COMP 1

Molecular modeling of complex fluids

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The thermodynamics and phase behavior of complex fluid systems are central to chemical process design in the traditional chemical and petrochemical industries. The importance of a theoretical framework for interpreting and ultimately predicting phase equilibria increases as the need for accurate physical properties increasingly exceeds the rate at which new experimental work is being carried out. The statistical associating fluid theory (SAFT) is a molecular-based equation of state derived from thermodynamic perturbation theory that describes the thermodynamic properties of associating and non-associating chain molecules, and is a powerful tool with which to study the fluid phase equilibria of pure fluids and their mixtures. Results will be presented from recent new developments with the SAFT-VR equation1; a version of the SAFT approach that treats chain molecules formed from hard spherical segments with long-range attractive interactions described by a potential of variable range (SAFT-VR). In particular, we will discuss the development of a group contribution based SAFT-VR equation and the application of recent advances in the theory to model dipolar (SAFT-VR+D)2 and electrolyte fluids (SAFT-VR+DE)3.

1. A. Gil-Villegas, A. Galindo, P. J. Whitehead, G. Jackson, and A. N. Burgess, Journal of Chemical Physics, 106, 4168 (1997); C. McCabe, A. Gil-Villegas, G. Jackson, F. Del Rio, Molecular Physics, 97, 551-558 (1999); Y. Peng, H. G. Zhao and C. McCabe, Molecular Physics, 104(4), 571-586 (2006).
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3. H. G. Zhao, M. C. dos Ramos, and C. McCabe, Journal of Chemical Physics, 126(24), 4503 (2007).

COMP 2

Phase diagram calculations of alloys using density functional theory

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A theoretical approach to calculate the correlation functions in binary hard-sphere (HS) liquid and solid mixtures is developed using the fundamental measure density functional theory. The method is motivated by the theory of correlations in one-component hard-sphere (HS) solids [C.Rascon, L.Mederos, and

G.Navascues, Phys.Rev.E 54, 1261(1996)] and the exact statistical mechanics sum rules of mixtures are used to find the parameters of correlation functions. The computed correlation functions are in quantitatively agreements with the numerical simulations results. Using these correlation functions and the perturbation theory we have calculated the phase diagram of Cu-Au alloy. The obtained phase diagram and other thermodynamic properties are in very good agreement with simulation results and experimental measurements.

COMP 3

Quantum Statistical Mechanics of rigid and semirigid molecular condesed matter

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Path integral simulations of condensed molecular matter at or below room temperature have been a formidable challenge; the convergence rate for the energy and its derivative is greatly affected by the presence of intramolecular degrees of freedom that are predominantly in the ground state. We present methods to perform path integral simulations of rigid tops designed to overcome the technical difficulties associated with handling ellipsoids of inertia and the axes precession in the lab frame. Results are presented for water, ammonia and other linear hydrogen bonded clusters.

COMP 4

The nonbulk like phase behavior for nanocluster systems

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Nano-clusters are a special state of matter in between vapor and condensed liquid or solid phases. Evidence is mounting that these particles are distinct from bulk materials by exhibiting a variety of intermediate phases/structures. The fact that their properties are tunable through the size and structure not only opens up an opportunity to tailor-design these nano-objects for specific applications but also poses a request for a fundamental understanding of their unique phase/structural behavior. Here we will present an extension of the aggregation-volume-bias Monte Carlo approach for the efficient computation of the size-dependent phase diagrams for nano-clusters involving not only liquid- but also

crystalline-like phases. This presentation will focus on two subjects. One is on the disorder-to-order phase transition encountered by single-component clusters consisting of monatomic argon, molecular water, carbon dioxide, macro-molecular proteins, and metallic species. The other is on the non-ideal mixing and demixing behavior observed for multi-component clusters containing water, n-alkanes, and alcohols.

COMP 5

Modeling the kinetics of nanocrystal growth

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Specific control of nanocrystal size and shape is integral to the development of advanced nanotechnologies. Currently there exists no a-priori means of describing specific conditions that will optimize the synthesis procedure or that will provide better understanding of the Oswald and digestive ripening phenomena that occur during later stages of crystal growth. To do so we have developed a multiscale theoretical approach. We apply a mean field theory in order to study the role of ligands in nanocrystal synthesis, with particular emphasis on the kinetics of crystal growth and the related ripening phenomena. We then employ potentials obtained from these calculations in Monte Carlo simulations of digestive ripening. We examine the effects of ligand type and concentration on thermodynamic and structural properties, and compare our results with available data. We focus on the changes in nanocrystal growth kinetics and nanocrystal ripening that occur as the relative concentrations of metal (semi-conductor) and ligands are changed.

COMP 6

Simulation of pure component phase equilibrium properties using a modified Stockmayer potential

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The prediction of pure component and mixture properties is important for the design of industrial separation and reaction equipment. In recent years, molecular simulation has made considerable advances in the prediction of pure component properties. This work describes the modification of the Stockmayer dipolar potential by replacing the Lennard-Jones interaction with a Buckingham exponential-6 potential. Simulation were conducted to produce reduced

coexistence density, reduced vapour pressure and reduced heat of vaporization data and these results have been correlated. Using a simple set of properties, namely the critical temperatures, the critical density, one liquid density point and one vapour pressure point, the pure component phase behaviour can be predicted. Results are given for several short chain alcohols, chlorofluorocarbons and aldehydes. In general, this modification has enabled this simple dipolar potential to better predict pure component critical points, vapour pressures and heats of vaporization over a wider temperature range for the short-chain molecules studied.

COMP 7

Replica-exchange method and its generalizations

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Replica-exchange method (REM) and its generalizations such as replica-exchange multicanonical algorithm (REMUCA), multicanonical replica-exchange method (MUCAREM), replica-exchange simulated tempering (REST), simulated tempering replica-exchage method (STREM), and multidimensional/multivariable replica-exchange method (MREM) are explained, and the results of their applications to biomolecular systems are presented.

COMP 8

Multiplexed replica exchange molecular dynamics simulations of protein folding with a physics-based coarse-grained force field

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The replica exchange (RE) method is used increasingly to improve sampling in simulations of biomolecular systems. Recently, we implemented a physics-based coarse-grained force field (UNRES) for mesoscopic molecular dynamics (MD), Monte Carlo (MC) and Hybrid Monte Carlo (HMC). UNRES simulations facilitate studies of folding events which take place in a microsecond or even a millisecond time scale. To speed up the conformational search, we applied the multiplexed variant of the RE method introduced by Pande which differs from the original RE

method in that several trajectories are run at a given temperature. The RE method for umbrella sampling simulations has also been enhanced by applying a multidimensional extension in which pairs of replicas, not only at different temperatures, but also with different parameters of the potential energy are exchanged. Here, we present a comparison of RE UNRES simulations with MD, MC and HMC as a basic algorithm for canonical simulations.

COMP 9

Improving the convergence of replica exchange simulations for complex systems

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Replica exchange molecular dynamics (REMD) has facilitated the exploration of free energy landscapes for complex molecular systems. These can be useful for the study of transiently populated states that are difficult to directly characterize experimentally, such as the unfolded state of proteins under conditions that favor folding. Application to large systems, particularly those employing explicit solvent, is hampered by several limitations, including the scaling of number of required replicas with increasing system size and the long times required to reach equilibrium. We will present variations of REMD with modified exchange probability that decouple conformational search from the computationally expensive simulation of multiple replicas in explicit solvent. These REMD simulations draw from a conformational diversity “reservoir” and converge much more rapidly than standard REMD simulations. This permits use of different solvent models and search techniques for initial exploration of the free energy landscape while still providing rigorous Boltzmann-weighted ensembles for the REMD replicas.

COMP 10

Replica exchange with solute tempering

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The number of CPUs required in the replica exchange method scale as the square root of the number of atoms in the system. We discuss a method for reducing the effect of this poor scaling by using a different potential function at each temperature. This method, called replica exchange with solute tempering

(REST), is applied to three large solvated peptide systems: an alpha-helix, a beta-hairpin, and a TrpCage, with these peptides defined as the “central group”.

We discuss the advantages and shortcommings of REST. In addition we discuss a new serial method based on Replica exchange.

COMP 11

Biasing potential replica exchange to enhance sampling of peptide and protein conformations during molecular dynamics simulations

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Molecular dynamics-replica exchange (RexMD) simulations that allow exchanges between MD simulations at different temperatures are frequently used to sample peptide and protein conformations. However, a drawback of the standard RexMD method is the rapid increase of the number of replicas with increasing system size to cover a desired temperature range. To limit the number of replicas we have developed new Hamiltonian-RexMD methods that employ various biasing potential levels associated with soft degrees of freedom of the biomolecule for each replica run. One approach is designed to enhance the sampling of peptides and proteins by applying a backbone biasing potential. The biasing potential lowers the barrier for backbone dihedral transitions and promotes enhanced backbone transitions along the replica coordinate. In the second method a coarse-grained elastic network model (ENM) of a protein is used to construct a biasing potential that controls the motion along soft directions compatible with the ENM model. Both biasing potential (BP)-RexMD methods require only a very modest number of replicas and were successfully tested on several peptide and protein systems. Applications of the methods to simulate peptide folding and structural transitions in proteins will be presented.

COMP 12

Abandoning the rigid receptor approximation: Side-chain flexibility in GOLD

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In the rapid and ongoing development of ligand docking methods a recent goal has been to abandon the use of a single ‘low'-energy structure of the receptor. It has long been clear that Fischer's famous lock and key concept, although attractive, is an oversimplification of reality - Especially in the field of drug discovery where the goal is often to disrupt an enzyme's function: as the key changes so may the lock!

The use of fully flexible ligands is considered standard for all ‘state of the art' docking programs, and most programs are fast and efficient in finding the correct poses, even if the search for the perfect energy function continues. Today most programs also include a way to treat receptor rearrangement upon ligand binding (induced fit). Methods range from ‘simple' solutions such as soft potentials to more sophisticated methods relying on homology modelling packages. The problem is complex due to the potentially large conformational space coupled with the requirement for rapid computations.

In this study we have used the recently implemented flexible side-chains option in the docking program GOLD to probe induced fit in important drug targets. Cross-docking has been performed on publicly available protein structures together with virtual screening using the challenging DUD-set to demonstrate the potential usefulness and pitfalls of docking with flexible receptors in modern-day drug discovery.

COMP 13

Accurate docking and scoring of fragment molecules for lead discovery and optimization

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In previous work we described a method to generate structure-based pharmacophore hypotheses derived from fragment docking. In this work we focus on methods to accurately dock and score fragments. While fragments generally bind weakly, we find that accounting for receptor flexibility is still important and show that our Induced-fit Docking methodology can accurately predict binding modes of fragments and the conformational reorganization of the protein. Next, we look at database virtual screening of fragments and show that it is possible to obtain substantial enrichment of actives, although not on par with virtual screening studies of drug-like compounds. We discuss the reasons for this and why false positives in computational fragment screening are more common and less problematic for drug discovery. Finally, we apply methods such as fragment joining and fragment growing to generate drug-like compounds from initial fragment hits.

COMP 14

Advances in induced-fit docking with applications toward predicting binding energies of diverse molecules

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The ability to accurately predict the structure of a flexible ligand-receptor complex is a key challenge in computational drug discovery. Obtaining an accurate structure can provide insights into important interactions that drive ligand binding and is necessary to predict binding energies. In this work we present recent advances in our induced-fit docking methodology. Significant improvements to accuracy and speed have been made by incorporating an adaptive softening potential that allows key receptor residues detected by the algorithm to be fully flexible while more rigid parts are treated with less flexibility. We present a much more extensive set of cross-docking cases covering a broad range of targets and ligands, and show that results from the new method are substantially improved over our previous induced-fit docking results. Finally, we couple the induced-fit structures with a new version of Glide XP to obtain significant correlations between predicted and experimental binding free energies.

COMP 15

Improved water handling in structure-based molecular docking

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The proper handling of water in active sites is still a largely unsolved problem in structure-based drug design. We propose a novel strategy that allows for water molecules to be taken into consideration during placement generation in docking. The water can be either placed manually and fixed in orientation or kept rotatable, so that according to the ligand poses, it can best possibly form interactions with the protein and the small molecule. Also, the water can be made permanent or displaceable, so that the ligand placements and scores determine whether the water stays or is removed. This treatment is important for modelling buried or conserved water that is replaced by stronger binding ligands. Finally, aside of the manual placement, FlexX can suggest potential water positions which are then subjected to either of the above ways of handling such water. We

present this novel technology together with application examples, illustrating the usefulness of the procedure.

COMP 16

Predicting absolute binding free energies with physics-based methods

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Accurate and reliable predictions of binding free energies would be a tremendous aid to drug design, but this has proven extremely challenging. We discuss recent work applying rigorous alchemical free energy calculations to compute absolute binding free energies in a predictive context in several different model binding sites. We highlight lessons learned, including the relative contributions of multiple ligand orientations, protein conformational changes, and protein flexibility. We also present highlights from work in progress on applying these techniques to realistic binding sites.

COMP 17

Protein loop flexibility around ligand binding sites: Implications for drug design

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A common procedure in deriving binding models for ligand-protein interactions is to treat the protein rigidly while allowing ligand flexibility. While this often gives reasonable binding models, there are numerous instances where the size and shape of the protein binding pocket changes quite dramatically upon ligand binding. Such structural changes are, as expected, most significant in the ″structurally variable regions″ of a protein, most commonly the loops. This study shows a variety of therapeutically interesting proteins that exhibit significant loop conformational changes upon binding different ligands. The drawbacks of generating binding models using ″incorrect″ loop geometries is discussed, underscoring the need to consider an ensemble of loop conformations rather than a single structure for ligand docking.

COMP 18

Role of quantum mechanical energies in binding sites of metalloproteins

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As commonly acknowledged, binding between protein and other molecules is a fundamental phenomenon in biological processes. A protein binding could involve a number of different interactions including Coulombic, van der Waals, and hydrogen bond, all of which have their origin in electric charge. In order to model these processes on a computer, one needs to use the right blend of theories. Force field based molecular mechanics has primarily been used to simulate protein binding. However, in some cases, especially those involving highly polarized binding sites, fixed charge model molecular mechanics fails to describe binding modes of two molecules accurately. Quantum mechanical / molecular mechanical (QM/MM) method has gained popularity in last few years for description of such systems since one can use quantum mechanical level theories for only part of the system in question to obtain better description and yet maintain reasonable computational cost. In particular, when electron transfer is suspected within the binding site of a protein, quantum mechanical theory is needed to fully understand the binding process. We use QM/MM method to study systems in which electron transfer occurs, such as metalloproteins. We also devise a docking protocol which covers extended regions with quantum mechanics and apply it to various systems. The results show that the employment of QM/MM methods greatly improves prediction of binding modes in a few classes of proteins, including metalloproteins.

COMP 19

Structure-based lead optimization of small molecule β-secretase (BACE1) inhibitors

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Alzheimer's Disease (AD) is a progressive neurodegenerative disease and the leading cause of dementia. It is believed that the deposition of β-amyloid peptide

(Aβ) resulting from the cleavage of Amyloid Precursor Protein (APP) may cause the development of of AD. β-secretase (BACE1) is a membrane-tethered aspartyl protease that cleaves the β-amyloid precursor protein (APP) and generates the N-terminus of Aβ, and therefore the reduction of brain Aβ levels through the inhibition of BACE1 is being pursued as an attractive approach for AD therapy. Despite extensive research over the past decade, it is only recently that high-affinity small molecule BACE1 inhibitors have emerged. We present here the optimization of a weak HTS lead WY-24454 (IC50 = 40 uM) to highly potent and selective BACE1 inhibitors through an iterative structure-based approach with the aid of the X-ray crystallography and molecular modeling. A variety of computational methods were applied in this endeavor to assist structure-based lead optimization effort, ranging from GRID analysis, quantum mechanical studies, QSAR modeling, and molecular docking with improved scoring function. The approach enabled us to identify key interactions in the enzyme site, to understand the role of the FLAP region (with regard to selectivity over BACE2), and to assess the physical parameters for improving cell-based activity and brain penetration. This approach enabled us to rapidly explore the rather large ligand-binding pocket of BACE1 and produce structurally diverse, and highly potent (IC50 ~10 nM) BACE1 inhibitors. These potent and selective BACE1 inhibitors will potentially lead to the identification of disease-modifying AD therapeutics.

COMP 20

Cation binding and quadrupole moments of substituted cyclopentadienyl rings

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Recently, our group reported a correlation between substituted benzene quadrupole moments (Θ_{zz}) and the cation binding energies of the substituted benzenes. We have extended this line of research to cation binding of substituted cyclopentadienyl rings (Cp) due to our interest in metal-Cp complexes as reaction catalysts. Here we report on the correlation between the Θ_{zz} value of substituted Cp rings and the Cp–Li^+ and Cp–Na^+ binding energies. During the course of this work it quickly became apparent that a significant difference exists between the effect of substitution pattern on benzene Θ_{zz} values and the effect of substitution on Cp Θ_{zz} values. Namely, while for substituted benzene rings there are numerous examples of both positive and negative Θ_{zz} values, substituted Cp rings almost exclusively have positive Θ_{zz} values. Molecular orbital and electron density analysis will be employed to explain this difference between substituted benzene and Cp rings.

COMP 21

Effects of the crystal environment on potential energy surfaces for proton transfer in aspirin

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The potential energy surfaces for proton transfer in crystalline aspirin and related compounds are explored computationally using fragment models of the crystals and ab initio DFT methods. Such approaches have proved useful for modeling the potential energy surfaces for CF_3 rotation in substituted phenanthrenes, and in understanding the disorder observed in X-ray structures of these compounds. Disorder in neutron diffraction structures of aspirin and other carboxylic acid dimers likewise has implications for the shape of the proton transfer potential energy surface. The influence of the local environment on these surfaces is explored.

COMP 22

Evaluation of several correlated electronic methods in the context of calculations common to drug design

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As the cost ratio of computational infra-structure continues to decrease and scientific algorithms become more efficient, quantum chemical methods are becoming integral to routine modeling work. Torsional potentials, QM-MM studies of protein ligand complexes, and complete conformational energy surfaces of flexible, drug-sized molecules are not uncommon. Over the years several correlated electronic models have been developed offering superior performance in terms of increased speed with little purported loss in accuracy compared to higher level calculations. How efficient are these methods, and how do they compare in real life tasks which industrial modelers face on a day to day basis? In this report, we compare the performance of several correlated methods, including TRIM-MP2, LMP2, RI-MP2 and several recently developed DFT functionals in terms of relative conformational and tautomeric energies and torsional potentials. Results are evaluated relative to benchmarks obtained using explicit MP2 or higher levels of theory.

COMP 23

Influence of molecular oxides on transition metal tricarbonyls

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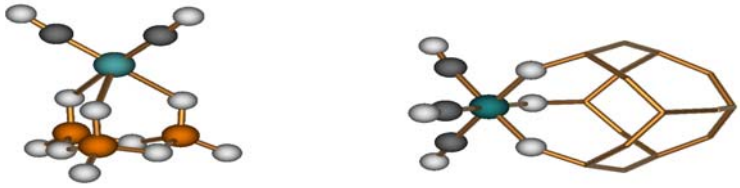
The catalytic activity of metal carbonyl clusters and metal carbonyls supported on surfaces has been extensively studied. In this work, calculations have been performed on a series of mononuclear d^6 metal di- and tri-carbonyls supported on molecular oxide cages. The molecular cages were chosen both as models for phosphate, silicate, and aluminosilicate surfaces and because experimental data is available for some of these molecular complexes. By systematically varying the nature of the oxide surface, qualitative estimates of metal binding affinity toward CO, metal carbonyl geometry, and CO stretching frequencies can be determined for a range of transition metals. Most of the trends observed correlate with expectations, but several exceptions were found. For example, while decreased M-C bond lengths are generally accompanied by an increase in CO bond lengths, this was not observed in all cases.



COMP 24

Novel QM/MM investigations of enzyme catalysis

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Enzymes facilitate specific chemical reactions by lowering the reaction's Gibbs free energy of activation (∆G‡);it would be advantageous to understand exactly what within the enzyme leads to this lowering of the activation energy. The energy gap fluctuation between two states can be used to calculate a free energy function for the reaction coordinate between these states. We present, the

progress thus far, at developing a novel approach for obtaining the energy gap between two states using computer modelling, and apply it to the rate limiting hydride transfer step catalysed by the extensively studied horse liver alcohol dehydrogenase (LADH) enzyme. Two, independent, equilibrium trajectories of the states either side of this rate limiting step are propagated classically using the AMBER force field and then post-processed using a QM/MM method to obtain the ground state energy of each state. Due to the independent nature of the simulations, one cannot simply subtract the energy of one state from the other to obtain the energy gap between the states. Instead, both state's time ordered ground state energies are Fourier transformed and then subtracted in the frequency domain, with the inverse Fourier transformation of the difference of these two spectra yields a phaseless approximation to the time ordered energy gap between these states. The subtracted spectrum of oscillators gives insight into which modes within the system contribute to the catalytic effect.

COMP 25

Minding the gap: Lowering the barrier to the Bergman cyclization of enediynes

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Naturally occurring anticancer agents, such as Dynemicin A, contain reactive, electron rich enediyne moieties. Under the proper conditions, the enediyne group undergoes a Bergman cyclization that results in a p-benzyne diradical that can abstract hydrogen atoms from DNA resulting in cancer cell death. In this project, the cyclization energetics of five, seven, and eight-membered enediyne molecules are studied using a variety of theoretical methods. Structures and energetics for the reactant, product and reactive intermediate along the cyclization pathway will be presented.

COMP 26

The contribution of electronic and conformational constraints to the selectivity of P450-catalyzed oxygenation vs. dehydrogenation reaction mechanisms during tamoxifen metabolism

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Hepatic cytochrome P450 (P450) enzymes are responsible for the metabolism of the majority of drugs in use today. The promiscuity of these enzymes in their substrate selectivity, as well as the ability to catalyze a number of different chemical reactions allows these enzymes to perform their physiological role in detoxification and metabolism of numerous exogenous and endogenous compounds. These characteristics of P450 enzymes also present significant challenges to the accurate prediction of how a given drug is metabolized. To gain insight into the contributions of substrate-enzyme interactions during P450 catalysis we are using a combination of theory and experiment to study the P450 isozyme-specific metabolism of a commonly used anti-cancer drug: tamoxifen. Here we present the results of ab initio Hartree-Fock (HF) / 6-31G* level calculations for tamoxifen and key metabolites formed during P4540-catalyzed oxygenation and dehydrogenation reactions. Our calculations for the oxygenation products are in agreement with earlier published work and our calculations for the species formed during P450 catalyzed dehydrogenation reactions indicate a unique cis/trans ethylene-quinone interaction that contributes to the stabilization of these quinone methide species. Additionally, molecular dynamics simulations of various P450-drug interactions provide further insight into the broad substrate specificity. These results provide encouraging insights into the electronic and conformational constraints that contribute to the selectivity for oxygenation versus dehydrogenation reaction mechanisms by certain P450 enzymes with specific substrates.

COMP 27

ACE, a virtual screening tool for asymmetric catalysts

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ACE (Asymmetric Catalysis Development) has been developed for taking virtual screening techniques in the field of drug design and applying them to asymmetric catalyst development. Initial results in screening asymmetric Diels-Alder and Aldol reactions show promise and have lead to further developments. New modifications to ACE will be discussed, such as solvation along with new applications to asymmetric reactions.

COMP 28

Assessing the performance of density functional theory for metal-salen catalysis

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Density functional theory has become the electronic structure method of choice for exploring metal-ligand catalyzed transformations. However, assessing the performance of density functional theory for such systems has been hindered for several reasons. Experimental results for metal-ligand catalysts are often scarce and direct comparisons to experiment remain difficult. Furthermore, comparisons against ab initio results are limited by the size of the systems and the presence of near degeneracies. This presentation will highlight recent and ongoing research in our group to assess the reliability of density functional theory for metal-salen catalysts, comprising the most important and versatile ligand systems in asymmetric catalysis. Stressing the successes and failures of the most common functionals, the trends observed in the electronic structure and the applicability of density functional methods to such systems will be discussed. It is anticipated that the results will guide future applications of density functional theory to metal-ligand catalyzed chemical transformations.

COMP 29

Born-Oppenheimer molecular dynamics simulations of enzyme catalysis with ab initio QM/MM methods

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In order to elucidate enzyme catalysis through computer simulation, a prerequisite is to reliably compute free energy barriers for both enzyme and solution reactions. By employing on-the-fly Born-Oppenheimer molecular dynamics simulations with the ab initio QM/MM approach and the umbrella sampling method, we have determined free energy profiles for the methyl-transfer reaction catalyzed by the protein lysine methyltransferase and its corresponding uncatalyzed reaction in aqueous solution, respectively. At each time step, the forces on atoms in both QM and MM sub-systems as well as the total energy are calculated with a pseudobond ab initio QM/MM method on the fly, and Newton equations of motion are integrated. Our simulations have yielded activation free energy barriers consistent with experimental results, and provided detailed theoretical understanding of enzyme catalysis and methylation state specificity in histone lysine methylation. Meanwhile, we are further pushing the limit of the ab initio QM/MM MD approach in its feasibility and applicability.

COMP 30

Dehydrogenation of ammonia-borane catalyzed by N-heterocyclic carbene nickel complexes: A DFT study

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Density functional Tao-Perdew-Staroverov-Scuseria calculations with all-electron correlation-consistent polarized valence double-zeta basis set demonstrate that N-heterocyclic carbene (NHC) nickel complexes catalyze the dehydrogenation of ammonia-borane, a candidate for chemical hydrogen storage, through proton transfer from nitrogen to the metal bound carbene carbon, instead of the B-H or N-H bond activation. This new C-H bond is then activated by the metal, transferring the H to the metal, then forming the H2 by transferring a H from B to the metal, instead the β-H transfer. This reaction pathway explains the importance of the NHC ligands in the dehydrogenation and points the way to finding new catalyst with higher efficiency and stability, as partial unsaturation of the M-L bond may essential for rapid H transfers.

COMP 31

Kinetics of oxidation of monosaccharides by protonated N-bromosuccinimide using nano-amount of chloro-complex of Rh(III) as homogeneous catalyst

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Kinetics of oxidation of arabinose (ara) and ribose (rib) by protonated N-bromosuccinimide (N^+BSH) using chloro-complex of Rh(III) in its nano-concentration range as homogeneous catalyst have been investigated at 40^0 C for the first time. Almost constant values of pseudo-first-order rate constant (k_1) throughout the variation of N-bromosuccinimide (NBS) in the oxidation of both the reducing sugars clearly demonstrate that order of reaction with respect to [NBS] is unity. This result is further supported by the plots of initial rates of the reactions versus [NBS], where straight lines passing through the origin were obtained. First-order kinetics with respect to each [Rh(III)], [sugar] and [H^+] is evident form the observed values of k_1 which show increase in the same proportion in which the concentration of each reactant is increased. Negligible effects of [Hg(II)], [Cl^-] and [succinimide] on the rate for the oxidation of each reducing sugar have been observed. Variation in ionic strength (μ) and dielectric constant (D) of the medium have not influenced the oxidation rates. Protonated N-bromosuccinimide, N^+BSH, and chloro-complex of Rh(III), $[Rh(H_2O)Cl_5]^{-2}$, have

been postulated as the reactive species of NBS and Rh(III) chloride in acidic medium respectively. Various activation parameters have been calculated.The proposed mechanism, with the most reactive activated complex formed as a result of interaction between the complex species, $[RhCl_5.NBSH]^-$, and a sugar molecule, is supported by kinetic data, spectrophotometric evidence, positive entropy of activation and by the observed nil effect of the dielectric constant and ionic strength of the medium. Almost the same values of fourth-order rate constant (k') observed for the variations of [sugar], [NBS], [Rh(III)] and $[H^+]$ in the oxidation of both the reducing sugars provide further support to the proposed reaction path. Formic acid and erythronic acid are the most probable oxidation products of the reactions under investigation.

COMP 32

Comparison between regular and replica exchange molecular dynamics simulations and their applications in protein folding

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Replica exchange molecular dynamics (REMD) method helps a system to escape from local energy traps and enhance the conformational sampling. In an earlier work, we studied the accuracy and efficiency of REMD by comparing to the conventional molecular dynamics (MD) simulations. An excellent agreement between the REMD and the extended MD simulation results was observed for T > 300 K, showing that REMD can accurately reproduce long-time MD results with high efficiency. We also found that REMD can significantly enhance the sampling efficiency by 14.3 +/- 6.4, 35.1 +/- 0.2, and 71.5 +/- 20.4 times at, respectively, 360, 300, and 275 K in comparison to the regular MD. Convergence was less satisfactory at low temperatures (T < 300 K) and a slow oscillatory behavior suggests that longer simulation time was needed to reach equilibrium. In a series of protein folding simulations, we further compared REMD and long-time conventional MD simulations. It was found that the free energy landscapes obtained from two types of simulations qualitatively agree with each other.

COMP 33

Enhanced sampling via replica methods

***Adrian E. Roitberg**, Department of Chemistry, Quantum Theory Project, University of Florida, Gainesville, FL 32611-8435*

We will present some recent advances pursued in our group regarding enhanced sampling with replica exchange-like methods.

We will show that increasing the frequency at which exchanges are attempted substantially helps convergence without hindering equilibration. We will some measures of convergence for replica-based simulations.

Results related to our implementation of constant pH replica exchange simulations will be shown, as well as our work on multicanonical simulations.

COMP 34

Simple continuous and discrete models for simulating replica exchange simulations of protein folding and binding

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Replica exchange (RE) is a generalized ensemble simulation method for accelerating the exploration of free-energy landscapes which define many challenging problems in computational biophysics, including protein folding and binding. Although temperature RE (T-RE) is a parallel simulation technique whose implementation is relatively straightforward, kinetics and the approach to equilibrium in the T-RE ensemble are complicated; there is much to learn about how to best employ RE to protein folding and binding problems. Protein folding rates often slow down as the temperature is raised above a critical value and this “anti-Arrhenius” behavior represents a challenge for RE. However, it is far from straightforward to systematically explore the impact of this on RE by brute force molecular simulations, since RE simulations of protein folding are very difficult to converge. In studies over the past two years using both atomistic and simplified models, we have clarified some of the obstacles to obtaining converged thermodynamic information from RE simulations. In my talk I will describe some simple continuous and discrete models we have constructed to explore the behavior of replica exchange sampling under a variety of conditions. Comparison of the efficiencies obtained using the continuous and discrete models makes it possible to identify non-Markovian effects which slow down equilibration of the RE ensemble on the more complex contiuous potential. In particular, the rate of temperature diffusion and also the efficiency of RE is limited by the timescale of conformational rearrangements within the free energy basins of the corresponding macrostates. Finally, I will discuss some of the obstacles to using

RE to construct pathways for protein folding and binding and how they might be overcome.

