Al2O3 interface is key to facilitating combustion reactions in small scale reactors. Although there are many computational studies which detail the complete reaction mechanism for reactant and product species interacting with the catalytically active metal-cluster, few studies consider the pathways that arise due to presence of the Pt/Al2O3 interface. In this paper, we first study the chemisorption of small Pt clusters on Al(100) surface and identify two unique adsorption structures for Pt trimer clusters and three adsorption structures for atomic Pt. We then investigated the thermochemistry and kinetics for dissociation and surface diffusion processes involving small molecular fragments such as water, hydroxyl, hydrogen and oxygen molecules on both the support and at the support/metal interface. The reaction barriers for dissociation and diffusion processes were calculated using the Density Functional Theory (DFT)- Generalized Gradient Approximation (GGA) and compared to experimental data, when available.

COMP 232

Docking simulation on the inhibitor of exo-polygalacturonase

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Docking simulation on the inhibitor of a protein called polygalacturonase (PG), which is relevant to control cell walls, was performed to slow down the ripening of fruit. The simulation was conducted by using a docking program, Glide by applying the various structure of inhibitors to Exo-PG of Yersinia enterocolitica, YeGH28. In order to find proper inhibitors that have more affinity and are structurally similar to natural inhibitor of Exo-PG found in X-ray structural data, a trial set is prepared by changing positions of –OH attached carbon atoms. In addition, substitution was made in the linkage of the natural inhibitor to research the effect of different binding. Result showed that the ligand whose –OH is positioned alternately had the strongest affinity to the protein. Redocking was conducted to find whether there is any synergestic effect between the positional effect and substitution.

COMP 233

Dynamics of nitrous oxide in lipid bilayers at different hydrations: A molecular dynamics study

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In previous work, we have presented evidence that nitrous oxide is an effective probe of both hydrophobic and aqueous sites in lipid bilayer systems. The rate of vibrational energy relaxation of nitrous oxide depends on both the total hydration of the lipid and the local environment: the acyl tail region, interfacial water region, and bulk water region. Further interpretation of the experimental results can benefit from a detailed computational study of nitrous oxide in lipid bilayers at different hydration levels. To this end, we present molecular dynamics simulations of nitrous oxide in 1-palmitoyl-2-oleoyl-phosphatidylcholine (POPC) and 1,2-Dioleoyl-sn-Glycero-3-phosphocholine (DOPC) bilayers in the liquid-crystalline state and at three hydration levels ranging from 12 to 50 water per lipid head group. The dynamics of nitrous oxide in different solvation environments and the influence of nitrous oxide on water solvation structure and dynamics are reported.

COMP 234

Effect of the nucleotide modification on the conformation and stability of the triple DNA formation

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Triple helix-forming oligonucleotides (TFOs) represent a DNA sequence-specific tool that can be prepared to target specific sites on naturally occurring genes. Such tools can be very effective in controlling gene expression. Although triplexes can be formed with high specificity, they are generally less stable than duplexes under typical physiological conditions. Triple helix stability can be enhanced by the use of modified nucleotides. Using molecular dynamics simulations we have studied the interaction of 17-mer RNA oligonucleotide

(TTTCTCTXTTTTCTTCT) (X = T, or C) with the 32 base pair (bp) duplex (GACATTCTAGAAGAAAAYAGAGAAATAAAAAT): (Y=A, C, or G)

(ATTTTCATTTCTCTZTTTTCTTCTAGAATGTC), (Z=T,G, or C). Detailed conformational analyses of all the triplexes is done to asses the changes induced at a double-triple helix junction by the 3rd strand containing either RNA, DNA or RNA-2'-OMe and to understand their differential stability.

COMP 235

Elucidation of binding profile similarities across structurally diverse ligands using a 3D dopamine transporter model

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The dopamine transporter (DAT), a protein belonging to the neurotransmitter sodium symporter (NSS) family, is responsible for the reuptake of dopamine from the synaptic cleft. It is well known that the DAT is the principal target for addictive psychostimulants such as cocaine and amphetamine. Recently LeuTAa, a leucine transporter and distantly related NSS family homologue, was crystallized, providing a template for the construction of 3D DAT homology models. Potential low and high affinity binding pockets were identified using these models. Docking of structurally diverse ligands having different affinities towards the DAT will be used to characterize the low and high affinity binding sites, thus aiding rational design of new DAT-targeted therapeutics.

COMP 236

Enzymatic DNA base flipping mechanism examined via nudged elastic band simulations

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A central mechanism of 8-oxoguanine repair by the glycosylase Fpg concerns the path by which the damaged base is everted from an intrahelical position to an extrahelical position in the active site of the enzyme. To elucidate the effect of mutations, which confer a loss of function, on the Fpg-DNA complex, we present a study of the conformational changes which occur during this base eversion process as modeled using the nudged elastic band (NEB) model. The NEB model determines the minimum potential energy pathway of a conformational transition based on endpoint configurations. Decoupling of the forces applied to each image on the chain results in a minimum energy path. The implementation of the NEB model on the explicitly solvated Fpg-DNA system (60000+ atoms), will be discussed.

COMP 237

Implementation of a novel coarse-grain model using rhodopsin in a lipid bilayer

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A recent coarse-grain model was introduced to give a more accurate simulation to increasingly large protein systems (DeVane et al. *J. Chem. Theory Comp.* **2009**, submitted). Coarse-grain models implemented in molecular dynamics simulations allow larger time scales and systems under study. This model has been implemented on rhodopsin, and also has been incorporated into a lipid bilayer. All-atom molecular dynamics simulations was compared to it's coarse-grain counterpart in order to validate the model. Results from rhodopsin will be further simulated on other G-protein coupled receptors, as well as other transmembrane proteins.

COMP 238

Intrinsic Lewis base strength based upon valency

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Gilbert Lewis originally defined a base as a molecule that donates a lone pair of electrons. When an acid coordinates to a base, an adduct is formed. Due to its importance, chemists have searched for a way to gauge the strength of a Lewis base. Base strength cannot be determined by direct measurement. Consequentially, it is usually indirectly inferred from the adduct bond strength. However, the adduct bond strength involves other forces which may stabilize or destabilize the bond. Thus, the bond strength does not always correlate with Lewis base strength. Density functional theory and natural bond orbital analysis have been employed to determine the base strength in the gas phase. Based upon Lewis' original ideas concerning valency, we define an “intrinsic Lewis basicity” index based upon excess electron population in the valence orbitals of the coordinating atom, which defines its tendency to donate an electron pair.

COMP 239

Key role of computational CNS penetration studies in selecting and advancing compounds in P2X7 analgesia project

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This poster describes a successful in-silico CNS prediction based compound screening approach that was integrated into a project cascade, with an objective to find new antagonists in a P2X7 Neuropathic Pain (NP) project. Due to an availability of multiple LI and LO chemical series from a P2X7 project imported from another Research Area, an opportunity existed to exploit these by cross testing in NP targets. However, an absence of an understanding of their CNS penetration potential stood as a barrier from advancing compounds in PK experiments. Lack of synthetic resources also prevented from running a normal LI optimization protocol. Our approach therefore employed in-silico Blood Brain Barrier (BBB) models to validate and then predict the CNS penetration of these

compounds. The predicted CNS profile was combined with other known key experimental attributes, such as P2X7 rat potency, Metabolic Clearance, Permeability etc. These considerations led to a short-listing of a small set of compounds that was eventually tested in rat NP models and some were found to yield positive results, in both CNS penetration as well as in-vivo pain models.

COMP 240

Ligand-supported homology modeling of the human melanin concentrating hormone receptor 1 (MCH-R1)

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Melanin concentrating hormone (MCH) is a cyclic peptide secreted mainly in the hypothalamus. It is involved in the control of energy homeostasis, feeding behavior and body weight. Many studies have proved that administration of MCH-R1 antagonists significantly reduces food intake and causes weight loss in animal models. In this study, a homology model of the human MCH-R1 was constructed based on the crystal structure of bovine rhodopsin (PDB: 1u19). It was observed that MCH-R1 can bind ligands with high chemical diversity. To address this problem, the initial model was subjected to an extensive ligand-supported refinement using antagonists of different chemotypes. The refinement protocol involved several rounds of energy minimizations and molecular dynamics simulations. The refined model is able to explain the binding mode of MCH-R1 antagonists with diverse chemical structures. Moreover, it reveals new insights into the critical recognition sites within the receptor.

COMP 241

Mechanism of anesthetic binding to lipid bilayer

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Our research combines computational and experimental work on interaction of the drug Dibucaine to the lipid bilayer POPC (1-palmitoyl-2-oleoyl-sn-glycero-3-phosphatidylcholine). The study of drug interaction with lipid bilayer is essential for drug design, efficacy, and toxicology. For a detail molecular understanding, we have conducted investigations into the mechanism of drug binding to the lipid bilayer using both computational and experimental technique. Specifically, we measure the binding of Dibucaine with both experimental isothermal titration calorimetry (ITC) and molecular dynamics simulations (MD). ITC measures the binding energy, enthalpy, and entropy of Dibucaine to lipid bilayer. MD simulations are used to understand the molecular contributions of the binding energy, enthalpy, and entropy of the drug to the lipid bilayer. We hypothesize that the increased entropy comes mainly from the tails of the lipids, while the enthalpy term is dominated by the headgroup-drug interaction. The combination of the computational and experimental data allows for insight into the mechanism of drug binding. These investigation lead to the rational drug design to improve efficacy, efficiency, and reduced toxicity of therapeutic agents.

COMP 242

Modeling of pillared covalent organic frameworks as the hydrogen storage material

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Pillared covalent organic frameworks (PCOFs) have been modeled with the density functional theory (DFT) calculations. Based on the COF-1 structure, one of covalent organic frameworks (COFs), synthesized by the condensation reactions of phenyl diboronic acid $\{C_6H_4[B(OH)_2]_2\}$, we inserted “pillar” molecules between the organic layers for the improvement of physisorption ability for the hydrogen molecules. Pyridine was considered as a candidate for the pillar molecule. The system was extended from the cluster to the periodic systems for the estimation of the effect of insertion, inter-layer distance and energetic stability. We also considered the effect of packing method for COF layers in the presence of “pillar” molecules. Among all the feasible packing structures, two structures in staggered and eclipsed form influence the morphology of the crystal

structure. With this calculation, we proposed new PCOF structures to enhance hydrogen storage capacity. Grand canonical Monte Carlo (GCMC) simulations showed the effect of insertion of pyridine molecule into COFs by the prediction of loading of the hydrogen molecules.

COMP 243

Models for the nucleation and growth of calcium carbonate

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The nucleation and growth of calcium carbonate is important in fields from biomineralization through geology to industrial processes. We show how the growth and morphology of calcite can be controlled by organic molecules such as polysaccharides, peptides and proteins or by molecular arrays by calculating absorption energies (for molecules) and interfacial energies (for the arrays). We have considered the nucleation of calcite using mechanisms other that those based on classical nucleation theory. Simulation of nano-particles allows size and shape-dependent properties to be studied directly. The presence and structure of surface water and the effects of organic molecules and arrays are all important in determining their structure. Simulations using metadynamics have shown both that amorphous calcium carbonate is the stable form for small particles and that it is stabilised by proteins. We shall also present results on the interactions of nanoparticles and proteins and their relevance to the structure of egg-shells.

COMP 244

Molecular dynamics of proteins embedded in a lipid bilayer

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The aggregation of amphipathic peptides in a membrane have been studied using novel computational methods. In order to gain a better understanding of the structural and dynamical aspects of peptide assembly within lipid bilayers, a series of coarse grain (CG) molecular dynamics (MD) simulations of four synthetic transmembrane peptides were performed. The LS2 synthetic peptides, which are model amphipathic peptides, have been constructed using two structurally distinct models with hydrophobic and hydrophilic side residues. It is essential to design both models with accurate structural details such as amphipathicity and length, because these properties are critical for the formation of ion channels. The hypothesis of this research was that the formation of an ion channel is enthalpically and entropically driven. From these simulations, we confirm that ion channel formation is both enthalphically and entropically driven. However, we did not anticipate the solvation of the peptides by the phospholipid head groups and horizontal diffusion of the peptides to aggregate. By understanding the assembly of peptides in membranes, it will provide a detailed description of the biophysical properties of membranes, further it will help facilitate the design of antimicrobial, antiviral, and other pharmaceutical agents which will target ion channels.

COMP 245

Molecular dynamics of second-shell interactions in zinc finger binding sites

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Zinc finger domains bind zinc with a tetrahedral motif consisting of cysteine and histidine residues. These zinc binding sites are generally believed to have either a solely structural function, or to be redox-regulated. The solvent accessibility of the thiolate atoms in the zinc-binding cysteines, among other factors, influences their vulnerability to oxidation into disulfides, with concomitant release of zinc and domain unfolding. Second-shell interactions with positively charged residues surrounding the zinc binding site are important for stabilizing and shielding the

negatively charged thiolate atoms. However, in a survey of NMR structures of the p300 transcription factor we have found significant differences in these second-shell interactions between different structures in the NMR ensemble. Here we present a series of molecular dynamics simulations of several different zinc fingers of various types. We explore the dynamics of the second shell interactions, and whether significant differences between structural zinc fingers and redox-regulated ones can be observed.

