COMP 1

Docking performance accelerated 30-50 fold on the Cell/BE processor

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The eHiTS flexible docking has proven to be among the most accurate pose prediction tools (http://www.simbiosys.ca/ehits/ehits_validation.html) providing one of the highest enrichment factors based on comparative evaluation studies (http://www.simbiosys.ca/ehits/ehits_enrichment.html). The accurate results of eHiTS have been achieved at the price of longer CPU times in the past, but that has changed with the recent port of the algorithm to the Cell/BE processor (http://www.bio-itworld.com/issues/2008/july-august/simbiosys.html). The revolutionary hardware that powers RoadRunner (the world's current fastest supercomputer) and also available in the low cost SONY PS3 game console, gives eHiTS 30-50 fold speedup compared to a single core Intel/AMD processor. The advantages of the Cell/BE platform over other acceleration techniques (FPGA,GPGPU) will be described, along with the challenges faced during the porting effort. A new proximity data structure is introduced that is optimized for SIMD architectures. It allows efficient evaluation of short range pairwise interactions with optimum cache locality.

COMP 2

Large-scale computational approaches: New tools to enable biomass conversion to ethanol

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Liquid fuel derived from biomass shows great promise as a major source of renewable energy for the future. One approach is to use enzymatic degradation of plant cell wall polymers, especially cellulose, to monosaccharides that can subsequently be fermented to alcohols or converted to other useful fuels. Natural biomass deconstruction processes are, unfortunately, very slow. We are addressing the problem of the remarkably slow rate of conversion of cellulose using small- to large-scale molecular dynamic and molecular mechanic computations. Studies of all components of the problem, including the elusive cellulose structure, the plethora of cellulose-degrading enzymes, and very large structures such as cellulosomes, require simulations of very large systems for long times. More loosely coupled simulations of many multiple copies of a system

to gather reaction path and thermodynamic information are also required. This presentation will detail several of our larger simulations and the methods we are using to gather useful information to pass on to the experimentalists to aid in their effort to create a faster, more efficient process via engineering the enzymes and/or their substrates.

COMP 3

Accurate modeling of biomolecular structure and dynamics using atomic-detail simulations

***Carlos L Simmerling**, carlos.simmerling@sunysb.edu, Department of Chemistry, SUNY Stony Brook, Stony Brook, NY 11794, Fax: 631632-1555*

Experimental methods have been highly successful in determining 3-dimensional biomolecular structures. However, most approaches provide only time- and ensemble-averaged data. Atomic-resolution simulations are highly complementary to experiments, and can provide data with unparalleled resolution in time and space. This seminar will summarize our recent work, including development of an accurate force field model and improving efficiency through the sharing of information between multiple simulations. Results will be presented for HIV-1 protease, a key model system for structure-based drug design, with quantitative comparison against experimental data from crystallography, NMR and EPR. Coarse-grain modeling along with microsecond-length atomistic simulations in explicit water provide insight into the dynamic behavior of the protease, including characterization of the transition pathway between experimentally observed structures, comparison of drug-resistant mutants and development of a model for the fully open form in which the active site becomes accessible to protein substrates and vulnerable to inhibitors.

COMP 4

Multiscale simulation of cellular cytoskeleton proteins and their assemblies

***Gregory A. Voth**, voth@chem.utah.edu, Center for Biophysical Modeling & Simulation, University of Utah, Department of Chemistry, 315 S. 1400 E. Rm 2020, Salt Lake City, UT 84112-0850*

In this talk it will be shown how large scale molecular dynamics simulations combined with coarse-graining and other multiscale techniques can characterize key proteins and multi-protein assemblies of the cellular cytoskeleton. These studies will be used to elucidate actin filament behavior as a function of both bound nucleotide state and the underlying actin protein conformations, the effect of cofilin binding to actin filaments, the structure and dynamics of the critical

Arp2/3-actin branch junction, and the self-assembled properties of microtubules as they relate to the underlying structure of the tubulin heterodimer components. In the spirit of this symposium, these studies highlight the current computational state-of-the-art in addressing complex biomolecular problems of relevance to cellular processes.

COMP 5

Insights into the activation pathway of the adenovirus protease enzyme: Large scale nudged elastic band simulations on NSF supercomputers

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The adenovirus proteinase (AVP) is essential for adeno virus replications and hence is a target for antiviral drugs aimed at treating infections such as bird-flu and SARS. The enzyme is activated upon the binding of a small peptide via a 53 amino acid signal transduction pathway. Recently obtained crystal structures of both the inactive and active forms of AVP provide the two end points of this pathway. This talk will highlight attempts, in combination with experimentalists at Brookhaven National Laboratory, to characterize this pathway. This includes a combination of standard molecular dynamics simulations, replica exchange simulations and a complete characterization of the structural motions involved in the activation pathway using a simulating annealing based Nudged Elastic Band (NEB) algorithm that is implemented within the AMBER software. Simulations to date, carried out on NSF supercomputers, have revealed some interesting features of this pathway and it is hoped that this insight, coupled with experimental feedback, will provide valuable data that can aid in identifying novel drug targets other than the active site and in finding drugs that prevent the utilization of the pathway.