COMP 35

Exploring the energy landscape of protein folding using replica exchange and conventional molecular dynamics simulations

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Replica-exchange molecular dynamics (REMD) simulations with explicit water were performed of the Trp-cage mini-protein, starting from both native and nonnative conformations. Beginning with the native conformation, the predicted melting temperature is 50-150 K higher than the experimental value. In simulations from a nonnative conformation, there was no evidence of folding. Transitions from the unfolded to folded state did not occur on the timescale of the simulations, despite the expected improvement in sampling of REMD over conventional molecular dynamics (MD) simulations. The combined 1.42 μs of simulation time was insufficient for REMD simulations with different starting structures to converge. Conventional MD simulations at a range of temperatures were also performed. In contrast, the conventional MD simulations provide an estimate of Tm in good agreement with experiment. Furthermore, the conventional MD is a fraction of the cost of REMD and continuous, realistic pathways of the unfolding process at atomic resolution are obtained

COMP 36

Limitations of temperature replica exchange (T-REMD) in protein folding simulations

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The replica exchange/parallel tempering method and its variations offer the hope of improved sampling for many challenging problems in molecular simulation. Like all sampling methods, however, the effectiveness of replica exchange is highly dependent on the specific physical system being studied. We have carried out large scale temperature replica exchange (T-REMD) simulations of peptides and proteins in explicit water and encountered a number of issues that limit the effectiveness of the method in sampling biomolecular conformations. In particular, our results suggest the need to either replace or augment the

temperature variable with an alternative extended variable, such as Hamiltonian scaling.

COMP 37

Ab initio molecular dynamics simulations of water under shock compression: Chemistry behind shock fronts

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We report herein first principles simulations of water under shock loading of velocities from 5 – 11 km/s. Accurate description of the plateau in the ionic conductivity at high pressures and temperatures is of particular importance to models of the planetary dynamo mechanism in Neptune and Uranus. We attribute this plateau to the exceedingly short-lived molecular and ionic states that occur in water under these extreme conditions. In particular, at the intersection of the shock hugoniot and Neptune isentrope we observe transient metallization that we attribute to the formation of short-lived negatively charged species that contribute electronic states at or around the band gap. Our results represent the first quantum mechanical description of water under shock loading that we know of, to date.

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COMP 38

Conformational and isomeric free energy differences from cluster-based simulations

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The solvation of ions, peptides and other biomolecules plays an important role in a wide range of biochemical processes. Cluster systems can provide detailed molecular level information about solvation effects by singling out particularly

important solvent molecules, which can be difficult to identify in the bulk due to statistical averaging. Experimental and theoretical evidence has also suggested that sufficiently large clusters can serve as good models for bulk systems. We have developed a cluster based computational approach utilizing the AVUS-HR algorithm combined with ab initio molecular dynamics data to probe these effects. Having successfully applied this approach to ion pairs in solution, we have extended it to a number of other systems. Topics will be selected from i) the conformational properties of small peptides, ii) the relative stability of neutral and zwitterionic amino acids in water and iii) solvent mediated interactions between hydrophobic solutes

COMP 39

Photoisomerization of azobenzene: A quantitative force field-based implementation and simulation of assemblies with layered silicates in comparison with experiment

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Classical MD simulation is a suitable tool to investigate trans-cis isomerizations as a function of various molecular environments and conditions (temperature, pressure). A temporary modification of the C–N=N–C torsion potential in azobenzene is presented to model quantitatively the input of photon energy. The relative energies of the trans and the cis isomer, the excited state energy, the thermal conversion barrier, and the time scale of the conversion (1 ps) are accurately accounted for in this force field-based implementation, using a standard three-term torsion potential as available in the polymer consistent force field or in OPLS-AA. MD simulations were carried out for layered silicates with attached photoactive azobenzene-containing surfactants, and reversible changes up to 2.8 Å (14%) in basal plane spacing between montmorillonite layers have been identified upon trans-cis isomerization. The best responses are indicated for (4,4'-pheylazophenyl)diammonium ions and (4-phenylazophenyl)ammonium ions in pillar-like, upright orientation on the mineral surface. Experimentally, optical switching of more than 1 Å has still remained challenging without support from excess amounts of solvent [Okada et al. J. Mater. Chem. 2005, 15, 987], and the simulation helps explain the orientation of the azobenzene units relative to the surface and the reorganisation in the interlayer space upon excitation in the context of UV/VIS absorption measurements and X-Ray diffraction data.

COMP 40

Using wide-angle X-ray scattering and molecular mechanics to explore the conformational ensemble of a hexameric porphyrin macrocycle: Evaluating CHARMM's ability to reproduce large amplitude motions

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Wide-angle x-ray scattering measurements in combination with coordinate-based modeling offer new possibilities for gaining atomic scale insight into the conformational dynamics of supramolecular architectures in solution. A comparison has been made between the configurationally broadened x-ray scattering patterns for dilute toluene solutions of a hexameric, diphenylethyne-linked porphyrin macrocycle with scattering patterns calculated from structural ensembles from constant pressure and temperature molecular dynamics simulations. Thermal fluctuations sampled at 0.5 picosecond intervals within nanosecond time scale dynamic simulations show large amplitude motions that include extended macrocyclic ring “breathing” motions. This motion produces characteristic, angle-dependent dampening of scattering features that are needed to qualitatively reproduce experiment. Mis-matches in the magnitudes of experimental and simulated dampening indicate that large amplitude, breathing-type motions are significantly under-represented in the simulated ensembles. The comparison between experiment and simulation provides a means to interpret x-ray scattering data in terms of an explicit atomic model, and additionally suggests the opportunity to use wide-angle x-ray scattering as experimental benchmarks in the development of simulation methods that more accurately predict function-linked configurational dynamics of supramolecular assemblies.

COMP 41

Ultrafast transformation of graphite to diamond: An ab initio study of graphite under shock compression

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We report herein *ab initio* molecular dynamics (MD) simulations of graphite under shock compression, in conjunction with the Multi-Scale Shock Technique (MSST). Our simulations reveal that a novel short-lived layered diamond intermediate phase is formed within a few hundred fs upon shock loading at a shock velocity of 12 km/s (longitudinal stress > 130 GPa). The layered diamond state differs from the experimentally observed hexagonal diamond intermediate found at lower pressures and previous hydrostatic calculations in that a rapid buckling of the graphitic planes produces a mixture of hexagonal and cubic diamond. Direct calculation of the X-ray absorption spectra (XAS) in our simulations reveals that the electronic structure of the final state closely resembles that of compressed cubic diamond.

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COMP 42

Simulations of phase transitions and activity coefficients in ionic systems

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A fundamental molecular-level understanding of ionic systems is important for many physicochemical processes. The unifying characteristic of these fluids is the close interplay between microstructure and macroscopic roperties and the existence of strong interactions or multiple relevant length scales. Systems with short-range interactions in addition to the Coulombic forces show a variety of phase behaviors including tricriticality, ionic criticality and conventional (non-ionic) criticality. For highly charged colloids, the gas-liquid critical point becomes metastable with respect to a gas-solid phase eparation at colloid charges Q > 20. Employing approximate free energy calculations, we were able to determine the critical line below which a broad gas-solid phase separation occurs for highly charged colloids up to Q = 2000. The effects of added salts on the interactions and phase separation in colloidal suspensions has also been investigated. Even away from phase transitions, electrolyte solutions show strong non-idealities at low concentrations, especially for multivalent ions. We describe computational methodologies to obtain effective interactions between ions that correctly represent activity coefficients in concentrated solutions.

COMP 43

Comparing the Gibbs Ensemble and Grand-Canonical Transition-Matrix Monte Carlo methods in the determination of fluid phase equilibria

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In spite of the number of existing simulation methods capable of determining fluid phase equilibria, the Gibbs ensemble remains the most popular one due its conceptual simplicity and, in part to, its historical significance. In recent years, so-called flat-histogram sampling methods have emerged as an efficient and powerful means for locating the conditions phase coexistence. However, these methods have not yet been compared directly with Gibbs ensemble. In this work, we compare systematically the performance of the Gibbs ensemble and grand-canonical transition-matrix Monte Carlo (GC-TMMC) methods to determine fluid-phase equilibria in a variety of pure molecular fluids. Ethane, n-octane, cyclohexane, 2,5-dimethylhexane, 1-propanol, and water comprise the range of molecules used in this study. We first show that the GC-TMMC method is able to reproduce Gibbs ensemble results found in the literature. Next, we compare directly the performance of Gibbs ensemble and GC-TMMC simulations at both low and high reduced temperatures by monitoring the relative uncertainties in the saturation properties as a function of computational time. In general, we find that the GC-TMMC method yields limiting uncertainties in the saturated vapor density and pressure that are significantly lower, in some instances by an order of magnitude, than those of the Gibbs ensemble method. Limiting Gibbs ensemble uncertainties for these properties were generally in the 1.0 - 10 % range. However, both methods yield comparable limiting uncertainties in the saturated liquid density, which fall within the range of 0.1 - 1.0 %. In the case of water at 300 K, we find that the Gibbs ensemble outperforms GC-TMMC. The relatively poor performance of the GC-TMMC method in this situation is tied to the slow convergence of the density probability distribution at this low temperature. We also discuss strategies for improving the convergence rate under these conditions.

COMP 44

Free energy calculations of molecular solutes in polymeric microstructures

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Solubilities of additive molecules whose molecular sizes exceed the typical dimensions of free volume cavities pre-existing in amorphous polymer melts and glasses cannot readily be computed in molecular simulations. In this contribution, we discuss two methods for calculating excess chemical potentials of large molecular solutes in a bisphenol-A polycarbonate polymeric melt: (1) fast-growth thermodynamic integration using Jarzynski's non-equilibrium work theorem and (2) free energy perturbation based on a soft-cavity reference state ensemble. We illustrate that the first method is particularly useful to linking solubility to preferential interactions in the polymer matrix while the second method offers a fast route to obtaining relative solubilities of many solutes from a single simulation of the reference state.

COMP 45

Molecular simulation of equilibrium properties of fluids: From understanding toward quantitative predictions

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Over the last decades, algorithms have made numerous progress in the field of molecular simulation, and the increase of computer capacity has made many realistic systems accessible to such simulations. The purpose of this talk is to review what kind of thermodynamics properties can be predicted, either qualitatively or quantitatively, with molecular simulation. After a short introduction on Monte Carlo simulation methods and interaction potentials, different uses of molecular simulation in the oil and gas industry will be considered. One of the field of application that will be investigated is the prediction of fluid phase equilibria by Gibbs Ensemble Monte Carlo simulation, exemplified by the systematic determination of full phase diagrams, including liquid-vapour critical points, for pure components as well as binary systems. In some of the studied cases, the account for chemical reactions in the system is achieved using the Reaction Ensemble Monte Carlo method. The study of interfacial properties using two-phase Monte Carlo simulations will also be discussed, with an illustration of the calculation of liquid-vapour interfacial tensions in the case of several pure components. Application to gas production will also be illustrated by the calculation of gases solubility in polymer materials at high pressure, using Osmotic Ensemble Monte Carlo simulations. For each type of studied problem, molecular simulation has provided useful predictions together with a better understanding of the relation between properties and chemical structure.

COMP 46

Predicting phase equilibria using efficient Monte Carlo simulations

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In this presentation, we will review the application of efficient Monte Carlo algorithms using transferable force fields or GGA density functionals for predicting phase equilibria. Topics include the vapor-liquid coexistence curve of water, the retention mechanism in reversed-phase liquid chromatography, the formation of hydrates for pharmaceutical solids, and the miscibility of silica and water at extreme conditions.

COMP 47

Discretized transferable Lennard-Jones united atom models for phase equilibria

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Discontinuous molecular dynamics (DMD) is combined with thermodynamic perturbation theory (TPT) to provide an efficient basis for characterizing molecular interactions based on vapor pressure and liquid density data. The Lennard-Jones potential model is discretized to permit treatment by Barker-Henderson perturbation theory. The potentials are characterized by 11 wells ranging over radial distances from the site diameter to three times that diameter. This work develops a consistent mapping between the continuous LJ potentials of the TraPPE-UA and Step LJ potentials. The Step LJ potentials have been optimized and refined globally and rapidly by the DMD/TPT methodology and applied to continuous LJ potentials through the mapping. The primary database includes all the hydrocarbons of the TraPPE-UA development. The key step is to optimize the diameters of the step potential to match the density results of the TraPPE-UA model as closely as possible. This is made difficult by the temperature dependence of the equivalent hard sphere diameter inherent in the LJ model. Deviations in vapor pressure are similar to those of the TraPPE-UA model, while deviations in density are slightly higher. We conclude that DMD/TPT can be used to characterize continuous potentials with comparable accuracy to other characterization methods while maintaining the efficiency of the SPEADMD methodology.

COMP 48

Problem oriented sampling design via the replica exchange strategy

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Enhanced sampling is one of the most important issues in computational biophysics research. In recent years, there have been some significant progresses in algorithmic development for systems of interest to both physicists and biophysicists. Those methods are related in their mathematical foundations, but also different in their applications. Typical examples include recent development on various generalized-ensemble-based sampling methods including those using Replica Exchange Method and Wang-Landau sampling scheme. The impact on studying complex biological macromolecules of these advanced simulation methods has just begin to emerge. In many cases, such as in free energy simulation of biomolecular processes, those new methods have shown to be transforming in terms of speed of calculation and efficiency of sampling. In the present talk, a series of developments, designed based on the combinations of these basic sampling schemes, will be introduced to realize various aspects of simulation accelerations such as in free energy simulations, quantum mechanical potential based simulations, and the solutions of diffusion sampling problems.

COMP 49

Extrapolating to equilibrium from early simulation results of replica exchange calculations on proteins

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Replica exchange molecular dynamics simulations of protein folding provide two benefits. First, the enhanced sampling offered by the algorithm helps to provide a more thorough representation of conformation space for Boltzmann averaging. Second, it naturally produces "melting curves," which show how the distribution of any observable changes with temperature. Melting curves are very useful for comparison of simulation and experimental results. In a fully converged simulation, after equilibration and adequate sampling, the resulting melting curves should be independent of the starting state of the simulation, and stable with respect to continued simulation time. Convergence of results is usually fast at high temperature, even without the benefit of the replica exchange. However, even for relatively small molecular systems, we have seen that at intermediate and low temperatures convergence can be very slow. With varying degrees of success, we have worked on extrapolation methods to estimate fully converged

melting curves early in the simulation process. These methods assume that at each temperature, there is a simple exponential relaxation to equilibrium. Although this is an approximation, since one always hopes that replica exchange results converge in a multiexponential fashion, in practice there is rarely enough data to characterize more than a few fitting parameters. The talk will present some of our experiences with the slow convergence of simulation results and with such extrapolation.

COMP 50

New replica exchange methods for spanning large temperature ranges

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Replica exchange is a powerful method for increasing the sampling efficiency of computer simulations but scales poorly with system size, limiting its usefulness for larger systems. Two replica exchange methods which require far fewer replicas to span a given temperature range are presented. Both these methods use a potential scaled with a parameter treated either as a dynamical variable or with a simple explicit time dependence. This results in a method that can reduce the number of replicas by a factor of 5 to 10, allowing replica exchange to be applied to larger systems. The methods are applied to the alanine dipeptide and the twelve residue tryptophan zipper polypeptide. The method can also easily produce equilibrium averages for a range of temperatures using a single replica.

COMP 51

Conformational sampling of peptides in different dielectric environments

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The conformational sampling of peptides in different solvent environments is examined with replica exchange simulations. The effect of different environments is modeled through different dielectric constants with implicit, continuum-based solvent as implemented in the GBMV Generalized Born method. Replica exchange simulations in temperature-space are applied to characterize the sampling of peptides in different dielectric environments. Furthermore, novel replica exchange simulation in dielectric constant-space are used to explore to what extent a change in solvent polarizability can be used to speed up folding

and re-folding of mis-folded peptides in analogy to the function of biological chaperones.

COMP 52

Advanced sampling in exploring pH-dependent conformational transitions in proteins and peptides

***Charles L. Brooks III**, Department of Chemistry, University of Michigan, 930 North University Avenue, Ann Arbor, MI 48104, Fax: 858-784-8688*

In this talk I will describe recent developments and applications in the areas of pH modulated conformational transitions. I will review our recently developed continuous constant pH molecular dynamics method and how it is integrated with replica exchange sampling methods to explore a range of physical processes in biological molecules that are both dependent on conformational sampling and solvent pH. Examples will focus on the calculation of protein pKa values and the role of replica-exchange sampling in improving the convergence of these calculations, as well as pH-dependent conformational transitions associated with protein folding and amyloid fibril formation.

COMP 53

Temperature intervals with global energy reassignment (TIGER): Algorithm development and application to protein folding

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We have developed a new sampling algorithm called Temperature Intervals with Global Energy Reassignment (TIGER), which overcomes two of the major problems encountered when using replica-exchange molecular dynamics (REMD) simulations: requirement for a large number of CPUs and slow diffusion across temperature space. This algorithm overcomes these problems using heating/quenching cycles with energies globally compared at the base-line temperature. The equations underlying this algorithm have been formally developed and demonstrated to meet the detailed balance condition. The application of TIGER to predict conformational distributions for two relatively simple systems using CHARMM (butane/vacuum and alanine dipeptide/TIP3P water) resulted in similar distributions as with REMD, but with about 8-fold fewer CPUs. Simulations being conducted for peptide folding in TIP3P water also show performance enhancement compared to REMD. Because the number of CPUs for TIGER is independent of system size, this algorithm has substantial potential for the simulation of large molecular systems.

COMP 54

Identification of Pyk2 FERM ligands by combining protein similarity assessment, mutagenesis study, pharmacophore prediction, and in silico screening

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The strong tendency of malignant glioma cells to invade locally into surrounding normal brain precludes effective surgical resection and reduces the efficacy of radiotherapy, Pyk2 (proline-rich tyrosine kinase 2) contributes to in vitro glioma migration and disease progression in vivo. The N-terminal FERM domain is functionally critical for Pyk2-mediated effector signaling. A three-dimensional model of Pyk2 was generated (PDB: 2FO6) and compared with available bound structures of related FERM domains. Important Pyk2 FERM residues were identified by similarity and confirmed by mutagenesis study. A protein pharmacophore model was subsequently created and used to search the LeadQuest small molecule database. Molecules identified in the screen were refined by docking. Top compounds (n=67) were screened by competition ELISA using an active site-specific antibody targeting the Pyk2 FERM. This methodology yielded 9 confirmed actives and validated this combined approach for identifying Pyk2 FERM ligands.

COMP 55

Improving enrichment rates: A practical solution to an impractical problem

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The weights of the terms in many of the empirical scoring functions used for docking were trained by regression against binding affinity (Ki) values for a set of protein-ligand complexes. Although it would indeed be very useful to be able to calculate accurate binding energies, the practical problem in protein-ligand docking is simply to distinguish active molecules from inactives. This suggests that information on inactive poses, or negative data, should be incorporated into the training procedure.

We have recently introduced a scaling function into the ChemScore scoring function used by GOLD, which is based on the burial depth of an interaction in the binding site. By training using negative data, we show that the discrimination between active and inactive molecules is greatly increased.

COMP 56

Annotated DB of chemically feasible scaffolds: Key point for an efficient scaffold hopping

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Our main goal in drug discovery is reaching clinical phases with a good candidate in terms of PK/PD and with a solid IP position. Along this process there are too many barriers to overcome, from chemical feasibility, ADME related issues… to IP status. Therefore, looking for alternative chemotypes to main chemical series, its bioisosteric replacement, is a highly recommended approach if we want to achieve our goal.

Ideas for addressing the scaffold hopping in the most efficient manner are presented. Key starting point is building up an annotated DB with hundreds of thousands of unique, and chemically feasible, scaffolds. Details describing the process to build and use this DB will be discussed.

In addition, a case study where this approach was applied, providing a real added value to a drug discovery project, is presented.

COMP 57

Fragment based de novo design using an existing fragment based docking program, eHiTS

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Fragment based drug discovery has become a hot topic in recent years. The eHiTS docking program has been using a fragment based approach to docking since its inception. The algorithm divides input molecules into fragments and docks each fragment independently of the others before reconnecting to re-form the input molecule. Applying this methodology to fragment based de novo ligand design is a natural extension resulting in an efficient new tool. BACE-1 is a well studied flexible enzyme with implications in the treatment of Alzheimer's disease and over 30 public crystal structures. Using a set of co-crystallized ligands, we fragment the ligands and dock the fragments. By comparing the fragment poses to the original ligand pose, we can validate the ability of this protocol to reproduce known binders from fragments. It will be demonstrated how fragment docking results from various known ligands can be recombined and linked with additional common fragments to form some novel potential BACE-1 inhibitors.

COMP 58

Identification of a potent novel nonsteroidal progesterone receptor modulator from a virtual screen

Ray J Unwalla[1]*, Andrew Fensome*[1]*, Michael Marella*[1]*, Jason Cross*[1]*, Edward Melenski*[1]*, James Wilhelm*[1]*, Andrea Olland*[1]*, Scott Wolfrom*[1]*, Hassan Elokdah*[1]*, Jay Wrobel*[1]*, Richard C. Winneker*[2]*, Matthew Yudt*[2]*, Sunil Nagpal*[2]*, and Jeff Cohen*[2]*. (1) Chemical and Screening Sciences, Wyeth Research, 500 Arcola Rd, Collegeville, PA 19426, (2) Women's Health and Musculoskeletal Biology, Wyeth Research, Collegeville, PA 19426*

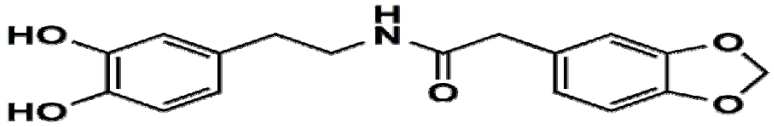
Progesterone plays an important role in the regulation of female reproductive functions. Synthetic steroidal progestins are widely used as oral contraceptives and for treating a variety of other endocrinological diseases and disorders, however, concerns of side effects due to cross reactivity with other steroid hormone receptors such as the glucocorticoid receptor (GR) and androgen receptor (AR), have prompted us to search for novel non-steroidal progesterone modulators with improved receptor and tissue selectivity. A virtual screen of the Available Chemical Database was performed using in-house docking program i.e PharmDOCK on the x-ray structure of the human progesterone receptor(PR) and after applying physical properties and undesirable chemical functionality filters, 103 compounds were submitted for testing in the T47D alkaline phosphatase assay. This approach proved to be successful with 10 of the 103 compounds showing PR antagonist activity with Ic50 values ranging from 5 nM to 500 nM (~10% hit rate). In this presentation we will discuss the identification and characterization of one of the hits. We will also discuss our approach to build a nuclear hormone focus-screening library using ligand-based virtual screening of published x-ray structures.

COMP 59

Virtual screening discovered catechol-containing compounds as STAT3 SH2 domain inhibitors

Yongbo Hu[1], *Wenshan Hao*[2], *Xinyi Huang*[3], *Chao-Pei Betty Chang*[2], *Jay Gibbons*[2], *Jun Xu*[2], *and Christine Humblet*[3]. *(1) Department of Structural Biology & Computational Chemistry, Wyeth Research, Pearl River, NY 10965, (2) Department of Oncology, Wyeth Research, Pearl River, NY 10965, (3) Chemical and Screening Sciences, Wyeth Research, Collegeville, PA 19426*

Excessive activation of STAT3 (Signal Transducers and Activators of Transcription 3) has been correlated with a wide spectrum of cancers. Activation of STAT3 requires homodimerization between a pTyr (phosphotyrosine)-containing peptide of one monomer and the SH2 domain of another. To find leads from which to develop STAT3 SH2 inhibitors as anti-cancer agents, a proprietary Wyeth library of 112,386 lead-like compounds was screened. Compounds were docked to the STAT3 SH2 domain, using Glide SP. The top 1,000 virtual screening hits were tested in biochemical assays and 74 competitive STAT3 SH2 inhibitors were found. Among the active compounds, a group of 15 hits shared a common catechol structural moiety. The binding model of Hit 1 suggested that this catechol portion occupied the pTyr-binding pocket. The catechol mimicked pTyr by hydrogen bonding to Arg609 and Glu612, which are conserved cross most SH2 domains. In biochemical assays, 1 inhibited STAT3 DNA-binding and competed with pTyr peptides in binding to the STAT3 SH2 domain. This suggests that the catechol moiety may be a pTyr bioisostere and might be generally used for designing novel cell-permeable SH2 inhibitors.



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COMP 60

Searching for new targets for the inhibition of Acetyl-CoA carboxylase

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Current research on the inhibition Acetyl-CoA carboxylase(ACCase) could lead to novel antiobesity and antimicrobial agents. Bacterial ACCases contain three different subunits, a central biotin carrier protein which transfers the biotin between the biotin carboxylase subunit and carboxyltransferase subunit. We used the ZINC database and the AutoDock program to screen for potential targets on both of these subunits. Since biotin is the natural ligand in both of these subunits, similar top dockers and binding motifs are found. These top docked ligands are checked with an experimental inhibition study. This presentation will explore the similarities between the tight binding ligands of these two subunits and the reasons why certain ligands showed no experimental inhibition.

COMP 61

Computer-aided design of novel Akt inhibitors targeting to the pleckstrin homology domain

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PI3K/Akt pathway represents a new cancer target for drug discovery. We have employed multiple molecular docking approaches to design and study non-lipid based inhibitors targeting to Akt PH domain. Guided by computational modeling, several hits have been identified and their anticancer activities were experimentally tested. The most active compound exhibits binding affinity as high as 25 nM. However, in silico ADMET studies were conducted and demonstrated that compounds with nitrobenzyl moiety were possibly toxic, consistent to known facts that they are usually mutagens and carcinogens. Based on docking results, we have proposed a series of analogues in which the nitrobenzyl groups were replaced but protein-ligand interaction patterns were maintained. Further lead identification and optimization is in progress to improve the ADME/Tox properties of these compounds. In conclusion, molecular modeling has been successfully employed to guide our chemical design and optimization of novel Akt PH domain inhibitors.

COMP 62

Computation of acidity constants in solution from vertical energy gaps

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The question of how to compute acidity constants (pKa) treating solvent and solute at the same level of theory remains of some interest, for example in the case of high or low pH conditions. We have developed a density functional based molecular dynamics implementation of such a method. The method is based on a half reaction scheme, i.e. free energies are computed from the vertical energy gaps for insertion or removal of protons. Finite size effects are large, but approximately cancel when half reactions are combined to full reactions. We verified the method by investigating a series of organic and inorganic acids and bases spanning a wide range of pKa values (20 units). We find that the response of the aqueous solvent to vertical protonation/deprotonation is almost always asymmetric and interpret this nonlinearity in terms of solvent reorganization in analogy with the picture for electronic ionization.

COMP 63

Dual-basis methods: Energies and derivatives with application to noncovalent interactions

***Ryan P. Steele**, Robert A. DiStasio Jr., and Martin Head-Gordon, Department of Chemistry, University of California at Berkeley, Berkeley, CA 94720, ofer4@bastille.cchem.berkeley.edu*

The expansion of a wavefunction in a fixed, finite basis set is one of the most common approximations in electronic structure theory. Convergence of results with respect to basis set size--particularly in correlated methods--is slow, while the cost grows steeply and renders many acceleration techniques (linear-scaling) inapplicable. Dual-Basis methods strike a pragmatic balance between cost and accuracy. An SCF calculation is performed in a subset of the target basis; the remaining basis set relaxation effects are treated perturbatively. Cost savings for DFT and MP2 energies are on the order of 90%, while errors are only 0.025 kcal/mol for bond breaking energies and 0.0009Å for equilibrium structures, orders of magnitude smaller than using the smaller basis set alone. Demonstrations for energies and analytic first & second derivatives are presented. The method is applied to non-covalent interactions in substituted benzene (1,4-phenylenediisocyanide) dimers, yielding insight into the formation of self-assembled monolayers.

COMP 64

Semiempirical PM6 modeling of organic crystal structures

***James J. P. Stewart**, Stewart Computational Chemistry, 15210 Paddington Circle, Colorado Springs, CO 80921, MrMOPAC@OpenMOPAC.net*

The new semiempirical method PM6 has been used for modeling the structures of several hundred organic solids. This involved using the Born Von-Kármán periodic boundary conditions (PBC) to construct the interaction matrices, and evaluation of the density matrix using the Cluster or Large Unit Call technique. A wide spectrum of intermolecular interactions involving both organic and organometallic species was studied, ranging from weak van der Waals interactions, through hydrogen bonding, to fully ionic. A discussion of the accuracy of prediction of the structures involved will be presented, along with a description of some of the weaknesses in the PM6 method.

COMP 65

Evaluating the accuracy of semi-empirical QM/MM methods using replica exchange and AMBER 10: Phi/Psi free energy calculations of peptides in solution

***Ross C Walker**, Strategic Applications Computing, San Diego Supercomputing Center, University of California, San Diego, 9500 Gilman Drive #0505, La Jolla, CA 92093, rcw@sdsc.edu, Gustavo de M. Seabra, Department of Chemistry, Quantum Theory Project, University of Florida, Gainesville, FL 32611-8435, and Adrian Roitberg, Department of Chemistry, University of Florida, Gainesville, FL 32611-8435*

Recent improvements to AMBER 10 include a fully featured semi-empirical QM/MM implementation that offers improved performance over previous versions as well as support for PME long range electrostatics and enhanced sampling methods such as replica exchange, umbrella sampling and thermodynamic integration. Support is included for an array of semi-empirical methods including MNDO, AM1, PM3, PM3/PDDG, MNDO/PDDG, RM1 and SCC-DFTB.

Here we present calculations of the free energy surfaces of various small peptides in solution calculated using QM/MM replica exchange simulations. We compare the results for all the methods supported by AMBER, both QM and classical and compare these to experimental NMR data.

An overview of the new QM/MM related features in AMBER 10 will also be presented.

COMP 66

Stacking and hydrogen bonding: Effective fragment potential modeling of DNA bases

Toni Smith[1]*, Lyudmila V. Slipchenko*[1]*, and Mark S. Gordon*[2]*. (1) Department of Chemistry, Iowa State University, 201 Spedding Hall, Ames, IA 50011, Fax: 515-294-5204, toni@iastate.edu, (2) Ames Lab/Iowa State University, Ames, IA 50011*

The generalized effective fragment potential (EFP2) method in GAMESS has previously been shown to model π-π interactions in substituted benzene dimers with an accuracy exceeding that of MP2 and approaching that of CCSD(T), though with a much smaller computational cost than either of these methods. DNA base stacking occurs via similar, dispersion-dominated π-π interactions, while base pairing operates through hydrogen bonding and is dominated by electrostatics. Here, the EFP2 method is used to model both types of DNA interactions and the results are compared with MP2 and estimated CCSD(T) data.