COMP 246

Molecular dynamics simulations of complex mixed lipid bilayers to model yeast membranes

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There has been growing interest in using molecular dynamics (MD) simulations to investigate membrane-protein systems. However, these simulations have heretofore consisted of no more than three types of lipids, greatly simplifying the compositions of actual membranes. CHARMM-GUI, a web-based graphical user interface for performing various CHARMM functions, has recently been used to generate more complex lipid bilayers composed of six different lipids – cholesterol, DOPC, DPPC, POPA, POPE, and POPS – in order to accurately and realistically model yeast membranes. Four bilayers containing varying amounts of chain saturation, cholesterol concentration, and surface tension were created. These yeast membranes were simulated for a total of 170 ns using the atomistic CHARMM27r force field at 303.15 K. MD simulations with a high concentration of unsaturated chains (73%) showed an increase in surface area per lipid and an decrease in the SCD order parameters for DPPC, as opposed to the membrane created with a high concentration of saturated chains (60-63%). Simulations of the more saturated membranes were in a liquid-ordered state and were in agreement with experimental cholesterol-containing membranes. The unsaturated membrane simulation exhibited a larger average tilt angle of cholesterol with respect to the bilayer normal. Moreover, cholesterol in the unsaturated membrane actually oriented parallel to the bilayer surface for periods of less than a nanosecond. This result supports previous observations of parallel cholesterol existing at the center of polyunsaturated fatty acid membranes, and makes us the first to observe parallel cholesterol in a fully atomistic simulation.

COMP 247

Molecular dynamics simulations of the quick micelle formation of Azotab in D_2O solution: Micellar structure and the swing of two benzene rings

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Azotab, CH_3-CH_2-(C_6H_4)-N=N-(C_6H_4)-O-$(CH_2)_4$-$N(CH_3)_3$-Br, is a photo-controlled surfactant with both cis and trans structrures. Unlike other surfactants, azotab carries with a big tail, a pair of benzene rings. Starting as random configurations, the molecular dynamics simulations plus DIP3P water model were performed. This study suggested that the swing of the two benzene rings contributes the fast diffusion rate as well as the quick micelle formation of azotab within 20 ns at the concentration near CMC (~10 mM). We measured the swing rate for each benzene ring and the diffusion rate for a single azotab in D_2O solution. We also defined the compact degree of micelle and compared the structural analysis between cis and trans azotab-micelles and see if any structural difference for various sizes of micelles. The simulation told us that the mixture of cis and trans azotabs in D_2O solution possibly forms a micelle. Our predicted gyration radius distribution corresponds to the experimental data.

COMP 248

Molecular modeling of interaction between sAnk157-122 and obscurin6322-6339 in striated muscle

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Binding of obscurin (obsc) to the muscle-specific small ankyrin1 (sAnk1) is important for organizing the sarcoplasmic reticulum in striated muscle. Experimental work investigating this interaction has been performed on $obsc_{6322-6339}$ and $sAnk1_{57-122}$. We used molecular modeling methods to obtain additional information on this interaction. Initial interaction between $obsc_{6322-6339}$ and $sAnk1_{57-122}$ was modelled using 10,000 Brownian dynamics simulations followed by the minimization of the complex, with solvation treated using the Generalized-Born method. Obsc is predicted to interact with

R67,R68,R69,K73,K100,K101,R104,K105,R108 in sAnk1, in agreement with experimental results. 30ns MD simulations were then performed on six selected obsc-sAnk1 complexes. Results show that the alpha helical conformation of obsc is maintained in the complex, where it is stabilized by the interaction with the positively charged binding groove in sAnk1. Results from the simulations also predicted that K6337 on obsc interacts with D111 on sAnk1, a prediction that we recently confirmed by experiments. The modeling observed the dynamic and heterogeneic properties in $sAnk1_{57\text{-}122}$-$obsc_{6322\text{-}6339}$ interaction.

COMP 249

Navigating molecular worms inside chemical labyrinths

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Predicting if a molecule can traverse into a pocket buried inside a protein or through a channel system of a porous material is a difficult question to answer. Even using a simplified model where physical interactions and dynamical effects are excluded, chemists are not able to reach an answer. The current state-of-the-art solutions can find paths of a spherical probe that mimics the molecule inside a convex hull constructed from atoms of a protein or material's framework. Nevertheless most molecules interest rarely have a spherical shape. Therefore they would be better modeled as complex objects built from solid blocks connected by flexible links – molecular worms. Then, studying their possible movement paths inside a chemical system would not only include translational degrees of freedom as in the case of spherical probe, but also rotational and internal degrees of freedom.

Our presentation will demonstrate the application of the Fast Marching Method (FMM) to study the paths of “molecular worms” inside the labyrinths of complex chemical structure. Our study aims to be the most complex application of FMM to the problem of robotic navigation as it considers at least a six-dimensional space to account for translational, rotational and internal degrees of freedom.

This work is supported by the U.S. Department of Energy under Contract No. DE-AC02-05CH11231.

COMP 250

Novel protocols for modeling flexible loops: Implications for drug design

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The accurate modeling of loops is one of the key challenges in protein structure modeling. This is especially true in cases where protein loop conformations change based upon ligand binding. Several examples are known in the literature where the size and shape of a protein binding pocket changes when comparing the Apo structure to protein complexes with diverse ligands. In this study, we examine a series of therapeutically relevant protein structures that contain loops that exhibit significant ligand-dependent conformational changes. Two methods for generating accurate loop conformations for these proteins are described; an improved protocol for induced fit docking, Sample-IFD-Refine (SIR) and a new method, Delete-Dock-Resample (DDR).

COMP 251

Numerical integration of the coupled rate differentials via a discretized Adomian decomposition

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Adomian polynomials are used to approximate the integrated chemical rate equations. The solution to the coupled integro-differential equations and numerical methods developed by the authors outperform high-order Runge-Kutta routines in the arenas of computational time and discretization error. The speedup is highly significant to kinetic inversion problems where hundreds of numerical integrands are needed. An order of magnitude decrease in computational time is observed. The inclusion of up to fourth-term polynomials in the solution gives a truncation error of order $O(h^8)$. This extremely low-order error yields solutions that are step-size independent. The problem of rapid polynomial divergence is addressed through discretizing the time axis.

COMP 252

On the applicability of homology models of G protein-coupled receptors to computer-aided drug discovery

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We recently built and compared to the corresponding crystal structure molecular models of the β_2-adrenergic receptor (β_2-AR) in complex with the inverse agonist Carazolol. The homology models were built using rhodopsin as template and docking was performed through an induced fit procedure that allows flexibility to the ligands and the receptor binding pocket. Here, to probe if homology modeling of G protein-coupled receptors (GPCRs) can generate structures applicable to computer-aided drug discovery, we subjected the crystal structure and our homology models of the β_2-AR to a simulated virtual screening. In particular, 67 β_2-AR ligands were dispersed within over 50,000 diverse molecules selected from the ZINC lead-like database, and the capacity of prioritizing the active over the inactive compounds through molecular docking was assessed by plotting ROC curves. Our results demonstrate that GPCR homology models are indeed applicable to virtual screenings, in some cases almost as effectively as the experimental structure.

COMP 253

Optimal design of paper mill process energy with mathematical programming and three-link modeling

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According to the paper mill characteristics, the total energy system of paper mill was classified into three-link: energy-conversion link, energy-use link and energy-recovery link. A new approach of process energy optimization for paper mill based mathematical programming and three-link modeling was introduced. According the papermaking process requirement and the minimum rebuilding cost, the best energy networks on energy-use link was provided with mathematical programming. Based on the energy-use link results, the best mill wide energy efficiency was obtained with three-link modeling with the aid of exergy analysis.

COMP 254

Parameterization of desipramine, imipramine, and clomipramine

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Antidepressants, narcotics, and other types of mood altering drugs bind to the dopamine active transporter (DAT). Certain molecules, like cocaine, block dopamine re-uptake from the synaptic cleft. This causes an excess of dopamine to remain in the synaptic cleft, which can lead to euphoric like feelings. How and why specific molecules bind to and inhibit DAT is of high pharmacological interest. In order to determine how these molecules bind, parameterization efforts for tricyclic antidepressants such as desipramine, clomipramine, and imipramine have been undertaken. Alterations for the tail end nitrogen and the corresponding proton were necessary to correctly model the partial charges. Free energies of hydration calculations and binding free energy calculations for each drug were performed to validate the accuracy of the parameterization. The parameters as well as the results from our calculations will be presented as part of this poster.

COMP 255

Potential of mean force calculations of the free energy of binding of Type I antifreeze proteins at water/ice interface

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Antifreeze proteins (AFP) are highly specialized proteins which can protect select cold-surviving organisms from freezing by a non-colligative mechanism of the freezing point depression. This protective mechanism relies on the subtle functional design of these proteins which skillfully utilizes both polar and non-polar residues to minimize the free energy at the water/ice interfacial region.

We investigate the role of both polar and non-polar residues in the non-equilibrium antifreeze activity of winter flounder (WF) Type I AFP by carrying out AMBER9 molecular dynamics simulations of WF AFP and its selected mutants at the water/ice interface. Free energies of binding of WF AFP and its mutants are estimated using the Potential of Mean Force method, allowing the role of both polar and non-polar residues in non-equilibrium antifreeze activity at the water/ice interface to be examined.

COMP 256

Prediction of fold resistance for inhibitors of EGFR using all-atom molecular dynamics simulations

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The tyrosine kinase domain (TKD) of Epidermal Growth Factor Receptor (EGFR) is an important and validated drug target for many types of cancers including non-small cell lung (NSCL) and breast. Despite the clinical success of ATP-competitive inhibitors such as erlotinib, which target EGFR, drug resistance mutations in the TKD can occur which alters drug potency. Here, in an effort to characterize fold resistance, we describe computational structural models and results from molecular dynamics simulations for inhibitor complexes with several EGFR variants including wild type, L858R (cancer causing mutant), and L858R&T790M (drug resistance mutant). Free energies of binding, per-residue contributions to binding, and structural differences which occur as a result of the mutations for different inhibitors will be discussed.

COMP 257

Probing protein-ligand interactions by ab initio NMR chemical shift calculations

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We have developed an automatic fragmentation quantum mechanics/molecular mechanics (AF-QM/MM) approach to routinely calculate NMR chemical shifts for biological systems. This approach shows excellent agreement with full system calculations as tested on a small protein Trpcage. We have applied this approach to study the FKBP-GPI complex. Good agreement between our calculated ligand proton chemical shifts with experiment was obtained for ten NMR structures, but not for the decoy poses. Therefore, CSP RMSD offers a straightforward measurement for scoring different poses. Our results have demonstrated that the comparisons of ab initio/DFT NMR chemical shifts with experimental values can provide insights into protein-ligand interactions at the molecular level. The AF-QM/MM approach has potential applications in the structure-based drug discovery process such as SAR by NMR.

COMP 258

Properties of alcohol water mixtures by computer simulation

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We have used computer simulation to study the properties of a series of alcohols and water mixtures in an attempt to validate a force field specifically designed to reproduce the experimental Kirkwood-Buff (KB) integrals. Mixtures covering the entire composition range where studied for methanol, ethanol, n-propanol, n-butanol, n-octanol, i-propanol, t-butanol, ethylene-glycol and glycerol. The results suggest that, to a very good approximation, the parameters developed for the simulation of methanol and water mixtures also provide a reasonable description of other alcohol and water mixtures. Other properties besides the KB integrals were also well reproduced including the enthalpy of mixing, translational diffusion constants, and dielectric properties. The results strongly suggest that the hydroxyl group parameters are both transferrable and additive between these molecules.

COMP 259

QSAR modeling and knowledge discovery of a large unbalanced dataset of hERG K+ channel blockers and openers

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The human ether-a-go-go related gene (hERG) K+ channel can be target and antitarget in drug discovery. It is important to screen out hERG channel blockers that cause QT prolongation and fatal arrhythmia, or tune out QT liability in a lead at early stage, and find openers as potential therapeutics for LQTS. For a diverse imbalanced dataset of 1878 compounds (including openers, blockers, and inactives) with class overlap, we combined k-nearest-neighbor (kNN) QSAR classification algorithm with the class boundary cleaning, class boundary mining

and active learning techniques, then built models for (i) blockers vs. openers, (ii) blockers vs. inactives, (iii) hits (openers & blockers) vs. inactives. Models with prediction accuracy exceeding 90% each were obtained for training, test and external validation sets; false positive/negative rates were below 10%. Our results compare favorably with those generated using other algorithms for imbalanced dataset. Knowledge discovered will extend application scope of hERG in drug development and regulatory.

COMP 260

Quantitative conformationally sampled pharmacophore for μ opioid ligands

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μ-opioid ligands, the most effective analgesics, have been the constant object of lead modification and optimization for the purpose of overcoming their adverse effect. However their structural diversity and significant differences in pharmacological activity associated with subtle modifications hampered development of a consensus pharmacophore to differentiate agonists and antagonists. The recent development of the Charmm General Force Field (CGenFF) and Conformationally Sampled Pharmacophore (CSP) method provides a new approach for this challenging task. CGenFF is an organic force field for drug-like molecules and parameterized based on large set of model compounds. CGenFF was extended to cover the opioids and validated based on the reproduction of quantum mechanical and crystal data. Based on 33 nonpeptidic and peptidic compounds, which have been selected as representative ligands, we carried out CSP modeling to discriminate agonists from antagonists. Efforts include implementation of an automated pharmacophore searching procedure and regression models for affinity and efficacy were explored. Predictability of the model and its physical meanings will be discussed.

COMP 261

Representation, searching, and enumeration of Markush structures: From molecules toward patents

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Cheminformatics systems usually focus primarily on handling specific molecules and reactions. However, Markush structures are also indispensable in various areas, like combinatorial library design or chemical patent applications for the description of compound classes. The presentation will discuss how an existing molecule drawing tool (Marvin) and chemical database engine (JChem Base/Cartridge) are extended to handle generic features (R-group definitions, atom and bond lists, link nodes and larger repeating units, position and homology variation). It will be shown how Markush structures can be drawn and visualized in the Marvin sketcher and viewer, registered in JChem databases and their library space searched without the enumeration of library members. Different enumeration methods allow the analysis of Markush structures and libraries. These methods include full, partial and random enumerations as well as calculation of the library size. Furthermore, unique visualization techniques will be demonstrated on real-life examples that illustrate the relationship between Markush structures and the chemical structures contained in their libraries (involving substructures and enumerated structures). The presentation will focus on the most recent developments (position variation, repeating units, homology variation), and further developments will be discussed towards full patent handling.