COMP 6

Elucidating protein function through high-performance molecular dynamics simulation

Ron O. Dror*, D. E. Shaw Research, 120 W. 45th St, 33rd Floor, New York, NY 10036*

Molecular dynamics (MD) simulations provide a promising method to characterize the conformational changes that are critical to protein function, but

many relevant biomolecular events occur on timescales beyond those accessible by simulation. Recent advances in algorithms for high-performance parallel MD have allowed us to address a substantially broader set of questions regarding protein function, by enabling both longer-timescale simulations and iterative exploration based on fast turnaround time for individual simulations. This talk will describe the application of these techniques to membrane proteins, including a transporter, a channel, and a G-protein-coupled receptor. In each of these studies, we used high-performance MD to either deduce an atomic-level mechanism for protein function or to reconcile apparent discrepancies among recent experimental observations.

COMP 7

Lessons learned from predicting binding free energies in model binding sites

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Binding affinity prediction has long been a goal of computational modeling of protein-ligand interactions, but it has proven an elusive one. Many methods struggle even to discriminate between binders and nonbinders and fall far short of predicting affinities. We will recap recent work predicting binding free energies, using molecular dynamics free energy calculations, in a model nonpolar binding site, and the quantitative insights gained from that work. Then we will discuss ongoing work making and refining predictions in a polar model binding site that presents additional challenges beyond the nonpolar cavity, such as additional unforseen protein flexibility and other factors. We also provide some comparison between approximate endpoint free energy calculations using MM-PBSA and our full alchemical free energy calculations.

COMP 8

MD study of origin of enantioselectivity in CPO-catalyzed epoxidation

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The binding of selected substrates at the active site of chloroperoxidase (CPO) and along the narrow channel, and the influence of particular binding site residues on measured enantiomeric excesses, are reported. The results have implications for bioengineering CPO as a chiral biocatalyst for the synthesis of epoxides. The work is based on simulation with some input from NMR.

COMP 9

Modeling glycine tautomerization and glycyl-glycine peptide bond formation using a reactive force field

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Neutral to zwitterion tautomerization of glycine and glycyl-glycine peptide bond formation are two of the most important and fundamental chemical processes that involve bond breaking and bond making. A polarizable and reactive force field, ReaxFF, has been parameterized to simulate these processes in the gas phase and in water. An ab initio derived training-set of several molecular clusters with variable geometries were used to fit the force-field parameters. The relative energies of different conformations of glycine have been assessed. The predicted free-energy barrier for the glycine tautomerization reaction matched well with experiment. A reaction mechanism for glycyl-glycine peptide bond formation has also been proposed. The effects of water catalysis, presence of ions, and temperature variation, have been studied for these two reactions. These studies will lead ReaxFF to successfully simulate important and complex chemical reactions involving polarization, charge transfer and bond breaking.

COMP 10

Multiscale approach to developing universal coarse-grained peptide force fields

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Reducing the complexity of molecular systems via coarse-grained (CG) modeling allows larger length and longer time scales to be simulated. We recently described a method to obtain multiscale coarse-grained (MS-CG) peptide models directly from all-atom simulation data. This study extends that approach to generate a single MS-CG force field able to describe structural properties of peptides displaying disparate secondary structural motifs. This is accomplished by systematically incorporating information from different peptide ensembles into the multiscale procedure. In principle, this strategy allows MS-CG models to be finely tuned to study processes that encompass transitions between distinct regions of configuration space. Successes of the method as well as its limitations are discussed. The systematic nature of the approach suggests straightforward paths to future improvement. We anticipate that this scheme will be of general utility in the development of MS-CG models.

COMP 11

Statistically optimal free energy estimates from sparsely chosen states

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We recently presented a minimum variance method (J. Chem. Phys. 129, 124105 (2008)) to calculate free energies and ensemble averages from multiple equilibrium simulations conducted at different thermodynamic states, which gives the same results as WHAM in the limit of vanishingly small histogram bins, but does not require histograms, eliminating bias due to binning. This new estimator is especially useful for highly multidimensional problems where histograms cannot be well populated and additionally yields an expression for the statistical uncertainty of the estimates. However, this estimator (like WHAM) requires reevaluation of the potential energy of the system at all other thermodynamic states under study. This can become a computationally unreasonable burden when there are many states, such as 3-dimensional potentials of mean force obtained through umbrella sampling or alchemical simulations with many intermediates. To solve the problem of efficiently computing averages and free energies with large numbers of states, we derive a modification of the multistate minimum variance method that uses only states with sufficient mutual phase space overlap. We present a number of test cases of this method, including small molecule solvation, and 3D potentials of mean force of small molecules in the ribozyme exit tunnel.

COMP 12

Stochastic thermostat induced synchronization of MD trajectories in biomolecules

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Molecular dynamics simulations starting from different initial conditions with subsequent averaging of experimental observables are commonly used as a way to mimic the behavior of an experimental ensemble. While recent studies have shown that stochastically thermostatted trajectories evolving within a single potential basin with matched random number seeds tend to synchronize, we show that there is a partial synchronization effect even for complex, biologically relevant systems, and even when the trajectories are initiated from substantially different geometries corresponding to different conformational basins. We demonstrate this effect in simulations of Alanine trimer and pentamer and we show an example of synchronization in a simulation of a temperature-jump experiment for peptide folding of a 14-residue peptide. Even in replica-exchange simulations, in which the trajectories are at different temperatures, we find partial synchronization is clearly evident when the same random number seed is employed. Our results suggest several ways in which mishandling selection of the a pseudo random number generator initial seed can lead to corruption of simulation data.