COMP 67

Multicentered ONIOM method for weakly bound noncovalent clusters: Recent advances and applications

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By taking advantage of the recently developed multicentered integrated (or hybrid) QM:QM method [J. Comput. Chem., 24, 1563-1568 (2003); Mol. Phys., 103, 309-315 (2005)], it is possible to recast the classic 2-body:n-body treatment of weakly interacting clusters in the ONIOM formalism. The resulting integrated QM:QM technique provides an extremely accurate description of weakly bound clusters. The approach is extremely efficient since it essentially reduces the problem to a series of dimer calculations with the high-level method and one low-level calculation on the entire cluster. Furthermore, this formulation allows the technique to (1) be extended to analytical 1st and 2nd energy derivatives and (2) readily take advantage of the latest developments in high-accuracy electronic structure theory for weak interactions. An overview of recent advances in and applications of this MC ONIOM method for clusters will be presented.

COMP 68

First principles study on the effect of metal and interface identities on thin film surface activity

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An atomic level understanding of the role that a support material plays in altering the physical and chemical properties of a metal can be used to tune the selectivity and reactivity at the surface of metal catalysts. Using ab initio methods we examine the electronic structure of three different metals (Pt, Pd and Rh) supported on alpha-alumina. We find that in all three cases there is a coexistence of charge-transfer valence-bond and band-like metallic states. Applying an orbital specific tight-binding model we demonstrate that these changes in the electronic structure are directly correlated with changes in the adsorption and diffusion of carbon monoxide at the metal surfaces. Our work also shows that the magnitude of the support induced changes in the metal electronic structure is strongly dependent on basic metal properties.

COMP 69

Computational study of hydrogenated transition metal clusters on zeolite support

Notker Roesch[1]*, Galina P. Petrova*[2]*, Georgi N. Vayssilov*[2]*, Elena A. Ivanova Shor*[3]*, Vladimir A. Nasluzov*[3]*, and Aleksey M. Shor*[3]*. (1) Department Chemie, Theoretische Chemie, TU Muenchen, Lichtenbergstr. 4, 85748 Garching, Germany, Fax: +49-89-2891 3622, (2) Faculty of Chemistry, University of Sofia, 1126 Sofia, Bulgaria, (3) Institute of Chemistry and Chemical Technology, Russian Academy of Sciences, 660049 Krasnoyarsk, Russia*

Small supported transition metal clusters activate H_2 and mediate transfer of hydrogen from or to the surface of the support. Our QM/MM DFT results for metal clusters M_6/zeo in a hydroxylated faujasite cage showed that for transition metals of the groups 8-11 the hydrogenated state, M_6(3H)/zeo, is energetically preferred over the bare form M_6/zeo(3H), except for gold. We also quantified the successive adsorption of hydrogen on Ir_4 clusters, supported either on hydroxylated or dehydroxylated models of faujasite, and found adsorption to be favorable at least up to H/Ir = 3. The calculated average Ir-Ir distance of the cluster models increased with the number of adsorbates, by ~1.9 pm per hydrogen atom. We suggest that the tetrairidium species in Y zeolite, investigated by EXAFS, are hydrogenated with up to 12 hydride centers. Using these results we constructed a thermodynamic model of hydrogen uptake by supported Ir_4 clusters.

COMP 70

Surface chemistry of gold nanostructures deposited on oxides: Oxide-specific O2 interactions with supported gold and the oxidation state of gold

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Oxide-supported Au nanostructures are promising low-temperature oxidation catalysts. It is generally observed that Au supported on reducible oxides is more active than the Au supported on irreducible oxides. Recent studies also suggest that cationic Auä+ is responsible for the unique Au/oxide catalytic activity. This observation is contrary to the conventional perception that oxide supports donate electronic charge to Au. We have utilized DFT calculations and ab initio thermodynamic studies to investigate the oxidation state of Au nanostructures deposited on reducible and irreducible supports. We find that there are fundamental differences in the electronic structure of Au deposited on the different oxides. We propose a simple model, grounded in the first principles calculations, which attempts to explain the oxide-specific catalytic activity of Au nanostructures and which can account for the presence and the role of cationic Auä+.1

1. Laursen S, Linic S, “Oxidation catalysis by oxide-supported Au nanostructures: The role of supports and the effect of external conditions”, Physical Review Letters, 2006, 97 (2), 026101

COMP 71

Density functional theory study of Pt and Pd-based pseudomorphic monolayer alloy catalysts for NOx storage reduction applications

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One of the consequences of our need to conserve our finite petroleum resources is a transition to more efficient diesel engines and lean burning gasoline engines. Associated with the switch to these lean burning engines is an increase in NOx production which results in a need to improve exhaust catalysts. One strategy for handling higher NOx levels is through the use of a so-called NOx storage reduction catalysts system. This catalyst (paired with a NOx carrier material, often barium oxide), must be able to operate in two distinct regimes: one highly oxidizing, one reducing. Using density functional theory, we have begun to

examine these processes by looking at two highly simplified and fundamental reactions: the oxidation of NO to NO2 and the hydrogenation of N atoms to NH. At this point, we have focused on Pt and Pd based alloys as a launching point in our investigation of periodic trends for these reactions.

COMP 72

First principle calculations of supported catalysts: CO binding on MgO supported gold clusters and nanoparticles

Giannis Mpourmpakis *and Dionisios G. Vlachos, Center for Catalytic Science and Technology, Department of Chemical Engineering, University of Delaware, Colburn lab, 150 Academy Street, Newark, DE 19716, gmpourmp@udel.edu*

First principle theoretical calculations have been performed to examine CO binding on all possible binding sites of gold clusters in the gas-phase and when supported on a MgO support. The gold clusters ranged in diameter from a few angstroms to approximately 1.5 nm. The largest systems are amenable only via novel quantum mechanical techniques described in our work. Our results concerning CO adsorption on gold clusters showed that suitable binding energy relations can be developed. Planar gold structures, when supported on MgO, slightly deform from their initial structural configuration, due to support-cluster interactions and the charge transferred from the support to the clusters. As a result, new binding sites are created on supported clusters for CO adsorption. When the deformed gold structures were isolated from the support, their reactivity to CO adsorption was decreased. Our simulations isolate for the first time electronic from strain effects regarding CO binding on gold nanoparticles.

COMP 73

Believe it or not: Understanding prediction confidence in computational drug discovery

Derek Debe*, Discovery Scientific Computing, Abbott Laboratories, 100 Abbott Park Rpad, Abbott Park, IL 60064*

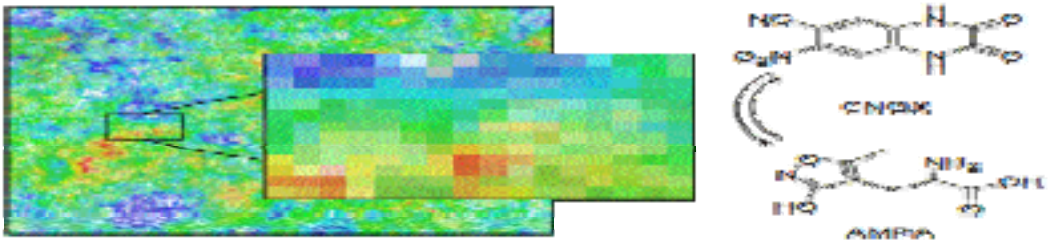
A well known drawback of computational chemistry approaches is the lack of confidence one has in the resulting prediction. This lack of confidence naturally limits the role that computational methods can play during hypothesis generation. Hence, an important frontier in the field of computational drug discovery is developing useful methods that also provide an accurate assessment of prediction confidence. This talk will discuss the potential of Belief Theory approaches to provide accurate confidence estimates in problems related to the activity and conformation prediction of drug molecules.

COMP 74

Exploration of chemical space for drug discovery by database generation

Jean-Louis Reymond*, Department of Chemistry and Biochemistry, University of Berne, Freiestrasse 3, Berne 3012, Switzerland, Fax: 41-31-6318057, reymond@ioc.unibe.ch*

Organic chemisty is the study of molecules made by forming covalent bonds between atoms of carbon, hydrogen, oxygen, nitrogen, halogens, and a few other elements (S, P, Si). The ensemble of all possible molecules forms the so-called chemical universe, or chemical space. Our aim is to explore chemical space in depth by exhaustive generation in silico, going beyond what nature and chemists have synthesized or imagined to date. In one approach, we have generated a database of all molecules up to 11 atoms of C, N, O, F that are possible under simple chemical stability and synthetic feasibility rules, and found that 99.8% of these are unknown and mostly feature new structural types [1]. In another approach, we travel through chemical space between known ligands using a mutational algorithm to produce large databases of intermediates, which are almost exclusively novel, and display a broad range of properties (illustration: map of chemical space between AMPA and CNQX, colored for polar surface area. The map contains 3.2 millions structures ordered by structural similarity). We have used these databases for drug discovery by combining substructure classification methods and docking with organic synthesis and testing of the most promising ligands, and discovered new types of bioactive ligands. Our findings challenge the commonly held notion that all the molecular types that nature may ever need are already available as natural products, and point to a plethora of novel structural types as new targets for synthesis. [1] a) T. Fink, H. Bruggesser, J.-L. Reymond, Angew. Chem. Int. Ed. 2005, 44, 1504-1508; b) T. Fink, J.-L. Reymond, J. Chem. Inf. Model. 2007, 47, 342-353. [2] R. van Deursen, J.-L. Reymond, ChemMedChem 2007, 2, 636-640.



COMP 75

Considering a treatment of induced electronic polarization based on the Poisson equation

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Currently, two physical models have been developed for use with explicit solvent to introduce electronic polarization in classical force fields: fluctuating charge and point dipole polarizability (Drude oscillators are included in the latter category). In this work, we explore a new way of using Poisson equation and the Poisson Boltzmann solver ZAP to introduce electronic polarization in an explicit classical force field. In this treatment, the polarizable electronic density of a molecule is represented as an intramolecular continuum dielectric constant. Our preliminary work show encouraging results in some important aspects. This simple model shows itself capable of describing naturally and well highly anisotropic molecular dipole polarizabilities; also key biologically relevant and polarizability driven cation-pi interactions are inherently well described.

COMP 76

Extracting configurational entropy changes using a mutual-information expansion: Binding in the TSG101/PTAP complex

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The current state-of-the-art of binding affinity computation for host/guest and protein/ligand complexes in modern drug design is predominantly energetics based. However, binding affinities assessed using even highly accurate potential energies are often over-estimated due to neglect of configurational entropy changes, information that is in principle available from molecular dynamics (MD) simulations. Our recently developed method of extracting classical solute configurational entropy from MD simulations uses a mutual-information expansion (MIE) which systematically accounts for correlations amongst all degrees of freedom, producing the exact configurational entropy when the full expansion is employed. The MIE has the advantage that it can be truncated at any correlation level and does not assume a presupposed form of the underlying probability distribution. We report first application of the MIE in evaluating the

entropy changes on binding for a microsecond-scale MD simulation of a protein/ligand system: TSG101, a potential HIV drug target, with a PTAP-motif peptide ligand.

COMP 77

Natural linear scaled coupled cluster theory with local transferable triple excitations: Applications to polymers

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The natural linear scaled coupled cluster (CC) method is extended to include hybrid triple excitations in which CCSDT-3 is embedded in a CCSD region. This approach uses the extensivity of the CC wavefunction to be represented in terms of transferable natural localized molecular orbitals (NLMOs) or effective functional groups thereof. We consider the transferability of NLMOs deriving from a variety of density matrices, for example exchange only density functionals as well as non-canonical RHF and UHF wavefunctions. Storage of the non-canonical triples amplitudes are avoided by applying the unitary localization matrix to the final canonical CC wavefunction instead of to the reference function. Our results indicate that the triples contributions are quite large for double bonds suggesting an interesting active space method for triples. Applications include translationally periodic polyacetylene and polyglycine and for a more realistic three dimensional example we consider met-enkephalin.

COMP 78

Dispersion in combined ab initio/effective fragment potential systems

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Dispersion, an attractive intermolecular force arising from a temporary dipole-induced multipole interaction, plays a major role in many systems of chemical and biological interest. An accurate description of dispersion is essential for modeling benzene dimers, DNA base stacking, and other systems involving π-π interaction, as well as solvation in general. The general effective fragment potential (EFP2) method, an explicit solvation method in GAMESS, already accounts for fragment-fragment dispersion interaction, but an EFP2/QM method is presently in development. A means of modeling the dispersion interaction

between an EFP fragment and an *ab initio* molecule is presented, and demonstrated on a water dimer and a benzene dimer.

COMP 79

Statistical correlation approach to improved thermodynamic predictions from DFT

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Statistical properties of the errors in enthalpy of formation as predicted by 18 different density functionals have been analyzed using a test set of 675 molecules. After accounting for some systematic errors, correlations of the errors for different functionals allow improvements in the accuracy of thermodynamic predictions. The best linear unbiased estimator (BLUE) method was used to determine linear combinations of energies from different functionals that make more accurate predictions than any single functional. For example, the best combination of five functionals (Poly-Functional 5, or PF5) has a mean absolute deviation (MAD) from experiment of 2.4 kcal/mol on the G3 set of 271 molecules, compared to 4.8 kcal/mol for B3LYP and 1.2 kcal/mol for the more costly G3 method. On the larger set of 675 molecules, the MAD for PF5 is 2.8 kcal/mol.

COMP 80

Pushing the limits of MCSCF

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Occupation restricted multiple active spaces (ORMAS) is a general CI/ MCSCF method showing promise as a reliable means to approximate CASSCF calculations. A brief introduction to the methodology of ORMAS will be presented. ORMAS will be shown to be an effective method to obtain a qualitatively accurate zeroth order wave function for the Si (100) surface and providing quantitative accuracy with respect to CASSCF. In addition, the example of Ga on the Si(100) surface will illustrate the usefulness of ORMAS as a way to circumvent large active spaces from conventional CASSCF problems.

COMP 81

Reaction path analysis: Approximations and applications

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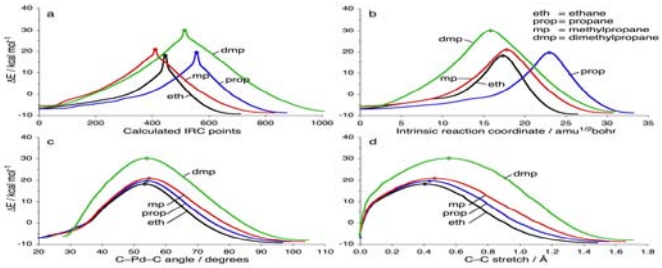
The appearance of a reaction profile or potential energy surface (PES) associated with the reaction path depends on the choice of reaction coordinate onto which the intrinsic reaction coordinate (IRC) is projected. Here, we address this issue by analyzing a number of reaction coordinates for a set of oxidative addition reactions of C-X bonds to palladium. Different choices affect the appearance of the PES and we discuss which qualities make a particular reaction coordinate most suitable for comparing and analyzing the reactions. Besides this, we introduce the TV-IRC approximation, where the Transition Vector is used to approximate a significant part of the IRC path. We also present a recently developed program, PyFrag, which streamlines reaction path analysis by extending the ADF energy decomposition analysis along any set of coordinates. The program makes it easy to plot a large set of chemical relevant data along any reaction coordinate.



COMP 82

Coarse-grain simulations of complex systems

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This talk will describe the use of coarse-grain simulations to explore complex nanosystems.

COMP 83

Optimized expanded ensembles for simulations involving molecular insertions and deletions

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Monte Carlo simulation methods that involve the insertion-deletion of molecules are of widespread use for the study of thermophysical behavior of complex systems; e.g., for the estimation of chemical potentials in closed-system ensembles and for establishing chemical potential equilibrium in open-system ensembles. In this work, efficient expanded ensemble methods are described to overcome the lack of ergodicity that often plagues such molecular moves, wherein an arbitrary physical parameter Lambda is used to gradually couple and decouple a partial molecule to and from the system. In particular, we describe the use of methods for the robust estimation of free-energy changes associated with transitions between Lambda states of the partial molecule, (2) Non-Boltzmann sampling of the probability density of Lambda states so that one can achieve an optimized histogram based on the minimization of either the time per round trip between the lambda bounds or the free-energy variance, and (3) an approach to select optimized intermediate stages of the Lambda parameter. The validity of the advocated methods is demonstrated by their application to several model single- and multi-component systems.

COMP 84

Use of the AUA intermolecular potential to determine the solubility of hydrogen in oxygenated solvents

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In order to respect the French commitments on bio-fuel production and use, the valorisation of lignocellulosic biomass (LCB) by means of thermochemical processes appears to be a promising solution. One of the current research topics consists in upgrading the bio-oils obtained after LCB flash pyrolysis by means of a hydrodeoxygenation. The development of this technology requires that new tools be available to accurately describe the behaviour of molecular compounds present during LCB conversion. These compounds correspond mainly to a large proportion of oxygenated molecules.

Molecular simulation has become widely used in industrial applications, specially when measurements are costly or involve specific risks due to the substances and / or the extreme experimental conditions. In this work, we use the molecular simulation technique based on Monte Carlo sampling to calculate the solubility of hydrogen in different alcohols; these data are required in the simulation of bio-oils hydrodeoxygenation processes. A previous study [1] showed that the

hydrogen/hydrocarbon interactions can be considered non-polar and modelled through simple Lennard-Jones intermolecular potential for hydrogen and the non charged AUA4 potentials for hydrocarbons [2]. This representation permits an adequate representation of phase diagram of such mixtures. For the case of hydrogen/oxygenated mixtures, strong electrostatic interactions are present in the mixtures due to collective hydrogen bond between solvent molecules. Therefore we will explore different hydrogen intermolecular potentials able to mimic the quadrupolar interactions of this gas and its interactions with the AUA potentials of oxygenated compounds [3], used in this work to model the solvent molecules.

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[3] Bourasseau E., PhD Thesis, Université Paris-Sud, 2003

COMP 85

Monte Carlo simulations for phase equilibria: Polymer solubility and quantum effects

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Molecular simulations studies investigating the phase behavior of polymer-carbon dioxide mixtures, and the effects of nuclear quantum effects on the phase behavior of water were carried out. Modeling polymer-carbon dioxide phase equilibria required a combination of Gibbs Ensemble Monte Carlo, connectivity-altering Monte Carlo, and identity exchange moves between polymer chains of various lengths. Results found that polymers with relatively high miscibility in carbon dioxide had a significant amount of surface area available for favorable interactions with carbon dioxide, and not just strength of interaction. For the understanding of the effect of nuclear quantum effects on the phase equilibria of pure water, both path integral Monte Carlo and semiclassical approaches were used with the TIP4P water model. The effect of nuclear quantum effects was to consistently shift the phase diagram to lower temperatures by around 20 K, and the semiclassical approach did not give good agreement with the path integral results.

COMP 86

Thermodynamics of solvent reorganization in solvent/co-solvent mixtures

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Gibbs free energies of transferring molecular solutes between different phases are routinely being calculated today in Monte Carlo and Molecular Dynamics simulations. Transfer entropies, enthalpies, and heat capacities require considerably more expensive calculations but offer additional information on the thermodynamics of structural solvent reorganization in the solvation shell. We present recent calculations of the transfer thermodynamics of nonpolar solutes between pure water and water/organic co-solvent mixtures and discuss the preferential solvation of the solute in relation with the calculated Gibbs free energies, entropies and enthalpies of transfer. Solvent reorganization contributions to the entropies and enthalpies will be discussed as well and interpreted in terms of the molecular reorganization processes in the solution.

COMP 87

Structure of liquid water from ab initio molecular dynamics at the complete plane wave basis set limit

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Water the most important liquid on Earth. Due to its critical role in many chemical and biological processes, a detailed understanding of the structural and dynamical properties of water is essential. As a result of many experimental and theoretical studies, a qualitative picture of the local solvation shell structure and dynamics of liquid water has emerged.

Unfortunately, the results obtained from different ab initio molecular dynamics (AIMD) studies of liquid water do not always agree with each other and often show disagreement with experiment. It has been even argued that the lack of agreement results from an irreproducibility of AIMD simulations of liquid water at ambient condition leading to a wide range of structural and dynamical properties.[1] Recently, this issue has been addressed by the another computational approach employing a discrete variable representation (DVR) basis set rather than plane wave basis set.[2] This study showed more accurate RDF values compared to earlier works.

In an effort to access this problem we performed series of AIMD very near the complete basis set limit. Comparison with the results obtained with the common setup demonstrates the effects basis set completeness on the structural and dynamic properties of liquid water.

References

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COMP 88

Treatment and importance of conformations in COSMO-RS

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COSMO-RS is a novel predictive method for thermodynamic properties of fluids. COSMO-RS calculates the thermodynamic data from molecular surface polarities resulting from quantum chemical calculations of the individual compounds. The molecular interactions, i.e. electrostatics, hydrogen bonding and dispersion, are represented as functions of surface polarities. Using an efficient thermodynamic algorithm COSMO-RS converts the molecular polarity information into thermodynamic data of fluids, i.e. vapor pressures, activity coefficients, excess properties, etc.

Originally, COSMO-RS considered only one conformation per compound, but since 2001 the COSMOtherm implementation of COSMO-RS enables a thermodynamically consistent treatment of multiple conformations in COSMO-RS simulations. This is of importance, because some molecules may occupy considerably different conformations in polar and non-polar solvents, respectively. In this talk we will report on our experience regarding the importance of conformational treatment, demonstrate some example cases, and discuss a strategy how to find the relevant conformations of molecules in polar and non-polar solvents.

COMP 89

Computing properties determining the stability diagram of a miniprotein in dilute aqueous solution by full atomic detail computer simulation

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We report replica exchange molecular dynamics (REMD) simulations of the equilibrium folding/unfolding thermodynamics of an all atomic detail model the Trp-cage miniprotein in explicit solvent. Simulations of at least 100 ns length seem to be required to provide converged simulations results. Recognizing that isochores cover a large portion of the experimentally accessible P,T-range, we use data sampled from different isochores to gain information on (P,T) free energy landscape of model Trp-cage. A Hawley-type model representing the $\Delta G_u(P,T)$-landscape is found to describe free energy difference and their derivatives in reasonable agreement with simulated data. We find the derived stability diagram exhibit similar features than for globular proteins with increasing hydrostatic pressure destabilizing the native fold. The data seems to suggest a hill shaped stability diagram for model Trp-cage, although however, indicating rather large large unfolding temperatures and pressures, which might reflect a weakness of the employed forcefield model.The observed energy differences ΔE_u are roughly linearly temperature dependent and approach $\Delta E_u=0$ with decreasing temperature strongly suggest approaching the region of cold denaturation. In the denatured low temperature state, the native helical secondary structure elements are largely preserved, while the cages changes to an "open-clamp" configuration. A tighter packing of water around nonpolar sites, accompanied with an increasing solvent accessible surface area of the unfolded ensemble, seems to stabilize the the unfolded state at elevated pressures. Based on data sampled from the all-atom/explicit solvent simulations we will discuss possible schemes for this type REMD simulations which will allow faster equilibration and perhaps introduce a certain degree of scalability.

COMP 90

Convergence of folding free energy landscapes via application of enhanced sampling methods in a distributed computing environment

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The Replica Exchange Method (REM) and Simulated Tempering (ST) enhanced sampling algorithms have been widely used for sampling the conformational space of bimolecular systems. We have implemented a serial version of REM (SREM) and ST in the heterogeneous Folding@home distributed computing environment in order to calculate folding free energy landscapes. We have applied both algorithms to the 21 residue Fs peptide, and SREM to the 23

residue BBA5 protein. For each system, we find converged folding free energy landscapes for simulations started from near-native and fully unfolded states. To our knowledge, this is the first time anyone has computed a converged free energy landscape for a protein system like BBA5 at atomic resolution in explicit solvent. We give a detailed comparison of SREM and ST and find that they give equivalent results in reasonable agreement with experimental data. Such accuracy is made possible by the massive parallelism provided by Folding@home, which has allowed us to run approximately five thousand 100ns simulations for each system with each algorithm. Our extensive sampling shows that the AMBER03 force field gives better agreement with experimental results than previous versions of the force field.

COMP 91

Structure and dynamics of the Aβ21-30 peptide from the interplay of NMR experiments and molecular simulations

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While significant progress has been made in the interpretation of NMR observables for disordered protein systems, combining structural constraints often leads to an inadequate description of the ensemble diversity. By contrast molecular dynamics simulations of disordered systems has the opposite challenge where the simulated ensemble is directly observable but the accuracy has been difficult to assess due to uncertainties of the underlying empirical force fields. We present high precision structure and dynamics of the Aβ21-30 peptide by multiple NMR methods and molecular simulations using AMBER99-SB and TIP4P-Ew and a vanilla replica exchange sampling technique. Faithfully predicting the experimental ROESY cross peaks for partially structured peptides and natively unfolded proteins present a new challenge for simulations since the ROESY experiment singles out the sub-populations of close range interactions based on an observable with a steep power dependence on distance. We show that while there is significant improvement in new generation force fields, it now reveals imperfections in the convergence of the equilibrium ensemble to dramatically affect ROESY cross peak predictions.

COMP 92

Sampling sequences: Engineering protein structure and function with theoretical protein design

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Protein design opens new ways to probe the determinants of folding, to facilitate the study of proteins, and to arrive at novel molecules, materials and nanostructures. Recent theoretical methods for identifying the properties of amino acid sequences consistent with a desired structure and function will be discussed. Such methods address the structural complexity of proteins and their many possible amino acid sequences. Several computationally designed protein-based molecular systems will be presented that have been experimentally realized, including novel proteins tailored to accommodate nonbiological cofactors.

COMP 93

Pharmacophore fingerprints and application to target class modeling

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This presentation describes a GSK in-house pharmacophore fingerprint (pFP) toolkit and lead ID model building tool, pFPbitrank. Fundamental issues relating to pFP descriptors will be addressed in the talk- including lead hopping capacity- and a detailed description of pFPbitrank will be provided. pFPbitrank builds a model by identifying the 3- or 4-point pharmacophores (i.e. pFP bits) that preferentially discriminate a training set of active compounds from inactives. Randomization trials are conducted to assess the level of statistical signal amongst the most informative bits and to decide how many of these bits should comprise the pFP model. The pFPbitrank methodology will be applied to both single-target and multi-target activity data and the resulting models will be used to perform virtual screens; enrichment will be evaluated via ROC curves. Particular attention will be paid to a 7TM target class model, which has been used extensively at GSK to conduct 7TM-focused enhancement of the corporate screening collection via external compound acquisition and the design of large combinatorial libraries.

COMP 94

Applications of target class pharmacophore fingerprint modeling and multi-objective genetic algorithm optimization to large-scale combinatorial library design for corporate compound collection enhancement

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Corporate HTS collections in the pharmaceutical industry are a patchwork of sets of compounds that were either made/acquired for a particular molecular target or were designed to cover chemistry space as completely and efficiently as possible. The former approach produces compound sets of great “depth” – i.e. compounds densely clustered in particular chemotypes, such as those identified via focused virtual screening or pursued via lead optimization efforts. The latter approach produces compound sets of great “breadth” – i.e. that cover chemical space very thinly via large numbers of small chemotype clusters. Historically, little collection enhancement effort has been spent in between these extremes of depth and breadth. This presentation will discuss applications of target class pharmacophore fingerprint (pFP) modeling1 and multi-objective genetic algorithm (MoGa) optimization2 to the design of large combinatorial libraries that begin to fill this gap. Advantages of target class focused MoGa library design over pure compound collection enhancement-based MoGa library design will be presented in a detailed case study of a large 7TM-focused array design. The impact of target class focused MoGa library design on the GSK HTS collection will also be discussed.

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COMP 95

Confirm: Connecting fragments in receptor molecules

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A novel algorithm for the connecting of fragment molecules is presented and validated for a number of test systems. Within the CONFIRM (Connecting Fragments in Receptor Molecules) approach a pre-prepared library of bridges is searched to extract those which match a search criterion derived from known experimental or computational binding information about fragment molecules within a target binding site. The resulting bridge ‘hits' are then connected, in an automated fashion, to the fragments and docked into the target receptor. Docking poses are assessed in terms of root-mean-squared deviation from the known positions of the fragment molecules, as well as docking score should known inhibitors be available. The creation of the bridge library, the full details and novelty of the CONFIRM algorithm, and the general applicability of this approach within the field of fragment-based de novo drug design are discussed.

COMP 96

Fast and accurate method for flexible ligand superposition and shape-based screening

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The use of 3-dimensional molecular shapes has been demonstrated to be useful in comparing small molecules. We have developed a novel method that allows for rapid superposition and scoring of flexible molecules. The core algorithm is based on the alignment of a set of optimal atom triads followed by volume overlap scoring. The method can process approximately 1000 conformations per second on a modern computer. For flexible superposition we demonstrate on a large data set of crystal structures how accurate alignments can be obtained rapidly (less than one second per molecule) in an automated fashion. Next, we apply the method to virtual screening and show high enrichment rates across a broad range of targets and ligands. A one million compound database (100 conformations per compound) can be processed in approximately 15 minutes on a 100-processor cluster, making this method attractive for pre-screening large databases before downstream pharmacophore-based or docking screens.

COMP 97

Combining clique-detection, MOGUL and MOGA for pharmacophore generation

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Pharmacophore elucidation is a difficult problem involving the determination of the 3D description of interactions between a small molecule and a protein without knowledge of the protein structure. A Multi-Objective Genetic Algorithm (MOGA) has been developed with the aim of generating multiple feasible solutions (Cottrell et al, JCAMD,20,735-749,2006). However the solution space of potential pharmacophores is very large and increases with the number of molecules. In this work we have combined a clique-detection algorithm with the MOGA in order to limit the MOGA exploration to a feasible reason of solution space to increase both the efficiency and effectiveness of the program. In a further enhancement we bias the search towards reasonable conformers using MOGUL (Bruno et al., J. Chem. Inf. Comput. Sci., 44,2133-2144,2004). We report the results of these enhancements in terms of both speed and solution quality on datasets of up to ten molecules.

COMP 98

QSAR-based design of novel anti-HRV 2 agents

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The objectives of the present study were development of QSAR analysis of antiviral activity of a set of [(biphenyloxy)propyl]isoxazole derivatives that inhibit human rhinovirus 2 (HRV-2) replication and design of novel potential antiviral agents on the base of obtained results.

The QSAR approaches applied were simplex representation of molecular structure (SiRMS) and Lattice Model (LM). The relationship between antiviral activity against the HRV-2, cytotoxicity in HeLa cells, selectivity index and

structure of [(biphenyloxy)propyl]isoxazole derivatives has been studied systematically.

Quite adequate QSAR models have been obtained using PLS method and have been used as consequent virtual screening tool. Structural fragments with positive or negative influence on cytotoxicity as well as antiviral activity have been determined on the base of these models. This information has been used for directed drug design of novel antirhinoviral agents. High level of antiviral action and selectivity of several designed compounds has been verified experimentally.

COMP 99

Modeling the Fischer-Tropsch synthesis catalyzed on a Fe(1,0,0) surface

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The adsorption and reactions of organic fragments containing C1-C3 unit on the iron surface have been investigated employing periodic density functional theory with a plane-wave basis set and pseudopotentials, , as well as a slab model representing the p(2 × 2) Fe(100) surface topology. The calculations demonstrate that the most favorable Cn species on the Fe(100) surface are those containing the acetylenic carbon at the position (i.e., C-CH, C-CH2, and C-CH3). Both the hydrogenation reactions and C-C bond coupling that are responsible for the chain growth process have been explored; it is observed that the most likely mechanism of C-C bond propagation involves the recombination of adsorbed C and CH2/CH3 followed by the migratory insertion of hydrogen at the C atom. The subsequent -hydride or reductive elimination results respectively in the evolution of ethylene or ethane. The present computational study indicates that the production of ethane is preferred over ethylene, which agrees with the product selectivity observed in the industrial Fischer-Tropsch synthesis catalyzed by iron.