COMP 262

Search for inhibitors of S100B-p53 interaction

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S100B protein is known to interact with the p53 tumor suppressor protein in melanoma cells, inhibit wild-type p53 functions and thus contribute to cancer progression. Inhibition of S100B using siRNA provides a proof-in-principle for designing small molecule inhibitors of S100B-p53 interaction. The strategy for designing inhibitors involves a combination of computer simulation, structural biology, and molecular biology approaches. The p53 binding site on S100B was

identified as the inhibition target and virtual screens were performed using a database of drug-like molecules. High scoring compounds were used in biochemical and biological assays. Fluorescent binding assays were used to detect compounds that to bind to S100B and 7 were shown to interact with the p53 binding site with high affinity. Structures of the inhibitor-S100B complexes were determined by X-ray crystallography. In order to understand the biophysics of the inhibitor-S100B interaction, molecular dynamics simulations of the complexes were performed using parameters from CHARMM and CHARMM general force field (CGenFF). The atomistic picture from the simulations of different complexes shed light on the key interactions and residues in S100B, which are responsible for inhibition by the small molecules. The poster will present the results of the simulations and possible strategies to optimize the inhibitors.

COMP 263

Simulation study of interprotein electron transfer in hemoglobin tetramers

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Experiments [1] have shown differential dynamics for forward and backward electron transfer (ET) rates in mixed metal (αZn, βFe) Hemoglobin (Hb) tetramers as the viscosity of the solvent medium is altered. The dynamic docking model [2] explains the different viscosity dependence of the forward and backward ET rates in terms of having two species (ET reactive and ET non-reactive) in the ensemble of bound conformations which can interchange into one another at experimental temperatures. Molecular dynamics simulations coupled to ET calculations are performed on a fully solvated Hb tetramer unit to assess the dynamic docking model. We employ the empirical pathways model [2] as well as Greens function calculations parametrized by quantum chemistry calculations, to the MD ensemble to characterize the ET reactive and ET non-reactive species both structurally and energetically. The role of the solvent and the protonation states of heme propionate groups will also be discussed.

[1] Patel, A. D.; Nocek, J. M.; Hoffman, B. M. J. Am. Chem. Soc. 2005 127 16766

[2] Patel, A. D.; Nocek, J. M.; Hoffman, B. M J. Phys .Chem. B, 2008, 112 11827

[3] D. N. Beratan, J. N. Betts, J. N. Onuchic, Science, 1991, 252, 1285.

COMP 264

Structure-based drug design against pandemic influenza using all-atom molecular dynamics and docking

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Avian influenza strain H5N1 has been identified as a serious pandemic threat due to its extremely high mortality rate and risk of developing into a human pathogenic strain. Although H5N1 is sensitive to currently approved drugs oseltamivir and zanamivir, which target the viral enzyme neuraminidase (NA), point mutations H274Y and N294S in NA have been identified in some strains which confer drug resistance. In this study, we are using crystallographic structures as a starting point for simulations of NA tetramers, bound with known inhibitors, with the goal of elucidating the origins of drug resistance due to mutation. In parallel, we are developing and applying virtual screening protocols using the program DOCK, for targeting NA using the IBM BlueGene platform, with the goal of discovering novel drug leads. Results from these studies which include free energy calculations and analyses, as well as DOCK benchmarking, cross-docking, and enrichment for virtual screening, will be presented.

COMP 265

Surface tension, contact angle, and line tension in a liquid nanodroplet

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The surface tension of an oil/water interface is recognized as having tremendous potential to control the organization and assembly of nanoparticles. However, it is extremely difficult to directly measure the surface tension at a nanoscale level. One possible solution is to relate the surface tension with the contact angle, but the current theory is not applicable to nanoparticles. For our research, we report our progress to correct this theory, specifically by including three-phase

contributions to the line tension, the curvature dependence of the surface tension, and their relation with the contact angle.

We also report a new method to compute the surface tension using the internal energy density. We suppose that the internal energy density can be interpreted as the microscopic pressure, and from the difference in pressure the surface tension follows. We compare this new method with other standard methods.

COMP 266

Targeted design of dual kinase inhibitors for breast cancer

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The ErbB family of tyrosine kinases, as well as the kinase IGF-IR, are both important targets for development of anti-cancer drugs in the class known as "molecular targeted therapeutics." A precise understanding of the determinants which drive inhibitor specificity and affinity for these targets will be important for development of next generation drugs using techniques such as virtual screening. Results from all-atom structure-based modeling approaches (molecular dynamics, free energy calculations, and structure activity relationships) will be presented from simulations of inhibitors with kinase cancer targets which include EGFR, HER2 (structure obtained by homology modeling), ErbB4, and IGF-IR.

COMP 267

The development of an affinity evaluation and prediction system by using protein-protein docking simulations and parameter tuning

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To elucidate the partners in protein–protein interactions (PPIs), we previously proposed an affinity prediction method called affinity evaluation and prediction (AEP), which is based on the shape complementarity characteristics between proteins. The structures of the protein complexes obtained in our shape complementarity evaluation were selected by a newly developed clustering

method called grouping. In this study, we set a data scale (84×84 = 7056 protein pairs) including 84 biologically relevant complexes and then designed 225 parameter sets based on four key parameters related to the grouping and the calculation of affinity scores. AEP was able to provide prediction accuracy for a maximum F-measure that statistically distinguished 23 target complexes among 84 protein pairs. We have also been developing a workflow for protein-protein docking affinity prediction using the Konstanz Information Miner (KNIME). We apply KNIME to operate graphical/seamless protocols between users and analysis steps in the docking affinity prediction.

COMP 268

The effects of conformational variations on the packing of cup shaped molecules

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Crystallographic studies have shown that cup-shaped cyclotriveratrylene (CTV, CSD refcode: CUVHAC01) molecules assume geometries that do not maximize symmetry by deviating from the C_{3v} point group and forming jagged stacks[1]. The constituent methoxy groups in the crystal also align in directions that do not correspond to the lowest energy conformation obtained by density functional theory for an isolated molecule. These counterintuitive conformations are expected to be results of local dipoles, dispersion forces, electron distribution, and angle strains. In this study, we monitor these properties and evaluate how each affects the packing structure. Adjustments will then be made to develop an optimized molecular crystal structure with the lowest energy conformation. The packing preferences obtained in this analysis will be used to attempt the interpretation of several CTV structures used as container molecules.

[1]Zhang, H.; Atwood, J. L. *J. Cryst. Spect. Res.* **1990**, *20*, 465.

COMP 269

The energetics of stop codon recognition on the ribosome

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Ribosomal release factors successfully decode mRNA stop codons without the help of a kinetic proofreading mechanism. Recent medium resolution x-ray crystal structures of ribosomal termination complexes have shown that release factor recognition of stop codons in the decoding center is structurally distinct from sense codon recognition. Presented herein are molecular dynamics simulations and free energy calculations on six different cognate and non-cognate termination complexes. The calculated binding affinities are in good agreement with published experimental data, and the simulations predict that several specific interactions with conserved water molecules may be crucial for stop codon recognintion. Furthermore, a modified mechanism for the recognintion of both A and G nucleotides in the third stop codon position by Gln181 of RF1 is suggested.

COMP 270

The nature of intermolecular interactions in water-methanol complexes

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The differential stability between water-methanol complexes, when the roles as a hydrogen bond donor and acceptor are switched, has been studied by ab initio methods and density functional theory. The origin of increased stability when water is the hydrogen bond donor (WdM) compared to when it is the hydrogen bond acceptor (MdW) has been evaluated using symmetry-adapted perturbation theory (SAPT), natural energy decomposition analysis (NEDA), and natural bond orbital analysis (NBO). Electrostatic and stereo electronic contributions to the intermolecular interaction that determines the stability of the two complexes have been investigated. The results obtained are important in understanding the conformational properties of carbohydrates, where the subtle balance between the weak intramolecular hydroxyl group interactions and those between the carbohydrate and the solvent dictates the conformation.

COMP 271

The role of human skin emanation in understanding how a mosquito repellent works

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The mechanism of a mosquito repellent is unclear though a lot of efforts have been made either experimentally and theoretically. Previous theoretical studies only focused how the chemical structure of repellents may affect the biological activities of the repellents. However, there are missing information between repellents and the host. Recent study showed that the inclusion of the constituent of the human skin emanations may be important in understanding the repelling mechanism. In this study, the similar approach was extended to more mosquito repellents previously investigated by Katritzky and Suryanarayana. Theoretical geometry optimization was performed at the HF/6-31G(d) theory level and the subsequent QSAR was applied to compare the repellent-only results and the results of the repellent-human skin emanation complexes.

COMP 272

Theoretical studies for the crystal structure prediction: Tests on indenopyrazine

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The crystal structure of core component of blue OLED materials, 6,12-Dihydrodi-indeno(1,2-b:1,2-e)pyrazine was predicted using the Materials Studio 4.4 Polymorph Predictor in combination with XRPD patterns. After generation of the possible structures using Monte Carlo method they are minimized by the

molecular mechanics methods and we compared the X-ray powder diffraction between the experimental powder patterns and calculated ones for the simulated structures. The crystal structures which are best fitted to the experimental X-ray powder patterns were searched in the space group P21 and P21/c, respectively. The predicted structures were in agreement with the experimental structures stored in the Cambridge Structural Database and previously published structures. The structures which have low energy are possible structures for other polymorphs that has not been published. This work shows the possibility to predict the crystal structures using the Monte Carlo Simulated Annealing search procedure and X-ray powder diffraction patterns.

COMP 273

Training pKa and logP prediction

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pKa and logP prediction methods are based only on a limited number of molecule types in the training set. The accuracy of these models is not always satisfactory. Practically in most cases only those types of structures will be predicted correctly which were present in the training set. We decided to develop a training method for the pKa and the logP calculations to allow users to build models relevant for their structures.

The identification of acidic and basic ionization centers is defined in our default pKa prediction modul. 120 predefined atom types are implemented in the logP prediction model. The learning algorithm is based on a linear regression method called as Single Value Decomposition (SVD). The training set, a collection of experimental pKa or logP values, should be provided by the user. The collected data should be imported as an SDF or MRV file, which can be compiled for example using Instant JChem.

The training algorithm of pKa prediction creates a correction library containing correction values for interacting functional groups. In the case of logP prediction, a full set of atomic contributions is calculated.

COMP 274

Vibrational and spin properties of radicals derived from ubiquinol (dihyroubiquinone)

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Ubiquinol (dihydroubiquinone) is an important electron transfer cofactor and its radicals are implicated as intermediates in bacterial photosynthesis, plant photosynthesis, and mitochondrial respiration. Because of their transient nature, these radicals are often characterized only spectroscopically. This contribution describes B3LYP hybrid Hartree-Fock calculations to characterize the vibrational and spin properties of ubiquinol-derived radicals and compares calculated properties with published experiments.

COMP 275

Web services to promote GPCRs peptide mimetics

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G-Protein Coupled Receptors (GPCRs) are one of the most important targets for pharmaceutical medicines. Recent study revealed that many GPCRs are able to form homo- and/or hetero-oligomers, and the functional importance of the oligomerization has been extensively investigated. These studies revealed the combinations of subtypes required for complex formation and the wide variety of functions of the oligomers. In contrast to this situation, the molecular mechanisms of oligomerization are not fully understood yet. Under such restrictions, accurate predictions of the interfaces will accelerate investigations of the molecular mechanisms of oligomerization and promote the drug discovery for GPCRs based on peptide mimetics approach. Therefore, we recently launched a web service to predict the interfaces for GPCR oligomerization, named G-protein coupled Receptors Interaction Partners (GRIP) (http://grip.cbrc.jp/GRIP/index.html). In addition, we are developing a database for providing information about GPCR oligomerization.

COMP 276

Simulating protein folding on experimental timescales in all-atom detail

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One of the major challenges of connecting simulation to many application areas, especially biological applications such as protein folding, is the relatively long time scales found experimentally (milliseconds to seconds) compared to what is typically possible computationally (nanoseconds to microseconds).

I will describe our efforts to break past these time scale barriers with Markov State Models (MSM's). In our MSM formulation, we have means to automatically identify relevant states, very efficiently sample transitions from these states using adaptive methods, and then to finally statistically test and compare models. I will discuss recent applications of these methods to the simulation of the folding of small proteins, especially in connection to experimental data.

I will also touch on the differences between protein folding in vitro and folding in vivo, highlighting recent results we have found regarding a new hypothesis for the mechanism of chaperonin function.

COMP 277

Hydration effects on peptide stability in confinement

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Understanding the stability of peptides and proteins in confinement is

important in a number of biological situations, including

encapsulation in a chaperonin cage, translocation through nanopores

and the ribosome exit tunnel. While polymer theory predicts that

proteins will be stabilized in confinement due to entropic effects,

recent coarse-grained simulations [O'Brien et. al., Nano Lett., 2008,

v8, 3702] have shown how the stability of peptide helices in carbon

nanotubes depends on a number of factors such as the amino acid

sequence, solvent conditions, nanotube dimensions and the strength of the nanotube-peptide interactions.

A complete understanding of hydration effects is still lacking -- some studies show enhanced peptide stability in confinement [Vaitheeswaran et. al., Proc. Natl. Acad. Sci. U.S.A., 2008, v105, 17636], while others suggest the opposite [Sorin et. al.,J. Am. Chem., Soc., 2006, v128, 6316]. Here, we report on the results of MD simulations to study hydration effects on the conformations of short peptides, ranging in length from 3 to 10 amino acid residues, in carbon nanotubes immersed in a water reservoir.