COMP 13

Synergistic regulation and ligand-induced conformational changes of tryptophan synthase

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Tryptophan synthase (TRPS) is a bifunctional, tetrameric enzyme that is composed of two α and two β subunits, arranged in a linear fashion as αββα complex and catalyzes the last two steps in the biosynthesis of L-tryptophan in prokaryotic and lower eukaryotic organisms. The center of the active sites of both α and β subunits are far apart from each other and are connected via a 25 Å long

tunnel, which allows for the direct substrate channeling of the reaction intermediate. In ligand-free state both α and β subunits are proposed to exist as an equilibrium between an open and a partially closed conformations. However, as the α-site ligand (ASL), such as 3-indole-D-glycerol 3'-phosphate (IGP) binds to the α-active site the equilibrium distribution shifts towards the closed conformation state, the more active form. These ligand-mediated conformational changes in the protein substructure and the molecular basis of allosteric communications at inter-subunit level have been a subject of interest since decades for both experimental and computational chemists.

The current work comprises of molecular dynamics (MD) simulations of ligand-free and ligand-bound protein complexes at nano time scale in both implicit and explicit water solvent in order to evaluate the effect of ligands on loops (L2 and L6) and communication domain (COMM) movements. The dynamics of residues α-Gly181 (L6) and β-Ser178 (COMM), α-Asp60 (L2) and α-Thr183 (L6), α-Asp56 (L2) and β-Lys167 (COMM) were of particular interest as these residues are proposed to be involved in allosteric communications, switching of the loops to open and closed conformations and substrate channeling processes.

COMP 14

Coarse-grained models to reflect functional dynamics of large biomolecules obtained by an elastic network model

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We have developed a new and systematic methodology called essential dynamics coarse-graining (ED-CG), which variationally determines the CG sites that reflect the functional essential dynamics characterized by principal component analysis (PCA) of a molecular dynamics (MD) trajectory. The present work extends the ED-CG scheme to define CG sites in a biomolecule that approximate the low-frequency normal modes obtained by a one-site per residue elastic network model (ENM) of the system. Numerical calculations for the HIV-1 CA protein dimer and ATP-bound G-actin indicate similar ED-CG models to the published data by PCA of atomistic MD trajectories, but only a single structure of the biomolecule is needed here. The ED-CG with the ENM model is particular useful to these huge biomolecules when the MD simulations are computationally expensive or the atomistic structures are not available. As an example, the ED-CG models of the thermus thermophilus 70S ribosome have been defined.

COMP 15

Quantum chemical and detailed chemical kinetic modeling of methylamine oxidation: Applications to atmospheric and supercritical water chemistries

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Previous attempts to model both low-temperature atmospheric and supercritical water oxidation of methylamine have failed due to a lack of elementary kinetics for peroxy radical reactions involving methylamine and its free-radical derivatives. We have explored the potential energy surface (PES) for the reaction of CH_2NH_2 + O_2 using ab initio quantum chemical calculations with the CBS-QB3 method. Using the information from the PES, we have computed reaction rate constants from transition state theory. These rate constants are then used as input to improve an existing detailed chemical kinetic model to describe the homogeneous oxidation of methylamine under both atmospheric and supercritical water conditions. In both cases, we use our mechanistic simulations to determine global reaction orders and activation energies. Reaction pathway and sensitivity analyses are used to identify the main routes of chemical transformations and most important elementary reactions.

COMP 16

Force-field development for heavy elements using ab initio data and the force matching method

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An algorithm has been developed for fitting classical force-fields, based upon the force matching method. It is interfaced with the electronic structure codes Gaussian03 and Crystal06 and the molecular dynamics codes DL_POLY, LAMMPS, and Amber. The quality of force-fields fit solely to the ab-initio data and PES (rather than experimental observables) has been examined with an emphasis upon the fitting of different functional forms with varying accuracy to the local minima vs. the entire dissociation curve for a given potential. The efficacy of different minimization methods has also been examined as a function of the analytic expression of the force-field. This method has been applied to the

fitting of force-fields for trivalent lanthanides in aqueous solution that have relevance to both environmental remediation and nuclear fuel cycle processes.

COMP 17

Shot-noise-limited detection of conformational states and photoblinks in single-molecule FRET trajectories

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As the methods of single-molecule spectroscopy advance, so does the complexity of the systems being studied. In particular, many biological systems show complexity not only in the ensemble regime, where multi-step enzymatic reactions are quite commonplace, but in the single-molecule regime as well. Mechanistic heterogeneity and conformational dynamics combine to create single-molecule FRET trajectories that are bursting with buried information. In order to distinguish noise from experimental information, various statistical models, such as hidden-Markov models, have been developed and implemented with relative success. This work presents an algorithm using a combination of statistical methods that, when applied to a single-molecule time trajectory, will simultaneously detect the presence of photoblinks and distinct conformational states within the limits of the experimental data in question.

COMP 18

Path sampling for nonequilibrium processes in many-dimensional order-parameter spaces

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Many systems of interest in the chemical sciences take energy and matter from their surroundings by one means and return it by another; this exchange can drive them far from equilibrium. These include, but are not limited to, molecular motors, molecular electronics, polymers under shear, and regulatory modules of living cells. My group and I recently introduced an umbrella sampling method for obtaining nonequilibrium steady-state probability distributions projected onto an arbitrary number of coordinates that characterize a system (order parameters). Here, I show how the procedure can be adapted to restrict sampling to the vicinity of a path in a many-dimensional space of order parameters. For the study of transitions between stable states, the adapted algorithm results in improved

scaling with the number of order parameters and the ability to progressively refine the regions of enforced sampling. Results will be presented for a coarse-grained model for nucleation under shear.