COMP 100

First-principles modeling of $Ba(Ce_{1-x},Pd_x)O_{3-x}$: Redox, structure, and chemistry

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Our recent experimental and theoretical work demonstrated the reversible incorporation of Pd into $BaCeO_3$ (BC), forming $Ba(Ce_{1-x},Pd_x)O_{3-x}$ (BCP). The Pd cations are observed to be highly active catalysts for oxidation. In the current work, we further examine BCP with first-principles density functional theory (DFT) calculations. The relaxed structures match closely with recent experimental scattering studies, and also provide a local picture of how the BC perovskite lattice accommodates Pd. Both stoichiometric and oxygen-deficient materials are considered, and structures with an O vacancy adjacent to each Pd are predicted to be favored. The oxidation state of Pd in each doped structure is investigated through a structural analysis, the results of which are supported by an orbital-resolved projected density of states. The HOMO and LUMO orbitals are discussed in detail. O-vacancy stabilization by Pd in BCP is explained through redox chemistry and lattice strain relief.

COMP 101

First-principles investigations of oxygen vacancies, copper adatoms, and their interactions on TiO_2 (110)

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Using density functional theory and Monte Carlo simulations, we explore the structural phase diagram for oxygen vacancies on the (110) surface of rutile TiO_2 over a broad range of temperature and surface chemical potential. These studies reveal a rich variety of structural motifs, including persistent oxygen pairing at high vacancy concentration, quasi-ordered 1D vacancy structures, and two distinct 2D long-range ordered phases at 25% and 50% vacancy concentration, respectively. With the goal of better understanding catalytic metal/support interactions, we introduce copper adatoms andinvestigate their binding, diffusion, and clustering properties. We compute the optimal binding sites and geometries for adsorbed copper monomers, dimers, and trimers, both on the stoichiometric surface and in the presence of oxygen vacancies. Furthermore, we identify pathways and barrier heights for copper adatom diffusion, and we find that oxygen vacancies play a crucial role, not only in diffusion, but also in copper clustering and island formation.

COMP 102

Identification of surface intermediates through the combined use of molecular modeling and vibrational spectroscopy

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Identifying the molecular structure of novel surface intermediates often poses a difficult challenge. Vibrational spectroscopic techniques such as infrared spectroscopy and high resolution electron energy loss spectroscopy often provide a high level of detail regarding adsorbate structure; however, interpretation of these results is, in many cases, less than clear. When used in combination with vibrational specroscopies, density functional theory calculations of surface intermediate structures can be used to identify the detailed molecular structure of adsorbates. Multiple examples of this approach, with applications to intermediates on both metal and metal oxide surfaces, will be discussed.

COMP 103

NO oxidation thermodynamics and kinetics at high O coverage on Pt(111)

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NO_x (x = 1 or 2) formed during fuel combustion is harmful to health and to the environment, and therefore there is interest in their effective removal from emissions. One of the most elementary and generally important reactions of this remediation is the catalytic oxidation of NO to NO_2 with O_2. Platinum is a common catalyst for this reaction, and evidence suggests the (111) face to be highly active for the catalysis. The thermodynamic driving force for NO oxidation is quite small, ΔH^{rxn} = –57 kJ/mol, so that high oxygen chemical potentials are necessary to promote NO_2 formation. Under these conditions the Pt(111) surface has a high oxygen coverage, and this coverage has a strong influence on both the thermodynamics and kinetics of various potential elementary reaction steps. In this work, we report DFT simulations of the oxygen-coverage-dependent rates of several steps in catalytic NO oxidation. The results illuminate the factors that limit the rate of catalytic oxidation and help guide the way to improved materials.

COMP 104

Density functional theory study of CO oxidation on Pd alloy surfaces

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Oxidation of carbon monoxide is important in many different applications including removing exhaust pollutants as well as preventing poisoning of fuel cells. We use density functional theory and periodic slabs to study the coadsorption and reaction of CO and O on Pd(111) and Pd alloy surfaces. For example, we find that the catalytic efficiency of Pd-Au bimetallic systems largely depends on the surface composition of Pd and Au. The addition of Au significantly improves the activity of Pd-Au bimetallic slab with Au-rich surface due to the dominant Au-induced ligand effect. This results in a lowering of the barrier by about a third compared the pure Pd(111) surface. In addition, our work on the nickel alloy will also be presented.

COMP 105

Investigating allosteric communication in protein systems with new conformational fluctuation covariance analysis methods

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The Ni(II)- and DNA-binding protein NikR is involved in nickel regulation in the bacterium Escherichia coli through transcriptional repression of the NikABCDE nickel permease. NikR is a homotetramer composed of 2 distinct domains. Fifty N-terminal amino acids of each chain contribute to two dimeric ribbon-helix-helix (RHH) domains, a known DNA-binding fold. Eighty-three C-terminal amino acids of each chain form a tetrameric interface composed of four βαββαβ domains. Each of these four domains form an ACT (aspartokinase, chorismate mutase, TyrA) fold, a domain class that typically binds small molecules and allosterically controls enzymatic activity. In this study we have utilized an equilibrium molecular dynamics (MD) simulation in order to explore the conformational dynamics of the NikR tetramer and determine important residue interactions within and between the RHH and ACT domains. Using two novel correlation measures based on fluctuations in atomic position and non-covalent bonding, we have defined a series of residue interrelationships that describe an allosteric communication pathway between the Ni(II) and DNA binding sites. In addition, we utilize a clustering algorithm to define groups of residues with similar correlation patterns for both types of correlation measure. Several of the residues identified by our analyses have been shown experimentally to be important for NikR function and may help coordinate the allosteric communication between the ACT and RHH domains. As an additional test of these new covariance methods, we have also examined cation-induced allosteric activation in the thrombin

system and compared the results with experimental data from structural and mutagenesis studies. These analysis tools will be made freely available for download from the Baker group web site (http://agave.wustl.edu/).

COMP 106

Brownian dynamics with hydrodynamic interactions: Application to lipid bilayers and biomembranes

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Abstract text not available.

COMP 107

Ensemble approaches yield new scaffolds and new binding sites

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In the multiple protein structure (MPS) method, a collection of protein conformations is used to represent the ensemble of states available to a flexible receptor. Each conformation is mapped with probe molecules and then combined to identify "consensus" regions where the requirements for complementing the receptor are consistent over many conformations. The probes in the consensus regions are translated into a pharmacophore model which describes the essential interactions but does not introduce any limits in the flexible areas. Experimental testing has shown that the technique is useful for pushing discovery into new chemical space with inhibitors of different sizes, shapes, chemical content and scaffolds. Applications to HIV-1 protease and the cancer target p53-MDM2 will be shown. In particular, inhibitors have been identified for a new pocket in HIV-1 protease; the inhibitors are half the molecular weight of existing therapies and may eventually yield new therapeutics with better pharmacokinetic properties.

COMP 108

Molecular simulations of macromolecular behavior in physiological conditions

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Attempting to model the behavior of biological macromolecules in physiological conditions presents a number of difficulties not encountered in modeling their behavior in vitro. This talk will describe our laboratory's efforts to tackle some of these issues and to develop a realistic simulation methodology, based on Brownian dynamics ideas, that is capable of modeling the dynamics of very large macromolecular systems. Example applications of our simulation methodology that will be discussed include: (a) synthesis of proteins in a dynamic model of a polyribosome, (b) capture of unfolded proteins by the chaperonin GroEL, and (c) immersion of both systems into a realistic model of the cytoplasm of Escherichia coli.

COMP 109

Adventures in computational chemistry

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This talk will describe some of the speaker's experiences and perspectives on computational chemistry. Projections for the near future will be suggested, particularly for computer-aided drug discovery.

Images and animations related to work in the speaker's group can be found at http://mccammon.ucsd.edu/

COMP 110

The generalized Born model: Past, present, future?

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The generalized Born (GB) approximation is a simple, but effective way to account for electrostatic effects of aqueous solvation. Since the model was first proposed more than 15 years ago, its accuracy has been gradually improving through the effort of many research groups. However, despite its well-documented successes, the model is still known to have serious flaws. Can it be

further improved at this stage? To answer this question, I will re-examine the physical foundations of the GB approximation to understand why (and when) it works in the first place. I will discuss the latest improvements and possible future directions.

COMP 111

Salt effects and explicit ions in continuum representations of water

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Continuum models usually represent bulk electrostatics effects using a Debye-Huckel-like screening parameter. However, biological processes occur in a broad range of salt concentrations, from highly diluted to nearly saturated conditions. Moreover, biomolecules interact with ions at specific locations, usually triggering/inhibiting functional responses; with counterions in the hydration shells; and with ions in the bulk phase, possibly at high concentrations (~0.5-5 M). A model is presented to introduce ions in a continuum representation of water. Ions are treated as part of the biomolecular system moving in a continuum background. For this, electrostatics and liquid-structure forces need be accounted for [JPC B 111, 227 (2007)]. First, transport, structural, statistical, and dynamic properties of ions in NaCl solution are studied in the 0.1-3 M range at 25 C. The ability of the model to describe structure and dynamics of counterions is then assessed in simple solutes. Finally, the model is used in dynamic simulations of calmodulin, where four Ca2+ ions and salt at physiological concentration are introduced. Results are compared with experiments and atomistic simulations.

COMP 112

Charge asymmetries in hydration of polar solutes

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We discuss our recent work on the solvation of polar molecules in water. The center of water's dipole moment is offset from its steric center. In common water

models, the Lennard-Jones center is nearer to the negatively charged oxygen than to the positively charged hydrogens. This asymmetry of water's charge sites leads to different hydration free energies of positive versus negative ions of the same size. We explored these hydration effects on some hypothetical neutral solutes, and two real solutes, with molecular dynamics simulations using several different water models. Like ions, polar solutes are solvated differently in water depending on the sign of the partial charges. Solutes having a large negative charge balancing diffuse positive charges are preferentially solvated relative to those having a large positive charge balancing diffuse negative charges. Asymmetries in hydration free energies can be as large as 10 kcal/mol for neutral benzene-sized solutes. These asymmetries are mainly enthalpic, arising primarily from first solvation shell water structure. Such effects are not readily captured by implicit solvent models, which respond symmetrically with respect to charge.

COMP 113

Molecular dynamics with generalized effective fragment potentials

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The Generalized Effective Fragment Potential (EFP) is a first principles method to evaluate intermolecular interaction in a fraction of the time required for traditional QM methods. EFP has been shown to achieve an accuracy between MP2 and CCSD(T) for gas phase and clusters. Molecular dynamics with the EFP potentials is used to model solvation and the

mixing of liquids. We investigate the ability of EFP to reproduce experiments and it's use as predictive method in the condensed phase.

COMP 114

Novel algorithms enabling practical microsecond-scale molecular dynamics simulations

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Although molecular dynamics (MD) simulations of biomolecular systems often run for days to months, many events of great scientific interest and pharmaceutical relevance occur on long timescales that have remained beyond reach. We recently introduced several algorithms that significantly accelerate classical MD simulations compared with current state-of-the-art codes. These algorithms include parallel decompositions that reduce interprocessor communication requirements and numerical techniques that maintain high accuracy even with single-precision computation. Using these methods, we have developed an MD code called Desmond which achieves unprecedented speed and parallel scalability for all-atom, explicit-solvent simulations, enabling simulation rates above a microsecond per week on commodity clusters. These simulation rates represent an order-of-magnitude performance improvement over several widely used MD codes, broadening the range of biological problems amenable to study by MD simulation.

COMP 115

Programming generalized Born models for a SIMD architecture

***Ingvar C Lagerstedt**, ClearSpeed Technology plc, 3110 Great Western Ct, Hunts Ground Road, Bristol BS34 8HP, United Kingdom, Fax: +44 117 317 2002, ingvar@clearspeed.com*

Many computations are today run in parallel to achieve good performance. Depending on the type of calculation different types of parallelization can be deployed. One choice is between using processors that work independently of each other and using more tightly coupled smaller processors in a SIMD (single instruction, multiple data) design.

The Generalized Born (GB) models 1, 2, and 5, together with the gas-phase GB 6 model from Amber 9, are used as an example of how to implement the non-bonded forces for a SIMD architecture using ClearSpeed's Advance board.

Relative to a Xeon processor an Advance board achieved up to 9X relative performance for the gas-phase model, and up to 5X for the GB models. The relative performance depends on several factors, including cutoffs and size of the problem. The model scales well over multiple SIMD-processor as long as there are at least 4 atoms per processor.

COMP 116

On the applicability of GPCR homology modeling to drug discovery: A comparison between crystal structure and in silico model of the β2 adrenergic receptor complexed with carazolol

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The publication of the crystal structure of the β2 adrenergic receptor proved that G protein-coupled receptors (GPCRs) share a structurally conserved rhodopsin-like 7TM core. Comparison of docking of carazolol to a homology model of the receptor with the corresponding crystal structure reveals a very similar mode of binding. Consistently with the crystallographic data, the ligand docks in the cavity formed by TM3, TM5, TM6, and TM7, with the aromatic carbazol moiety pointing toward TM5 – specifically toward Ser203(5.42), Ser204(5.43), and Ser207(5.46) – and the positively charged amino group pointing toward TM3 and TM7 – specifically toward D113(3.32) and N312(7.39). These results argue in favor of the applicability of homology modeling and in silico drug discovery to the field of GPCRs.

COMP 117

Decomposition of high-energy density materials using high-level coupled-cluster theory

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We used two new coupled-cluster methods to investigate key unimolecular decomposition pathways for the model high-energy materials nitromethane and nitroethane, as well as for 1,3,5-trinitrohexahydro-1,3,5-triazine (RDX). To properly describe reaction pathways, we used ΛCCSD(T), an extension of CCSD(T) that fixes bond breaking in spin-restricted reference. For a molecule such as RDX, the calculations are too costly using standard CC, so we used frozen natural orbital CC (FNO-CC), which systematically truncates the unoccupied space. We implemented analytical gradients for ΛCCSD(T) and FNO-CC, allowing us to optimize transition states and reaction pathways.

For nitromethane, our results support recent work suggesting that the rearrangement to methylnitrite is not energetically favorable. For nitroethane, our optimized transition states are similar to those calculated from DFT, but the relative energetics are different. We investigated the concerted decomposition of RDX, and found that the activation barrier was too high to play an important role.

COMP 118

Building aromatic oligoamide foldamers

***Jessica Amber Geer**, Zhiwei Liu, and Vojislava Pophristic, West Center of Computational Chemistry and Drug Design, University of the Sciences in Philadelphia, 600 South 43rd Street, Woodland Avenue, PA 19104, jgeer@usip.edu*

Over the past ten years, synthetic oligomers and the way that they fold in solution has been of great interest. The key in this study is to investigate compounds containing a benzene ring with a peptide bond which are the building blocks of synthetic oligomers that have medicinal functions. The torsions that occur around the backbone of these molecules control shape which consequently control their biological function. Presented here is a computational study of ortho-methoxy benzamide with side chains on the nitrogen atom of the molecule systematically grown. The torsional profiles of backbone dihedral angles are obtained using ab intio calculations. This approach helps us study the effects of side chain lengths on the flexibility of the backbone torsion, therefore on the conformational distribution of this type of synthetic oligomers. The information obtained in this study will enable us to develop new force field parameters that will accurately describe backbone torsion, taking into account the intramolecular environment. Consequently, molecular dynamic simulations with the modified force field will be used to study their specific biological funtion with a higher accuracy.

COMP 119

Salt effects on the conformational preferences of alanine peptides

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A molecular dynamics study of the effects of sodium perchlorate on the conformational preferences of a 21 residue alanine based peptide in water has been performed to understand the mechanisms of salt stabilization/destabilization effects on proteins. The peptide unfolding process in $NaClO_4$ was investigated and compared with the unfolding in NaCl solution and in pure water. The simulation in explicit water indicates that the peptide exists in alpha-helix conformations as well as in poly-proline conformations. The inclusion of $NaClO_4$ stabilizes the alpha helix conformations making the unfolding process unfavorable while the inclusion of NaCl destabilizes the folded states promoting a fast unfolding. A Kirkwood-Buff analysis and the preferential hydration and interaction parameters are also used to understand how sodium perchlorate affects the peptide stability.

COMP 120

Molecular dynamics of the RNA-binding domain of Influenza A NS1

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Molecular dynamics simulations of the RNA-binding domain of the Non-Structural protein (NS1) of influenza A virus, a homodimer, were performed for 10ns at 298K, as well as at higher temperatures. We focused our analysis on intermonomeric salt bridges that stabilize dimerization, centered on helices 2, which is the area involved in RNA binding. A salt bridge displaying instability was identified between Aspartate-29 of chain A and Arginine-46 of chain B. A "flipping" out and in of the two side-chains in this salt bridge occurred during the simulation. A recent paper describes a cavity in the surface of the side-chains of helix 2 of both monomers. We calculated the size of this cavity and found that the size and shape changes with time. Our results could have implications in computational screening studies searching for potential molecules blocking this salt bridge formation.

COMP 121

TAE augmented scoring functions: Application to enzymatic and nonenzymatic proteins

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In this study we attempt to build reliable scoring functions for 1296 curated protein-ligand complexes using a specific set of Atom Types, Transferable Atom Equivalent descriptors and QSAR based methods. Our initial results showed that partitioning enzyme-ligand complexes based on their function could result in models with strong correlation ($r2 > 0.7$) and lead to reliable prediction of their binding activities. We further the work by classifying protein binding sites with respect to atom types, in order to go beyond the limitations of Enzyme Nomenclature (NC-IUBMB) that was used in our previous study and derive reliable scoring functions for specific classes of both enzymatic and non-

enzymatic proteins. Both standard statistical model validation techniques and decoys are used to assess the reliability of the scoring functions.

COMP 122

A novel computational strategy for identifying peptides that bind pancreatic lipase

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Pancreatic lipase is an enzyme, secreted from the pancreas, which is involved in lipid metabolism. It is a diagnostic marker for pancreatitis and a promising target for therapeutic intervention. Recently, there has been considerable interest in developing peptide and peptidomimetic drugs. Given all of this, we developed a computational strategy to design peptides that bind pancreatic lipase. Our strategy employs rigid body docking, systematic residue substitutions, flexible side-chain modeling, and our own recently described scoring function. While more research is required, our preliminary results are very encouraging.

COMP 123

Hypothesis-driven computational biophysics: A possible explanation for trypsin-BPTI binding

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The trypsin S1 pocket appears designed to perfectly accommodate the P1 Lys of wild type (WT) bovine pancreatic trypsin inhibitor (BPTI). This explains the tight binding between WT BPTI and trypsin (-18.3 kcal/mol). Interestingly, hydrophobic, polar and even acidic P1 BPTI mutants also bind trypsin with a broad spectrum of affinities (-6 to -11 kcal/mol). Here, we hypothesize that the mutant P1 binding affinities can be explained in terms of (1) altered P1 contacts at the trypsin-BPTI interface and (2) mutant P1 side chains being forced into energetically unfavorable binding conformations. We quantitatively test this hypothesis using 10 trypsin-BPTI crystal structures, a molecular mechanics energy function, a side chain mutation algorithm, and a recently described empirical free energy function. We obtain good agreement between our binding affinity predictions and experiment, suggesting the validity of our hypothesis. We discuss the implications of our work for computational free energy prediction and the rational engineering of protein-protein interactions.

COMP 124

Theoretical study of the glutamate receptor ligand binding domain flexibility and conformational reorganization

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We present theoretical analysis of the conformational reorganization of the glutamate receptor ligand binding domain (the GluR2 S1S2 two-lobe protein). A range of atomistic and coarse grain computational methods (Molecular Dynamics simulations, Continuum electrostatics, Rigid Cluster Decomposition, Thermodynamic Integration and Umbrella Sampling) has been employed in this study to model the opening transition of this two-lobe protein, and compute the free energy associated with this transition. Our study indicates that electrostatic interactions play important role in stabilization of the protein in the closed conformation. In particular, modification of the E705 residue, centrally located in the ligand binding site, destabilizes the closed conformation allowing transition to the open conformation of the binding domain.

COMP 125

A new strategy to drug discovery: Systems-based drug discovery

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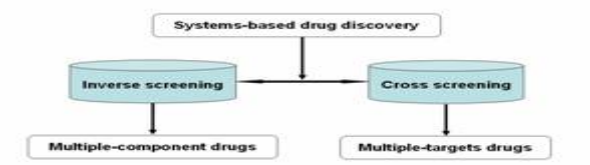
Modern drug discovery has been driven by the search for new molecular targeted therapeutics. Despite all recent technical innovations and advancement, the number of drugs produced by pharmaceutical companies remains at disappointingly low level. Recently, we have proposed a new drug discovery approach - systems-based drug discovery (SBDD), which is complementary to the target-based approach, to accelerate the identification of new leads with improved efficiency and reduced adverse effects. Systems-based drug discovery is a powerful drug discovery strategy that is based on the complexities of biological systems, using effective screening methods and software tools to discover systems-oriented drugs that take into account the robustness of biological systems to achieve the desired therapeutic goals. This new approach offers the prospect of a more efficient strategy to drug discovery, resulting in the generation of high-quality drugs with a better chance of success in clinical development.



COMP 126

Ab initio calculation of reaction between series of gilman cuprates and CH3I

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Gilman reagent can be used for selective creation of carbon-carbon bonds in Organic chemistry. We performed ab initio calculation at the level of B3LYP/LANL2DZ, 6-31G* to propose reasonable mechanism between Me2CuLi·LiX (X=I, SCH3, CN) and CH3I. The tetracoordinate, square-planar intermediate is found in the calculation, consist with the recent RI-NMR results. Based on our calculations, the reaction goes through the asymmetric, non-planar transition state to reach the long believed “copper(III) intermediate”. Then the intermediate overcomes a fairly low barrier to create C2H6. The schematic potential energy surface for this reaction illustrates the mechanism of new carbon-carbon bond formation.

COMP 127

Acute toxicity of polynitroaromatics and products of their biotransformation on *Vibrio fischeri*: 2-D QSAR- study

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The present study is devoted to the application of the Hierarchical Technology for Quantitative Structure - Activity Relationships (HiT QSAR) for the evaluation of the influence of such well known pollutants as polynitroaromatic compounds and products of their biotransformation on acute toxicity. 50% effective concentration (EC_{50}) of their reduction on bioluminescent bacteria *Vibrio fischeri* has been used to develop QSAR analysis based on simplex representation of molecular structure and it circular model. Based on obtained QSAR models the prediction

of toxicity for new nitroaromatic derivatives and determination of molecular fragments that promote and interfere with toxicity have been performed. Since obtained 2D QSAR PLS simplex models are quite satisfactory (R^2=0.95–0.96; Q^2=0.88–0.95; R^2_{test} =0.89–0.95), they can be and have been used as a powerful acute toxicity virtual screening tool for new (poly)nitroaromatics explosives and their metabolites. The results show that all these mentioned compounds are highly toxic pollutants.

COMP 128

Amyloidogenic intermediates: A computational study of the conversion of the β-sheet to α-sheet structure

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Many diseases and disorders are a result of aggregation and the progressive deposition of amyloid. Despite the fact that all of the amyloidogenic proteins vary significantly in their composition and structure, all of the mature fibrils are similar in that they consist of the cross β-sheet structure. One possible intermediate structure which could explain experimental observations is the α-pleated sheet, which has characteristic backbone dihedral (Φ,Ψ) angles in the and region. The structure of the α-pleated sheet was analyzed through geometry optimization and minimization of dipeptides. The optimization was performed using HF theory and a 6-31G* basis set. Dihedral constraints and hydrogen bond distance constraints were used in order to force the dipeptides into the α-pleated sheet structure, which was then minimized without constraints. The effect of implicit and explicit solvation was also analyzed.

COMP 129

Analysis of polarization effects in protein-water simulations

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Using the Atomic Multipole Optimized Energetics for Biomolecular Applications (AMOEBA) force field NPT ensemble simulations of protein Crambin with explicit water were performed at room temperature. The functional form of this force field uses permanent atomic multipoles through quadrupole and induced dipole to describe polarization. Two fixed charge force fields, namely CHARMM27 and OPLS-AA, were also considered.

We show that protein secondary structural properties have a better agreement with X-Ray experimental data when polarization is included. We also present evidence of an enhanced structural organization at the helical region indicating that nonadditive interactions also contribute to its stability. Local polarization effects were studied using two selected residues, serine and tyrosine. Measurement of dipole moment fluctuations provides consistent correlations with each hydration structure. This capacity to adapt to distinct environments is a characteristic signature of polarizable force fields, accenting their relevance when studying heterogeneous systems.

COMP 130

Analysis of torsional effects and ring flipping in heavily substituted oxazolidine rings

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Some compounds that contain the same 1,2-aminoalcohol moiety, such as in bestatin (a known protease inhibitor) exhibit anti-malarial activity. It is still unknown whether such activity is stereospecific. When preparing and separating individual stereoisomers, ^{1}H-NMR coupling constants can be used to distinguish between them. In this work, the oxazolidine derivatives of an active 1,2-aminoalcohol are used to examine structural differences between stereoisomers. Specifically, molecular orbital calculations are used to determine differences in dihedral angles between hydrogens that can potentially couple in the cis and trans isomers of the oxazolidine ring. In addition, the kinetic barrier for ring flipping in the trans isomer is calculated in order to determine whether such motion is likely to occur, thus changing the dihedral angle of interest.

COMP 131

Application of the fault-injection system algorithm for chips coated with silsesquioxanes

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In this work, the model R_T_S based on Catastrophe Theory is performed to describe the behavior of fault injection and the influence of fault injection on a system. The system was selected as a chip in a microelectronic device of

satellite, which is often failed to work by an error of the single-event upset (SEU). An FI_S algorithm based on the S attribute of the model R_T_S is designed to figure out the errors in the attacked system. Based on silsesquioxane derive from hydrolytic condensation of [(3-glycidoxy)propyl]trimethoxysilane (GPMS), vinyltrimethoxysilane (VMS) and [(3-methacryloxy)propyl]trimethoxysilane (MPMS), the nanofilm was coated on the surface of the chip to protect it from the fault. As the result of the testing with the FI_S algorithm, the errors in the coated chip decreased obviously. The protection mechanism was studied by the molecular dynamic simulation.

COMP 132

Artificial neural network prediction of metal hydride properties with experimental and/or computational data

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It has been shown previously that neural networks can accurately predict the percent weight of hydrogen storage for metal hydrides through DFT modeling properties. We have found that combining experimental data with the DFT calculation data (dipole moment, nuclear repulsion energy, Hartree-Fock total energy, and HOMOs and LUMOs) can dramatically improve predictability. This improvement over statistical methods is caused by the improved generalization procedures. The development of this technique will be discussed in our presentation.

COMP 133

Atomic level computational identification of ligand migration pathways between solvent and binding site in myoglobin

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Myoglobin is a globular protein involved in oxygen storage and transport. No consensus yet exists on the atomic level mechanism by which small non-polar ligands move between surrounding solvent and its binding site on the heme group buried inside the protein. This study uses multi-microsecond, room

temperature molecular dynamics simulations to complement experiment with a complete atomic-level picture of ligand migration. Specifically, we characterize: (i) Explicit full trajectories in which the CO ligand revesibly shuttles between the internal binding site and the solvent; and (ii) Pattern and structural origins of transient voids available for ligand migration. The computations are performed both in wild-type myoglobin and in V68F myoglobin mutant, which is experimentally known to slow ligand binding kinetics. The map of ligand visitation sites explicitly observed in the simulated trajectories closely follows the independent mapping of integrated free volume fluctuations.

COMP 134

Axial bonding in alkylcobalamins: DFT analysis of the inverse trans influence

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In B12 cofactors (generally referred to as cobalamins) containing a unique Co-C bond, central Co (III) atom is coordinated equatorially by the four nitrogen atoms from the corrin macrocycle and axially on the lower face by the 5,6-dimethylbenzimidazole (DBI) connected with corrin by the nucleotide side chain. In enzymes substituent on the upper face is the alkyl group being either methyl in methylcobalamin (MeCbl) or 5'-deoxyadenosyl in adenosylcobalamin (AdoCbl). Structural analysis of the existing X-ray data for different alkylcobalamins revealed correlation between the axial Co-C and Co-N bond lengths known as the inverse trans influence, reflected by the simultaneous elongation (or shortening) of both axial bond lengths.

Density functional theory (DFT) has been applied to study the origin of the inverse trans influence for several models of cobalamins with different electronic and steric properties of the alkyl group. It was shown that for certain systems inverse trans influence is observed, while normal trans influence for other. Steric and electronic properties of the axial substituents will be discussed in terms of molecular orbitals essential in interligand bonding.

COMP 135

Binding energies in dimers of N-methyl methyl carbamate, N-methyl S-methyl thiocarbamate, and N-methyl methyl dithiocarbamate

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Carbamates and thiocarbamates have been of interest lately in photoinitialized polymerization studies. In the current study we build upon that interest by investigating the relative binding energies in N-methyl methyl carbamate, N-methyl S-methyl thiocarbamate, and N-methyl methyl dithiocarbamate. Each dimer is formed with two identical hydrogen bonds. The hydrogen on the nitrogen of each monomer forms a hydrogen bond to either the oxygen of the carbonyl or the sulfur of the thiocarbonyl of the other monomer. Energies for the monomers are computed at the levels of SCF, DFT, and MP2. The density functionals used are the common B3LYP and O3LYP hybrid functionals. Correlation-consistent basis sets are employed and the basis-set-superposition errors are computed with the Counterpoise method. We gratefully acknowledge support from the NSF (MRI-0321397) and from the Mississippi College Catalysts.

COMP 136

Calculation of adsorption free energy for peptide interactions with a crystalline polylactide polymer surface

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The body's responses to implanted biomaterials are mediated by proteins that coat the material immediately upon implantation. A fundamental understanding of peptide-surface interactions is necessary if we are to control these responses. As an initial approach, we are using CHARMM to calculate the change in free energy for a nine-residue peptide over a crystalline polylactide surface as a function of its surface separation distance (SSD). Simulations are performed in two stages to overcome sampling problems: (1) Umbrella potentials are applied to the peptide to force sampling over the full range of SSD values, from which a nominal potential of mean force (PMF) vs. SSD relationship is calculated. (2) The negative of the PMF profile is then applied as a bias potential and replica-exchange molecular dynamics simulations are performed in order to sample conformational space of the peptide in addition to SSD. Adsorption free energy is then calculated from the trajectory.