COMP 278

The kinetics and structure of protein energy landscape

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The complexity of the physical interactions that guides the folding of biomolecules presents a significant challenge for atomistic modeling. Minimal representation protein structure prediction potentials have previously been used to predict protein structure from sequence. The resulting landscapes suggests the actual protein energy landscapes are funneled as predicted from theory. A reduced description of the energy surface comprised of connected sets of minima, transitions states, and minima can both reduces the complexity of the energy surface, and present opportunities for statistical mechanical treatment of the underlying reaction kinetics.

We show several disconnectivity graphs for the folding reaction a protein A, villin, and the 434 repressor using a database of minima and transition states. Using these databases we calculate the diffusion of the polypeptide chain as a function

of native contacts, and the kinetics between various basins of attraction. Finally we calculate disconnectivity graphs of funnelled energy functions with an increasing amount of randomness to identify the transition between random hetero-polymers, and proteins.

COMP 279

Action of urea: Molecular picture of protein chemical denaturing from large scale simulations

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The protein chemical denaturing mechanism is analyzed using extensive molecular dynamics simulations of several proteins (lysozyme, gamma-D crystallin, and CI2) in 8 M urea. We observe a 2-stage penetration of proteins in general, with urea penetrating the hydrophobic core before water, forming a ‘‘dry globule.'' The direct dispersion interaction between urea and protein backbones and side chains is stronger than for water, which gives rise to the intrusion of urea into the protein interior and to urea's preferential binding to all regions of the protein. This is augmented by preferential hydrogen bond formation between the urea carbonyl and the backbone amides that contributes to the breaking of intra-backbone hydrogen bonds. Meanwhile, we find little change in the structure of water on addition of 8 M urea except that a very small fraction of water engaged in two simultaneous H-bonds with the same urea molecule slow down the reorientational dynamics. Our study supports the ‘‘direct interaction mechanism'' whereby urea has a stronger dispersion interaction with protein than water.

COMP 280

Folding free-energy landscape of an alpha/beta fold protein from replica exchange molecular dynamics simulations

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We present the "ab initio" folding of a mini alpha/beta fold protein using replica exchange molecular dynamics simulations using an AMBER protein force field coupled with a recent implicit solvent model. The lowest Ca-rmsd from the NMR structure at 280 K is 0.92 Å and the Ca-rmsd of the centroid of the most

populated structural family at 280 K is 1.77 Á. The melting temperature Tm=321±6 K obtained from the heat-capacity profile is in a good agreement with the experimental value 315 K. The folding landscape can be partitioned into the native state, transition state and denatured state regions. While the denatured ensemble lacks the hydrophobic core as well as alpha and beta secondary content, the transition state structural ensemble is characterized by a folded C-terminal helix, an unfolded N-terminal beta-hairpin and a partially formed hydrophobic core. Our data is consistent with a nucleation-condensation folding mechanism.

COMP 281

Helix formation and helix-helix interactions in protein folding

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While much is known about the equilibrium properties of the helix-coil transition in proteins, there is no widespread agreement on the rates of helix formation in general - theoretical and experimental estimates varying widely, from picoseconds to microseconds. Factors such as peptide length, sequence composition and contacts between secondary structures all influence the rates of helix formation. We present results of molecular dynamics simulations of helix-forming molecules, including a helix-turn-helix protein and various polyalanine peptides. Using large-scale all-atom simulations with explicit water molecules, we study of the competition between secondary and tertiary contacts and the effect of sequence length on the rates of formation of helices and their stability. The helix-turn-helix motif allows a systematic study of the dynamics and sequential formation mechanism of both inter- and intra-helix contacts, as a first stage towards understanding the elementary steps of secondary and tertiary structure formation in the folding of larger proteins.

COMP 282

Probing the role of domain cooperativity in the mechanical unfolding of proteins

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Single molecule mechanical methods provide unique opportunities for directly probing the free energy landscape of complex biomolecules. An assumption

employed by many experiments to understand the force-unfolding of multi-domain proteins is that the ensemble is the sum of its parts. While this assumption applies to homo-protein tandems, for hetero-protein tandems or whenever units are connected by interfaces as in multi-domain complexes this assumption needs revisiting. I will present forced-unfolding simulations, employing a self-organized polymer model, of multi-domain protein complexes selected from fusion and cytoskeletal proteins. While our model reproduces the experiments, we find that the independence assumption fails. I will discuss the domain-domain interactions as a function of force, and the connection between the shape of the force peaks and the cooperativity in the protein. Remarkably, the degree of stabilization is determined by a combination between the stability of the interface and the internal fluctuations of a module.

COMP 283

Ligand free energy ranking using constrained fragment annealing (CFA): A step toward a practical analysis of full ligand/protein interactions

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Fragment-based design exploits optimal binding sites of chemical fragments on a protein, but cannot rank ligands with functional groups positioned at less than optimal sites. Further, some ligand interactions are impacted by complex intra-ligand non-bonded interactions between functional groups, confounding attempts to rank such compounds. CFA extends the method of free energy ranking by annealing chemical potential by the addition of constraint potentials. These potentials limit the motion of a fragment in a grand canonical Monte Carlo process to configurations compatible with ligand bond positions. This method enables deconvolution of the interactions by individually constraining fragments corresponding to functional groups of the ligand that may interact. To date we have used this with ligands containing up to 5 separate functional groups. Examples are given comparing the predicted ranking with IC50 data. Extension to free energy ranking of complete ligands will be discussed.

COMP 284

Machine learning and drug discovery: Never the twain shall meet?

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Numerate has developed a novel drug engineering platform wherein key design decisions are made by predictive computational models, developed by machine learning techniques, rather than by chemists. Previous attempts at using machine learning in drug discovery have met with limited success. The reasons for this rest on the inability or failure to address challenging statistical problems associated with ligand-based design. We will discuss the problems that have limited previous attempts and present results from two programs based on the solutions we have devised. In the first program we designed dual-acting compounds for addressing multiple aspects of cardiovascular risk. The 19 compounds synthesized represent four proprietary series and display differential pharmacology relative to statins in vitro and in vivo. In the second program we designed broad spectrum non-nucleoside HIV1 reverse transcriptase inhibitors. We identified compounds with whole cell activities comparable to Sustiva in 6 months with only 21 compounds synthesized.

COMP 285

Methods for structure based scaffold replacement

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Small molecule scaffold replacement techniques are an important part of drug discovery because of the need to find rapid "follow on" compounds or alternate series. Fragment-based drug discovery techniques also benefit from scaffold replacement methods because of the need to link fragments that bind to a receptor. We present methods for structure-based scaffold replacement that combine techniques from pharmacophore discovery and ligand receptor docking. Strategies for the creation of 3D virtual fragment databases are discussed as well as the results of computational experiments.

COMP 286

Modeling allosteric regulation in GPCRs: Toward rational structure-based drug design

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Allosteric interactions mediate highly specific ligand recognition and signal transduction in transmembrane protein receptors. We use theory and computer

simulations to explore allosteric regulation in two members of the G protein-coupled receptor superfamily, bovine rhodopsin and human beta2-adrenergic receptor (B2AR). The simulations reveal how specific structural motions can mediate signal transduction between different receptor sites, suggesting an explanation for the recently discovered and still puzzling effect of "biased agonism" (the selected activation of the G protein-mediated pathway or the beta-arrestin-mediated pathway in B2AR) [1,2]. The molecular basis for specific receptor responses to ligand binding is analyzed, and development of strategies for rational structure-based drug design is discussed.

[1] Shukla A.K., et al. (2008) Distinct conformational changes in beta2-arrestin report biased agonism at seven-transmembrane receptors. Proc. Natl. Acad. Sci. USA 105:9988-9993.

[2] Kenakin T. (2007) Collateral efficacy in drug discovery: taking advantage of the good (allosteric) nature of 7tm receptors. Trends in Pharm. Sci 28:407-415.

COMP 287

Modeling novel planar BACE1 inhibitors: Trying to hit a moving target

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Inhibition of BACE1 is a promising therapeutic target for treatment of Alzheimer's disease. BACE1 like other aspartic proteases has a flexible loop – “flap” – which gives rise to a multitude of possible and observed protein conformations.

Isothioureas and subsequently cyclized analogs were discovered as BACE1 ligands by fragment-based NMR screening. The iterative fragment optimization efforts relied on the integration of medicinal chemistry, docking and modeling calculations, NMR studies and X-ray crystal structures. During the optimization many unexpected and difficult to predict binding modes and protein conformations were encountered. Ultimately, this allowed the rational design and optimization of iminohydantoins as very potent BACE1 inhibitors.

This novel class of ligands induces a more open flap conformation than found in the substrate like complexes of statines and homo-statines. This leads to a significant extension of the mostly lipophilic S1- and S2'-pockets.

COMP 288

Modeling of prolyl-leucyl-glycinamide (PLG) analogs that modulate the dopamine D2 receptor: Method evaluation, pharmacophore mapping/database searching, and 3D-QSAR

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Prolyl-leucyl-glycinamide (PLG) is a unique endogenous peptide that modulates dopamine receptor subtypes of the D2 receptor family within the CNS. We seek to elucidate the structural basis and molecular mechanism by which PLG modulates dopamine receptors, toward the development of new drugs to treat Parkinson's and related diseases of the CNS. Toward this goal, we have applied a series of molecular modeling techniques to (a) evaluate the suitability of a wide variety of modeling techniques including MM, NDO, SCC-DFTB, DFT and HF methods for a family of novel PLG analogs; (b) derive pharmacophore maps for a subset of active compounds and use these to search databases for potential active compounds; and (c) develop novel and highly predictive 3D-QSAR (CoMFA and CoMSIA) models for a PLG analog subset with experimentally determined biological activities against the dopamine D2 receptor. We specify the best computational methods for this group of PLG analogs, along with a series of hit compounds from pharmacophore mapping and database searching which have not previously been identified as potential dopamine D2 receptor

binders, and visualizations of optimized 3D-QSAR models that elucidate key ligand-receptor interactions.

COMP 289

Of things that are rare: Iridium, dinosaur coprolite, and high quality protein-ligand structure databases

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Computational chemistry, like any other predictive science, uses models of physical phenomenon to make predictions. The Achilles heel of every model is the quality of the experimental data upon which it is built or validated. Unfortunately, in protein-ligand modeling too little time and attention has been paid to this important detail. We present here a protein-ligand structure database called Iridium, so called to reflect the scarcity of reliable information. The data in Iridium is from published sources, e.g. structures and electron density can be found in the RCSB; however, enormous time and effort have been taken in annotation and curation. For instance, all structures have been re-refined with MMFF94s used as the force field for the small molecule ligand. Structures are annotated with regard to the quality of the data and for approximately 90% of the structures binding affinity has been obtained from primary literature. We found that 19% of the ligands in this data set contained errors, e.g. incorrect bond orders, element types and/or stereochemistry and missing functional groups. The resultant database divides into three subsets: structure models that should never be used for validation, structure models of questionable reliability or utility and structure models of high reliability. The database will be made freely available with the hope it will reduce the prevalence of coprolite in modeling theory.

COMP 290

Assessment of DFT and NDDO models for Zn molecules, clusters, and biocenters

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Here we present benchmark databases of Zn-ligand bond distances, bond angles, dipole moments, and bond dissociation energies for Zn-containing model and coordination compounds with a variety of ligands incorporating H, C, N, O, F, Cl and S. We also include clusters with Zn-Zn bonds, and dipole moments and binding energies for Zn centers in coordination environments taken from zinc metalloenzyme x-ray structures representing both structural and catalytic zinc centers. The benchmark values are based on relativistic-core coupled cluster calculations, and are used to test the predictions of four density functionals: B3LYP and the more recently developed M05-2X, M06, and M06-2X theory levels; and six semiempirical methods, including neglect of diatomic differential overlap (NDDO) calculations incorporating the new PM3 parameter set for Zn called ZnB developed by Brothers and coworkers, as well as the recent PM6 parameterization of Stewart. We found that the best DFT method to reproduce dipole moments and dissociation energies of our Zn compound database is M05-2X, which is consistent with a previous study employing a smaller database and a larger set of density functionals. Here we show that M05-2X geometries, and single-point coupled cluster calculations with M05-2X geometries, can also be used as benchmarks for larger compounds where coupled cluster optimization is impractical. We find that the most predictive NDDO methods for our training set are PM3 and MNDO/d, and we note large errors in B3LYP for the coordination compounds based on experimental x-ray geometries.

COMP 291

Computation of interaction energies via density functional theory with empirical van der Waals corrections

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The computation of interaction energies between noncovalent complexes with common density functionals is often hindered by the exclusion of dispersion terms associated with van der Waals interactions. We have implemented a methodology to introduce empirical corrections due to van der Waals interactions on top of conventional density functional calculations. The methodology is based on finding parameters that moderate Lennard Jones potentials by comparison with available CCSD(T) and other reference data. Our results allow for computation of interaction energies for noncovalent complexes with an accuracy generally better than a few percent over several orders of magnitude. Possible applications to DNA and bioinorganic molecules will be discussed.

Supported, in part, by NSF CAREER award CHE-0349189 (JHR)

COMP 292

Density functional molecular dynamics calculation of the dissociation constant of liquid water

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Calculation of the dissociation constant (pKw) of liquid water using all atom density functional theory based molecular dynamics methods is a bench mark test for the computation of acidity constants in more complex aqueous systems. We have performed such a test using a recently developed proton insertion/removal method. Chemical species in this scheme must be explicitly defined by an appropriate classical force field chaperone potential. This enabled us to distinguish between a (hypothetical) Zundel and Eigen form of the solvated proton. The hydroxide anion is treated as a single species. The resulting BLYP estimate of the pKw values for dissociation in Zundel and Eigen ion are 13.6 and 13.3 respectively. A separate calculation in which the Zundel ion is reversibly transformed into the Eigen ion confirmed that these two forms of the excess proton are practically degenerate in free energy and moreover thermodynamically not stable.