COMP 19

The relative entropy in multiscale modeling and coarse-grained model development

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Many complex systems of interest cannot be simulated at the atomistic level due to long length and time scales. Instead, such problems require a multiscale approach in which simplified, “coarse-grained” descriptions are first derived from atomistic considerations and then used in simulation runs that are larger and longer than possible with all-atom models. A critical aspect of multiscale modeling is the need to connect coarse-grained models to atomistic physics in a manner that faithfully reproduces the relevant physical behavior. Though there have been several specific approaches to this problem, it has been challenging to identify general theoretical methods for linking coarse-grained systems of arbitrary design and scale to detailed all-atom models.

We show that the relative entropy, Srel = sum p_T ln(p_T/ p_M), provides a major solution here, serving as a fundamental and unifying framework for multiscale modeling problems that involve optimization of a model system (`M') to reproduce the properties of a target one (`T'). We demonstrate that the relative entropy serves as a generating function for variational mean field theory and uniqueness, and gives intuitive results for simple case scenarios. Moreover, we show that the relative entropy provides new numerical techniques for linking models at different resolutions, and we use these approaches to extract coarse-grained models for several systems. In particular, we use the relative entropy to investigate anomalous behavior in liquid water; we show that Srel permits a quantitative evaluation of water's departure from simple liquids, and enables the optimization of single-site coarse-grained water models. Moreover, we use the relative entropy to develop a family of coarse-grained peptide models from accurate all-atom folding simulations, and we investigate the ability of these to reproduce the correct folding behavior and landscape.

COMP 20

Surfactant formulation multiscale modeling with CULGI

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We discuss microphase formation in several complex polymer-surfactant mixtures, typical for industrial formulations. Examples include the interaction between Alkyl Benzene Sulfonate surfactants and Poly Acrylic Acid polyelectrolytes, the interaction between charged colloids and surfactants, and the phase modeling of cationic surfactants. We discuss in detail mapping procedures from atomistic to mesoscopic modeling using correlation functions and steered Monte Carlo builders, principles of our colloidal editor compared to molecular editors, mesoscopic titration modeling by the merging of Poisson-Boltzmann with weak acid/base equilibria, and the coupling of Low Reynolds CFD to mesoscopic particle and field models. In all cases, the desire is to retain the molecular picture suitable for rationalized chemical modification, while at the same time, one realizes such molecular model is not suitable to reach the long length and time scales that are necessary for thermodynamics and mechanics.

COMP 21

Molecular modeling as an important step in the multiscale study of the CVD process

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Zinc sulfide has received a significant amount of attention during the last decade. Compared to other semiconductors, zinc sulfide has a large direct band gap, which makes it useful in a broad range of optical applications. These applications demand high quality zinc sulfide films, which are produced through the chemical vapor deposition method. A common cause of defects in the deposited film is due to the fact that the morphology of adducts in the gas phase is different from that of the deposited film. These adducts affect the deposition efficiency and film quality by (a) consuming the gas phase precursors, (b) settling down due to gravity, (c) leaving the reactor, or (d) depositing on the substrate. Depending on the size of clusters, the latter create large distorted grains on the substrate that do not normally have the same morphology as the deposited film. The concern here is how big these clusters grow—the larger the clusters, the more chance of having defects in the deposited film.

We have employed a computational approach to predict the size distribution and morphology of the clusters. With this information we have attempted to explain the link between the cluster size and the morphological defects on the deposited film. To achieve this aim, we employed a multi-scale modeling approach to

predict the particle formation, growth, and motion. The approach couples the macro-scale computational fluid dynamics with micro scale molecular dynamics and nano-scale ab-initio calculations in order to estimated the nucleation, growth, dynamics, and size distribution of the particles inside the CVD reactor. In this presentation, we will discuss various quantum chemistry methods (i.e. Density Functional Theory, Molecular Dynamics, and Transition State Theory) used to closely study the particle nucleation, surface growth, and deposition during the CVD process.

COMP 22

Approaching petascale biomolecular simulation

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In the year 2011 the Blue Waters sustained petaflop computing system will become operational at the University of Illinois. One of first programs to run on the machine will be the parallel molecular dynamics code NAMD, simulating a system of 100 million atoms. This talk will discuss the challenges and opportunities for biomolecular simulation as petascale machines become more common over the next decade.

COMP 23

Architectures and algorithms for millisecond-scale molecular dynamics simulations of proteins

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Our research group is currently building a specialized, massively parallel machine, called Anton, which should be capable of executing millisecond-scale molecular dynamics simulations of biological macromolecules at an atomic level of detail. The machine is based on 512 custom-designed integrated circuits, each incorporating (a) 32 specialized pipelines tailored to the rapid execution of particle-particle and particle-gridpoint interactions, and (b) a programmable subsystem designed to provide flexible support for other parts of the simulation process. Novel algorithms and architectural features are used to reduce the inter- and intra-chip communication requirements associated with distributing particle position data and aggregating the pairwise force vectors acting on each particle.

A small-scale prototype of the machine is now operational, and is currently executing multi-microsecond simulations for preliminary testing purposes. This talk will provide an overview of our work on architectures and algorithms for high-speed MD simulation, focusing on the tradeoffs between special- and general-purpose approaches.