COMP 137

Calculation of rotational barriers for two iminium cation stereoisomers

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Molecular orbital calculations are used to determine the relative size of three rotational barriers present in the interconversion of two iminium cation stereoisomers. Specifically, the lowest energy pathway for the interconversion is identified, as well as the relative stability of the two stereoisomers. This diphenyl-substituted iminium cation is the first intermediate in the aza-Cope rearrangement—Mannich cyclization, a cascade reaction that is used to form pyrrolidines. Since barriers for rotation affect control of product stereochemistry, the results are important in the design of iminium cation isomers that lead to a desired product stereochemistry.

COMP 138

Calculations of the acidities of n-butylbenzene protons in aqueous media under normal and supercritical conditions

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Ongoing studies in our laboratories are focused on the investigation of base catalyzed hydrogen-deuterium isotope exchange of organic compounds in superheated aqueous media. Thus, exposure of toluene to deuterium oxide at 400 °C and high pressure resulted in the rapid displacement of all organic hydrogen by deuterium. This reaction is of interest not only for the preparation of novel deuterium-labeled compounds, but also as model for C−H bond activation in aqueous media. It has been postulated that this exchange process occurs via carbanionic intermediates, but the deprotonation of hydrocarbons in aqueous media is difficult to accept due to the low acidities of these compounds. Quantum mechanical calculations to determine free energies of deprotonation and carbanion stabilities for n-butylbenzene were correlated with experimentally observed exchange behavior. Optimized geometries of n-butylbenzene and its carbanions served to calculate pK_as. We will show comparisons of pK_a values obtained by different calculation methods.

COMP 139

CCl_4 adsorption and dissociation on Si(111)- $\sqrt{3}$x$\sqrt{3}$- Ag surface from first principles

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In order to identify the reactivity of Si(111)- √3x√3- Ag surface, CCl_4 adsorption and dissociation reaction on this surface were studied by first principles calculations. All the possible adsorption sites and dissociation paths are studied. The results show CCl_4 adsorption on Si(111)- √3x√3- Ag surface is weak exothermic. The most stable adsorption structure is for CCl_4 sitting above the small Ag trimer, and the adsorption energy is about 0.2 eV. The interaction between CCl_4 and the surface Ag atoms is the overall interaction between the Ag d states and the non-bonding Cl p states. The dissociation reaction paths are also studied. The lowest reaction barrier is found to be 1 eV, showing that it would be impossible for CCl_4 to dissociate on Si(111)- √3x√3- Ag surface.

COMP 140

Combinatorial QSAR analysis of histone deacetylase inhibitors and QSAR-based virtual screening

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Histone deacetylase (HDAC) is a promising target for cancer therapy. Its inhibitors induce cell differentiation and/or cell apoptosis in malignant cells. We have applied a combinatorial QSAR modeling approach to 59 chemically diverse HDAC 1 inhibitors. MOE and MolConnZ based descriptors were combined with kNN and SVM approaches independently to achieve models with the highest external predictive power. Validated QSAR models were then used to mine large chemical libraries totaling over 9.5 million compounds. Concurrently, we applied fingerprint-based similarity search as well as pharmacophore search and compared results in terms of the receiver operating characteristic curve, the enrichment factor, and the robust initial enhancement. Virtual screening identified 47 consensus hits, including two reported HDAC inhibitors that were not present in the original data set. Computational hits were confirmed experimentally and two novel HDAC 1 inhibitors were identified with the best inhibitory activity (IC50) of ca.1 μM.

COMP 141

Comparing the thermodynamic stability of skipped diene radicals: A model for the peroxidation of arachidonic acid

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Lipid peroxidation is the oxidative modification of polyunsaturated fatty acids (PUFA) which leads to a hydroperoxide. Hydroperoxides that are derived from the lipid arachidonic acid serve as regulators of the enzymes involved in prostaglandin synthesis. Further oxidation of these hydroperoxides produces short chain aldehydes, such as 4-hydroxynonenal. The mechanism of lipid peroxidation is well established, yet it is difficult to predict the ratio of aldehydes produced. Since these aldehydes are markers of biological activity, quantitative prediction of product ratios is desirable. In this work, the relative thermodynamic stability of all possible cis-trans isomers of the 2,5-heptadiene and the 2,5-octadiene radicals is examined. In addition, relative stabilities are calculated for the corresponding peroxyl radicals. Results for these model systems are used to explain the experimentally observed ratio of products of peroxidation of arachidonic acid.

COMP 142

Comparison of density functionals and semiempirical methods for protonated creatinine

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Creatinine concentrations in blood and urine can be used to detect renal insufficiencies and muscle diseases. Our research team seeks to fabricate an ion-selective electrode (ISE) to measure creatinine with high selectivity and robustness, which current chemical sensors lack. To make such an ISE, a receptor that selectively binds protonated creatinine (creatininium) is required. Computational methods have proven valuable for the rational design of similar receptors, but systematic studies, which have not yet been reported, are necessary to understand the reliability of specific in silico methods for creatininium. Here we examine the accuracy of DFT (density functional theory) and WFT (wavefunction theory) calculations for the creatininium ion structure, validated against two experimental crystal structures. We tested seventeen local

and nonlocal density functionals, Hartree-Fock theory, four semiempirical molecular orbital methods of the neglect of differential overlap (NDO) type, and two tight-binding methods. We specify the best methods for protonated creatinine and discuss important hydrogen bonding interactions that are elucidated by our calculations.

COMP 143

Comparison of DFT and MP2-based electronic models in the estimation of relative conformational and tautomeric energies and torsional potentials of drug-like moieties

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Current computational resources have grown enormously over recent years, to the extent that quantum chemical methods are taking a place along side forcefields in the context of therapeutic program support at many pharmaceutical companies. Several efficient correlated methods are now available, among them LMP2, TRIM-MP2, RI-MP2, as well as several recently introduced DFT functionals that have been parameterized to take into account dispersive interactions. How does the overall efficiency of these methods compare in terms of time and accuracy? In this study, a comparison of several methods is performed over a range of tasks common to pharmaceutical molecular modeling.

COMP 144

Comparison of pose generation and virtual screening accuracy for several molecular docking programs

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Molecular docking programs are regularly used to position ligands within the protein binding pocket during lead optimization and to identify new leads through structure-based virtual screening. In an effort to assess the relative merits of six molecular docking programs (DOCK, FlexX, GLIDE, ICM-Dock, PhDock, Surflex), we evaluated them based on docking accuracy and hit enrichment rate. To investigate the ability of these docking tools to reproduce the X-ray pose of a ligand, docking studies were performed using 90 diverse, high-resolution protein-

ligand complexes. Virtual screening performance was assessed using the Directory of Useful Decoys (DUD), which is a dataset of 40 protein targets with associated lists of active and decoy compounds. Detailed analyses of the docking and virtual screening results will be presented.

COMP 145

Computational studies of gas phase and heterogeneous sulfur oxide reactions

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Sulfur oxides are important species in atmospheric chemistry, for example in the formation of acid rain. Heterogeneous chemistry, including reactions taking place on ice surfaces, plays a key role in reactions of sulfur oxides in the atmosphere since it is estimated that 50 percent of atmospheric sulfur dioxide reactions occur heterogeneously. In this work, we report the results of density functional theory studies of sulfur trioxide interacting with large water clusters of up to 39 water molecules in order to model the interaction with an ice surface. Results have been obtained at the B3LYP/6-31G(d) level of theory. Optimized geometries and vibrational frequencies have been computed for all structures, and minima on the potential energy surface as well as transition states for conversion to sulfuric acid have been located. The calculated binding energy of sulfur trioxide to the water clusters ranges from 13-20 kcal/mol and the activation barrier for conversion to sulfuric acid ranges from 3-6 kcal/mol. The results will be correlated with previous studies of the interaction of sulfur trioxide with small water clusters.

COMP 146

Structure-activity relationships in FF neuropeptide studied with computational simulations

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NPFF1 and NPFF2 are G protein-coupled receptors that respond to Neuropeptide FF (NPFF, a neurotransmitter involved in the intricate modulation of pain and opiate tolerance in mammals. To date, little information has been obtained as to the exact functions of NPFF receptors and the specific receptor-peptide interactions. Parallel tempering (replica-exchange) molecular dynamics (REMD) methodology is applied to NPFF and its most dominant conformational

states are predicted using hydrogen bonding, NMR and clustering analyses. Calculations were carried out for both implicit and explicit solvent models and for different FF variants, in order to monitor the most probable conformations for the peptide, as well as any interactions between FF and the receptors. Our results provide important insight into the diverse pharmacological functions of neuropeptide FF.

COMP 147

Computational study of the interaction of sulfoindocyanine dye Cy3 with single- and double-stranded DNA

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Many fluorescent studies of biologically relevant systems employ sulfoindocyanine dye Cy3 as a label. Energy transfer and distance correlations are usually studied using Förster theory. To interpret such studies correctly one has to be able to separate the effects of the environment from the effects of the dynamics of the system on the fluorescence of the dye. In this work, we report results of the simulation of Cy3 dye attached to single- , double- and mixed-DNA. Our results indicate that Cy3-DNA interaction consists predominantly of two modes: interaction of Cy3 indole rings with nearby bases and hydrogen bonding of Cy3 CH2OH side-group to accessible H bond acceptors of the backbone and bases. We will use our data to help interpret recent experiment form the Levitus' lab at Arizona State University.

COMP 148

Density functional study on the reductive elimination at an (NCN)Pt(IV) center

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The mechanism of reductive elimination reaction at an (NCN)Pt(IV) center was investigated by density functional theoretical study. The rate of sp3–sp3 coupling

and that of sp2–sp3 coupling were evaluated by calculating the Gibbs free energy of activation. Intermediate states were located, and the Gibbs free energy of activation and the stability of the equilibrium mixture were in good agreement with the experimental results.

COMP 149

Density functional theoretical study on the proton migration in radical cations of substituted cytosine:guanine pair

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Role of the guanine N1 imino proton in the migration and reaction of radical cations in cytosine:guanine pair was investigated with a density functional theoretical quantum mechanical method in combination with the Poisson-Boltzmann continuum solvation model. The effect of fluorine substitution at 5-position of cytosine was studied. The ease of proton transfer was monitored by calculating the Gibbs energy for both cytosine:guanine pair before and after proton transfer. Gas-phase basicity and pKa values of the substituted cytosine and cytosine:guanine pair were also calculated.

COMP 150

Density functional theory calculations on Ti and Li decoration in MOF-5

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We carried out the density functional theory calculations on the adsorption of Ti and Li atom at three sites (Zn-O3, Zn-O2, and Hex sites) in MOF-5. For the Ti, the binding energy at Hex site is largest and that at Zn-O3 is smallest. Through the analyses of orbitals and density of states plots, we found out that the Ti binding at Hex site is made from direct orbital overlap between the d orbital of Ti atom and the p orbital of carbon atoms of phenyl ring. Meanwhile, Li binds at Zn-O2 site most tightly with the smaller binding energy than the largest binding energy of Ti. It may be due to the different binding characteristics of Li atom, that

is the electrostatic interaction without the direct orbital overlap. We conclude that the binding site and characteristics are different depending on the metal.

COMP 151

Deterioration of popular DFT model chemistries for electron affinities

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Careful calibration has revealed that popular density functional theory (DFT) methods (B3LYP, BP86, etc.) can be combined with the modest DZP++ double-zeta basis set to reliably predict adiabatic electron affinities of a wide variety of molecules [Chem. Rev., **102**, 213-282 (2002)]. This procedure has become one of the most popular prescriptions for the theoretical determination of electron affinities because DFT has rather modest computational demands and results are typically within 0.1-0.2 eV of experimental values. Recently, several groups have identified a variety of molecules for which this popular DFT approach dramatically overestimates the electron affinity. Here, we attempt to identify a common thread connecting these discrepancies in order to determine when this popular and well-established procedure is likely to fail. When feasiable, CCSD(T) adiabatic electron affinities are computed to provide reliable benchmark values.

COMP 152

Development of a QSPR method for the prediction of chemicals explosibility

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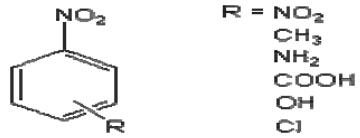
A step towards more stringent procedures for the risk control of chemicals has arisen with the recent promotion of European regulatory framework GHS and REACH. If quantitative structure property relationships (QSPR) methods have been up to now mainly devoted to screening toxic properties, their use to establish relationships between the explosibility of dangerous substances and structural, energetic or physicochemical descriptors could led to new perspectives. This contribution focused on the case of a series of nitroaromatic compounds. In particular, correlations have been observed between molecular descriptors, mostly based on ab initio quantum chemical calculations, and thermal stability taken as a macroscopic property related to explosibility.

Therefore, a promising multivariable model has been established (R^2=0.9) to predict the decomposition enthalpy. Moreover, the decomposition process of such compounds has been calculated. Finally the influence of substituents on the competition between the two major channels of decomposition has been examined.



COMP 153

Direct dynamics study of [1,3]-sigmatropic shift of bicyclo[3.2.0]hept-2-ene to norbornene

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Non-statistical behavior is studied for the [1,3]-sigmatropic shift of bicyclo[3.2.0]hept-2-ene to norbornene. Previous studies by Carpenter with AM1 and PM3 establish non-statistical behavior, but involve diradical minima, whereas, this reaction has a flat potential energy surface and no diradical minima at the B3LYP/6-31G* level. Quasiclassical direct dynamics simulations have been performed on the B3LYP/6-31G* surface. Among all the trajectories initiated by TS normal mode sampling at 573 K, there exist numerous direct trajectories which have non-statistical behavior. Each trajectory starts from the TS region and goes forward to product and backward to reactant. Initial results show that out of 72 trajectories, 34 are effective, meaning the trajectory connects reactant, TS and product. The direct trajectories have very short lifetimes of ~ 400 fs, while statistical trajectories have lifetimes of > 600 fs.

COMP 154

Docking based pharmacophore modeling of combined AT1-PPAR gamma ligands

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The metabolic syndrome is a common precursor to various cardiovascular diseases and type-II diabetes and is characterized by a variety of symptoms including insulin resistance, dyslipidemia and increased blood pressure. Drugs that activate peroxisome proliferators activated receptor (PPARγ) have been proven effective in prevention and treatment of insulin resistance and type-II diabetes. The discovery of unique antihypertensive angiotensin II type I receptor (AT1R) blockers (ARBs), telmisartan and irbesartan, as partial agonist of PPARγ, has provided us with a novel approach for developing new generation ARBs with benificial metabolic effects. A 3D pharmacophore model was developed using the docked poses of telmisartan and irbesartan in the X-ray crystal structure of PPARγ (PDB ID: 2PRG). Superimposition of the binding poses of telmisartan in AT1R and PPARγ were carried out to gain insight into the dual binding capability of this ligand as well as its interaction within both receptors. The developed pharmacophore model could be used to design new leads possessing the desired polypharmacological profile and improved activity in comparision to existing compounds.

COMP 155

Doublet-quartet gaps of substituted carbynes

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Carbynes are monovalent carbon molecules with three non-bonding electrons and are found in interstellar space where they may play a role in the formation of larger organic molecules. While a number of experimental and theoretical studies have appeared on a few simple carbynes, there have been few efforts to understand factors influencing the doublet-quartet gap of these species. We present a systematic study of the doublet-quartet splittings in a series of substituted carbynes, CX (X = NH_2, OCH_3, F, $N(CH_3)_2$, Cl, Br, CH_3, H, CF_3, CN, NO_2). Density functional and multi-reference molecular orbital calculations were combined with natural bond orbital (NBO) analysis to identify the primary factors that influence the doublet-quartet gap. Each carbyne examined has a doublet ground state and the trend in the doublet-quartet gaps correlates well with the Taft σ_R substituent constants and with the magnitude of interaction between the subtituent and the carbyne center as determined by NBO second order perturbation energy analysis.

COMP 156

Effects of salt concentration on the HIV Rev-RRE complex using molecular dynamics simulations

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Recognition of the rev responsive element (RRE) by the rev protein is critical to the human immunodeficiency virus (HIV) life cycle, allowing unspliced and partially spliced viral RNA to exit the nucleus. NMR studies have shown increasing salt concentration affects side-chain dynamics. Two NMR structures of the complex were simulated under four different NaCl concentrations with explicit water. Each system (~72,000 atoms) was equilibrated for a minimum of 10.0 ns before statistics were calculated on every 1.0 ps snapshot of a 10.0 ns production run. All systems were converged after 10.0 ns as shown by RMSD plots, and monitoring of structural properties. Hydrogen bonding and arginine side-chain dynamics were examined in all systems. Preliminary analysis suggests agreement with both structural experiments and bioassays. Interestingly, major structural changes do not occur with increasing salt presence. Current analysis focuses on an examination of electrostatics in the presence of increasing salt concentration.

COMP 157

WITHDRAWN

COMP 158

Enhanced stacking interactions between nucleic acid base pairs upon hydrogenation

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We have explored the effect of base hydrogenation on the stacking interactions between nucleic acids base pairs. We show that the hydrogenation at the N3 position of guanine in a CG step leads to enhanced stacking interactions and a decrease in the rise parameter. Our calculations were performed with the B3LYP hybrid functional and 3-21+G** basis set. We expect the trend of increased stacking, inolving hydrogenated radicals, to persist with larger basis sets.

COMP 159

Enthalpies of formation of TNT derivatives by homodesmotic reactions

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TNT (2,4,6-trinitrotoluene) is a well known explosive. We focus on the computation of the standard enthalpy of formation of TNT and similar aromatic compounds by homodesmotic reactions. The enthalpy of all of the reactants and products in each homodesmotic equation is computed by various levels of theory and basis sets. From the resulting enthalpy of reaction, the desired enthalpy of formation is determined by use of reference values for all other systems in the reaction. Several different homodesmotic equations are used for each TNT derivative. Results are consistent with the exception of those obtained from reactions that utilize the experimental enthalpy value for 3-nitroaniline. Better convergence is obtained with our theoretical value for this system, leading us to believe that the reference value is incorrect. We gratefully acknowledge support from the NSF (MRI-0321397) and from the Mississippi College Catalysts.

COMP 160

Establishing a balance between prediction accuracy and applicability domain of QSAR models

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An approach for excluding outliers from the external evaluation set (EES) has been developed. Applicability domain (AD) of QSAR models is defined by a threshold distance between a compound in EES and its nearest neighbor of the modeling set (MS): $D_{thresh}=D_{av}+Z*\sigma$, where D_{av} and σ are the average and standard deviation of distances between nearest neighbors in the MS, and Z is a user-specified cutoff value. In this procedure, Z is increased from zero to the value for which correlation coefficient R^2 between predicted and observed activities of compounds of the EES within the AD decreases below a predefined value, or all compounds of the EES are included in the AD. The maximum acceptable Z defines the final AD. Compounds within this AD are used for external validation. We demonstrate that our approach gives a realistic estimate of predictive power of QSAR models for *T. pyroformis* and Fathead Minnow aquatic toxicity datasets.

COMP 161

Evaluation of density functionals, semiempirical methods, SCC-DFTB and molecular mechanics force fields for prolyl-leucyl-glycinamide (PLG) analogs designed as dopamine D2 receptor modulators

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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 evaluate the suitability of a wide variety of molecular mechanics (MM) force fields, semiempirical neglect of differential overlap (NDO) methods, self-consistent-charge density-functional tight-binding (SCC-DFTB) methods, density functional theory (DFT) levels, and Hartree-Fock theory for a family of novel PLG analogs designed in our laboratory, using crystal structures as benchmarks. We also present benchmark databases, obtained by coupled-cluster calculations with single, double and quasiperturbative triple (CCSD(T)) excitations, of bond distances and partial charges for a representative fragment common to our PLG analogs, and use these to test a selection of popular density functionals. We specify the best methods for this class of PLG analogs, and we recommend the M05-2X hybrid meta GGA functional to obtain accurate geometric parameters on these and similar peptidomimetic compounds.

COMP 162

Exploring pharmacophore generation programs

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The identification of structural features responsible for ligand-receptor binding is an important part of drug discovery process. When the receptor structure is unknown, such information is typically derived from SAR data available for relevant ligand sets. With such specific pharmacophore features, or pharmacophore model in hands, potential leads can be retrieved from structural databases to assist the lead optimization process. However, alignment of multiple ligands based on their common pharmacophoric features can be tricky and challenging. It not only depends on the alignment algorithms used, but also ligand training set, target of interest, coverage of conformational space, as well as understanding of the SAR across chemical series. In this study, we have

compared a variety of pharmacophore generation programs including Catalyst and PHASE for their ability to identify “true” pharmacophore models observed in X-ray protein-ligand complexes. Six training sets were analyzed to cover different protein families including cyclin dependent kinase 2 (CDK2), thrombin, dihydrofolate reductase (DHFR), HIV reverse transcriptase (HIV-RT), thermolysin and β-secretase (BACE1). Also, several conformational sampling methods (OMEGA, MacroModel, Catalyst Best, Catalyst Fast, and CAESAR) were applied to assess the conformational searching impact on pharmacophore model generation. This study describes results obtained with those popular software tools and offers practical observations toward automatic pharmacophore generation with existing methods.

COMP 163

Fast folding of peptides and small proteins using the “temperature intervals with global energy reassignment” (TIGER) method

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A new advanced sampling method for molecular simulation based on temperature intervals with global energy reassignment (TIGER) has been developed, validated, and applied to fold peptides and small proteins. The validity of this method has been demonstrated by sampling the conformation space of a butane molecule in vacuum and alanine dipeptide in TIP3P water. The efficiency of TIGER and replica exchange molecular dynamics (REMD) methods are being compared by observing the computational cost for folding a model peptide {(AAQAA)3} in TIP3P water. The TIGER method is also being applied to fold two small proteins (Trp-cage and chignolin) in TIP3P water. The folding mechanisms of the two molecules predicted by the TIGER simulations will be presented and its structural parameters compared with NMR. The simulation results thus far indicate that the TIGER method can greatly increase sampling efficiency and decrease the number of CPUs required to adequately sample a system compared to REMD, thus providing an accelerated method for protein folding simulations in explicit solvent.

COMP 164

Finding the right path: Computational approach to DNA base eversion

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8-oxoguanine (8OG) is the most prevalent form of DNA damage, caused by reactive oxygen species. Formamidopyrimidine glycosylase (Fpg) is the enzyme in E. coli responsible for recognition and repair of 8OG opposite a cytosine base. This project's goal is to characterize how Fpg locates and recognizes the 8OG lesion. The driving hypothesis is that innate structural differences between 8OG and an unlesioned guanine aid in recognition by Fpg. Molecular dynamics simulations of lesioned and unlesioned duplexes have been performed in explicit and implicit solvent using AMBER9. Changes in the backbone dihedral angles of the lesion base show a significant conformational switch between G and 8OG that correlates with an increase in the distance between the 8OG base and the phosphate backbone. Simulations show the lesioned base is held to a more localized position than its unlesioned counterpart, suggesting initial destabilization of the lesion by the Fpg enzyme promotes its catalytic activity.

COMP 165

FITTED: A docking-based virtual screening tool for flexible and complex systems

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FITTED is a docking-based virtual screening tool for medicinal chemists. By accounting for the protein flexibility and displaceable water molecules increases in the accuracy of docking results are seen. The most current developments will be discussed as well as new additions such as docking of covalent inhibitors. A docking comparative study will also be presented comparing FITTED against some of the most popular docking methods. Along with the comparative study some of the current biases in docking will be discussed and examined.

COMP 166

Formic acid tetramer: Hydrogen-bonding vs. π-stacking

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The formic acid tetramer exhibits an interesting competition between hydrogen bonding and π-stacking. Twelve low-energy structures have been identified [*J. Chem. Phys*. , **124**, 224313 (2006)], and there is only a very small energy difference between the most stable hydrogen bonded structures and the most

stable π-stacked structures. This system presents a unique challenge for the multicentered QM:QM method for clusters developed by our group [*Mol. Phys* , **103**, 309-315 (2005)] because the cooperative effects in hydrogen bonded networks tend to be quite different than those associated with π-stacking. In this work, the structures are first re-optimized at the MP2 level with relatively large basis sets using analytic MC ONIOM gradients. Then, a series of single point MC ONIOM energies are calculated to estimate the CCSD(T) complete basis set limit relative energies of the most stable structures of the formic acid tetramer.

COMP 167

HiT QSAR analysis of chiral AchE inhibitors

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Hierarchical QSAR technology (HiT QSAR) has been used for consensus QSAR analysis of AchE inhibition by chiral organophosphates. Different chiral organophosphates represented by theirs (R)-, (S)-isomers as well as racemic mixtures have been used as objects of investigation.

The aims of investigation were: application and tuning of HiT QSAR for description and explanation of AchE inhibition by chiral organophosphates according to theirs structure and detailed analysis of behaviour of chiral center as well as different substituents in it for racemates and (R) and (S) enantiomers.

Successful 3D QSAR PLS models have been obtained using simplex and field descriptors. Statistic characteristics for 2D QSAR simplex models with additional consideration of Phosphorus chirality are also very satisfactory. In most cases (R) isomers are less active than (S) and racemate. It was shown that atom individuality that also describes chiral moieties of Phosphorus play a very important role in AchE inhibition.

COMP 168

Homology modeling: Studying conformationally flexible loops near ligand binding sites

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The modeling of loops is one of the great challenges in protein structure modeling. This is especially true in cases where conformational change of a loop occurs upon ligand binding. Several examples are known in the literature where the size and shape of the binding pocket are significantly altered between the Apo protein structure compared to the ligand bound structure or between binding modes of structurally diverse ligands. In this study, we examine a set of therapeutically relevant protein structures that exhibit a significant conformational change of loops which participate in ligand binding. The impact of correct loop conformation in terms of generating accurate binding models is discussed, as well as the benefits of using an ensemble of loops to identify the best loop conformation.

COMP 169

How do SET-domain protein lysine methyltransferases achieve the methylation state specificity? An ab initio QM/MM molecular dynamics study

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Histone lysine methylation plays a pivotal role in regulating chromatin structure and gene expression. The distinct methylation states give rise to different functional consequences. We have carried out ab initio quantum mechanical/molecular mechanical (QM/MM) molecular dynamics simulations to elucidate how such a remarkable product specificity is achieved. We found that the methylation state specificity is mainly controlled by the methyl-transfer reaction step.

COMP 170

Identification of inhibitors for blocking S100B-P53 interaction using virtual database screening

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Virtual database screening was applied to identify small molecule inhibitors of the calcium-dependent S100B-p53 tumor suppressor interaction. Docking calculations of 60,000 compounds were performed individually targeting two binding grooves on calcium bound S100B, one known to interact directly with p53 and the other pentamidine. Fluorescence polarization competition assay (FPCA) was employed to validate the in silico selected hits and 34 active compounds were identified. Among them, ten have K_D values < 10.0 μM. Comparison of the activities of compounds selected via the *in silico* screening and compounds in a library of diverse lead-like compounds indicates that database screening using the program DOCK is able to provide more active compounds than experimental high throughput screening alone.

COMP 171

Interplay of π-stacking and hydrogen bonding: An *ab intio* study of diacetylene/water and cyanogen/water clusters

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Recently our group identified the linear diacetylene (HCCCCH) and cyanogen (NCCN) molecules as new prototypes for delocalized π-type interactions [PCCP, **9**, 1550-1558 (2007)]. Unlike acetylene, the π electron system in cyanogen and diacetylene is substantially delocalized which causes their dimers to closely mimic the interactions found in the benzene dimer. In this work, *ab initio* electronic structure computations have been used to examine the structures and energetics of small clusters composed of diacetylene, cyanogen and water molecules. Results for these clusters are compared to work that has already been reported in the literature for acetylene/water and benzene/water complexes in order to gain some insight into changes that occur as heteroatoms are introduced and as the π electron system delocalizes.

COMP 172

Iterative refinement of parameters for computer simulation of peptides and proteins

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An iterative protocol was developed for the refinement of energetic parameters used in computer simulations of peptides and proteins. Two small peptides of known structure, “trp-cage” and “trpzip2,” were simulated with an implicit solvent model based on screened Coulomb potentials. The energy landscapes were explored and modified in an iterative attempt to simultaneously distinguish each of the two native conformations from the many misfolded alternatives. The refinement protocol, folding simulations, and the functional form of the energy function will be discussed.

COMP 173

Kinetic aspects of the oxygenation reaction mechanism in COX-1

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Polyunsaturated fatty acids (PUFAs) exhibit very different rates of oxygenation in the cyclooxygenase (COX) active site of prostaglandin endoperoxide H synthase-1. The first and rate-determining step of the proposed oxygenation mechanism is the abstraction of one of the bis-allylic *pro*-S hydrogens on the substrate by the Tyrosyl-385 radical. In this work, we compare the relative activation barriers for the rate determining step among four PUFAs at the B3LYP/6-31G level of theory. The crystal structures of arachidonic, eicosapentaenoic, linoleic, and dihomo-γ-linolenic acids in the COX-1 active site are used to determine the reactant energy. A simple model of the abstraction process is used as a template to approximate the transition state energy in each of the PUFAs. Results of the calculations provide insight into the reasons why arachidonic acid is the preferred substrate for COX-1.

COMP 174

Kirkwood-Buff derived force fields for mixtures of thiols in water

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A force field based on the Kirkwood-Buff theory of solutions will be presented for mixtures of sulfur containing side-chain analogs of amino acids in water. The force field values will be compared with existing united-atom (GROMOS96) and all-atom (Amber, OPLS) parameters.

COMP 175

Mechanism of hydrogen production by [Fe-Fe]-hydrogenase in DdH and CpI: A QM/MM study

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[Fe-Fe]-hydrogenases are a class of metalloenzymes that catalyze the production of H_2 from two protons and two electrons. Crystal structures have been solved for [Fe-Fe]-hydrogenases found in two species: the anaerobic soil microorganism Clostridium pasteurianum (CpI) and from the sulfate-reducing microorganism Desulfovibrio desulfuricans (DdH). While the active sites in the structures from CpI and DdH are very similar, it has been inferred from the manner in which the crystals were obtained that the CpI structure represents an oxidized state and that the DdH structure represents either a reduced state or a mixture of anaerobically oxidized and reduced states. We employed density functional theory (DFT) within a QM/MM method to investigate the mechanism of hydrogen production in CpI and DdH and its dependence on the protein environment of the active sites. We included in the QM region the Fe_2S_2 and the Fe_4S_4 subclusters as well as the cysteine residue than links them; we showed previously the importance of including the Fe_4S_4 subcluster. The rest of the protein was modeled by the OPLS2001 forcefield. Preliminary results for the oxidized active site of CpI show that optimal geometries obtained using QM/MM are in better agreement with the crystal structure than those obtained from DFT optimizations of the isolated active site.

COMP 176

Mixed quantum/classical studies of Trypanosoma Cruzi's Trans-sialidase

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Chagas' disease is an incurable and lethal chronic disease prevalent in Central and South America and is transmitted by insects carrying the infectious protozoan, Trypanosoma Cruzi. This pathogen is responsible for the devastating effects of Chagas' disease and, as such, is the target for possible therapies. Instrumental to T. Cruzi's survival is its Trans-sialidase enzyme. Trans-sialidase removes sialic groups from sugar chains emanating from the host cells' membranes and reattaches them to the membrane of the protozoan. Because sialic groups are instrumental in cell recognition, T.Cruzi is effectively able to evade immune response. Since Trans-sialidase is not expressed in humans, it presents a good target for inhibition. Utilizing mixed QM/MM methodologies, a reaction simulation is carried out to elucidate the mechanism of the reaction at the active site of this enzyme. By determining the reaction mechanism, transition states can be isolated and inhibitors more effectively designed.