COMP 293

Density functional theory studies of doping in both bulk- and surface-state titania

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The structural, energetic and electronic properties of substitutional Ge, N/W, Bi/S (co)doped bulk anatase-titania systems have been investigated, along with those of a range of adsorptive and substitutional S- and P-doped rutile-titania (110) surfaces, by first-principles density functional theory (DFT) calculations. The stability of the various doping configurations was compared on the basis of their calculated formation/adsorption energies, and preferred dopant states were identified and characterised in terms of structural features. In many cases, red-shifts in optical absorption edge and reductions in photon transition energy were observed, along with synergistic effects between electronic states introduced by

co-dopants. These observations have been used to rationalise various recent experimental observations under these dopant conditions.

COMP 294

Electronic coupling matrix elements from charge constrained DFT calculations: A plane wave basis set implementation

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Electron transfer rates are largely determined by the electronic coupling matrix element

between donor and acceptor states, H12. Accurate calculation of H12 usually requires

expensive wavefunction based ab-initio methods, and as such is limited to rather small

electron transfer systems. Computationally less demanding methods based on ground state

density functional theory (DFT) are in principle available as an alternative, but their success

in practical applications is hampered in part by the self-interaction error of uncorrected

exchange-correlation functionals. Recently Van Voorhis and co-workers have suggested a

method for an approximate calculation of H12 using a special variant of DFT calculations,

termed constrained density functional theory (CDFT). In this method the diabatic states 1

and 2 are obtained from two DFT calculations with the excess electron or hole constrained

on the donor (state 1) or acceptor (state 2), respectively. Approximating the two diabatic

wavefunctions by their Kohn-Sham determinants, H12 can be computed from quantities that

are solely derived from localized diabatic states. The electron self-interaction error

of these two states is suppressed (though not eliminated) due to their localized nature.

We have implemented the CDFT method in the Car-Parrinello molecular dynamics package.

In our contribution we present calculations of H12 for simple electron transfer systems and

discuss the accuracy of this approach by comparing to the results obtained from wavefunction

based ab-initio methods. Applications to electron transfer in more complex systems will be

presented thereafter. Our implementation of CDFT into the CPMD code allows us not only to

compute coupling matrix elements for condensed phase systems such as ionic solutions or solids,

but also to probe the fluctuations of H12 along a finite temperature ab-initio molecular

dynamics trajectory, allowing us to investigate the validity of the Condon approximation.

COMP 295

Binding free energy calculations of protein-ligand complexes using fragment molecular orbital method combined with continuum solvent model

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The fragment molecular orbital method (FMO) [1,2] has made feasible the quantum chemical calculations of large molecular systems such as whole

protein-ligand complexes. In order to incorporate solvent effect into the calculations, FMO has been combined with the polarizable continuum model (PCM). We will report the binding free energies of several protein-ligand complexes obtained from FMO/PCM calculations at the MP2/6-31G* level.

[1] D. G. Fedorov, K. Kitaura, J. Phys. Chem. A, 111, 6904 (2007).

[2] D. G. Fedorov, K. Kitaura, Eds, "The Fragment Molecular Orbital Method:

Practical Applications to Large Molecular Systems", CRC press, in press.

COMP 296

Electronic properties and intermolecular binding in drug-like molecules

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Semiempirical molecular orbital calculations are fast enough to be able to treat databases of many hundreds of thousands of molecules on modern hardware. The resulting wave functions can be used to calculate local properties that relate directly to intermolecular interactions and hence binding and physical properties. In this lecture, I will show how these local properties can be used for drug design applications and how they allow “non-standard” interactions such as halogen bonding to be detected. Modeling and docking techniques based on molecular surfaces will be discussed.

COMP 297

Quantum mechanics in drug discovery and design

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Quantum chemical (QM) methods have had tremendous impact on our understanding of chemical and biological systems. In this presentation we will focus on the application of ab initio QM methods to solve relevant problems in structure-based drug design (SBDD) using NMR techniques. We will describe our novel automated fragmentation (AF)-QM/MM method and show that it

efficiently gives accurate NMR chemical shift information. We will discuss application of this new approach to refining protein structures, selecting ligand poses and studying protein dynamics by NMR. Finally, we will briefly summarize our vision of the future application of quantum chemistry to SBDD.

COMP 298

Use of quaternions in biomolecular structure analysis

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In this presentation we will describe a new method for measuring and visualizing "straightness" and "structural integrity" of proteins and nucleic acids. In the case of proteins, the method relies on heretofore unrecognized relationships between Ramachandran angles and unit quaternions representing amino acid residue orientation. In the case of nucleic acids, we will show how an extrapolation of these measures provides valuable information in that context as well. Several recent advances in the Jmol molecular visualization applet were necessary in order to allow these visualizations. These advances will be demonstrated as part of the presentation.

COMP 299

Sirius: A versatile desktop visualization environment

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Sirius is a component-based visualization system originally developed at San Diego Supercomputer Center and available for all major operating systems. Sirius provides tools for molecular modeling, drug discovery, protein structure analysis, as well as data mining and sequence-based work. It includes Structure Viewer (3D display), Sequence Viewer, and Structure Browser. These components are linked to allow simultaneous updates to the displayed data in response to changes, such as structure edits and appearance changes.

Sirius features a powerful structure editing capability. Small organic compounds can be easily built from scratch, and peptides can be assembled from individual amino acids. Sirius provides the flexibility to render, color, show/hide, label any

given atom of the structure independently of other parts of the display, as well as edit existing atomic structure and protein sequence. Hydrogen bonds and steric clashes are detected automatically and updated in real time as the structure or its parts are moved.

Sirius provides a convenient interface for several third-party applications. These include Modeller (homology modeling of protein structures), Amber and CHARMm (molecular dynamics setup and trajectory visualization), POV-Ray (high-quality ray tracing for scene rendering), as well as structure and sequence alignment functionality. A dedicated data access component provides the ability to run BLAST and InterProScan searches in the Uniprot database. Current feature set of Sirius is being expanded to include diverse surface rendering models, as well as extension capability for use in data-driven projects as a structure display module.

COMP 300

Molecular visualization and animations using PMV

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PMV is a mature, Python-based software environment for advanced visualization and manipulation of biological molecules. It has been used as a platform for producing specialized graphical user interfaces for several software packages including: FLIPDock, a protein-ligand automated docking allowing for flexible receptors; pyARTTK, an augmented reality software application; and last but not least, AutoDock, the well known automated receptor-ligand docking program.

We will give an overview of PMV's capabilities with a particular emphasis on: 1) its extensibility through the Visual Programming environment, 2) newly added animation story boarding and production capabilities, and 3) the latest developments in rendering molecular structures. We will shortly describe how Vision allows new functionality to be added to PMV without having to learn the syntax of the Python programming language or becoming familiar with the complex data structures in PMV. It also enables the definition of workflows that can contain web services and remote calculations. We will describe our latest addition to PMV allowing users to define animation using a paradigm similar to PowerPoint's custom animations. We will show how simple animations can be created with a few mouse clicks and saved as MPEG movies. Finally we will introduce some of the new rendering capabilities including 3D labels, cheap ambient occlusion, and generalized stroke outlines.

COMP 301

UCSF Chimera

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UCSF Chimera is a program for the interactive display and analysis of molecular structure at multiple scales and associated data of multiple types. Chimera is free for noncommercial use and can be downloaded for Windows, Linux, and Mac from http://www.cgl.ucsf.edu/chimera. Development is funded by the NIH National Center for Research Resources (grant P41-RR01081).

Menu and command-line interfaces provide a rich and overlapping set of features. Standard display styles are available and visual effects such as silhouette edges can be adjusted. Geometric objects and text labels can be placed in the display. Images can be saved at high resolution. Animations can be scripted or captured with the interactive Movie Recorder.

Data can be opened from local files or fetched over the Web from sources including the Protein Data Bank, Electron Density Server, Electron Microscopy Data Bank, ModBase (comparative models), and Pub3D (small molecules).

Measurements and interactive bond rotations can be performed. Atom types are determined automatically and used for detecting hydrogen bonds and contacts. Amino acid rotamers can be displayed and substituted into structures. Ensembles can be clustered or viewed as trajectories. Trajectories can be read from files or created by morphing.

Supramolecular assemblies can be shown as low-resolution surfaces. Density maps can be shown as contour surfaces or transparent solids. Maps can be filtered or otherwise edited, and atomic structures fitted into the density.

Chimera can display individual sequences, create alignments of structures and their sequences, and/or read sequence alignment files from external sources. Structures are automatically associated with sequences within some tolerance. Crosstalk includes bidirectional highlighting, superimposing structures using the sequence alignment, and displaying conservation on structures. Properties such as B-factor, hydrophobicity, and conservation can be shown with colors and/or "worm" thickness. Users can easily define new properties for custom analysis.

COMP 302

PyMOL molecular viewer: Updates and refinements

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PyMOL was first released to the internet as Open-Source software in the year 2000, and has since become a widely used tool for communicating results from structural biology and computational chemistry. PyMOL's main benefits lie in the areas of image quality, cross- platform compatibility, animation support, and scripting (via commands or through Python). Of course, there is also the project's open-source status, which permits free use of the open-source version. Here we cover the software's present capabilities and primary use cases and discuss how the package is likely to evolve in coming years in response to changing hardware and software infrastructure.

COMP 303

The energy landscape for folding and molecular motors: The kinesin story

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Globally the energy landscape of a folding protein resembles a partially rough funnel with reduced energetic frustration. A consequence of minimizing energetic frustration is that the topology of the native fold also plays a major role in the folding mechanism. Some folding motifs are easier to design than others suggesting the possibility that evolution not only selected sequences with sufficiently small energetic frustration but also selected more easily designable native structures. The overall structure of the on-route and off-route (traps) intermediates for the folding of more complex proteins is also strongly influenced by topology.

Many cellular functions rely on interactions among proteins and between proteins and nucleic acids. The limited success of binding predictions may suggest that the physical and chemical principles of protein binding have to be revisited to correctly capture the essence of protein recognition. Going beyond folding, the power of reduced models to study the physics of protein assembly will be discussed. Since energetic frustration is sufficiently small, native topology-based models, which correspond to perfectly unfrustrated energy landscapes, have shown that binding mechanisms are robust and governed primarily by the protein's native topology. These models impressively capture many of the binding characteristics found in experiments and highlight the fundamental role of flexibility in binding. Deciphering and quantifying the key ingredients for biological self-assembly is invaluable to reading out genomic sequences and

understanding cellular interaction networks. Going even beyond binding, we will be discussing the energy landscape for the molecular motor kinesin.

*supported by the NSF

COMP 304

Working principle of biomolecular motors revealed by molecular dynamics simulations

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All cells possess various kinds of molecular motors that transfer some free energy input, such as ATP chemical energy, into mechanical work. For ATPases, for example, the free energy transduction is achieved by interplay among three players, the bound nucleotide, structure of the enzyme, and mechanical work. Change in the type of bound nucleotide affects the enzyme structure, which is transmitted to the mechanical work. Simultaneously, in the reverse direction, the mechanical work has to regulate the chemical reaction of the bound nucleotide. Through various computer experiments by coarse-grained molecular dynamics simulations, we study structure-based coupling among these three factors in molecular motors. We present some of our works on F1-ATPase, myosin V, AAA+ motor and kinesin.

COMP 305

Computer simulations of protein unfolding and translocation by Clp ATPase nanomachines

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Clp macromolecular machines, found in all domains of life from prokaryotes to multicellular eukaryotes, are critical components of the quality control system that performs selective destruction of proteins and disassembly of protein aggregates. We focus on the powerful ATPase components of these nanomachines, which effect protein unfolding and translocation through narrow pores to deliver substrates to the peptidase subunit. Functional forms of Clp ATPases are homo-hexameric assemblies that enclose narrow central channels. Protein unfolding and translocation through these channels is hypothesized to result from mechanical pulling due to ATP-driven conformational changes that occur in the ring subunits. We use coarse-grained molecular dynamics simulations to study

the unfolding and translocation of a four helix bundle protein coupled with ATP-driven conformational changes in the ClpY ATPase. Our simulations suggest that protein unfolding occurs prior to translocation and that unfolding pathways contrast those resulting from mechanical pulling of the protein ends in solution.

COMP 306

Viral shell mechanics

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The mechanical properties of viral shells are crucial for viral assembly and infection. To study their distribution and

heterogeneity on the viral surface, we performed atomistic force-probe molecular dynamics simulations of the complete shell of

southern bean mosaic virus, a prototypical T 1/4 3 virus, in explicit solvent. The simulation system comprised more than 4,500,000

atoms. To facilitate direct comparison with atomic-force microscopy (AFM) measurements, a Lennard-Jones sphere was used as

a model of the AFM tip, and was pushed with different velocities toward the capsid protein at 19 different positions on the viral

surface. A detailed picture of the spatial distribution of elastic constants and yielding forces was obtained that can explain corresponding

heterogeneities observed in previous AFM experiments. Our simulations reveal three different deformation regimes:

a prelinear regime of outer surface atom rearrangements, a linear regime of elastic capsid deformation, and a rearrangement

regime that describes irreversible structural changes and the transition from elastic to plastic deformation. For both yielding

forces and elastic constants, a logarithmic velocity dependency is evident over nearly two decades, the explanation for which

requires including nonequilibrium effects within the established theory of enforced barrier crossing.

COMP 307

Molecular simulations of large-size protein assemblies on graphics procesors

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Although the mechanical properties of fibrin network, that determine how blood clots and thrombi respond to the shear stress of blood flow, are well known and have been related to fibrin fiber structure, the molecular mechanisms of clot mechanical deformation are poorly understood. Dynamic force spectroscopy experiments have enabled direct characterization of the mechanical response of large protein assemblies, and molecular simulations can now be used to interpret the experimental results. However, because of the extremely large system size (~1,000-10,000 residues), computer modeling of fibrin deformations under physiologically relevant force loads in atomic detail is unfeasible. We have overcome this problem by employing graphics processing units (GPUs), rather than CPUs, and coarse-grained models of proteins. These advanced methods allow the application of physiologically relevant pulling speeds of 1μm/s-10μm/s (unfolding forces of 50-500pN) to access the forced unfolding transitions in fibrin molecules on real timescales (0.001-1s). The force-induced unfolding transitions in fibrin monomers are determined by the interplay of mechanical deformations in the coiled-coils and in the globular C-terminal regions of the gamma chains. The unfolding forces (50-150pN) and molecular extensions (20-50nm) of the force-extension curves agree well with experimental data. The developed computational methodology (pseudo-random number generators, integration schemes), implemented on CUDA-enabled graphics cards (from NVIDIA), can now be used to explore large-scale biomolecular systems, including protein fibers, molecular motors, and viral capsids among many others.