COMP 24

Folding@home: Scalable algorithms for computational biology, running today on a sustained-petaflop class cluster of processors

***Vijay S. Pande**, pande@stanford.edu, Departments of Chemistry and Structural Biology, Stanford University, Stanford, CA 94035*

For those running grand-challenge class HPC calculations, all we really want is a single processor with petaflop scale speed. Unfortunately, we may likely never get such a system. Instead, we can get today petaflop (sustained) class performance from clusters of exotic "stream" processors, such as the Cell processor in PS3's or modern GPU's. While distributed computing of these stream processors is by no means a panacea for petaflop computing, one may be surprised to what degree algorithms that were traditionally tightly coupled can be ported to this platform. I will talk about our experience in this area, in particular with applications to simulations of biomolecular kinetics and thermodynamics performed on the Folding@home computing platform (which currently sustains over 4 petaflops of aggregate performance); I will also discuss how these methods could impact and influence HPC computing for other groups and other disciplines in the future.

COMP 25

GROMACS 4: Algorithms for highly efficient, load-balanced, and scalable molecular simulation

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Molecular simulation is an extremely useful, but computationally very expensive tool for studies of chemical and biomolecular systems. Here, a new implementation of the molecular simulation toolkit GROMACS will be presented, which now both achieves extremely high performance on single processors from algorithmic optimizations and hand-coded routines, and simultaneously scales very well on parallel machines. The code encompasses a minimal-communication domain decomposition algorithm, full dynamic load balancing, a state-of-the-art parallel constraint solver and efficient virtual site algorithms that

allow removal of hydrogen atom degrees of freedom to enable integration time steps up to 5 fs for atomistic simulations also in parallel. To improve the scaling properties of the common particle mesh Ewald electrostatics algorithms, we have in addition used a Multiple-Program, Multiple-Data approach, with separate node domains responsible for direct and reciprocal spacei nteractions. Not only does this combination of algorithms enable extremely long simulations of large systems, it also provides that simulation performance on quite modest numbers of standard cluster nodes.

COMP 26

PMEMD: A high performance implementation of AMBER molecular dynamics

***Robert E Duke**, rduke@email.unc.edu and Lee G. Pedersen, Department of Chemistry, The University of North Carolina at Chapel Hill, Chapel Hill, NC 27599*

The AMBER molecular dynamics package is widely used for simulation of chemical and macromolecular assemblies at the atomic level. Beginning in 2002, we have undertaken an effort to make longer timescale simulations of larger systems more feasible for the AMBER user community. We have done this by design and development of PMEMD (Particle Mesh Ewald Molecular Dynamics), a separate high performance executable that implements the most useful functionality of SANDER, the comprehensive molecular dynamics executable in AMBER. In development of PMEMD, we have emphasized efficient utilization of a wide range of hardware as well as high throughput via scaling on parallel supercomputers. We have carefully maintained results compatibility with SANDER, making no compromises in the precision of calculations. We will discuss the key design features of PMEMD that make possible its performance on a wide range of hardware.

COMP 27

Combined QM and MM approaches for vibrational spectroscopy: Applications to water and proteins, including comparisons with experiment

***James L. Skinner**, skinner@chem.wisc.edu, Department of Chemistry, University of Wisconsin, Madison, WI 53706*

Theoretical vibrational spectroscopy for liquids and other complex many-body systems depends on the accurate generation of configurations and the dynamics that connects them, and on the ability to assign accurate vibrational frequencies and transition dipoles for each configuration. We use conventional MM force fields for the former, and QM calculations on clusters, together with electric-field

maps, for the latter. This allows us to calculate IR and Raman line shapes, ultrafast observables, and vibrational sum-frequency susceptibilities. We give examples for liquid water, the water liquid/vapor interface, and membrane proteins, in all cases comparing with experiment.

COMP 28

Shedding light on photochemical reactions: Computer simulation as a tool for time-resolved spectroscopy

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Organisms have evolved a wide variety of mechanisms to utilize and respond to light. In many cases, the biological response is mediated by structural changes that follow photon absorption. These reactions typically occur at femto- to picosecond timescales. As the relevant time and spatial resolutions are notoriously hard to access experimentally, Molecular Dynamics (MD) simulations are the method of choice to study such ultra-fast processes.

We use a multi-configurational quantum mechanical (QM) description (CASSCF) to model the electronic rearrangement for those parts of the system that are involved in the absorption. For the remainder, typically consisting of the apoprotein and the solvent, a simple forcefield model (MM) suffices. QM/MM gradients are computed on-the-fly, and a surface hopping procedure is used to model the excited state decay. In addition to providing quantities that are experimentally accessible, such as structural intermediates, fluorescence lifetimes, quantum yields and spectra, the simulations provide also information that is much more diffucult to measure experimentally, such as reaction mechanisms and the influence of individual aminoacid residues.

COMP 29

Investigating biological spectroscopy with QM/MM methods

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We present here our investigation of several biologically important systems using QM/MM techniques with particular emphasis to interpreting and predicting U/V, IR and 2D-IR spectra. In particular we will illustrate the importance of being able

to predict 2D-IR spectra and the technical challenges associated with this methodology within a QM/MM framework.