COMP 177

Molecular dynamics studies of human immunodeficiency virus RSG-1.2-RRE recognition

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Recognition of the human immunodeficiency virus (HIV) Rev responsive element (RRE) RNA by the Rev protein is an essential step in the viral life cycle. A synthetic peptide, RSG-1.2, recognizes RRE with greater affinity and specificity than the native Rev peptide. Simulations of the RSG-1.2-RRE complex have been performed under four different salt concentrations in the presence of explicit solvent (~72,000-79,000 total atoms) with AMBER 8.0. Each trajectory was equilibrated for 10.0 ns prior to collection of statistics for an additional 10.0 ns. Intermolecular hydrogen bonding has been extensively analyzed, and arginine residues in RSG-1.2 have been specifically evaluated. Simulations have shown that RSG-1.2 changes conformation with increasing salt concentration, appearing quite malleable to the electrostatic environment. Hydrogen bonding analysis also indicates that RRE effectively clamps down on the synthetic peptide, perhaps explaining the ability of RSG-1.2 to bind RRE tighter than the native Rev peptide.

COMP 178

Molecular modeling of nonpeptidic agonists of glucagon-like peptide 1 (GLP-1) receptors

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Type 2 diabetes mellitus is a major and growing health problem throughout the world. The high prevalence of diabetes is combined with the associated increased mortality and morbidity, primarily as a result of macrovascular disease and microvascular longterm complications. Two orally-available small molecules (S4P and Boc5) with GLP1-like activity have been reported recently, which may represent a new class of therapies for type 2 diabetes and other metabolic disorders. In this study we use molecular modeling techniques to investigate the structure characteristics of these nonpeptidic GLP-1R agonists through molecular dynamics simulation and quantum chemical calculation. Our study will be of help to identify key features of these small molecules and may prompt the exploration of orally available GLP-1R agonists. This work is supported by grant 2 G12 RR003048 from the RCMI Program, Division of Research Infrastructure, National Center for Research Resources, NIH.

COMP 179

Novel derivatives of bicyclo[2.2.2]octane and their strain energies

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Recently, a new derivative of bicyclo[2.2.2]octane was synthesized at Mississippi College. To our knowledge, this ester derivative, 8,8-dimethyl-2,6-dioxa-bicyclo[2.2.2]octane-3,5-dione, has not been previously reported in the chemical literature. In the current study, we investigate the conventional strain energy of this system and other related derivatives of the parent compound to see how substitutions in and on the ring affect the strain. For each compound, the conventional strain energy is determined within the isodesmic, homodesmotic, and hyperhomodesmotic models. Optimum equilibrium geometries, harmonic vibrational frequencies, and corresponding electronic energies are computed for all pertinent molecular systems using SCF theory, second-order perturbation theory (MP2), and density functional theory. The DFT functional employed is Becke's three-parameter hybrid functional using the LYP correlation functional. Two correlation consistent basis sets are employed: cc-pVDZ and cc-pVTZ. We gratefully acknowledge support from the NSF (MRI-0321397) and from the Mississippi College Catalysts.

COMP 180

ONIOM investigation of nucleotide selectivity in phosphodiesterases 3, 4, and 5

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The cyclic nucleotide phosphodiesterases (PDEs) are drug-targeted enzymes that down regulate cyclic nucleotide concentrations in the cell by catalyzing the hydrolysis of the O3'-phosphorous bond, yielding the non-cyclic nucleotides. Selectivity for cAMP vs cGMP (cyclic 3',5'-adenosine/-guanosine monophosphate) as the favored substrate is primarily attributed to the orientation of a conserved glutamine residue which binds to the adenine/guanine ring. We use ONIOM hybrid quantum methods to accurately describe substrate binding within the catalytic sites of the cAMP-specific PDE4, the cGMP-specific PDE5, and the cGMP-inhibited, dual-specific PDE3 in order to understand subtle aspects of substrate selectivity. Our results are consistent with the PDE3's kinetic specificity for cAMP hydrolysis and the known competitive inhibition of PDE3 by cGMP.

COMP 181

Predicting ligand binding affinity to the rat α4β2 neuronal nicotinic receptor: Lessons from bayesian categorization modeling

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We have used the bayesian categorization method to derive predictive models for ligand binding to rat α4β2 Neuronal Nicotinic Receptors (NNR). Training sets were derived from a total of 2636 compounds representing a diverse chemical space. An accuracy of 0.85 was obtained for our best model, with a positive predicted value of 0.89, and a negative predictive value of 0.82, as determined from a test set. Good and bad structural features related to ligand binding at the rat α4β2 NNR were also derived. When the frequency of such structural characteristics in a large data set of nicotinic ligands was calculated, we found that 72% of good features appeared in molecules with binding affinity <=500 nM, whereas 39% of bad features appeared in molecules with binding affinity > 500

nM. We also found that there is no correlation between the similarity of nicotinic ligands to nicotine and their binding affinity to rat α4β2 NNR. These findings can aid in the rational design of ligands with therapeutic potential in the NNR landscape.

COMP 182

QSPR predictions of an aqueous solubility for military compounds using SiRMS

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The objective of this study was development of new QSPR equations which will accurately predict aqueous solubility for compounds of US Army interest (explosives and their metabolites) using SiRMS approach.

Training set consists of 135 compounds and test set totally includes 156 compounds. The set of well-fitted, robust and predictive (internally and externally) QSPR models (R^2 = 0.90 – 0.95; Q^2 = 0.85 – 0.91; R^2_{test} = 0.85 – 0.87) has been obtained. External validation using four different test sets also reflects high level of predictivity (R^2_{test1} = 0.7 – 0.87; R^2_{test2} = 0.82 – 0.88; R^2_{test3} = 0.75 – 0.76; R^2_{test4} = 0.89 – 0.91). These models were united in consensus model – powerful solubility virtual screening tool.

Comparison of predicted values for test set compounds by our SiRMS results with SPARC and EPI SuiteTM techniques indicates significant improvement of predictions accuracy. Virtual screening of solubility for military compounds has been carried out using consensus model.

COMP 183

Quantitative method for computational investigations of enzyme and antibody catalysis: The Kemp Elimination

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Nature's proficient catalysts are responsible for a great variety of difficult chemical transformations that occur under mild conditions with remarkable efficiency and unmatched specificity. The design of novel enzymes has the potential of making these features accessible to synthetic organic catalysis, which constitutes a considerable practical value to biotechnology, pharmaceutical synthesis, and industrial processes. This highly collaborative project focuses on the quantum mechanical evaluation of catalytic antibodies and de-novo designed enzymes that promote the conversion of benzisoxazoles to cyanophenoxides, a series of ring-opening reactions initially studied by Kemp and co-workers. The goal is to develop a computational method that is capable of accurately describing the catalytic reaction path of the Kemp elimination for these systems, in order to address unresolved mechanistic questions and guide the development of future catalyst generations. Theoretical calculations are conducted on the three dimensional structures of these proteins which we obtained from our collaborators. The catalytic reaction of each system is scrutinized with a variety of quantum mechanical models, ranging from simple theozyme-like descriptions to full quantum mechanical treatments of the entire catalytic site.

COMP 184

Quantitative structure-activity relationship modeling of the A_{2B} adenosine receptor agonists

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The A_{2B} adenosine receptor (AR) is one of the four known subtypes of ARs: A_1, A_{2A}, A_{2B}, and A_3, which are G protein-coupled receptors of the rhodopsin family. A_{2B} receptor agonists have been proposed for the treatment of several diseases, including septic shock, cardiac ischemia, and kidney disease. In the present study, the binding modes of seventy-two agonists of the A_{2B} receptor with known biological activity were studied by molecular modeling. The compounds in their receptor-docked conformations were used to build CoMFA and CoMSIA quantitative structure-activity relationship models. The best statistical parameters were obtained with the joint CoMFA and CoMSIA model: R^2 = 0.960, Q^2 = 0.676, *SEE* = 0.175, F = 158, R^2_{test} = 0.782, for an independent test set containing 18 compounds. The model can be used to design new agonists of the A_{2B} adenosine receptor.

COMP 185

RankScore2: A novel scoring function for ligand-protein binding affinities

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Docking methods are becoming increasingly popular in modern drug design campaigns. One of the key issues remaining to be addressed is the prediction of small molecule-macromolecule binding affinities. We developed a force field-based scoring function for the docking of small ligands to proteins. Starting from a challenging training set of protein-ligand complexes judiciously selected from the Protein Data Bank, we screened different molecular mechanical force fields to evaluate their predictivity for binding affinity prediction. Additional terms were included to account for entropic effects, such as an advanced consideration of loss of torsional degrees of freedom, and solvation energies via a GB/SA term. Benchmarking of the resulting scoring function against other available ones demonstrate its accuracy.

COMP 186

Reduced point charge approximation for speeding up the computation of electrostatic potential in biomolecular systems

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Estimating electrostatic forces in biomolecular calculations is generally computationally demanding. Presented here is a reduced point charge approximation for speeding up this computation for biomolecular systems. The approximation is based on multiple levels of natural partitioning of biomolecules into spatial subunits, e.g. amino acids, nucleotides, and chains. The charge distribution for these subunits are then approximated by a small number of point charges, much fewer than the number of atoms in the biomolecule. For short distance interactions, the electrostatic potential is calculated exactly using the full set of atomic charges. For long distance interactions, the reduced set of point charges are used instead. We test this approximation on a large number of biomolecules, compare its speed and accuracy to other commonly used approximations, such as the cutoff and Ewald methods, and discuss its implications for biomolecular simulations.

COMP 187

Relative stability of isomers of 2,3-disubstituted 1-aminoindenes

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One of the most fundamental types of reactions in organic chemistry is the rearrangement of the carbon framework. Several examples are well known, such as the Cope rearrangement and isomerizations of cyclopentadienes. Some examples of the isomerization of indene derivatives have been reported, but these examples almost always require high temperature conditions or irradiation with UV light. However, recently, Yoichiro Kuninobu and co-workers at Okayama University reported the rearrangement of an aminoindene derivative that proceeds at room temperature without UV radiation. Specifically, they report the isomerization between two isomers of 2,3-disubstituted 1-aminoindenes. Furthermore, their experiments with slightly different aminoindene derivatives, one deuterated and one not, indicate that the rearrangement is intramolecular. In the current study, we determine the relative thermodynamic stability of the two isomers and investigate slight alterations which may alter the relative energetics. We gratefully acknowledge support from the NSF (MRI-0321397) and from the Mississippi College Catalysts.

COMP 188

Relative stability of isomers of a dipseudoacid

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Pseudoacids are cyclic oxocarboxylic acids. One example would be the cyclic lactol form of levulinic acid, but the open form of this species is favored. Another example would be the cyclization product of 2-formylbenzoic acid. Here the interacting groups are forced to be nearer to each other by the rigidity of the aromatic ring, and the cyclic form is favored. Recently Liskin and Valente reported the synthesis and characterization of the first dipseudoacid, an arylpyran dipseudoacid, C16H18O6. Crystals of trans-4,4,8,8-tetramethyl-3,7-dihydroxy-1,2,3,4,5,6,7,8-octahydro-2,6-dioxaanthracen-1,5-dione occur in the monoclinic system and form linear hydrogen-bonded chains. This molecule has inversion symmetry, but an isomeric form with a two-fold rotation axis can be conceived. In the current study, we compare the relative stabilities of the two isomers to determine if the isomer with two-fold rotational symmetry might also be a candidate for synthesis. We gratefully acknowledge support from the NSF (MRI-0321397) and from the Mississippi College Catalysts.

COMP 189

Relativity aromaticity in pentacene derivatives

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As all chemists know, aromatic compounds are characterized by their high degree of stability. However, 6-methylpentacene undergoes hydrogen migration to form 6-methylene-6,13-dihydropentacene in which the aromaticity of the central ring is lost. The synthesis of pure 6-methylene-6,13-dihydropentacene was first reported in Nature by Clar and Wright in 1949. More recently, stable derivatives of 6-methylpentacene have been reported by Tamotsu Takahashi and coworkers. The stability is explained by the existence of substituted electron-withdrawing groups such as methoxycarbonyl groups which are believed to destabilize the transition state of the [1,5]-sigmatropic hydrogen rearrangement that leads to the dihydropentacene isomer. In the current study, we examine several amino and nitro derivatives of 6-methylpentacene and 6-methylene-6,13-dihydropentacene to investigate the relative energetics which arise from activating or deactivating the aromatic rings. We gratefully acknowledge support from the NSF (MRI-0321397) and from the Mississippi College Catalysts.

COMP 190

Significance of electrostatics at hydrogen bond donor and polarization at hydrogen bond acceptor: Insight through QM/MM simulation

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Water dimer hydrogen bond donor and acceptor substitutions have been studied using second-order Moller-Plesset theory and DFT with the 6-311++G(3d2f,2p) basis set. A full range of electron donating and withdrawing effects from 10 substituents have been studied. The effect of hyperconjugation, $n(O) \rightarrow \sigma^{*}(O—H)$, on the binding energy and structure has been approximated using NBO. It is found that the modulation of electron density from the n(O) orbital of the hydrogen bond acceptor significantly impacts hydrogen bond strength yielding a strong correlation (R2 = 0.83 & slope = -21.25) between binding energy and sigma meta. Hybrid ONIOM computations have been carried out to probe the acceptor control of hydrogen bonding. Polarization of electron density on the hydrogen bond acceptor is critical to model hyperconjugation and the hydrogen bond correctly.

COMP 191

Simulated interactions between structured peptides and functionalized surfaces

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Conventional molecular dynamics and replica-exchange molecular dynamics simulations are being conducted to study the conformational behavior of structured peptides, both in solution and when adsorbed on functionalized alkanethiol self-assembled monolayer (SAM) surfaces. Our model systems include a 14-residue LK alpha-helical peptide and a pair of 6-residue LK beta-turn peptides solvated in 140 mM NaCl aqueous solutions of TIP3P water over a 50%-deprotonated COOH-SAM surface and a CF3-SAM surface plus counterions for system neutrality. The system size in all cases is approximately 4.5 x 4.3 x 4.5 nm^3. Nanosecond-scale molecular dynamics simulations using the CHARMM c32b2 simulation engine have been completed with nonbonded interactions treated using particle-mesh Ewald. Simulations results are being used to theoretically investigate how interactions with various surfaces influence the conformation of peptide structures when adsorbed and how different surface chemistries influence this behavior. Results are being compared to NMR studies of these same systems.

COMP 192

Simulations of polypeptide folding using new efficient replica exchange methods

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The folding of even relatively small (50-100 amino acid) proteins in explicit water is currently beyond the scope of conventional replica exchange, a method which has proven very powerful for smaller systems. For larger systems, the required number of replicas becomes too large for the method to be practical. We present two methods in which 10 replicas can be replaced by one modified replica which effectively spans the same temperature range. Both these methods use a potential scaled with a parameter treated either as a dynamical variable or with a simple explicit time dependence. The methods are applied to a test case, the

alanine dipeptide, and a more complex system, the tryptophan zipper, a twelve amino acid polypeptide which folds into a beta hairpin structure.

COMP 193

Strain energies in isomers of 1,3-cycloheptadiene and bicyclo[3.2.0]hept-6-ene

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Recently, Steven Davis and co-workers at the University of Mississippi reported a study of the rearrangement of (E,E)-1,3-cycloheptadiene to (E,Z)-1,3-cycloheptadiene by one pathway and to trans-bicyclo[3.2.0]hept-6-ene by another. The further rearrangements of these products to cis-bicyclo[3.2.0]hept-6-ene and (Z,Z)-1,3-cycloheptadiene were also investigated. In addition, relative stabilities and the barriers to rearrangements were compared to the strain energies of the different cyclic systems as computed by homodesmotic model reactions. In the current study, we attempt to quantify the conventional strain energies of the different systems by hyperhomodesmotic as well as homodesmotic model reactions. Furthermore, we explore the possibility of computing the strain energies of each ring separately in the two bicyclic systems with different hyperhomodesmotic equations to see if strain energies might be additive. We gratefully acknowledge support from the NSF (MRI-0321397) and from the Mississippi College Catalysts.

COMP 194

Structural effects of interstrand crosslinks on DNA through molecular dynamic simulations

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Nitrogen mustards (HN2) are a cytotoxic class of bifunctional alkylating agents that form various DNA crosslinks. Among the adducts that form in the reaction of these compounds with DNA, interstrand crosslinks (ICLs) cause the greatest cytotoxicity to the cell. ICLs form covalent bridges between two complementary strands of DNA inhibiting essential processes such as DNA replication and transcription. Various DNA repair pathways, including NER, homologous recombination and translesion synthesis work together to repair ICLs, but the

details of how repair is achieved are not understood. In particular, the relationship between the structure of the ICL and its repair are not known. Investigating the effect due to variations of length and charge on these ICLs may lead to a better understanding of the recognition pathways involved in crosslink repair. In this work we use computational methods to investigate and predict helical distortions caused from various ICLs.

COMP 195

Surflex-Docking into the minor groove of DNA

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Nucleic acids are targets of increasing interest for drug discovery; in particular, ligands that can bind noncovalently in the B-DNA minor groove are an attractive source of novel anticancer agents. Here we present our initial validation studies for docking small molecules into the DNA minor groove using Surflex-Dock. We discuss the unique challenges posed by this target family, compared to protein structures, and suggest modifications to docking protocols to accommodate these differences.

COMP 196

Targeting the protein-protein interaction of Bcl-xL for drug discovery

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The Bcl-2 protein family acts as regulators of apoptosis or programmed cell death. In the first phase of our study, one of the Bcl-2 family members, Bcl-xL was targeted for structure based virtual screening. The Gold program was used to conduct a cross-docking based virtual screening using two significantly different protein structures of Bcl-xL. The publicly available ZINC database, containing around 1.8 million compounds was virtually screened against the target, using a extensively validated docking protocol, in conjunction with docking-pose based descriptors (Silver) and a receptor-based pharmacophore pre-filter (Catalyst). High scoring virtual hits common to both the target structures were biologically evaluated for their ability to bind Bcl-xL. Using the docked

poses of series of known Bcl-xL inhibitors, a predictive docking-pose based pharmacophore model (Phase) and a Linear Interaction Energy (LIE) model (Liaison) were generated. A similar pharmacophore model was generated to predict the undesired binding of putative Bcl-xL inhibitors with HSA. A molecular dynamics simulation study was carried out on a Bcl-xL-inhibitor complex to understand the induced-fit effects present in the surface groove of the Bcl-xL protein and its effect on the ligand binding process.

COMP 197

Temperature dependent structural dynamics of the Villin Headpiece Helical Subdomain: An ultrafast folding protein

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The villin headpiece helical subdomain (HP36) is the shortest naturally occurring sequence which has been shown to fold cooperatively. Infrared temperature jump, laser fluorescence, and NMR line shape analysis techniques have been used to determine the folding of HP36 occurs on the microsecond time scale. Fluorescence and temperature jump experiments suggest that HP36 may not follow a 2-state mode since multiple phases are observed. One phase is on the nanosecond time scale while the other occurs on the microsecond time scale and is due to the global folding transition. The fast phase has been suggested to be due to either a helical coil transition, or helix fraying or protein solvent fluctuations in the native basin. In order to gain a better understanding of this rapid transition, we have conducted multiple constant temperature and temperature jump simulations ranging from 276 to 339 K. These simulations can help describe the structural details of these early transitions.

COMP 198

The free energy and entropy of a water molecule in hydrophobic cavities

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Single water molecules in cavities consisting of hydrophobic molecules are examined using molecular dynamics simulations to determine the free energy and entropy of inserting a water molecule into the cavity. Various cavities in which hydrophobic molecules are replaced with hydrogen bond forming molecules are examined as well. The cavities are constructed to mimic those found in protein interiors in terms of volume and packing. Results will be presented using a new method in which equilibrium averages over a range of temperatures can be found from a single simulation at one temperature.

COMP 199

The radical enhanced nucleation of water

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The HOx family of molecules has been well studied due to their importance in atmospheric ozone chemistry. The uptake of these radicals by aerosols and cloud particles can significantly affect the rates of both ozone formation and destruction. Recent experimental evidence has indicated that these radicals may also serve as sites for enhanced water nucleation. We have used the AVUS-HR method, developed in our group to quantitatively examine the effect of these radical species on the nucleation of water.

COMP 200

The role of the active site solvent in the thermodynamics of factor Xa-ligand binding

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Understanding the underlying physics of the binding of small molecule ligands to protein active sites is a key objective of computational chemistry and biology. It is widely believed that displacement of water molecules from the active site by the ligand is a principal (if not the dominant) source of binding free energy. Although continuum theories of hydration are routinely used to describe the contributions of the solvent to the binding affinity of the complex, it is still an unsettled question as to whether or not these continuum solvation theories describe the underlying

molecular physics with sufficient accuracy to reliably rank the binding affinities of a set of ligands for a given protein. Here we develop a novel, computationally efficient, descriptor of the contribution of the solvent to the binding free energy of a small molecule and its associated receptor that captures the effects of the ligand displacing the solvent from the protein active site with atomic detail. This descriptor quantitatively predicts (R2=0.81) the binding free energy differences between congeneric ligand pairs for the test system factor Xa, elucidates physical properties of the active site solvent that appear to be missing in most continuum theories of hydration, and identifies several features of the hydration of the factor Xa active site relevant to the structure-activity-relationship of its inhibitors.

COMP 201

Unusual participation of the counterion in charge transfer copper(I) complexes

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Charge transfer in copper(I) complexes with bidentate nitrogen ligands and a strongly coordinating tetraphenyl borate counterion, [CuI(L)][BPh4] (L = 2,2'bipyridine; 3,4,7,8-tetramethyl-1,10-phenanthroline), has been investigated using density functional theory in conjunction with several basis sets. The strength of counterion coordination was found to be the primary result of σ donation from the counterion to the empty *n** orbital of copper. While there is some degree of π back bonding from copper to the π* orbitals of the phenyl rings, this interaction is less significant than the σ donation, in agreement with NMR data. Donation to the copper *n** orbital occurs not only from the π bonds of the phenyl rings, but also from the boron-carbon σ bonds, contributing to the unusually strong coordination of the counterion. The influence of counterion bonding upon the observed structures and binding constants, and a possible connection with observed kinetics from cyclopropanation reactions will be discussed.

COMP 202

Virtual screening with pharmacophore model: Application in search of novel CB1 antagonists

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CB1 receptor antagonists have proven to be clinically effective in treating obesity and related disorders. We developed a pharmacophore model based on the structures of known representative CB1 antagonists using the Catalyst software. This pharmacophore model highlights the interactions crucial for receptor binding, and agrees with most of the findings from recently CB1 receptor homology models. The pharmacophore model was employed to screen a database of about a half million Schering-Plough compounds. A large number of hits were identified from the virtual screening, and they had never before been tested in a CB1 receptor binding assay. To reduce the number of hits to a manageable scale for biological testing, we applied a stepwise filtering protocol that constituted molecular weight, compound availability, a modified “rule of 5”, Bayesian modeling and clustering. We combined Bayesian modeling and clustering techniques to maximize the chance of finding new chemotypes while retaining top scoring compounds. In the end, 420 compounds were selected for in vitro testing. Five compounds were found to have >50% inhibition at 100 nM in a CB1 competitive binding assay, and were further characterized using both CB1 and CB2 assays. The most potent compound has a CB1 Ki of 53 nM and more than five fold selectivity against the CB2 receptor. These hits represent a novel structural class of CB1 selective antagonists, and can be subjected to further chemical optimization for the treatment of obesity and its related diseases.

COMP 203

Considering a treatment of induced electronic polarization based on the Poisson equation

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Currently, two physical models have been developed for use with explicit solvent to introduce electronic polarization in classical force fields: fluctuating charge and point dipole polarizability (Drude oscillators are included in the latter category). In this work, we explore a new way of using Poisson equation and the Poisson Boltzmann solver ZAP to introduce electronic polarization in an explicit classical

force field. In this treatment, the polarizable electronic density of a molecule is represented as an intramolecular continuum dielectric constant. Our preliminary work show encouraging results in some important aspects. This simple model shows itself capable of describing naturally and well highly anisotropic molecular dipole polarizabilities; also key biologically relevant and polarizability driven cation-pi interactions are inherently well described.

COMP 204

Coupled-cluster theory on supercomputers

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The proliferation of parallel computers with thousands of processors has the potential to open up totally new areas of computational chemistry. We report on the marriage of high-level coupled-cluster methods with state-of-the-art supercomputing hardware. The computational chemistry software suite NWChem has been ported to the BlueGene/L and Cray XT4 platforms, allowing the ab initio study of molecules of an unprecedented size. We focus on coupled-cluster properties, including excited-states and dynamic polarizabilities and hyperpolarizabities for conjugated polymers and other small chromophores at the CCSD level of theory, as well as benchmark CCSDT and CCSDTQ response property calculations on small molecules. The chemical results allow us to analyze lower-level approximate methods, such as density functional theory (DFT) as well as the basis set dependence of correlated calculations. Computational benchmarks suggest new parallel strategies and allow us to evaluate the utility of various types of supercomputing hardware.

COMP 205

FORECASTER: A new platform for drug discovery

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Computer-aided drug design methods are a key emerging technology, enabling faster and more cost-efficient drug development. We developed FORECASTER, a drug discovery platform encompassing FITTED, a flexible protein docking program, SMART and PROCESS, two modules used to prepare ligand and protein

structures for FITTED simulations, and REACTOR, a tool for the generation of virtual combinatorial libraries. While FITTED has been optimized for virtual screening applications, virtual SAR becomes possible when used in conjunction with REACTOR. Recent advances in the development of this suite of programs, such as the implementation of a novel scoring function, as well as applications to pharmacology and drug design will be described.

COMP 206

Hydrophobic interaction in acidic aqueous solutions

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The hydrophobic interaction, which is believed to be the primary driving force for many fundamental chemical and biological processes, is known for decades to be rather different in acidic aqueous solutions than in neutral salt solutions. In the present study, by investigating the aggregation/dispersion behavior of the non-polar neopentane molecules in aqueous solutions with varying proton concentrations by means of molecular dynamics simulations incorporated with the methodology of SCI-MS-EVB, the formation of neopentane-hydronium cores was observed for the first time ever, as a result of the unique amphiphilic characteristics of hydronium. In contrast to the case of NaCl, high concentration of which eventually triggers a massive aggregation of neopentane molecules, the dispersion propensity of neopentane enhanced by HCl with respect to that in pure water through an ion-pair like dissolution is essentially invariant up to a proton molarity as high as 3M.

COMP 207

Using computer simulations to explore pressure effects on proteins

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Recently, pressure has emerged as an important thermodynamic dimension in which to perturb biological systems. A fundamental framework for understanding pressure effects on biological systems is missing, however. Effects of high pressure on globular proteins in solution are particularly intriguing. Instead of being mechanically compressed at high pressures, proteins unfold into water-swollen denatured states! How do we think about these puzzling observations from a fundamental perspective? Can we employ molecular simulation studies to

measure or predict the volumetric quantities a priori? Secondly, how does pressure affect the water-mediated hydrophobic interactions that drive folding? We thus follow a two-pronged approach: (i) Pressure effects at a fundamental level: We focused on hydrophobic interactions and their pressure dependence. Hydrophobic interactions are weakened with increasing and the conceptual picture of pressure unfolding that develops is that water molecules penetrate into protein interior at high pressures causing it to subsequently unfold. Our recent simulations also show that with increasing solute size the hydration shell becomes increasingly "soft", and highly compressible. Our results have implications on understanding their pressure sensitivity of proteins and protein aggregates. (ii) Pressure denaturation through large scale simulations: The slow kinetics of protein folding makes it computationally prohibitive to access these processes. Based on the funadamental understanding above we developed an algorithm to generate representative conformations of the ensemble of pressure denatured state. This study shows for the first time that MD simulations can be used to generate pressure unfolded states of proteins as well as to predict the pressure stability of the protein. Collectively, our multi-scale approach combining studies on fundamental interactions and small solutes with those at mesoscopic protein structure level provides a strong foundation to develop a framework for interpretation and prediction of pressure effects on biological systems

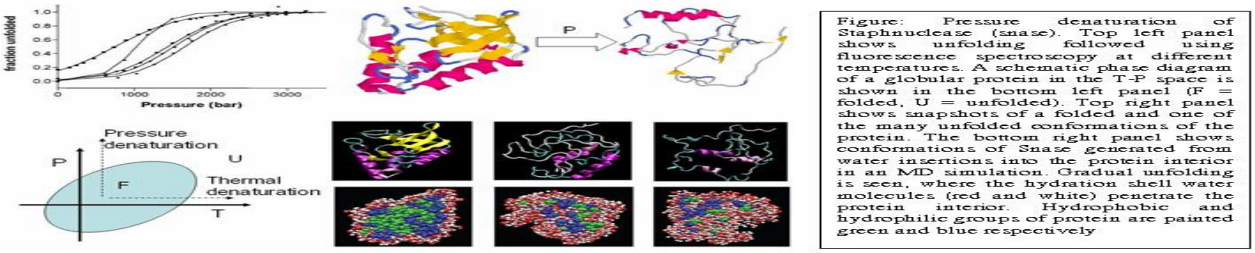

Figure: Pressure denaturation of Staphnuclease (snase). Top left panel shows unfolding followed using fluorescence spectroscopy at different temperatures. A schematic phase diagram of a globular protein in the T-P space is shown in the bottom left panel (F = folded, U = unfolded). Top right panel shows snapshots of a folded and one of the many unfolded conformations of the protein. The bottom right panel shows conformations of Snase generated from water insertions into the protein interior in an MD simulation. Gradual unfolding is seen, where the hydration shell water molecules (red and white) penetrate the protein interior. Hydrophobic and hydrophilic groups of protein are painted green and blue respectively

COMP 208

Determination of absolute configuration in solution

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The agreement between experimental measurements and theoretical calculations of chiroptical properties is often hampered by substantial contributions from electron correlation, basis set incompleteness, origin-dependence, vibrational and thermal motion, solvation, and conformational flexibility. Previous studies have shown that the neglect of a single one of these effects can result in the incorrect sign of the optical rotation or obscure a

transition in the circular dichroism (CD) spectrum. The zero-point vibrational contribution to the optical rotation for rigid molecules can be determined using perturbation theory, although it requires many individual property calculations along normal modes and potentially higher-order force constants to account for the anharmonicity in the potential energy surface. We have explored ab initio molecular dynamics as an alternative approach to estimate the effects of vibrational motion and explicit solvation on the calculated optical rotatory dispersion (ORD) and CD spectra. Our results suggest that short-time dynamics can cheaply estimate the magnitude of vibrational, thermal, and solvation effects on ORD and CD, thereby providing a useful diagnostic for the assignment of absolute configuration.