COMP 308

C^{I} channel antiporter function

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Only recently the E.coli chloride channel was found to be an anti-porter transporting protons opposite to Cl^- with stoichiometry of two Cl^- per proton. Homolog chloride channels in osteoclasts are used to remove excess bone tissue. Crystal structures with closed and open channel states are available. While the Cl^- pathway is traced in the crystal structure by three Cl^- sites the proton pathway is less well defined exhibiting a large hydrophobic gap bridged by a tyrosine (phenylalanine for a mutant) between a crystal water on the channel inside and the chloride gate Glu148 on the channel outside. Between the crystal water and the central chloride a chain of four additional water molecules can be placed, which are energetically stable. With electrostatic energy computations we can follow the proton pathway along the water chain between Glu203 and Glu148 on the channel outside. We also suggest a solution for the two-to-one stoichiometry.

COMP 309

Volatile anesthetic modulation of dynamic structure of water in α4β2 nicotinic acetylcholine receptor

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Water plays a significant role in shaping protein structures and dynamics. It is also implicated in mediating the action of volatile anesthetics on proteins. We performed 20-ns MD simulations on an anesthetic target, α4β2 nicotinic acetylcholine receptor, in the absence and presence of halothane (a volatile anesthetic). In the binding sites with access to bulk water, halothane was found to displace water molecules from the protein cavities, thereby reducing the amount of bound water. In other regions where the water presence was normally transient and scarce, halothane facilitated entrance of water to these sites. In all cases, the introduction of halothane substantially altered the hydrogen-bond network mediated by water molecules between protein residues. The disruption of the hydrogen-bond network dramatically changed the flexibility of the residues involved and conceivably has significant impact on the function of the protein. Supported by NIH (R01GM66358, R01GM56257, R37GM049202, T32GM075770) and NCSA through the PSC.

COMP 310

Paratope structural optimization during antibody-antigen docking

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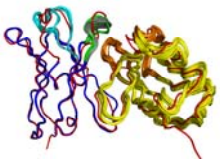
Success of several therapeutic antibody drugs has relied on homology modeling. However, inaccuracies in a homology model limit prediction of high resolution structure of antibody-antigen complexes, which are useful for analyzing the binding interface and making rational choices for antibody engineering. We illustrate a novel approach called SnugDock which predicts high resolution antibody-antigen complex structures by simultaneously optimizing (i) the antibody-antigen rigid body positions, (ii) the six complementarity determining region (CDR) loop conformations and (iii) the relative orientation of the antibody light and heavy chains. Local docking using SnugDock with the lowest-scoring RosettaAntibody homology model produced more accurate predictions than standard rigid-body docking. Performance of SnugDock is robust in that it can also make successful predictions using Web Antibody Modeling (WAM) server models or Prediction of Immunoglobulin Structure (PIGS) server models. We tested a new algorithm combining ensemble docking and SnugDock to capture conformer selection and induced fit. The fusion produced seven medium (Critical Assessment of PRediction of Interactions-CAPRI rating) and five acceptable predictions in a test-set of fifteen complexes. This work demonstrates that a new genre of general docking algorithms with flexible binding interfaces can compensate for inaccuracies in homology models and enable their use in high-resolution structure prediction needed for engineering improved specificity and affinity.

Figure: Conformational diversity generated by SnugDock for a representative antibody. (PDB ID: 1BQL) Crystal, red; Heavy and light chains, blue and yellow, respectively; Light and heavy chain CDRs, orange and cyan, respectively; SnugDock sampled CDR H3, grey; SnugDock+EnsembleDock sampled CDR H3, green.



COMP 311

Predicted 3D structure for the histamine H3 receptor and its binding site

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Now several human histamine H3 receptor (hH3HR) targeting drugs are under clinical trials in various diseases, allergic rhinitis, central nervous system diseases, and obesity. A 3D theoretical model of the hH3HR was predicted to investigate the binding mode of H3 selective agonists, Histamine/ (R)á-MeHistamine, and antagonists, Clobenpropit. Docking of these ligands in a Gensemble-based model revealed two major anchoring points at D3.32 and E5.46, consistent with mutagenesis studies. D3.32 and E5.46 in its anionic state interact with charged nitrogen and the N atom in the imidazole ring of histamine, whereas protonated D3.32 and E5.46 in neutral state through charge transfer formed H-bonds with neutral nitrogen and the imidazole ring. The proposed model for H3 selective ligand explains the observed difference in binding to other subtypes. The refined 3D model will guide the rational design of novel drugs for the hH3HR selective antagonists and agonists with reduced side effects.

COMP 312

Predicting druggable binding sites at the protein-protein interface

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Protein-protein interfaces are highly attractive targets for drug discovery because they are involved in a large number of disease pathways where therapeutic intervention would bring widespread benefit. Recent successes have challenged the widely held belief that these targets are 'undruggable'.

We have previously described a successful pocket finding algorithm – Q-SiteFinder – that we use to show marked differences between the binding pockets that define protein-protein interactions (PPIs) and those that define protein-ligand interactions (PLIs) of currently marketed drugs. Furthermore we

have undertaken molecular dynamics studies of a well characterized PPI inhibitor target.

In the case of PPIs, drug discovery methods that simultaneously target several small pockets at the protein-protein interface are likely to increase the chances of success in this new and important field of therapeutics.

COMP 313

Prioritizing ligand protonation states in docking

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Many drug-like molecules can access multiple protonation states at physiological pH. These states must be considered in in silico docking and scoring approaches, as they can have distinct binding modes and calculated affinities with receptors. While it is straightforward to enumerate the states, prioritizing them such that low population states are penalized (thereby reducing the frequency of false positives) is challenging. Furthermore, different populations of protonation states must be considered for molecules that interact with a metal in the binding site.

We have developed a method for calculating free energy penalties for protonation states. When these penalties are applied to the docking score in Glide, a significant increase in database enrichment is observed. We will describe how protonation states and penalties are assigned by Epik, and present validation results involving a diverse set of targets, including metal-containing binding sites.

COMP 314

Protein-ligand docking based on ant colony optimization

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In the past years, many different strategies for protein-ligand docking have been proposed. Especially the class of stochastic optimization methods turned out to be very suitable for this task. Methods like simulated annealing, genetic algorithms and evolutionary programming are well established in the chemistry community and have been investigated intensively for the docking problem. We recently introduced a new docking algorithm PLANTS (**P**rotein-**L**igand **ANT** **S**ystem) [1-3], which is based on a class of stochastic optimization algorithms called *ant colony optimization* (ACO) [4]. ACO is inspired by the behavior of real ants finding a shortest path between their nest and a food source. In the case of protein-ligand docking, an artificial ant colony is employed to find a minimum energy conformation of the ligand in the binding site of a protein.

After a short introduction to the general ideas, we will summarize the latest developments for PLANTS. This will include the pre-processing of the ligands and the protein performed by the program SPORES (**S**tructure **P**r**O**tonation and **RE**cognition **S**ystem) [5], parameterization of a new scoring function, as well as the inclusion of additional degrees of freedom into the docking process like flexible side chains and essential water molecules. Finally, an outlook towards the possible usage of the PLANTS approach for the flexible alignment of multiple ligands will be given.

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COMP 315

Screening rule of structure parameters in quantitative structure-activity relationships model

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A new screening rule of structure parameters in Quantitative Structure-Activity Relationships (QSARs) models applying Artificial Neural Networks (ANN) is given. The new screening rule overcomes the problem, which some important

nonlinear information between input nodes and output nodes may be omitted as screening input nodes in ANN-QSARs models. The structure parameters in multi-chlorophenol QSARs model can be screened fast and simply by using it. The results show that the structure parameters are cut down from 24 to 3, and the model quality and prediction ability in ANN are not reduced as the number of nodes in input layer is cut down, but are improved. In addition, the method expedites the convergence of networks model. So the method establishes the foundation for further developing the mechanism research of the toxicity of organic chemicals on biology and may be popularized in the other fields using ANN.

Key words: Screening rule, Structure parameter, Biological toxicity, Artificial Neural Network, Quantitative Structure-Activity Relationship

COMP 316

Self-organizing molecular conformations: From SPE to SOS

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Conformational search is a problem of central importance in computer-aided drug design. Virtually every 3D modeling technique, from pharmacophore modeling to protein docking, requires effective and efficient sampling of a molecule's conformational space. Here we review the evolution of a new class of conformational sampling algorithms based on a self-organizing embedding procedure for dimensionality reductions known as stochastic proximity embedding (SPE). While initial efforts concentrated on iterative refinement of individual distance, chiral and planar constraints, a more recent variant known as self-organizing superposition (SOS) utilizes an alternating scheme of pairwise distance adjustments of randomly chosen atoms, followed by fast geometric fitting of pre-computed templates of the molecule's conformationally rigid fragments. Both SPE and SOS have been thoroughly validated, and shown to significantly outperform many popular conformational search methods, particularly for molecules with complex topologies such as macrocycles and protein loops. Subsequent algorithmic improvements in the fitting procedure have afforded even greater efficiencies, making SOS the fastest, most widely applicable, and most robust conformational search algorithm reported to date. More importantly, additional constraints such as hydrogen bonds and salt bridges can be incorporated into the algorithm in a straightforward and inexpensive way, making this method ideal for more complex problems, such as NMR structure

determination, molecular alignment, multiple interlocking loop modeling, and many others.

COMP 317

Alchemical predictions of free energies, from hydration to binding

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We use molecular dynamics simulations in combination with alchemical techniques to compute transfer free energies and absolute binding free energies. Here I discuss recent prospective tests of these methods for predicting binding and hydration free energies, and insights gained. Binding free energy studies focused on two model binding sites in T4 lysozyme, and hydration free energy studies focused on several diverse sets of small molecules. Insights gained provide some guidance for future improvements to force fields, and highlight a variety of areas in which careful sampling is key to obtaining accurate results, and where more algorithmic developments are needed.

COMP 318

Benchmarks for validating and testing free energy calculations in molecular design

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There has been both intense interest and significant confusion in the simulation and theory community in determining the most efficient and reliable methods to perform free energy calculations. In this talk, I present a benchmark set for calculating free energies of molecular transformations in solution, and use this set to compare the performance of a range of published free energy methods, including thermodynamic integration, free energy perturbation, the weighted histogram analysis method, the Bennett acceptance method, transition matrix approaches, and the Wang-Landau based methods. I will describe efforts to generalize this benchmark set, including the distribution of initialization files for a number of different computational computation platforms to make it a truly general benchmark, which will hopefully provide significant guidance to the simulation field in the improvement of free energy methods.

COMP 319

Molecular dynamics simulations and free energy calculations for predictions of siRNA duplex stability

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For siRNA therapeutics, understanding the thermodynamic properties of the oligonucleotides can lead to a more stable and improved drug. For unmodified siRNA the use of neural network and parameter methods can be used to accurately predict these thermodynamic properties. However, when chemically modified nucleotides need to be considered, the problem is much more challenging with no accurate methods available. Herein we describe a method using CHARMm molecular dynamics (MD) simulations to predict the thermodynamic properties for both unmodified and chemically-modified siRNA duplexes. Simulation results show that the calculated free energies correlate well with the experimental melting temperatures. The method can also be used in understanding the significance of various physical forces in duplexes such as hydrogen bond patterns and nonconvalent energy distributions. In conclusion, this MD method demonstrates similar performance as current methods restricted to unmodified oligonucleotides. Moreover, it has a broader application allowing incorporation of chemical modifications and detailed structure profiling.

COMP 320

Structural and mechanistic modeling of the HER3/ErbB3 pseudo-kinase domain

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Overexpression and activating mutations of the ErbB kinases are implicated in cellular transformation and clinical malignancies including lung and breast

cancers. Recent studies have shown that some mechanisms of resistance to tyrosine kinase inhibition of EGFR and possibly HER2 in the treatment of some human malignancies are HER3 mediated. In this scenario, it is believed that a synergy between the c-Met-receptor activation and HER3-tyrosine phosphorylation possibly restores signaling through the PI3K-AKt pathway. However, the detailed molecular mechanism of this process remains an open question. In light of the implication of HER3 in resistance mechanisms and the recent interest in catalytic mechanisms of pseudo-kinases, we pursue, in this article, a theoretical study involving the structural and mechanistic modeling of the HER3 kinase domain. We construct and report a homology model of the ternary complex of HER3 kinase bound to ATP and tyrosine-containing substrate peptide, based on the crystal structure of the EGFR kinase. We also report a comparative study of the multiple pathways involved in the catalytic mechanisms of EGFR and HER3 kinase domains through molecular dynamics simulations, free energy calculations, and mixed quantum mechanics molecular mechanics simulations. Simultaneously, we are pursuing a collaborative effort involving the structure of the HER3 kinase domain with the group of Dr. Mark Lemmon at the University of Pennsylvania.