COMP 30

Multiscale modeling of electronic excitations at the nanoscale

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Complex interplay of confinement effects, localization and delocalization, exchange interactions, exciton binding energy, exciton fine structure, and coupling to molecular vibration (phonons) governs experimentally observed photoinduced dynamics and defines technologically important characteristics low-dimensional materials such as conjugated polymers, molecular aggregates and carbon nanotubes. Using concept of strongly bound excitons, we develop multiscale exciton scattering (ES) model, which attributes excited states to standing waves in quasi-one-dimensional structures. This method allows electronic spectra for any structure of arbitrary size within the considered molecular family to be obtained with negligible numerical effort. Complex and non-trivial delocalization patterns of photoexcitations throughout the entire molecular structure can then be universally characterized and understood using the proposed ES method, completely bypassing 'supramolecular' calculations. Consequently, computational design of molecular structures with desirable electronic and optical properties can be performed in real-time using graph-like representation of molecules.

COMP 31

A quantum of common sense in crystallography

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The traditional potential function used to model biological systems involves the use of simplified classical force field methodologies for no better reason than the inherent size of most biological systems and the associated computational expense. However, molecular systems are widely understood to have quantum mechanical features associated with their interactions. Indeed, quantum chemical

(QM) methods have had tremendous impact on our understanding of “small” molecular systems, which raises the question can QM methods impact biology in the same way? In this presentation we will focus on the application of QM/MM methods to solve relevant problems in structural biology and structure-based drug design (SBDD) that begin to address this question. In particular, we will focus on our developments aimed at using quantum mechanical methods in X-ray refinement. Finally, we will briefly summarize our vision of the future application of quantum chemistry to the solution of problems in structural biology and SBDD.

COMP 32

Toward a fully quantum mechanical force field for simulations of biocatalysis

***Darrin M. York**, york@umn.edu, Department of Chemistry, University of Minnesota, 207 Pleasant Street S.E, Minneapolis, MN 55455, Fax: 612-626-7541*

Novel linear-scaling electrostatic and quantum models are introduced to study chemical reactions catalyzed by biological molecules. The quantum models are highly efficient and can be applied in simulations in either a combined QM/MM context, or through a new linear-scaling formulation that affords speed-up by 2-3 orders of magnitude relative to conventional linear-scaling methods such as the ``divide-and-conquer'' approach. Systematic problem areas for conventional NDDO-based methods and SCC-DFTB methods are discussed, and a new DFT-based model is proposed that overcomes these limitations to afford higher accuracy and improved robustness. A new form of QM/MM interaction is developed that allows explicit coupling of polarization, exchange, dispersion and charge transfer such that the need for QM/MM atom-type parameters, and their associated problems in chemical processes that involve changes in charge state and bonding environment, is circumvented. Progress in the development and application of the methods to long-time simulations of phosphoryl transfer reactions in solution and catalyzed by RNA enzymes are presented.

COMP 33

Fretting about FRET: Breakdown of the ideal dipole approximation

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Brent needs to input proper text!!!

Ross -- I will plan to talk about QM calcs done with Benedetta looking at the breakdown of the ideal dipole approximation. I'll also mention older MD stuff we've done looking at correlated motions between the probe molecules. I'll VERY BRIEFLY talk about using these simulations to model experimental FRET data. However, I don't really have anything that looks any good, so I won't do anything cool like overlaying a simulated spectrum or single-molecule FRET histogram with real experimental data. But, I will at least talk about it.

COMP 34

Developing the promise of reactive molecular dynamics for performing kinetics experiments computationally

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To be completed

COMP 35

Surface nanostructure, diffusion and catalysis: The role of confinement and surface chemistry

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Chemical reactions are often carried out in nano-structured materials, which can enhance reactions due to interactions with the reacting mixture, high surface area and confinement effects. Diffusion of reactants and products to and from catalyst sites is frequently a limiting factor. Molecular dynamics studies of the effect of tube diameter and chirality for diffusion in single-walled carbon nanotubes are reported. For sufficiently narrow tubes the diffusion is via the single file mechanism, while for larger tubes there is a transition to the faster Fickian diffusion mechanism. The chirality of the carbon tubes has only a small effect at room temperature, but becomes important at lower temperatures.

A study of reactions in confinement is presented, using ab initio and semi-classical methods1,2. We consider several reactions to produce hydrogen, including the decomposition of methane and water on carbon surfaces, with and without the presence of defects and added transition metal atoms. These results provide examples of the influence on reaction mechanism, yield and rate of electrostatic interactions with the supporting material, surface defects and surface curvature.

1. Erik E. Santiso, Milen K. Kostov, Aaron M. George, Marco Buongiorno Nardelli, Keith E. Gubbins, “Confinement Effects on Chemical Reactions – Towards an Integrated Rational Catalyst Design”, Applied Surface Science, 253, 5570 (2007).

2. Liping Huang, Erik E. Santiso, Marco Buongiorno Nardelli and Keith E. Gubbins, "Catalytic role of carbons in methane decomposition for CO- and CO2-free hydrogen generation", Journal of Chemical Physics, 128, 214702 (2008).