COMP 209

Predictive electronic and vibrational many-body methods

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Predictive simulations of energetics, structures, and spectra of polyatomic molecules in the electronic ground, excited, ionized, and electron-attached states have been performed by employing combined linear, perturbation, and cluster expansions of (relativistic) wave functions. Computerized symbolic algebra has been developed and used to automate the lengthy and error-prone processes of formula derivations and parallel computer implementations of these high-rank electron-correlation methods. The same mathematical expansions have been used in vibrational problems to account for anharmonicity and mode-mode coupling of polyatomic molecular vibrations to any desired extent. The spectroscopic accuracy has been achieved in reproducing the frequencies of Fermi doublets of CO_2, in the Franck–Condon analyses of the photoelectron spectra of H_2O and H_2CO, and in the vibration-averaged indirect NMR spin-spin coupling constants of FHF^-.

COMP 210

Advances in potentials of mean force methodology for organic and biological simulations

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Combined quantum and molecular mechanics (QM/MM) simulations have been used to study reaction mechanisms and the origin of enzymatic rate

accelerations and selectivity. Speed and accuracy demands have led to the development of enhanced algorithms and a novel potentials of mean force (PMF) method for analytically reproducing free-energy profiles and surfaces with full sampling of solute and solvent coordinates. The methodology has provided excellent results for free-energies of activation for many reactions and has reduced average computation times from ca. 6 months to 3 weeks. The presentation will focus on the development of these methods and will feature recent examples including fatty acid amide hydrolase (FAAH), antibody 4B2, and a singlet oxygen ene reaction.

COMP 211

Integration of a bioinformatics approach to high-throughput docking and its application to the discovery of novel TNF receptor-associated factor 6 (TRAF6) inhibitors

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High-throughput docking (HTD) has been widely used in drug discovery. We have devised an efficient HTD package, termed HiPCDock, enabling us to dock millions of compounds within days. Also for the first time, to the best of our knowledge, a bioinformatics-based statistical model, motivated by BLAST, was applied to molecular docking to estimate the statistical significance of predictions because we found that the probability of binding free energy resulted from random screening conformed to an extreme value distribution. This statistical model gave us insight on the confidence of predictions and will help guide our decision-making during the hit/lead selection process. This integrated approach has been validated by efficiently and accurately recovering ten know thymidine kinase (TK) inhibitors from a 1000-compound pool. HiPCDock was also employed to successfully identify a series of compounds that have inhibitory effect on TRAF6, and currently structure optimization is undergoing to derive more potent agents.

COMP 212

A fast semiempirical approach to accurate rate constants

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A semi-empirical approach to calculating rate constants is under development for use in HyperChem™. The procedure uses canonical transition-state theory and a priori semi-empirical computation of the relevant molecular quantities. The procedure is extremely fast and has possibilities of being accurate because of the use of Typed Neglect of Differential Overlap (TNDO). TNDO introduces the molecular mechanics concept of "atom type" into quantum mechanics allowing an expanded space of semi-empirical parameters particular to the explicit bonding environment of the relevant molecular system. The increased parameterization potentially can allow one to obtain reasonably accurate rate constant A-factors and activation energies for systems similar to the training set used in developing the parameters. Examples will be described for a limited class of systems.

COMP 213

Rates of quantum states population and coherence relaxation during optical excitation of surfaces: A density matrix computational approach

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Light absorption by molecules and clusters adsorbed on solid surfaces leads to the excitation of electronic states that decay over time to thermal distributions. These phenomena involve energy dissipation due to coupling to electronic and vibrational excitations of their environment. A density matrix treatment has been developed to account for rates of instantaneous and delayed dissipation. The integrodifferential equations for the reduced density matrix of a many-atom system in a medium are solved using a diadic treatment and a generalized Runge-Kutta procedure. Instantaneous dissipation for the electronic states is described by a Lindblad term containing electronic transition rates,[D. A. Micha and A. Santana, J. Phys. Chem. A 2003, 107, 7311] while the delayed dissipation is given by a time integral with a memory supermatrix term derived from the time-correlation of atomic displacements in the medium.[A. S. Leathers and D. A. Micha, J. Phys. Chem. A 2006, 110, 749] Examples will be presented on recent results for a metal cluster on a semiconductor surface, of interest in the capture of solar energy.

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COMP 214

Efficient estimators for quantum instanton evaluation of the kinetic isotope effects

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The quantum instanton approximation is used to compute kinetic isotope effects for intramolecular hydrogen transfer in *cis*-1,3-pentadiene. Due to the importance of skeleton motions, this system with 13 atoms is a simple prototype for hydrogen transfer in enzymatic reactions. The calculation is carried out using thermodynamic integration with respect to the mass of the isotopes and a path integral Monte Carlo evaluation of relevant thermodynamic quantities. Efficient "virial" estimators are derived for the logarithmic derivatives of the partition function and the delta-delta correlation functions. These estimators require significantly fewer Monte Carlo samples since their statistical error does not increase with the number of discrete time slices in the path integral. The calculation treats all 39 degrees of freedom quantum mechanically and uses an empirical valence bond potential based on a molecular mechanics force field.

COMP 215

Kinetic analysis of the pyrolysis of phenethyl phenyl ether with different substituents: Computational prediction of α/β-selectivities

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We calculated overall α/β-selectivities for the pyrolysis of phenethyl phenyl ether with different substituents as a composite of the α/β-selectivities in the hydrogen abstraction reactions by the phenoxyl and by the benzyl radical with corresponding substituent that are in excellent agreement with experiment. We have developed a scheme to predict α/β-product selectivities in the pyrolysis of model compounds for the β-ether linkage in lignin. The approach is based on computation of the relative rate constant which profits from error cancellation in the individual rate constants. The Arrhenius pre-factors depend strongly on the description of the low-frequency modes for which anharmonic contributions are important. We use density functional theory in combination with transition state theory in this analysis. Diagonal anharmonic effects for individual low-frequency modes are included by employing a second-order Wigner-Kirkwood expansion in a semi-classical expression for the vibrational partition function. The composite

α/β-product selectivity is obtained by applying quasi-steady-state kinetic analysis for the intermediate radicals.

COMP 216

Transition state theory rate constants for intramolecular hydrogen transfer reactions in oxygenated radicals

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The β-hydroxyethylperoxy (A) and β-hydroxyethoxy (B) radicals possess intramolecular hydrogen bonds that facilitate hydrogen atom transfer, an important reaction in the troposphere and in combustion. We report quantum chemical reaction energetics and transition state theory rate constants. MPW1K and BB1K, unlike B3LYP, predict barriers that agree with the predictions of highly accurate multi-coefficient G3 calculations. For the 1,5-hydrogen shift in A at 298 K, the variational TST rate constant is ~30% lower than the conventional TST result, and the microcanonical optimized multidimensional tunneling (μOMT) method predicts that tunneling accelerates the reaction by a factor of 3. TST calculations on the 1,4-hydrogen shift in B reveal no variational effect, and a 298 K μOMT transmission coefficient of 10^5. The Eckart method overestimates transmission coefficients for both reactions. We also report preliminary results on the 1,4-hydrogen shift in syn acetaldehyde oxide, a major precursor of hydroxyl radical in the troposphere.

COMP 217

Two transition state model for radical-molecule reactions

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We will describe a two transition state model for treating the kinetics of radical-molecule reactions whose saddle point is below reactants. The outer transition state is treated with long-range transition state theory, while the inner transition

state theory is treated with standard rigid rotor harmonic oscillator assumptions. The rovibrational properties for both transition states are obtained from CASPT2 ab initio simulations. Comparisons with experiment are made over a wide temperature range (e.g., 10 to 1000 K) for $O(^3P)$ + alkene reactions and for OH + alkene reactions.

COMP 218

Parallel tempering techniques for simulation of proteins

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Rational drug design or the pathology of amyloid diseases are only two problems whose solution requires a detailed knowledge of the relation between chemical composition and structure (and function) of proteins. Despite decades of research, both experimental and in silico, this relationship is still only partially understood. Computer experiments offer one way to evaluate the sequence-structure relationship and the folding process but are extremely difficult for detailed protein models. This is because the energy landscape of all-atom protein models is characterized by a multitude of local minima separated by high energy barriers. Only over the last few years have been algorithms developed that allow one to overcome this multiple-minima problem in protein simulations. Prominent examples of these new techniques are parallel tempering and other generalized-ensemble sampling techniques. In the present talk I will focus on parallel tempering (also known as replica exchange sampling). I will discuss the underlying ideas behind this approach, its implementation to Monte Carlo and Molecular Dynamics, and strategies for further advancement of this popular approach. Recent results from folding simulations of small proteins (of order 50 residues) will illustrate the power of improved parallel tempering simulations.

COMP 219

Extracting averages and distributions from replica exchange simulations of large systems: A new version of WHAM

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The original multiple histogram method (Ferrenberg et al, PRL1989) and weighted histogram analysis method WHAM (Kumar et al, J. Comp. Chem. 1992) are problematic when applied to data generated from “temperature replica exchange” simulations of large systems (such a protein in explicit solvent). We discuss the difficulties associated with extracting averages and distributions from replica exchange data and present a new version of WHAM that overcomes many of these problems. Applications to biological systems, including peptide aggregation in explicit solvent, will be discussed.

COMP 220

Mechanisms of protein (un)folding and signaling state formation revealed with replica exchange

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We apply replica exchange molecular dynamics (REMD) to several systems. For the first, a WW-domain, we discuss the mechanism of folding and compare it to previous results. The second system is the bacterial sensor Photoactive Yellow Protein (PYP). PYP signals the presence of blue light by undergoing a photo-cycle, a series of conformational changes, ending with a partial unfolding to the signaling state. We explore the formation of the signaling state and the refolding to the receptor state.

PYP is at the limits of what REMD can handle, because of the large system size and energy. Much of the energy is in fact due to the explicit solvent. We discuss several recent improvements on the original REMD, e.g. solute tempering, bias exchange Metadynamics, Hamiltonian switching. In addition, we present a new Hamiltonian switching biasing function based on specific interactions in proteins, which does improve sampling folding dramatically.

COMP 221

A different architecture for expanded ensemble simulation: Adaptive AIS

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The annealed importance sampling (AIS) algorithm is a protocol which reweights an annealed sample into an equilibrium weighted ensemble (Neal, R. *Stat. and Comp.* **2001** *11*, 125-139). In contrast with exchange simulation, the ``information flow'' is in one direction---in the case of annealing in temperature, from high to low temperature. This ``top-down'' architecture provides a number of advantages over exchange simulation. First, correlations and therefore the effective size of the sample of configurations are easily monitored and controlled. Second, an adaptive ladder of replicas is easily implemented, so that the temperature steps automatically adjust to achieve a specified amount of overlap between neighboring ensembles. The adaptive AIS algorithm is demonstrated by folding and sampling implicitly solvated peptides.

COMP 222

Protein folding network, and energy landscape, studied by parallel Wang-Landau sampling

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Protein folding is a complex reaction proceeding through millions of conformations, but, for simplicity, the conformational space has often been projected onto few dimensions. Recent works suggested, however, that this projection might hide diverse heterogeneity in conformational space. Viewing energy landscape without severe projection is an important step to understand complexity in the protein folding problem. For the purpose, we performed large-scale conformation sampling for protein G and a random sequence using a parallel Wang-Landau sampling method coupled with the fragment assembly protocol. A parallel Wang-Landau method is somewhat similar in concept to, but can be superior to, the replica exchange method. We could achieve exhaustive sampling of conformations and estimate free energies through re-weighting technique. We then performed energy landscape analysis. Defining “state and connection”, we drew a network of conformations. Standard network analysis gives us various hypothetical folding pathways.

COMP 223

Protein folding using replica exchange and mechanism-based conformational searching

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In recent years it has become clear that sampling is the most significant bottleneck to the simulation of proteins with physics-based force fields. Replica exchange molecular dynamics (REMD) has now become a method of choice for simulating very small peptides and proteins, and extensive such studies by several groups have underscored the accuracy of modern energy functions. For proteins with more than ~20 amino acids, however, it has remained challenging to reach converged simulations.

Here, we pursue a strategy of combining REMD simulations with a mechanism-based conformational search. We believe proteins avoid extensive conformational searching with the zipping and assembly mechanism: a protein first explores local metastable structures in short segments all along its chain; some of these structures survive to longer timescales, and then reel in neighboring chain segments to form larger, more stable structures, until eventually, a fully structured chain is reached. Based on this ides, we have developed a methodology called the Zipping and Assembly Method (ZAM). ZAM uses the AMBER96 force field and integrates many multiple REMD simulations by: (1) breaking the full protein chain into small fragments (initially 8-mers), which are simulated separately; (2) then growing or zipping the fragments having metastable structures by adding a few new residues or assembling two such fragments together, with further simulations and iterations; and (3) locking in place any stable residue-residue contacts with a harmonic spring, enforcing emerging putative physical folding routes, without the need to sample huge numbers of degrees of freedom at a time. During this process, ZAM learns and pursues possible pathways by computing various contact free energies as fragments fold. We have found that this approach reaches highly native-like structures in proteins up to ~110 residues long, in both an in-house test of 9 small proteins and the blind structure prediction contest CASP.

COMP 224

Binding response: A method for the prediction of ligand binding sites on proteins

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Binding response is a novel descriptor to evaluate the response of a putative binding site on a protein to probe compounds using both the geometry and energies of binding poses. A complete approach has been implemented

including the generation of the protein surface, identification of putative binding sites, docking of a set of 1000 diverse compounds and evaluation of the putative binding sites using the binding response. This method is proposed to facilitate the identification of binding sites on protein surfaces for use in computational database screening studies targeting protein-ligand and protein-protein interactions. Analysis of 29 protein-ligand complexes shows a 90% success rate in identifying known binding sites.

COMP 225

Giving the Rule-of-5 a more accurate twist

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The much publicized “Rule-of-5” (Ro5) has been widely adopted in the pharmaceutical industry as the first step in the virtual screening of compound libraries, in an effort to pre-emptively eliminate hits that are deemed to have poor physicochemical properties for oral bioavailability.

LogP is a key parameter in the Ro5 and, although useful, fails to take into account variation in drug lipophilicity due to ionization under physiological conditions. Given that more than 95% of commercial pharmaceuticals contain an ionizable moiety, we propose that logD is a better descriptor for lipophilicity in the Ro5 (and similar filters). This alternative value should help reduce the number of potential false-positives eliminated in screening.

In this presentation we will discuss results from screening a number of commercially-available libraries using an adapted Ro5 applying logD in place of logP.

COMP 226

Virtual screening for superior R-groups

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Frequently during lead optimization, only a side chain or two are amenable to further structural variation, while established CADD methods are weak for choosing among even the limited number of candidates first coming to mind. Topomers provide an alternative possibility of "virtual screening for R-groups" within the largest structural databases, and on the basis of 3D-QSAR potency

predictions as well as shape similarity. However that possibility is so far untested. We will therefore report retrospective studies to address at least the following questions, starting from 25 reported topomer CoMFA models that statistically replicate published 3D-QSAR studies:

„« Within the ZINC database, how frequently do there indeed exist otherwise reasonable R-groups having higher predicted potencies?

„« How reliable are such predictions of higher potency? (How often do topomer CoMFA analyses omitting the most potent known structures correctly flag such omitted structures as promising? And what caveats are associated with such predictions?)

COMP 227

Histone deacetylase inhibitors: Reasons for isoform selectivity

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Histone deacetylases (HDACs) are promising targets in drug development, regulating gene expression through the deacetylation of histone tails. Eukaryotic HDACs have been classified into four groups on the basis of a phylogenetic analysis.

A wide range of structures have been identified that are able to inhibit the activity of the different classes, achieving significant biological effects in preclinical models of cancer. However, only few molecules are emerging as preferential inhibitors of class 1 versus class 2, and even fewer are able to discriminate efficiently among HDACs belonging to the same class. Nevertheless, common patterns, such as a low activity in HDAC8, have emerged.

Using x-ray structures, homology modeling, docking, and long-timescale MD simulations, possible reasons for the isoform selectivity are elucidated. The contributions of interactions in the binding, linker, and cap regions of the inhibitors to the potency and selectivity of a range of HDAC inhibitors are discussed.

COMP 228

Modeling the metabolic space in drug discovery

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In silico prediction of ADMET (absorption, distribution, metabolism, elimination, toxicity) properties is of special interest in the drug discovery process in order to detect and eliminate compounds with inappropriate pharmacokinetic properties at an early stage. A central step in the ADMET profiling of potential drug candidates is the assessment of drug metabolism. Some enzymes involved in the detoxification process show polymorphism and have multimodal binding sites. The majority of the oxidation reactions in phase I metabolism are catalyzed by cytochrome P450 enzymes.

This paper focuses on several aspects related to phase I metabolism by cytochrome P450 enzymes. Models for the prediction of the isoform specificity of cytochrome P450 3A4, 2D6, and 2C9 substrates [1] as well as for the prediction of potential inhibition of cytochrome P450 2D6 and 2C9 will be presented. The impact of descriptor selection, the choice of the model building method and the selection of training and test data set will be carefully discussed. A comprehensive scheme of cross-validation experiments was applied to assess the robustness and reliability of the models developed. In addition, the predictive power was inspected by predicting an external validation data set. The final models that perform with a predictability of over 80% are implemented in the program system isoCYP.

[1] Terfloth, L.; Bienfait, B.; Gasteiger, J. Ligand-Based Models for the Isoform Specificity of Cytochrome P450 3A4, 2D6, and 2C9 Substrates. J. Chem. Inf. Model.2007, 47, 1688-1701.
[2] isoCYP is available from Molecular Networks GmbH, Erlangen, Germany and available for testing at www.molecular-networks.com/online_demos/cyp450.

COMP 229

Surface segregation in nanoalloys under reaction conditions

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Determination of surface composition is crucial to understand reaction mechanisms. Surface segregation phenomena are well-known in bulk alloys, but

less-well defined in alloy nanoparticles. Further, how surface segregation trends may change under the presence of adsorbates and under dynamic reaction conditions may help rational design of nanocatalysts. We use density functional theory to analyze surface segregation behavior of bimetallic and trimetallic alloys, and investigate the effect of the presence of adsorbates on the segregation trends. The study includes random and ordered structures, and various crystallographic phases.

COMP 230

First principles studies of electrochemical oxidation reactions at model solid oxide fuel cell (SOFC) anodes

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Electrochemical oxidation of hydrogen and hydrocarbon fuels over solid oxide fuel cell (SOFC) anodes is crucial to the performance of SOFCs. Although SOFC technology has been evolving over the past few decades, not much is known about elementary electrochemical mechanisms that govern their performance. In this work we have employed quantum Density Functional Theory (DFT) and statistical thermodynamic calculations to investigate the underlying molecular mechanisms that govern the electrochemical oxidation of hydrogen and methane over Ni-based SOFC anodes. Aside from presenting the results of our calculations we will also discuss in detail the approach that was utilized to address the issue of electrostatic potential and electric field which are present in electrochemical systems.

COMP 231

Why PtVFe nanoparticles are better catalysts for oxygen reduction

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Alloying multiple transition metals has been illustrated as a powerful means to improve the catalytic activity for oxygen reduction. For instance, it has been demonstrated that PtVFe nanoparticles are about 4 times active towards oxygen reduction with respect to the pure Pt nanoparticles.(J. J. Luo, N. Kariuki, L. Han, L.Y. Wang, C. J. Zhong, and T. He, Electrochim. Acta 51 (2006) 4821.) In order to understand the mechanism of the increasing catalytic activity of the ternary

PtVFe nanoparticles, we use DFT calculations to study the effect of alloying V and Fe elements on the local electronic environment of Pt nanoparticles. The electron-ion interactions were described by the projector augmented wave method. The exchange and correlation energies were calculated using the PBE functional. A plane wave basis set was used with cut-off energy of 300eV. In this presentation, we will present the DFT results of PtVFe clusters with different compositions and comparison to pure Pt clusters will also be made, focusing on the differences in charge transfer and direct dissociation pathways.

COMP 232

Configurational correlations in the adsorption properties of atomic adsorbates on transition metal surfaces

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We have been investigating the adsorption properties of atomic adsorbates as a function of coverage on close-packed late-transition metal (Pd, Pt, Ag, Au) surfaces. Our approach is to use density functional theory in conjunction with cluster expansions to fully explore the phase space. With this approach we are able to show how the adsorption energy depends on the detailed configuration of the adsorbates on the surface, and to use this information to calculate the phase diagrams of the adsorbates at 0K, and ultimately at realistic pressures and temperatures. Although each surface has different adsorption properties, we have discovered a strong correlation between the adsorption energies of configurations on these surfaces. We will discuss these findings and their significance.

COMP 233

First-principles prediction of switchable stoichiometry at interfaces

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We present a first-principles density functional theory (DFT) study of the relative thermodynamic stability of ferroelectric (FE) lithium niobate ($LiNbO_3$) (0001) surfaces of different stoichiometry. We predict that the equilibrium stoichiometries are different for the positively and negatively polarized $LiNbO_3$ surfaces under the same conditions. A correct way of calculating surface charges for ferroelectric

materials with intrinsic polar stacking is developed. It is found that surface charge passivation by ions is thermodynamically favored over passivation by mobile carriers in a wide range of chemical potentials. This study helps rationalize polarization-dependent surface reactivity of FE $LiNbO_3$.

COMP 234

Thermochemistry and kinetics of steam methane reforming on Ni(111) under realistic conditions

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We report an extensive study of the thermochemistry of steam methane reforming (SMR) on Ni(111) using planewave density functional theory. In particular, we use statistical thermodynamics to model the process at realistic temperatures (900-1200 K) and pressures (10-20 bar) that mimic the conditions of an industrial steam reforming reactor. The thermochemical data are used to develop a kinetic model of industrial steam reforming that is used to study the reforming pathway on the catalyst surface. A key concern in SMR is catalyst deactivation due to carbon formation. The model is modified to account for computationally investigated carbon formation routes. Combined with sensitivity analysis, the kinetic model provides information about rate limiting steps as well as the most abundant reaction intermediates. The reaction intermediate CH* is found to be an important carbon-containing intermediate, while the reaction CH* + O* = CHO* is found to be a key rate limiting step.

COMP 235

Domain applicability of ligand and structure-based virtual screening

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We present results on the virtual screening behavior of docking and shape-based ligand methods as applied to large test sets such as DUD. In addition to lessons on the applicability of methods to particular systems, we demonstrate significant synergy between methods with substantial independence of domain applicability, some limits on the expected behavior of systems that are similar but not identical, and some suggested best practices for virtual screening.

COMP 236

Testing the limits of a QSAR model: How many cases are actually needed to develop a reliable predictive model?

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During this talk, key indicators of the predictive power of a statistical learning model will be presented as a function of the number and distribution of molecules in the training set, and the descriptors and learning method used. The study was based on the development of QSAR models for several representative datasets where the number and distribution density of the training data was gradually changed. The modeling performance of the remaining data was then evaluated for all descriptors, as well as for for selected subsets of descriptors with different levels of information content. Molecular features used in the study included MOE 2D and i3D descriptors as well as TAE / RECON, wavelet and PEST shape/property hybrid descriptors.

COMP 237

Automatic detection of outliers prior to QSAR studies

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We have developed automatic procedures for detection and elimination of outliers prior to QSAR studies. Two types of outliers are distinguished: leverage outliers and activity outliers. The former are compounds dissimilar from all other compounds in the dataset. They can be found using a sphere-exclusion algorithm. In contrast, activity outliers are compounds that are similar to some compounds in the dataset, but their activities are significantly different from those of their nearest neighbors. These compounds are of particular concern in QSAR studies: e.g., they can form so-called Maggiora's cliffs (Maggiora G.M., J Chem

Inf Model. 2006, 46, 1535) in the descriptor space. We will discuss the automatic detection and elimination of outliers as applied to several datasets. We show that taking into account activity outliers affords the significant increase in predictive power of QSAR models.

COMP 238

Combining global and local approaches to model domain applicability

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The goal of an in-silico predictive model is to predict a biological or physical property of a molecule based on its structural features. The model is built using a training set of molecules with the assumption that any new molecule to be predicted will have a degree of structural similarity with the training set. However, even though a new molecule may be structurally similar to the training set from the perspective of the model, it may still be predicted poorly because it incorporates some feature to which the model is blind. We describe a two-step approach to the quantification of model applicability. First, we consider the relationship between a new molecule and the structural features encoded in a model. This step is based on a determination of the point density of the region of model space that a new molecule is located in. The second step takes into account the differences between a new molecule and the training set in the context of a "global" chemistry space, represented by a structural key fingerprint. Our initial results indicate that a descriptor-weighted similarity between the new molecule and the model leads to a better measure of domain applicability. In addition we will present some initial results that highlight the importance of considering both model-specific and global aspects of domain applicability.

COMP 239

QSAR model stability: How much information is in the data?

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The evolution of a good QSAR or QSPR predictor can require significant expertise and effort. Frequently this work produces a single final model or ensemble of models which are then applied to new problems. When the model hypersurface is explored and multiple nearly-equivalent models are generated, the model stability can be viewed as an indication of model robustness and

applicability. Stability can be assessed by the impact of these variations on predicted rank ordering of cases. This in turn can be cast as a form of entropy. When multiple quasi-equivalent models produce a consistent rank ordering, the information content of the predictor set is high and the entropy is low. Conversely if multiple models lead to shuffling of rank ordering, then the Rank Order Entropy is high. The ROE metric can be used as a measure of the information power of a dataset. These concepts will be illustrated with several datasets and problem types.

COMP 240

Domain applicability: How far are ideal and reality?

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Domain applicability (DA) estimation is absolutely necessary for increase of QSAR predictions reliability. However, the situations when molecules belonging to model DA are badly predicted and vice versa are widespread. Present work is devoted to analysis how close are existing and developing DA procedures to their ideal sense.

Three different approaches for DA estimation (developed by us DA ellipsoid, DA rectangle and popular leverage method) have been applied for lattice and simplex 2D and 3D QSAR models developed for several different QSAR/QSPR tasks. Certainly, elimination of compounds which aren't belonging to model DA from prediction set increases quality of prediction during virtual screening or soft drug design. However, at the same time it leads to narrowing of chemical space covered by new compounds and impedes transgressing the bounds of investigated activity limited by training set. More drastic drug design is more risky but it allowing getting much more dramatic results.

COMP 241

Solvation of carbon nanotubes using de-novo peptide helices: A molecular dynamics approach

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The extreme hydrophobicity of Single-walled carbon nanotubes (SWNTs) strongly limits their current biological applications. Dieckmann et al. (J. Am. Chem. Soc. 125:1770-1777) have utilized designed amphiphilic peptide helices, called nano-1, to disperse SWNTs into aqueous solutions. The peptide is designed to interact with the SWNT mainly through the pi-stacking interactions between the phenylalanine residues and the SWNT aromatic side wall. Our research focuses on studying the conformation and the inter-molecular interactions inside the peptide – SWNT complexes using molecular dynamics (MD) simulation. The simulations are conducted with the program NAMD under the CHARMM31 force field. The peptide helicity and the peptide-nanotube contact area were analyzed to characterize the peptide conformation and amphiphilicity. Hydrogen bonds formed between the peptide and water molecules were counted to study the surfactant-like properties of the peptide. Inter-peptide hydrogen bonds can be formed and stablize the multiple peptide-SWNT complexes. Understanding the peptide – SWNT interaction at the molecular level will aid rational modifications of the peptide motif in the future.

COMP 242

Examination of proposed intercalation models for imidazoacridone related compounds

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In this study we examined DNA intercalation as an approach to understanding the minor and major groove binding nature of imidazoacridone derivatives.We report the binding affinity of imidazoacridone related compounds to the tetradecamer B-DNA duplex 5'-d(CATATGCGCATATG)-3'. Molecular dynamics simulations were explored to understand the intercalating behavior of imidazoacridone derivatives. A total of 108 models with intercalators and 22 models without intercalators were built, differing in binding geometries for each of the imidazoacridone derivatives. All calculations were carried out using AMBER with explicit solvent. We report the intercalator's movement within the binding site and we used HINT analysis to help interpret the experimental data. We explored differences in the minor and major groove widths especially in proximity to where the drug binds and compared these to equilibrated DNA without drug bound. The hydrogen bonding patterns, unwinding angle of the DNA helix caused by intercalation and other results have also been analyzed.

COMP 243

Computational studies of structure-activity relationships in FF neuropeptide

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Neuropeptide FF (NPFF) is a neurotransmitter involved in the intricate modulation of pain and opiate tolerance in mammals, via its G protein-coupled receptors, NPFF1 and NPFF2. To date, little information has been obtained as to the exact functions of NPFF receptors and the specific receptor-peptide interactions. Parallel tempering (replica-exchange) molecular dynamics (REMD) methodology is applied to NPFF and its most dominant conformational states are predicted using hydrogen bonding, NMR and clustering analyses. Calculations were carried out for both implicit and explicit solvent models and for different FF variants, in order to monitor the most probable conformations for the peptide, as well as any interactions between FF and the receptors. Our results provide important insight into the diverse pharmacological functions of neuropeptide FF.

COMP 244

Computational study of the interaction of sulfoindocyanine dye Cy3 with single- and double-stranded DNA

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Many fluorescent studies of biologically relevant systems employ sulfoindocyanine dye Cy3 as a label. Energy transfer and distance correlations are usually studied using Förster theory. To interpret such studies correctly one has to be able to separate the effects of the environment from the effects of the dynamics of the system on the fluorescence of the dye. In this work, we report results of the simulation of Cy3 dye attached to single- , double- and mixed-DNA. Our results indicate that Cy3-DNA interaction consists predominantly of two modes: interaction of Cy3 indole rings with nearby bases and hydrogen bonding of Cy3 CH2OH side-group to accessible H bond acceptors of the backbone and bases. We will use our data to help interpret recent experiment form the Levitus' lab at Arizona State University.

COMP 245

Role of ligand-receptor flexibility in the design of apoptosis targeting agents: Insight from molecular dynamics

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Detailed understanding of protein-ligand interactions is crucial to the design of more effective drugs. This is particularly true when protein targets have flexible, shallow or otherwise non specific binding sites. In this study, we use molecular dynamics and free energy calculations to explore the interactions of new classes of inhibitors with two apoptosis pahway cancer therapy targets: Bcl-xl and PTEN. We show how the activity of a new class asymmetric phospholipid based PTEN inhibitors is controlled by the flexibility of their alkyl chains, and investigate the role of cell membrane in mediating the binding process. Conversely, we demonstrate how receptor flexibility shaped the evolution of the most potent class of Bcl-xl inhibitors. Based on our findings, we suggest several strategies for designing inhibitors for targets that exhibit substantial structural rearrangement upon ligand binding.