COMP 321

Structural changes and quantification of ligand affinity in lactose permease of Escherichia coli

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Lactose permease (LacY) of E. coli, an important member of Major Facilitator Superfamily of membrane transporters, transports various sugar molecules across the plasma membrane. Though the structure of LacY open to cytoplasm has been determined, the structure open to periplasm, which is crucial in understanding the transport mechanism, is unrevealed. Molecular Dynamics simulations with an explicit lipid bilayer were carried out with conformations of LacY obtained from previous implicit lipid bilayer simulations. Simulations were carried out in NPAT ensemble with the Glu^{269} of LacY protonated. Pore radius analysis confirms opening of periplasmic end beyond the implicit bilayer simulations. The helix-helix distances of LacY were compared and agree favorably with the DEER experiments results (Smirnova et al., PNAS, 2007). To quantify the anomeric binding affinity of sugars to LacY, free energy calculations were done using alchemical free energy perturbation method with restraining potentials applied on sugar molecules for efficient sampling.

COMP 322

Peptide-based functional nanostructures

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We are developing the fundamental tools of molecular biomimetics as an enabling new field towards highly addressable, molecularly engineered functional materials systems using peptides as molecular synthesizer, erectors, and assemblers. Through in vivo and in vitro combinatorial biological selections, we first identify short peptide sequences that selectively bind to inorganic materials such as metals (Au, Ag, Pt, Ti), oxides (SiO2, Al2O3, TiO2, ZnO, Cu2O, ITO), semiconductors (GaN, ZnS), and minerals (mica, hydroxyapatite, graphite). We then examine fundamentals of solid binding by peptides using kinetics and thermodynamics via a plethora of quantitative techniques (SPR, QCM, AFM). Based on the elementary principles of genome-based design, molecular recognition, and assembly, and through computational biology and bioinformatics, we can now evolve second, third and fourth generation of peptides for solids and synthetic functional molecules as synthesizers, erectors, and assemblers, key utility for nanotechnology and medicine. Supported by NSF-MRSEC & BioMater, and NIH.

COMP 323

Directed assembly in biomineralization, amyloid fibrils, and viruses

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We will address general concepts behind (a) biomineralization, (b) protein fibrillization, and (c) virus assembly, based on statistical mechanics theory, Monte Carlo simulations, and Brownian Dynamics simulations. Specifically, new models and theories will be presented for (a) the selection of morphologies of inorganic crystals mediated by polypeptides, (b) nucleation and growth of amyloid fibrils mediated by the Oswald ripening process, and (c) complexation of DNA/RNA by virus proteins.

COMP 324

Computational modeling of biopolymers on carbon nanotubes

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Computational modeling and tools have been used to examine the interactions of short polypeptides and polynucleotides with carbon single wall nanotubes (SWNTs). For polypeptides, modeling has been used to identify an amino acid sequence in an odor binding protein primarily responsible for odorant binding. This has been linked to a polypeptide (identified by phage display) known to associate with SWNTs. The conformational properties of the combined polypeptide have been analyzed in solution and adsorbed on a SWNT, yielding results consistent with experimental observations. For polynucleotides, single- and double-stranded DNA segments have been modeled in their association with SWNTs. The objective of these simulations has been to examine binding affinities that might lead to selectivity based on the chirality of the SWNT.

COMP 325

A quantum of common sense in crystallography

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The traditional potential function used to model biological systems involves the use of simplified classical force field methodologies for no better reason than the inherent size of most biological systems and the associated computational expense. However, molecular systems are widely understood to have quantum mechanical features associated with their interactions. Indeed, quantum chemical (QM) methods have had tremendous impact on our understanding of “small” molecular systems, which raises the question can QM methods impact biology in the same way? In this presentation we will focus on the application of QM methods to solve relevant problems in structural biology and structure-based drug design (SBDD) that begin to address this question. In particular, we will focus on our developments aimed at using quantum mechanical methods in X-ray refinement. Finally, we will briefly summarize our vision of the future application of quantum chemistry to the solution of problems in structural biology and SBDD.

COMP 326

Quantifying adsorption of amino acids and surfactants on Au {111} surfaces in aqueous solution

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Employing all atom classical molecular dynamics with force fields of the Consistent Valence Force Field (CVFF) and the Chemistry at HARvard Molecular Mechanics (CHARMM22), which are extended for accurate Lennard-Jones parameters for fcc metals (pH=7), the adsorption of 20 essential amino acids on Au{111} surface in aqueous solution have been analyzed. The two force fields are in good agreement with each other for most amino acids except for aromatic amino acids. Additionally, common capping agents and surfactants have been examined and the results show that their binding abilities are in the same range as for amino acids. The information from simulations of single amino acids has been used for estimates of the adsorption energy of oligopeptides, which are compared with direct simulations of the oligopeptides. Furthermore, the effects of surface topology on the adsorption have been studied. The computed energies and binding mechanisms are in agreement with available experimental data.

COMP 327

An effective Hamiltonian approach to study zinc binding to a zinc-finger

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We study Zn^{2+} binding a zinc-finger domain with a hybrid molecular-mechanics/elastic network model. We divide the protein into a metal-binding site and the bulk. Site-bulk and bulk-bulk interactions are truncated at second order, thereby allowing integration over bulk protein coordinates to obtain an effective site Hamiltonian. This Hamiltonian comprises detailed site-site interactions plus an additional quadratic term mimicking (to within a scale-factor) the field imposed by the bulk of the protein. The scaling is chosen to reproduce the binding energy distribution $P(\varepsilon)$ of Zn^{2+} with the site obtained from a classical MD simulation. In this test-of-concept study, the effective Hamiltonian is propagated with a Monte-Carlo scheme using classical potentials, although we envision using an *ab initio* method in the future. We use the method to estimate the free energy of exchanging Zn^2 with Co^{2+} or Fe^{2+} from *ab initio* calculations. Limitations and applications to other metalloprotein systems is noted.

COMP 328

New methods for connecting protein NMR data to structure and dynamics

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In principle, molecular dynamics simulations of proteins ought to provide valuable information about the motions responsible for NMR relaxation. In practice, the value of such connections has been rather limited, both for statistical reasons (simulations were too short to look at overall tumbling, for example), and because existing force fields (for both water and proteins) showed significant problems in reproducing observed behavior. I will show that a "new generation" of simulations makes great strides towards solving both of these problems. Recent simulations can now deal with anisotropic overall tumbling, and show remarkably good agreement with N-H order parameters, at least for well-folded proteins. Special attention will be paid to the problem of describing NMR relaxation for floppier molecules, where a single rotational diffusion tensor cannot be used to describe overall rotation.

COMP 329

Reducing the essential side chain degrees of freedom in molecular docking

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Using MD simulations of separate component proteins taken from protein-protein complexes we have shown that key side chains frequently visit their rotameric states seen in the complex. Here we present an algorithm to efficiently search the conformational space of the key residues for the most likely rotameric states. The space is sampled by minimizations started from conformations given by an “end group position” library. After the minimizations the resulting conformations are re-clustered using a 1 Å cluster radius. Since the protein environment generally restricts the distribution of “key” side chains, the minimization trajectories from all the different states end up in a small number of clusters, corresponding to energy minima with broad regions of attraction. Thus, the application of the method can reduce the number of potential side chain conformations, thereby substantially increasing the efficiency of both protein-protein and protein-small molecule docking.

COMP 330

Identification of two distinct inactive conformations of the β_2-adrenergic receptor reconciles structural and biochemical observations

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Fully understanding the mechanisms of signaling proteins such as G-protein–coupled receptors (GPCRs) will require the characterization of their conformational states and the pathways connecting those states. The recent crystal structures of the β_2- and β_1-adrenergic receptors in a nominally inactive state constituted a major advance toward this goal, but also raised new questions. Although earlier biochemical observations had suggested that these receptors possessed a set of contacts between helices 3 and 6, known as the ionic lock, which was believed to form a molecular switch for receptor activation, the crystal structures lacked these contacts. The unexpectedly broken ionic lock has raised questions about the true conformation(s) of the inactive state and the role of the ionic lock in receptor activation and signaling. To address these questions, we performed microsecond-timescale molecular dynamics simulations of the β_2-adrenergic receptor (β_2AR) in multiple wild-type and mutant forms. In wild-type simulations, the ionic lock formed reproducibly, bringing the intracellular ends of helices 3 and 6 together to adopt a conformation similar to that found in inactive rhodopsin. Our results suggest that inactive β_2AR exists in equilibrium between conformations with the lock formed and the lock broken, whether or not the co-crystallized ligand is present. These findings, along with the formation of several novel structural elements in the β_2AR loops during our simulations, may provide a more comprehensive picture of the inactive state of the β-adrenergic receptors, reconciling the crystal structures with biochemical studies.

COMP 331

Probing the principles of dynamics and energy flow in proteins

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The elucidation of the fundamental principles defining energy transfer in proteins will only be possible through the parallel development of computational methods and theoretical models. A particular focus of our research is the development of increasingly accurate theoretical and computational models of protein vibrational

dynamics on the picosecond timescale. We will report on our efforts to gain insight into the nature of mode-specific energy transfer and signaling in heme proteins through the application of a non-Markovian time-dependent quantum mechanical perturbation theory informed by density functional theory calculations. Case studies involving excitation and energy transfer in heme proteins, each inspired by experiment, are considered. In each case, the pathways for energy transfer are identified, providing a state-by-state picture of protein dynamics and energy flow. Our results lead to the conjecture that the distinct mechanism of vibrational energy flow is “tuned” by and encoded in the detailed protein and porphyrin structure.

COMP 332

Effects of cosolvents on protein/polypeptide hydration and dynamics

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The effects of urea, tetramethyl urea (TMU), and trimethylamine N-oxide (TMAO) on the structure and dynamics of aqueous solutions are studied by molecular dynamics simulations. It was found in the simulations of three different systems, which include a model amide compound and two polypeptides, that the TMAO significantly weakens the interaction between the amide carbonyl group and the water molecules, while TMU and urea both appear to strengthen this interaction, although the effect of urea is much smaller compared to TMU. Consistent with earlier studies, we also found that urea interacts strongly with the carbonyl group directly. Through the analysis of the unfolding pathway of an originally folded polypeptide, GB1, it was found that the breaking of the protein backbone hydrogen bonds is mainly coupled to the formation of water/carbonyl hydrogen bonds, although the urea/carbonyl hydrogen bond formation also plays an important role. These results reveal the potential importance of the indirect effects in protein denaturation and structure protection by cosolvents, in particular through modifying the water amide interactions.

COMP 333

Non-equilibrium molecular dynamics study of electric and low-frequency microwave fields on hen egg white lysozyme

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Non-equilibrium molecular dynamics simulations of various mutants of hen egg white lysozyme have been performed at 298 K and 1 bar in the presence of both external static electric and low-frequency microwave (2.45 GHz) fields of varying intensity. Significant non-thermal field effects were noted, such as marked changes in the protein's secondary structure relative to the zero-field state, depending on the field conditions, mutation and orientation with respect to the applied field. This occurred primarily as a consequence of alignment of the protein's total dipole moment with the external field, although the dipolar alignment of water molecules in both the solvation layer and the bulk was also found to be influential. Substantial differences in behavior were found for mutants with and without overall net charges, particularly with respect to translational motion and hydrogen bonding characteristics.

COMP 334

Intrinsic mobility of rhodopsin photointermediates investigated by molecular dynamics simulations

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Rhodopsin is a light sensitive pigment belonging to the G protein coupled receptors (GPCRs) superfamily. Its structure includes a polypeptide – opsin – and a covalently attached chromophore – retinal. To study the conformational changes caused by light activation, we subjected several photointermediates of the rhodopsin light cycle, including ground state, bathorhodopsin, lumirhodopsin, and opsin, to multiple nanoseconds of unbiased in silico molecular dynamics using Desmond and NAMD. We also simulated opsin in complex with 11-cis all-trans-retinal. Besides the communalities, we detected several differences in the dynamic properties of specific structural domains of the various photointermediates. In particular, we noted a substantial change in the flexibility of the interhelical cavity in conjunction with the activation process. We also analyzed the behavior of the water molecules in the different states. Our study provides further insights into the mechanism of rhodopsin activation.

COMP 335

A computational workflow to identify and validate the druggable allosteric binding sites

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Allosteric binding sites are more diverse in nature as compared to traditional orthosteric binding sites. Consequently, they afford opportunities for designing compounds of high selectivity, divergent chemotypes, and the decreased potential for side effects. We have endeavored to develop and validate a computational workflow for identifying the allosteric site(s). The Elastic Network Normal Mode Analysis is employed to generate the conformational ensembles for a target protein. Next, binding site identification algorithms (CASTp, SiteMap, and Alpha Shapes) are employed. Finally, the site candidates are validated using ensemble docking techniques. It is expected that true allosteric sites will show greater enrichment for known allosteric binders vs. decoys. The application of this workflow to several test cases of apo- or orthosteric complex structures showed that we could identify allosteric sites successfully. The workflow can be utilized as a general approach for the effective identification of druggable allosteric sites and virtual screening.

COMP 336

SKATE: Decoupling systematic sampling from scoring to achieve more accurate docking

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SKATE is a docking program that decouples systematic sampling from scoring. This novel approach removes any inter-dependence between sampling and scoring to achieve better sampling and, thus, improved docking accuracy. SKATE systematically and exhaustively samples the ligand's conformational, rotational and translational degrees of freedom, as constrained by a receptor pocket, to find sterically allowed poses. Efficient systematic sampling is achieved by pruning the combinatorial tree using aggregate assembly, discriminant analysis, adaptive sampling, radial sampling and clustering. Because exhaustive sampling is decoupled from scoring, the poses generated by SKATE can be ranked by any published or in-house scoring function. To test the performance of SKATE, ligands from the Asetex/CDCC set, the Surflex set, and the Vertex set, a

total of 266 complexes, were re-docked to their respective receptors. The results show that SKATE was able to sample poses within 2 Å RMSD of the native structure for 98%, 95%, and 98% of the cases in the Astex/CDCC, Surflex, and Vertex sets, respectively. X-Score, energy functions in Rosetta and FRED were used to rank the sampled poses. The best performing scoring function was able to rank a pose that is within 2 Å RMSD of the native structure as the top-scoring pose for 87%, 84%, and 77% of the cases in the Astex/CDCC, Surflex, and Vertex sets, respectively. Compared to published data, SKATE has a higher self-docking accuracy rate than ICM, GOLD, Surflex, Glide, and RosettaLigand. Decoupling searching from scoring allows SKATE to sample more accurately, thus enabling more accurate docking.