COMP 36

Using molecular simulation to understand wetting behavior

Jeffrey R. Errington*, Department of Chemical and Biological Engineering, Univeristy at Buffalo, The State University of New York, 303 Furnas Hall, Buffalo, NY 14260-4200, Fax: 716-645-3822*

Fluids in the presence of one or more surfaces exhibit a rich variety of phase transitions that are absent in bulk fluids. Examples include wetting, prewetting, layering, and capillary condensation transitions. Even the simplest of systems display a broad range of phase behavior, with surface phase diagrams depending qualitatively upon the relative strengths and ranges of the fluid-fluid and fluid-substrate interactions and the structural characteristics of the substrate. In this presentation, we describe our recent efforts aimed towards obtaining a better understanding of surface phase behavior through the use of molecular simulation. We will focus on the role nanoscale roughness plays on wetting behavior. More specifically, we will examine the evolution of the contact angle with variation of the magnitude of geometric heterogeneities. Our simulation-based results will be compared with macroscopically-based expressions for describing the influence of roughness, such as those due to Wenzel and Cassie.

COMP 37

Identification of dynamical hinge points of L1 ligase using large scale molecular dynamics simulations

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L1 Ligase is an intriguing and unique catalytically active riboswitch. It is one of the five known ribozymes that specifically and regioselectively catalyze the 5' to 3'phosphodiester bond ligation and only one of the two ligases that make non-canonical base pairs with their substrate. Its crystal structure suggested its potential intrinsic flexibility, revealing two totally different (active and inactive) conformers in the same asymmetric cell. In this work we attempt to find how L1 Ligase riboswitch intrinsic flexibility impacts on its catalytic activity using large scale molecular dynamics simulations (overall ~800 ns) of the reactant and product states in different conformations. A limited set of internal coordinates is identified to contain the hinge points along which the conformational event that is used to allosterically control the catalytic step takes place. Our simulations show that in the inactive conformation one of the L1 Ligase stem C is largely flexible (deviations of ~20 Å) and makes specific contacts with stem B. These contacts are inter- mediated by a conserved base (U19) and are not revealed by any of the crystal structures. We postulate that these contacts might be used to stabilize intermediary states during the conformational switch and we probe this assumption with a series of mutations at position 19 to analyze the differential degree of stability of the interactions between the base in position 19 and stem B. Intriguingly, the non-canonically base-paired ligation site shows a high degree of variability, being observed to visit three distinct states characterized by specific hydrogen bond networks. These states are differentially correlated to initial steps of the catalytic reaction in the reactant simulations.

COMP 38

Simulating stimulating interfaces: Applications in adsorption and catalysis

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As the study of chemical processes and material science has reached the nanometer length scale, the physics of an interface has become an increasingly important topic. At the continuum level, bulk properties can be measured fairly accurately: thermodynamic relationships, transport properties, and fundamental constants. This same framework is not as reliable when the focus shifts to processes occurring at the nanometer length scale. In order to address this challenge, we are currently using molecular simulation methods and electronic structure calculations to investigate adsorption and reactions on surfaces and at interfaces. This presentation will demonstrate how these simulation approaches

can be used to guide the synthesis of new materials and chemical processes, including the deposition of metal oxide thin films, carbon nanotube transistors, more efficient fuel cells, and more robust heterogeneous catalysts. An overview of these projects will be given, which highlights some new targets for experimental synthesis.

COMP 39

Theoretical investigation of inverse spillover processes on alumina supported Pt catalysts

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Alumina supported catalytic nanoclusters have been used to promote a variety of reactions including the steam reforming of methane and Fischer-Tropsch synthesis. Although there are many computational studies which detail the complete reaction mechanism for reactant and product species interacting with the catalytically active cluster, few studies consider the pathways that arise due to the combination of the cluster and support. One example of such a pathway is the “inverse spillover” effect which occurs when water chemisorbs or dissociates on the support forming mobile species which then migrate to the catalytically active particle and further promote oxidation reactions. This effect has been experimentally observed during the steam reforming of methane on alumina supported Rh clusters. In our prior work, we provided a theoretical model for adsorption and dissociation processes that occur on the aluminum terminated alpha-alumina (0001) support. In this paper, we perform barrier calculations using DFT-GGA for the diffusion of the dissociated products across the support and analyze how these barriers are affected by the presence of the pre-adsorbed H and atomic Pt and Pt clusters. In addition, we identify four unique configurations for atomic Pt on the alpha-alumina surface and determine the complex structures that are formed when O diffuses to the Pt/alumina interface.

COMP 40

Fatty acid induced toxicity: Interactions with the lipid bilayer

***Amadeu K. Sum**, asum@mines.edu, Department of Chemical Engineering, Colorado School of Mines, Center for Hydrate Research, Golden, CO 80401-1887, Fax: 303-273-3730*

Understanding the effect of saturated and unsaturated fatty acids on biological membranes can provide insight into cures for diseases such as obesity-associated cirrhosis. In vitro experiments suggest that unsaturated fatty acids, such as oleate and linoleate, are less toxic, modify the membrane fluidity less, and potentially protect hepatocytes from palmitate induced toxicity. In this talk, we will show how recent advancements in molecular simulations of biological membranes help us to understand the how fatty acids interact with the lipid bilayer and in turn provide insight into their induced toxicity. Computational results indicate that the unsaturated fatty acid chain serves as a membrane stabilizer to counteract changes in the membrane fluidity. Unsaturated fatty acids have structural properties that can reduce the lateral compressibility of the lipid component in the membrane. Hydrogen bonding analysis indicate a uniform level of membrane hydration in the presence of oleate and linoleate compared to palmitate, which revealed as a possible mechanism of how unsaturated fatty acids reduce biophysical changes to the cellular membrane and protect the membrane structure. Also to be discussed in the talk is the characterization of lipid bilayers in terms of their fluidity, which is also directly linked to the changes of the bilayer structure with the accumulation and aggregation of fatty acids.