COMP 246

Improved software user interfaces for computational prediction of kinetic rate constants

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Versatile user-friendly computational packages for calculating chemical rate constants based on quantum chemistry, reaction dynamics, and transition state theory are being developed. The Extensible Computational Chemistry Environment (ECCE), a full-featured graphical user interface, has been enhanced to incorporate variational transition state theory (VTST) calculations based on the quantum chemistry code NWChem and the transition state theory

code POLYRATE. The transition state, reactants, and products are determined through a single graphical user interface, which is then be used to generate the potential over the reaction coordinate and to calculate the rate constant. This greatly simplifies the process of performing VTST calculations. The reaction dynamics code VENUS has been enhanced to perform direct dynamics using NWChem based forces. Direct reaction dynamics using VENUS with NWChem is designed to run on high-performance parallel supercomputers as well as conventional workstation clusters. A web-based user interface is being designed to simplify running simulations with VENUS.

COMP 247

The determination of reaction rate constants for H-atom abstraction from N2H4 by H, NH2, CH3, C2H5 and NO2

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H-atom abstraction reactions involving hydrazine: N_2H_4 +R → N_2H_3 +RH (R = H, NH_2, CH_3, C_2H_5 and NO_2), were computationally characterized via variational transition state theory (VTST) calculations that included quantum-mechanical tunneling corrections. Reaction path stationary points were identified via geometry optimizations performed with a MPWB95/6-31+G(d,p) model (abbreviated hereafter as B1K), and the electronic energies of these structures calculated using CCSD(T)/6-311++G(3df,2p), CBS-QB3, G3(MP2) and G3 models. The enthalpies of formation [ΔHf°(298)] of N2H4 and N2H3 were determined from the characterization of isodesmic working reactions modeled by W1U, APNO, G2, G3, CBSQ, CBS-QB3 methods. The contributions of vibrational modes to the entropies [S°(298)] and heat capacities [Cp(T) 300 K < T < 1500 K] of the structures were calculated based on the B1K-determined geometric parameters and vibrational frequencies, with rigid-rotor-harmonic-oscillator or hindered internal rotation formulae applied as appropriate. Based on the CCSD(T)/6-311++g(3df,2p)//B1K model results, the barriers to the abstraction of an H-atom from N_2H_4 abstraction by H, NH_2, CH_3, and C_2H_5 are 4.0, 3.2, 7.4, and 7.8 kcal/mol, respectively. The calculated rate constants are in agreement with the experimental data that is available. Three different channels were identified for the N_2H_4 + NO_2 system: (1) N_2H_3 + cis-HONO (2), N_2H_3 + HNO_2, and (3) N_2H_3 + trans-HONO. The barrier to cis-HONO formation is 1.3 kcal/mol lower than the barrier to HNO_2 formation and 4.2 kcal/mol lower than the barrier to trans-HONO formation.

COMP 248

Rate constants from biased and unbiased reactive path ensembles

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A noise space scheme for sampling reactive Langevin trajectories is extended to the calculation of rate constants. In this formulation of the path sampling problem, Monte Carlo is used to sample the distribution of noise leading to reactive Langevin trajectories. The efficiency of this approach is compared to an established stochastic path sampling strategy and some subtleties of the two methods are considered. Finally, a framework for accelerating dynamics is introduced which makes use of path sampling in the correction of biased rate constants.

COMP 249

Rate estimation rules for H abstraction reactions by H and CH3 from pure and oxygenated hydrocarbons

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The increasing demand for model predictions of complex chemical systems such as internal combustion engines, biomass pyrolysis or gas phase chemistry in anode channels of solid-oxide fuel cells requires the development of large reaction mechanisms. Whether such reaction networks are constructed manually or via sophisticated mechanism generating algorithms, a critical component of assembling those will be to find a way of assigning rate constants to the large fraction of reactions for which detailed kinetic information is not available. Rate estimation methods based on Evans-Polanyi relationships provide a suitable solution to this issue. This approach relates the activation energy of a reaction to its exothermicity and uses a pre-exponential factor expressed on a per reaction site basis. Although Evans-Polanyi plots have been successfully used in the past, an important question remains: How similar must a reaction be to the reference reaction to assure that a given rate rule provides reasonably good predictions? We address this question by computing transition state theory rate constants for H abstraction reactions by H atoms from a large set of pure and oxygen containing hydrocarbons. The data set covers various reaction sites including primary, secondary, tertiary, vinylic and allylic C-H bonds. Comparisons to the sparse data available suggest these calculated rate coefficients are consistent with the experimental measurements, especially at temperatures above 500K. An analysis of the rate expressions shows that the activation energies and pre-exponential factors for a given site are rather invariant with the overall size of the

molecule. On the other hand, a single estimation rule is not able to capture the reactivity of all C-H sites. We will also compare the rate constants for H abstractions by H atoms with those for CH3 radicals.

COMP 250

Theoretical study of serially coupled chlorite-iodide oscillators

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A group of serially coupled flow reactors containing chlorite-iodide oscillators were computationally modeled. Reactant concentrations and flow rates were independently varied to thoroughly explore the system and produce stability diagrams. It was found that variations in flow rates can lead to oscillatory systems with periods which vary by integral multiples. Three reactors were employed in this oscillatory regime to create a ‘true' chemical clock, whereby the reactors oscillate with a frequency of minutes, hours, and days.

COMP 251

An ab initio molecular dynamics study of the initial chemical events in nitramines: Thermal decomposition of CL-20

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CL-20 or (2,4,6,8,10,12-hexanitro-2,4,6,8,10,12-hexaazaisowurtzitane) belongs to the class of high-energy The nitramine explosives. To improve atomistic understanding of the thermal decomposition in gas phase and bulk CL-20 we performed series of ab initio molecular dynamics simulations.

Unlike other nitramines like RDX/HMX we found only one distinct initial reaction channel (homolysis of N–NO2 bond) during unimolecular decomposition. We did not observe any HONO elimination reaction under these circumstances. Whereas, ring breaking reaction followed by NO2 fission. Therefore, in spite limited sampling that provide mostly qualitative picture, we proposed scheme of unimolecular decomposition of CL-20 .The averaged products population over all trajectories is estimated at 4 HCN, 2-4 NO2, 2-4 NO, ~1 CO, and ~1 OH molecule per one CL-20.

Our simulations provide a detailed description of the chemical processes in the initial stages of thermal decomposition condensed CL-20. They allow us to elucidate key features of such process: composition of primary reaction products, reaction timing, Arrhenius behavior of the system, etc. They clearly indicate that the primary reactions leading to NO2, NO, N2O and N2 occur at very early stages. We also estimate activation barrier for the formation of NO2 which is essentially determines overall decomposition kinetics and effective rate constants for NO2 and N2. Calculated bulk decomposition pathways correlates with available condensed phase experimental data. Unfortunately, comparison of the predicted gas phase mechanism is not possible.

COMP 252

Simulations of hydrogen clathrate hydrates

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Clathrate hydrates have been proposed as a potential hydrogen storage medium, and hydrogen clathrate hydrates exhibit a variety of interesting phenomena. Some of the more interesting phenomenology of hydrogen clathrate hydrates will be highlighted with recent simulations. Included will be a discussion of ensuring ergodic sampling over a wide range of temperatures.

COMP 253

Calculation of the folding/unfolding thermodynamics of an RNA tetraloop by replica exchange molecular dynamics

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We report molecular dynamics simulations of the equilibrium folding/unfolding thermodynamics of the RNA tetraloop in explicit solvent. A replica exchange molecular dynamics study of the r(CGUUGCCG) oligomer that forms a hairpin is performed for 226 ns per replica, using 52 replicas. We are able to show the unbiased folding of all replicas starting from extended conformations. The equilibrium pressure-temperature free energy of folding, $\int$xG(P,T), is calculated from the averaged energy, pressure, and specific volume change upon folding of

the oligomer as a function of T at constant volume. We find this oligomer is destabilized by increasing hydrostatic pressure, similar to the behavior of globular proteins.

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COMP 254

Thermodynamic and transport properties of DNA from Monte Carlo simulations of a coarse-grained model

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In the interest of treating complex systems involving genomes with computer simulations, we have developed a coarse-grained mesoscale model for DNA. Each chemical moiety in DNA is represented by an effective interaction site. The model preserves physically relevant features, such as major and minor grooves, and supports the presence of electrically charged sites. The model also reproduces several important characteristics of DNA, including salt-induced melting, hybridization, and mechanical properties. The parametrization of the model has been achieved in the context of replica exchange molecular dynamics (REMD) and density-of-states simulation platforms. By resorting to an appropriate order-parameter representation, it becomes possible to examine phase transitions in DNA with an unprecedented level of precision, thereby leading to a new model that can be used with confidence over relatively large ranges of conditions.

COMP 255

Calculation of adsorption free energy for peptide-surface interactions using biased-REMD simulations

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Protein-surface interactions play a fundamental role in implant biocompatibility. We are conducting MD simulations to calculate adsorption free energy (ΔG) for a series of host-guest peptides over surfaces with varied surface chemistry using CHARMM. ΔG determination is problematic because peptides become trapped in low-energy states close to the surface; hence not sampling the full phase space of the system. To solve this, we are applying umbrella sampling of the peptide as a function of its surface separation distance (SSD) to estimate the PMF vs. SSD profile. The inverse of this relationship is then applied as a biasing energy in REMD simulations, hence providing sufficient sampling of both SSD and peptide conformation for the calculation of ΔG. Results are being compared with experimental values from surface plasmon resonance spectroscopy. These comparisons will enable us to assess the accuracy of the CHARMM force field for this type of molecular system.

COMP 256

Novel ligand-induced Survivin dimer conformation via replica exchange molecular dynamics (REMD) and receptor-based reverse virtual screening

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Survivin is an anti-cancer drug target due to its over-expression in cancer cells. It has two important binding hot spots - the BIR domain and its dimerization interface. In this study, we probe conformational “plasticity” in the dimerization interface aiming at design and discovery of dimerization inhibitors.

The Abbott laboratory has identified a small molecule binding site near the interface of the survivin dimer through NMR experiments [1]. A benchmarking of the Abbott8 compound binding modes aided in the refinement of the receptor conformation by exploring the survivin conformational flexibility. The REMD method was utilized to enhance the sampling of the dimer. A ‘reverse VS' with Abbott8 compound against a large set of conformations sampled via REMD allowed for a reproduction of the NMR experimental binding mode. Compared to the X-ray structure a prolific change in a survivin alpha-helix allows a new flexible loop conformation better suited for ligand binding.

[1] Wendt, M. D. et al. Bioorganic & Med. Chem. Lett. 2007, 17(11), 3122-3129

COMP 257

Testing, validation, and parameterization of density functionals and molecular orbital theory for zinc bio- and nanocenter coordination chemistry

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Here we present nonrelativistic and relativistic benchmark parameter databases (obtained by coupled cluster calculations) of Zn-ligand bond distances, dipole moments, and twelve bond dissociation energies in Zn coordination compounds with O, S, NH3, H2O, OH, SCH3, and H ligands. These are used to test the predictions of density functionals, Hartree-Fock theory, and more approximate molecular orbital theories for zinc bio- and nanocenters. We specify the most accurate methods for this test data in relativistic and nonrelativistic benchmark analyses, where the relativistic calculations incorporate a relativistic effective core potential. We find significant relativistic effects that cannot be neglected for accurate modeling, but the same density functionals that do well in all-electron nonrelativistic calculations do well with relativistic effective core potentials. Although most tests are carried out with augmented polarized triple zeta basis sets we also evaluate some functionals with an augmented polarized double zeta basis set, and we find, on average, that with the smaller basis set DFT has no loss in accuracy for dipole moments and only ~10% less accurate bond lengths. Finally, we examine the efficacy of new molecular orbital theory parameter sets designed specifically for Zn as compared to more general density functional and molecular orbital theory methods.

COMP 258

Methane and silane dimer potentials from quantum chemistry calculations

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We have calculated the methane-methane, methane-silane, and silane-silane dimer interaction potentials using Hartree-Fock (HF) method, Møller-Plesset (MP2) method, coupled cluster [CCSD(T)] method and density functional theory (DFT). Basis set effects on the equilibrium bond length, the binding energy, and the asymptotic behavior of the calculated potential are thoroughly studied. In general cases, it requires the aug-cc-pVTZ basis set to converge the binding energy to an accuracy ~0.01 kcal/mol. Only the basis set superposition error (BSSE) corrected results systematically converge to the expected basis set limit values. The DFT potentials can be correlated to the exchange and the correlation

enhancement factors at the low density limit. Molecular dynamics simulations have been performed using the calculated potentials and the simulated structural and thermodynamic properties are compared to the available experimental results and/or other theoretical results.

COMP 259

Nonequilibrium DFT properties of intramolecular hydrogen bonding in malonaldehyde, aminoacrolein, iminopropenylamine and derivatives

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The nonequilibrium properties of the intramolecular hydrogen bonding conformers of malonaldehyde, aminoacrolein, 3-iminopropenylamine, and their simple derivatives have been studied theoretically using density functional theory. The B3LYP/6-311++G(2d,p) method yields equilibrium structures in close agreement with experiment. In a series of constrained optimizations, the donor-acceptor distance was varied systematically from well below to well above the equilibrium geometry. It is revealed that the O-H...O interaction of malonaldehyde and the N-H...N interaction of 3-iminopropenylamine are able to form symmetric hydrogen bonds at short donor-acceptor distances, with an atoms-in-molecules (AIM) analysis revealing an essentially three-center, four-electron bond. In contrast, the N-H...O interaction in aminoacrolein becomes repulsive at short donor-acceptor distances. The results are rationalized in terms of molecular symmetry and the pseudo-Jahn-Teller effect.

COMP 260

Origin of Lewis acid strength within mixed boron halides

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The controversial understanding of Lewis acidity trends observed in boron halide Lewis acids has been investigated utilizing QCISD(T)/aug-cc-pVQZ and natural bond orbital analysis.The gas phase Lewis acidity trend of $BH_{(3-x)}F_x$, $BH_{(3-x)}Cl_x$, and $BCl_{(3-x)}F_x$ (X = 0, 1, 2, or 3) has been analyzed as a function of isolated Lewis acid reorganizational energies, steric repulsions, and stereoelectronic effects. It has been determined from multiple linear regression that only three stereoelectronic effects account for the observed trend in Lewis acidity. The

primary contributor is the dative donor–acceptor frontier molecular orbital interaction, n(N) → n*(B). The secondary effects are σ(B-X) →σ*(B-N) and σ(B-N) → σ*(B-X) hyperconjugative interactions (adjusted R^2 = 0.96, F-value = 83.2, and corresponding p-value = 0.0001, α = 0.05, 95% confidence). The statistics show that only the linear combination of stereoelectronic effects is significant. The new fundamental understanding is discussed in terms of organic reactivity and catalysis.

COMP 261

Quantum chemical calculations of surface photovoltages: Applications to adsorbates on Si(111)

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Photovoltages for adsorbates on semiconductor surfaces are obtained as functions of photon energy from ab initio calculations within a density functional treatment using atomic pseudopotentials and augmented plane waves. They are derived from time averages of surface electric dipoles, which follow from a time-dependent density matrix (TDDM) treatment using a basis set of Kohn-Sham orbitals and a steady state solution for the TDDM equations of motion. Applications have been done to a H-terminated Si(111) surface and to clusters of Ag atoms on Si(111):H . Changes of orbital shapes leading to surface electric dipoles are shown to provide physical insight. The location of large photovoltages versus photon energy are calculated and compared with available experimental data. Our treatment can be implemented for a wide class of photo-electronic materials relevant to solar energy capture.

COMP 262

Solid memory: Structural preferences in Group 2 dihalide monomers, dimers, and solids

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We examine, theoretically, connection between structural preferences in the monomers, dimers and extended solid state structures of the group 2 dihalides (MX2: M = Be, Mg, Ca, Sr, Ba and X = F, Cl, Br, I). Significant links between the bending in the MX2 monomers, the D2h/C3v M2X4 dimer structures have been

identified. The monomers that are bent prefer the C3v triply-bridged geometry, while the rigid linear molecules prefer a D2h doubly-bridged structure. A relationship observed between the structural trends in the MX2 and M2X4 series of structures, and the preferred structure types in the group 2 dihalide solids is discussed. The most bent monomers condense to form the high co-ordination number fluorite and PbCl2 structure types. The rigid linear monomers condense to form extended solids with low coordination numbers. The reasons for these correlations are explored.

COMP 263

3-D structural insights for DPP-IV inhibition with Abbott compounds

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Dipeptidyl peptidase IV belongs to a family of serine peptidases, and due to its indirect role in regulation of plasma glucose levels, DPP-IV has become an attractive pharmaceutical target for diabetes therapy. To elucidate details of the active site for structure-based drug design, the 3-dimensional structure of DPP-IV was determined using X-ray crystallography methods. The active site architecture provides important details for the design of selective inhibitory compounds, and experimentally determined structures of more than 100 inhibitor-protein complexes offer insight to structure-activity relationships that include protein movement. Integration of structural information by project team scientists contributed to the discovery of clinical candidates ABT-279 and ABT-341 at Abbott Laboratories. Details of this discovery process will be presented.

COMP 264

Structural biology and molecular modeling in the design of novel DPP-4 inhibitors

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Inhibition of dipeptidyl peptidase IV (DPP-4) is a promising new approach for the treatment of type 2 diabetes.1 DPP-4 is the enzyme responsible for inactivating the incretin hormones glucagon-like peptide 1 (GLP-1) and glucose dependent insulinotropic polypeptide (GIP), two hormones that play important roles in glucose homeostasis. The potent, orally bioavailable and highly selective small molecule DPP-4 inhibitor sitagliptin has been approved by the FDA as novel drug for the treatment of type II diabetes. The comparison between the binding mode of sitagliptin (a β-amino acid) and that of a second class of inhibitors (α-amino

acid) initially led to the successful identification and design of structurally diverse and highly potent DPP-4 inhibitors. Further analysis of the crystal structure of sitagliptin bound to DPP-4 suggested that the central β-amino butyl moiety could be replaced by a rigid group. This was confirmed by molecular modeling, and the resulting cyclohexylamine analogs were synthesized and found to be potent DPP-4 inhibitors. However, the right hand side triazolopyrazine was predicted to be distorted in order to fit in the binding pocket, and the crystal structure showed that multiple conformations exist for the right hand moiety. Additional molecular modeling studies were then used to improve potency of the cyclohexylamine series. In addition, a 3-D QSAR method was used to gain insight for reducing off-target DPP-8/9 activities. Novel compounds were thus synthesized and found to be potent DPP-4 inhibitors. Two compounds in particular were designed to be highly selective against off-target DASH enzymes while maintaining potency against DPP-4.

COMP 265

Lessons about molecular recognition from structure-guided targeting of DPP-IV

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Inhibition of the serine protease dipeptidyl peptidase IV (DPP-IV) offers a new therapeutic approach for type 2 diabetes. Supported by X-ray crystal structure information, we were able to optimize several chemotypes towards low nanomolar DPP-IV inhibition combined with a favorable physicochemical property profile. We describe our structure-guided optimization approach for the aminobenzoquinolizine hit series. Another focus of this presentation is placed on the analysis of the key molecular interactions in DPP-IV/inhibitor complexes and their exploitation by molecular modeling methods. Interesting insights into molecular recognition principles can be gained, which could be helpful for other drug design projects.

COMP 266

Structure, function and inhibitors of prolyl dipeptidase DPP8

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DPP8 is a prolyl dipeptidase capable of cleaving the peptide bond after the penultimate proline residue. Due to the proline cleaving activity and the potential to be drug targets, this family of proteases, including DPP-IV, DPP9, FAP and DPP-II, has attracted intensive investigation from both academia and industry. Despite of sequence homology and structural conservation, there are a number of differences on the structure and inhibitor profile between DPP8 and DPP-IV. First, we showed that DPP8 proteins are dimeric with small quantities of tetramers (Lee et al. 2006). Single site mutation at one of the dimer interfaces renders the enzyme inactive and these inactive DPP8 proteases remain dimeric (Lee et al., 2006), in sharp contrast to DPP-IV, whose mutations at the corresponding sites disrupt the dimers to inactive monomers (Chien et al. 2004 and 2005). We also showed that DPP8 is slightly more selective than DPP-IV at the P2 site by profiling against a dipeptide substrate library (Lee et al. 2006). Furthermore, a potent and selective inhibitor of DPP8 has also been discovered revealing significant difference on the P1 site between DPP-IV and DPP8 (Jiaang et al. BMCL 2005). Moreover, this inhibitor is devoid of inhibitory activity against DPP9 and other prolyl dipeptidases, making it the most potent and selective DPP8 inhibitors reported so far (Lankas et al. 2005). Understanding the biochemical properties of DPP8 and discovering its inhibitors will facilitate the identification of its substrates and biological function in vivo.

References:
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COMP 267

Homology models of Dipeptidyl Peptidases 8 and 9

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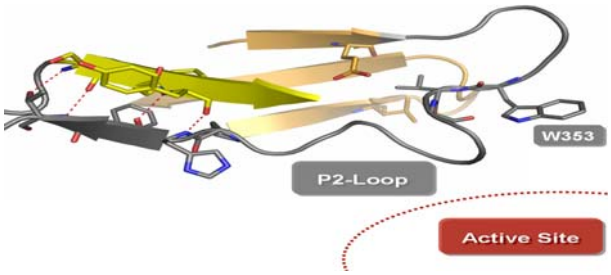
The first Dipeptidyl Peptidase 4 inhibitor as treatment for type II diabetes was launched in the US in January 2007 and several programs aiming at the same target are close behind. The selectivity of DP4 inhibitors towards the related but structurally unknown enzymes DP8 and DP9 has emerged as a possible source of drug-induced toxicity. We derived homology models of DP8 and DP9 in order to rationalize the SAR and selectivity of several chemical series in our in-house discovery project. The models are based on the X-ray coordinates of DP4 (sequence identity ~20%) involving meticulous overall sequence alignment and extensive modeling of two loops conformations close to the active site. The

influence of crucial parameters (e.g. water molecules, ligand, loop size) on the loop refinement was carefully evaluated in a study using several structurally known templates. The modeling approach using the Schrödinger PRIME software, the resulting sites of DP8/DP9 as well as the selectivity of known DP4-inhibitors will be discussed in light of our findings.



COMP 268

Applicability domains, space coverage, and predictive power of QSAR models

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For many years, our group has advocated the use of applicability domains (AD) as a mandatory component of QSAR modeling. The AD defines the boundaries of the chemistry space within which the models could be used reliably for predicting compounds' bioactivities. The specific definitions of AD depend on the descriptor types, similarity metrics, and particular modeling techniques. I shall discuss specific examples of AD implemented in our group in the context of k Nearest Neighbor (kNN) and Support Vector Machines (SVM) QSAR approaches as well as in special scoring function for protein-ligand docking. Expanding the AD naturally leads to higher coverage of the chemistry space; however it may also lead to lower prediction accuracy. Thus, I shall emphasize the challenges in finding optimal AD that afford a reasonable balance between chemical space coverage and prediction accuracy of QSAR models. I will also discuss the use of AD for outlier detection.

COMP 269

Testing the validity range of QSAR models using one-class support vector machines

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One-class Support Vector Machines (SVM) are a powerful method for outlier detection and anomaly detection. This presentation highlights the use of one-class SVMs for evaluating QSAR model validity. For example, one typical HIV RT inhibitor dataset contains at least five different molecular classes. In this case, five different QSAR models were built using PLS and K-PLS, each time leaving out all the molecules for a particular class. A one-class SVM was then applied to confirm that the activity of molecules from the remaining class cannot be adequately predicted if no training samples from that class were included. The general use for one-class SVMs for evaluating model validity for QSAR datasets in general will then be discussed. Modeling features include MOE, TAE/RECON and PEST shape/property hybrid descriptors.

COMP 270

Assessment of additive/nonadditive effects in SAR: Implications in the drug discovery iterative process

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Free-Wilson analysis of structure-activity-relationships is common practice in medicinal chemistry; and, nowadays, this additivity principle is becoming more prominent due to the popular modular approach for rational drug design: fragment-based drug design. In addition, additivity is implicit in most scoring functions used in structure-based design.

Our aims are to determine if we can estimate which effects, additive or non-additive, are taking place in near complete combinatorial libraries for the biological response(s) under study and then to determine the minimum attributes

of a data set (size, distribution of properties etc) necessary to reach the same conclusion about additive/non-additive effects.

Eight near complete combinatorial libraries have been utilized and they show the complexity of protein-ligand interactions: additive, non-additive and partially additive data sets. Then, a series of retrospective experiments are carried out providing some guidelines on when it is appropriate to apply Free-Wilson analysis and implications for iterative drug design.

COMP 271

Similarity based assessment of model applicability domain and quantitative evaluation of the reliability of the prediction

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Development of a methodology for the evaluation of Model Applicability Domain is presented using similarity analysis of the compounds in the training set. A novel methodology relying on the fact that any empirical in silico model works only for similar compounds was developed. The availability of similar compounds in the training set and experimental data consistency for such compounds was pivotal. This information is reflected in a corresponding Reliability Index (RI), which generates values from 0 (not reliable) to 1 (very reliable), assisting in interpretation of the results. The methodology is illustrated with examples of its application in estimating Model Applicability Domain for the models of logP, logD, solubility and toxicity. The reliability index is shown to be closely related to the overall quality of any given prediction that is represented by a clear correlation of the RI and RMSE values.

COMP 272

Localizing uncertainty in PLS predictivity

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Ordinary least squares regression (OLS) is convenient in that it provides a direct estimate of the uncertainty in prediction for any point in the descriptor space. Unfortunately, such estimates are only reliable when the underlying relationships

are linear, the descriptors are mutually independent, and the observations themselves are identically and independently distributed (IID). Partial least squares with projection to latent structures (PLS) is typically applied instead when there are more descriptors than observations. It is also more appropriate when the descriptors are not independently distributed, however, as is generally the case for structure-activity relationships. Here, we will examine the effectiveness of distributing the predictive sum of squares (PRESS) from PLS across the individual observations in a training set to model the predictive uncertainty in different parts of the applicability domain.

COMP 273

Ensemble QSAR

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Exhaustive searching for QSAR models through generation of all possible combinations of descriptors leads to dozens or even hundreds of models with r^2 and errors very close to the best result but differing in one or more descriptors. The models are so close that it is difficult to justify one model over the other. We use this to advantage by creating ensembles of models and using the ensemble to estimate the errors in predicted results. When making predictions with the ensemble model, in addition to checking the chemicals predicted for compliance with the training set chemical space and training set descriptor and property ranges, we find that the distribution of predicted values from the ensemble of models is an excellent diagnostic of model applicability. In this talk we describe the method and present examples of its use.

COMP 274

Advanced multicanonical replica exchange simulations

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Enhanced and efficient sampling in biomolecular simulations remains an important problem. The inherent rugged energetic landscapes of proteins inhibit sampling rates during computer simulations thus prolonging simulation times to unreasonable lengths. We have studied generalized-ensemble algorithms that take advantage of random walks in energy space to overcome potential barriers and hence alleviate kinetic trapping. The widely used replica exchange molecular

dynamics (REMD) method has gained footing in the community by using different walkers (usually in temperature space) to overcome energy barriers. Regular REMD suffers from the need to use a large number of replicas for large systems. This number can be shown to scale as the square root of the number of degrees of freedom. The multicanonical version of REMD substantially decreases the required number of replicas, hence increasing efficiency. We have optimized simulations to increase speed-up in generalized-ensemble algorithms including the multicanonical replica exchange method. We also implemented tools for measuring convergence and analyzing properties within the regime of generalized-ensemble algorithms.

COMP 275

Force field evaluation based on NMR experiments and molecular dynamics simulations involving folded proteins

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Molecular dynamics (MD) simulations provide an atomistic description of protein structure and dynamics, and recent advances in simulation algorithms have made possible individual simulations on a microsecond timescale. In this talk, we examine and evaluate several widely used molecular mechanics force fields based on information about the dynamics of folded proteins derived from long-timescale MD simulations and previously reported NMR data. The results of multiple MD simulations, each using a different force field, are systematically compared with the results of protein NMR experiments. Each MD simulation had a duration of several hundred nanoseconds (with an aggregate simulation time in excess of 9 microseconds), while the NMR experiments provide a detailed description of structural properties and fluctuations of both the backbone and the hydrophobic core of proteins on a wide range of timescales. The results of our systematic force-field comparisons suggest certain potential strengths and weaknesses of individual force fields.

COMP 276

Multiscale Monte Carlo sampling of proteins

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A multiscale Monte Carlo sampling scheme for macromolecules is presented that allows for hierarchical sampling of sidechain and backbone degrees of proteins and cyclic peptides in an implicit solvent model. The method uses the OPLS-AA 2001 forcefield, and a SGB/NP implicit solvent model for solvation. A variant of the multiple time step Monte Carlo algorithm is used to optimally sample coordinates within the SGB model of solvation.

The sidechains are sampled by perturbing the sidechain dihedrals uniformly. The backbone sampling is accomplished using our loop closure algorithm.

A novel algorithm for sampling of complex biomolecular landscapes and combining heterogeneous geometric move sets will be presented. Validation data will be presented on binding pockets, flexible loops, and cyclic peptides.

COMP 277

Predicting protein structure using inter-residue distances

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Knowledge of a protein's structure is important in understanding its function. The usual experimental structure determination methods can be costly and time-consuming. We present an idea for a fast and inexpensive protein structure prediction method that combines modeling with less expensive experimental data. Our method involves three steps: (1) building a decoy set, (2) measuring inter-residue distances in a target protein, and (3) comparing the measured distances with those calculated in each decoy. We postulate that structures with a small number of similar inter-residue distances will also have similar three-dimensional structure. We further hypothesize that the minimum number of distances needed to determine structure is much less than the total number of inter-residue distances in the protein. We will also present our refined scoring procedure which uses threading and molecular dynamics.

COMP 278

The coordination environments of Cu(I) in proteins: Cu(I) parameter development for CHARMM

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CHARMM force field topology and parameters for Cu(I) in proteins have been developed for both linear and trigonal planar coordination geometries. Two model compounds containing these coordination geometries were selected from the Cambridge Crystal Database and the parameterization strategy involves exploring four different methods: B3LYP, S-VWN, MPW1K and MP2 to determine which provides the most accurate results as compared to the experimental crystal structures. Interestingly, the MPW1K method provided the best results as compared to experiment for both models. The Cu-S bonds, angles and torsional terms were calibrated against structures and energies using the MPW1K/6-311+G(d,p) level of theory for the linear model and MPW1K/6-31G(3d) level of theory for the trigonal planar model. The resulting error between geometry-optimized CHARMM and MPW1K/6-311+G(d,p) computations for the linear model compound is 0.0028 ± 0.002 Å for the Cu-S bond distances and 6 ± 4° for the S-Cu-S bond angle. The resulting error for the optimized CHARMM and MPW1K/6-31G(3d) level of theory for the trigonal planar model compound is 0.022 ± 0.015 Å for the Cu-S bond distances and 4 ± 3° for S-Cu-S angles. A 2 ns molecular dynamics crystal simulation was performed on the Cu(I) chaperone, Hah1 containing a trigonal planar metal binding environment which resulted in an average RMSD between simulation and experiment of 1.40 ± 0.1 Å. The improved CHARMM force field for describing the Cu(I) coordination will allow for more accurate simulations of proteins.