COMP 337

Staying in the loop: Innovations in loop modeling at ligand binding sites

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Protein conformational change is an important consideration when assessing the accuracy of protein-ligand binding models. Several literature examples are known where the size and shape of the protein binding pocket can change quite dramatically upon ligand binding. Such structural changes are most significant in the ″structurally variable regions″ of a protein, most commonly the loops. In this study we describe two methods for deriving binding models for protein-ligand interactions. The two methods: an improved protocol for induced fit docking, Sample-IFD-Refine (SIR); and a new method, Delete-Dock-Resample (DDR), were tested on a set of therapeutically relevant protein structures that exhibit variable loop conformations dependent on ligand binding.

COMP 338

Synthetically accessible compounds from giant virtual chemistry spaces

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Today, the primary domain of VS applications are screening collections based on in-house repositories and vendor collections. However, any such library is tiny compared to the number of synthetically accessible compounds from validated chemistries available in any pharma company. It would be of great interest to perform searches against such “virtual chemistry spaces”. However, the number of possible compounds easily exceeds – by many orders of magnitude – the number of compounds that can be stored and searched using conventional methods.

We overcame these limitations by converting large numbers of existing (wet) combinatorial libraries into the now publicly available KonwledgeSpace covering 23 billion synthetically accessible compounds. FTrees - a fuzzy similarity calculator – is capable of searching such spaces within a few minutes. The result is a set of compounds similar to a query structure, plus an annotation through which of the synthetic routes these compounds can be made. FTrees is known for its scaffold hopping capabilities, thus chemically diverse results can be expected. Such output provides library design ideas for hit follow-up from high-throughput screening or lead hopping into novel series.

We present the design of the KnowledgeSpace and similar inhouse chemistry spaces as well as validation results and a number of successful applications including prospective results.

COMP 339

Using quantitative high-throughput screening (qHTS) results as biological descriptors to assist quantitative structure activity relationship (QSAR) modeling of rat acute toxicity

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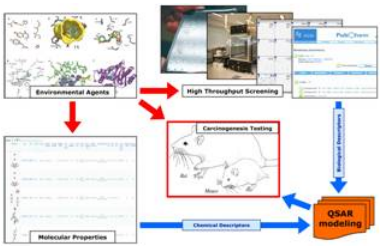
To develop effective means for rapid toxicity evaluation of environmental chemicals, the National Toxicology Program and the NIH Chemical Genomics Center have initiated a high-throughput screening (HTS) study. The cell viability

qHTS data for 1,408 compounds in 13 cell lines have been deposited in PubChem. We have identified 690 of these compounds, for which rodent acute toxicity data (i.e., toxic or non-toxic) was also available. The classification k Nearest Neighbor (kNN) Quantitative Structure-Activity Relationship (QSAR) modeling method was applied to these compounds using either chemical descriptors alone or a combination of chemical and qHTS biological (hybrid) descriptors as compound features. The external prediction accuracy of models built with chemical descriptors only was 76%. In contract, the prediction accuracy was significantly improved to 85% when using hybrid descriptors. Our studies suggest that combining qHTS profiles with chemical descriptors could considerably improve the predictive power of computational approaches for rodent acute toxicity.



COMP 340

Utilizing structure-based design to discover a potent, selective, in vivo active PDE10A inhibitor lead series for the treatment of schizophrenia

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Phosophodiesterase 10A (PDE10A) is a novel target for potential treatment of schizophrenia. Utilizing structure-based virtual library design and scoring, a novel chimeric series of PDE10A inhibitors was discovered by merging interactions and ADME properties of two difference series. Virtual libraries were generated and these libraries were docked and scored for prioritization. The docking score and visual inspection were used to prioritize analogs for parallel and traditional

synthesis, which yielded highly potent and selective compounds. Iterative structure-based design led to successful optimization of ligand efficiency and physical properties to produce in vivo activity and to modulate microsomal clearance and permeability.

COMP 341

Elucidating the two acidity constant behavior of silica with ab initio molecular dynamics simulations

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Understanding acid-base behavior of silica surfaces is critical for many nanoscience and bio-nano interface applications. Silica has been reported to exhibit two acidity constants, but the structural basis for the two deprotonation reactions ramins controversial. We here model deprotonation of silanol groups at representative crystalline silica interfaces using ab initio molecular dynamics (AIMD), which accounts for water and hydrogen bond network dynamics and reveals the role of cooperative hydrogen bonding on hydroxylated oxide surfaces. We show that previously proposed structural motifs, including hydrogen bonding between silanol groups and differing number of Si-O bonds to surface silanol groups, cannot account for the more acidic silanol reported, whereas locally strained regions with low silanol surface densities are consistent with high acidicity. Our simulations demonstrate the potential of large-scale AIMD for elucidating interfacial chemical reactions.

This work was supported by the Department of Energy under Contract DE-AC04-94AL85000. Sandia is a multiprogram laboratory operated by Sandia Corporation, a Lockheed Martin Company, for the U.S. Department of Energy.

COMP 342

Formalism and implementation of a continuous surface charge polarizable continuum model of solvation

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The Polarizable Continuum Model (PCM) of solvation has received much attention of over the last years, especially for its versatility. Unlike other solvent models, PCM can effectively predict - with semiquantitative accuracy - the solvent's effect on many of the structural and electronic properties of the solute. PCM requires the definition and the discretization of a solute-solvent interface as the surface of a cavity hosting the solute. Due to this discretization process it is very difficult to maintain the continuity of the energy and its derivatives. A possible solution was suggested years ago by Karplus and York, but never received the attention it deserved. In this contribution we describe how the whole PCM formalism can be recast in terms of a continuous surface charge. Expressions for the energy and its derivatives will be given in which model-dependent coefficients are separated from cavity-dependent terms. Also, other details of the implementation crucial to ensure robustness and computational efficiency will be discussed.

COMP 343

Quantum Monte Carlo study of low-lying electronic states and thermochemistry of small molecules

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Quantum Monte Carlo (QMC) is becoming an increasingly important tool for electronic structure calculations,

especially for transition metal systems with intrinsic multireference character in the wavefunction and for

excited states, due to its favorable scaling with system size. Recent progress in optimizing parameters of

general and flexible trial wavefunctions allows the fixed-node error in diffusion QMC to be reduced systematically and accurate energies can be obtained. We compare our calculations of the potential energy surfaces for the low-lying electronic states of FeS (5Sima, 5Delta and 7Sigma) and of C2 with experimental results and other quantum chemistry methods. Our results for the

thermochemistry of C2 and C3 are used to rationalize their relative abundance in comets.

COMP 344

Quantum Monte Carlo study of methylene excited states

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The energies of the $^1A_1$ and $^1B_2$ excited states of methylene, relative to the $^3B_2$ ground state are computed using diffusion Monte Carlo (DMC). The DMC excitation energies obtained using wave functions with all the parameters optimized within variational Monte Carlo agree with experiment to better than chemical accuracy (1 kcal/mole or 43 meV/molecule). The DMC excitation energies are insensitive to the size of the active space -- CAS(2,2), CAS(4,4) and CAS(6,6) energies are consistent with each other. The fluctuations of the local energy are much smaller using a Slater basis than using a comparable sized gaussian basis. Elimination of core electrons using a recently proposed nonlocal pseudopotential within the locality approximation results in excitation energy errors of approximately 1 kcal/mol.

COMP 345

The evaluation of QM/MM full Hessian and some applications

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We recently implemented the evaluation of QM/MM full hessian and the corresponding approximate hessian within the mobile block hessian (MBH) approximation. In this work, we discuss the technical aspects of this implementation and some of its application to molecular systems.

COMP 346

Variable-occupation-number perturbation theory

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The eigenvalues are the first derivatives of the energy with respect to occupation number in density functional theory. The second and third derivatives are the hardness and hyperhardness. Requiring the Fock and density matrices commute through each order of perturbation theory determines the off-diagonal (in the molecular-orbital representation) elements of the density matrix even as orbital occupation numbers change (metallic systems) or are changed (as they must be to compute hardness and hyperhardness numerically). The change in orbital occupancy required at each order of perturbation theory appears only in the diagonal elements of the density matrix. Analytic density-functional and perturbation theory give the hardness and hyperhardness of 56 molecules to machine precision that are in agreement with less precise, numerical approximations, J. Chem. Phys. 129, 244109 (2008).

The Office of Naval Research directly and through the Naval Research Laboratory supported this work.

COMP 347

Building a CHARMM polarizable force field for nucleic acids

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Electrostatic interactions help determine the structure and function of biomolecules, and an important aspect of the electrostatic interaction is polarizability, the response of the molecular dipoles to an external electric field. Towards development of a comprehensive force field for biomolecules, work on the CHARMM Drude polarizable force field for nucleic acids has focused on development of parameters for small molecule analogs of the sugar, phosphate and base moieties. Final stages of this small molecule parameterization are introducing minor modifications to: 1) correct for errors in ether dielectric constants; 2) accurately reproduce hydration free energies, and 3) finalize the nucleic acid base parameters. Assembling the building blocks into nucleic acids requires optimization of parameters associated with covalent connections between the constituent moieties, and careful assessment of macromolecular properties in comparison to experimental data. Such calculations are essential for validation of the model in condensed phase environments and will give new insights into the importance of polarizability in nucleic acid simulations.

COMP 348

Development and testing of protein backbone torsional potentials for the Kirkwood Buff derived force field of peptides and proteins

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Recently, we have been developing a force field for biomolecular simulations of peptides and proteins (KBFF) designed to reproduce the experimental Kirkwood-Buff (KB) integrals observed in solution mixtures. This ensures a reasonable balance between solute-solute interactions and solute solvation – usually by water. Here, we describe the development and testing of the backbone torsion potentials, required for accurate modeling of the conformational preferences of amino acids, which are consistent with the corresponding KBFF nonbonded parameters. Molecular dynamics (MD) simulations were performed for dipeptides of glycine, alanine, and proline and for polyglycine and polyglutamine in solutions. Comparisons with crystallographic data and quantum mechanics derived gas phase energy surfaces are also made.

COMP 349

Evaluating CHARMM parameters and the λ-dynamics free energy method for structure-based drug design

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Free energy calculations are fundamental to obtaining accurate theoretical estimates of many important biological phenomena including hydration energies, protein-ligand binding affinities and energetics of conformational changes. Using an extensive series of non-nucleoside inhibitors of HIV-1 reverse transcriptase and trimethoprim-like inhibitors of dihydrofolate reductase, we have evaluated the quality of recently developed ligand parameters that are consistent with the CHARMM22 force field. Thermodynamic integration simulations for over 50 pairs of compounds achieve a high level of success with an overall average unsigned error in the relative binding affinities of less than 1.5 kcal/mol; however, the accuracy is strongly dependent on the size differential between the substituents sampled. λ-dynamics simulations (in which the conventional "λ" is treated as a dynamic variable in the simulations) markedly improve the efficiency of these free energy calculations with no loss in accuracy for the binding free energies.

COMP 350

Improving the lipid force field of CHARMM: A quantum mechanical and experimental approach

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Biological membranes form a barrier to protect the cell from its environment and selectively control the entrance/exit of small molecules. Molecular simulations of these biological membranes require an accurate lipid force field (a major component of the membrane). Previously, extensive *ab initio* quantum mechanical (QM) calculations have been used to improve the aliphatic portion of the CHARMM27 lipid force field. Although this was a significant improvement, the lipid head group required additional modifications to agree with experimental lipid bilayer deuterium order parameters (S_{CD}) and solvation free energies. To

improve the solvation free energies, we modified the atomic charges in the carbonyl-glycerol region. The S_{CD}'s for the lipid head group of DPPC were improved by fitting dihedral energy terms to high-level QM calculations and/or to torsional conformational populations that result in agreement with experimental S_{CD}'s. Molecular dynamics (MD) simulations with this new force field resulted in a significant improvement in the S_{CD}'s and water hydration for DPPC lipid bilayers. A significant drop in the calculated electrostatic profile and lipid bilayer surface tension from our MD simulations was observed. MD simulations of other lipid bilayers and monolayers also agreed favorably with experimental densities, monolayer surface tensions, and SCD's, e.g., DMPC, DOPC, POPC, and POPE.

COMP 351

Simulation of cis-trans isomerization of the protein peptide bond

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The local change of the isomeric state of the prolyl peptide bond could act as a switching mechanism in altering the overall conformation of proteins. The timescale of cis-trans isomerization and even the timescale of the catalyzed process are beyond the sub-microsecond timescale of normal molecular dynamics. Therefore, we present an accelerated MD approach to study the mechanism of cis-trans isomerization of the protein peptide bond. We provide detailed description of cis-trans isomerization of the free substrate and the enzyme-assisted process and compare our simulation results to available experiments.

COMP 352

Toward an automatic force field parametrization engine: Assignment of parameters by analogy for the CHARMM General Force Field (CGenFF)

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Empirical force fields are presently the only computational methods fast enough to routinely perform molecular dynamics simulations of large biomolecular systems on relevant time scales. To facilitate the application of these methods to computer-aided drug design, a coordinated effort was started to build a computational engine that automatically assigns and optimizes parameters for drug-like molecules in the framework of biomolecular force fields. As a first step, an algorithm was developed that automatically assigns atom types, charges and bonded parameters to an arbitrary molecule in the framework of the recently released CHARMM General Force Field (CGenFF). The resulting program provides a good “initial guess” for the parametrization engine and can also be used in a standalone fashion as part of routine computer-aided drug design. Details and validation of the automatic parameter assignment will be presented and the current developmental status of the parametrization engine will be discussed.