COMP 41

Molecular dynamics and structural studies of cyclopentane modified peptide nucleic acids

***Anna K. Manukyan**, amanukya@odu.edu and Jennifer Radkiewicz-Poutsma, jradkiew@odu.edu, Department of Chemistry and Biochemistry, Old Dominion University, 4541 Hampton Blvd, Norfolk, VA 23529*

PNA molecule is a DNA strand where the sugar-phosphate backbone is replaced by N(2-aminoethyl)-glycine units. PNA binds strongly to both DNA and RNA. Analysis of the X-ray and NMR data show that the dihedral angles of PNA/DNA or PNA/RNA complexes are different from those of DNA/DNA or RNA/RNA. In addition, the PNA strand is very flexible. One way to improve the binding affinity of PNA for DNA/RNA is to design a more preorganized PNA structure. An effective way to rigidify the PNA strand is to introduce ring structures into backbone. In experimental studies, the

ethylenediamine portion of aminoethylglycine peptide nucleic acids has been replaced with one or more trans cyclopentyl units. This substitution has met with varied success in terms of DNA/RNA recognition. In present work we use MD simulations to determine how the cyclopentane ring improves binding and to

determine the contributions of both entropy and dihedral angle preference to the observed stronger binding.

COMP 42

Electronic structure theory at the petascale: Progress and challenges

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Extending scalable algorithms from tens or hundreds of processors to tens or hundreds of thousands of processors is a daunting task, especially for ab initio electronic structure theory. In this talk, many of the most problematic bottlenecks will be identified and discussed. Then, possible methods for addressing these bottlenecks will be presented, with illustrative examples.

COMP 43

Exposing more parallelism in quantum chemistry applications: Moving beyond the MPI and hybrid MPI/multithreaded programming models

Curtis L. Janssen*, cljanss@sandia.gov, Scalable Computing Research and Development, Sandia National Laboratories, MS 9158, PO Box 969, Livermore, CA 94551-0969*

Current approaches to the parallelization of quantum chemistry algorithms entails partitioning the problem into distinct steps and selecting a an associated level of granularity for each of these steps. This approach has flaws that increase the difficulty of getting good efficiency at large scales and reduces the ability to map the problem to the deep memory hierarchies in modern parallel machines. This talk will discuss alternative parallelization strategies and the implication for efficiency of quantum chemistry algorithms.

COMP 44

NWChem: Cutting-edge computational chemistry on large computing platforms

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With the availability now of machines of hundreds of teraflops, and with the first petaflop computers coming online, computational chemistry is on the verge of entering a new era of modeling. Large computing resources can enable researchers to tackle scientific problems that are larger and more realistic than ever before, and to include more of the complex dynamical behavior of nature. However, computational chemistry software needs to be available to the researchers to actually make effective use of petascale platforms and beyond. In this presentation we will discuss the development of scalable computational chemistry capabilities in NWChem, and we will demonstrate the scalability of our software on large scale computing platforms. NWChem is DOE's premier quantum chemistry software developed at the Environmental Molecular Science Laboratory at Pacific Northwest National Laboratory, and is freely available to the scientific community.

COMP 45

Overcoming difficulties in density functional theory: Calculation of nondynamical correlation and dispersion interaction

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The current standard DFT functionals suffer two major deficiencies: the lack of nondynamical correlation and the inability to describe dispersion interactions. Becke and co-workers have recently proposed some conceptually novel solutions to the two problems. At this conference, we will present efficient numerical algorithms to bring those models into practical applications. The main challenge of the nondynamical correlation method, real-space correlation (RSC), is the self-consistent solution and we have developed an efficient method to solve this problem. The effectiveness of RSC will be shown through the calculations of reaction barriers, dissociation energies, and other properties. We have also developed a self-consistent solution for the exchange-hole dipole moment (XDM) model for the calculation of intermolecular and intramolecular

dispersion interactions. The solution incurs little extra cost to the regular DFT calculation. XDM corrected DFT calculations will be shown to make qualitative structural difference for different types of systems of organic and biological interests.

COMP 46

Super instruction architecture of a parallel implementation of coupled cluster theory

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To develop a parallel version of the widely known and used program ACES II, that provides the most advanced implementation of Coupled Cluster theory, a new approach was used. The approach is based on a programming model called the super instruction architecture.

The programmer analyzes the work to be done and identifies basic chunks of data, called super numbers, with associated operations, called super instructions. The algorithm is programmed in a new language called super instruction assembly language (SIAL), which has some similarity to BASIC and which offers a number of distributed data structures, a PARDO construct, and synchronization. Writing and tuning SIAL programs turns out to be very efficient in programmer time.

Experience shows that ACES III shows excellent scaling to large numbers of processors on the most common hardware platforms in use today including Linux clusters with InfiniBand connects and the Cray XTn series.

COMP 47

Catalytic mechanism of cyclophilin

Donald Hamelberg*, dhamelberg@gsu.edu, Department of Chemistry, Georgia State University, Atlanta, GA 30302-4098, Fax: 404-413-5551, and J. Andrew McCammon, jmccammon@ucsd.edu, Howard Hughes Medical Institute, University of California San Diego, La Jolla, CA 92093-0365*

Peptidyl prolyl cis-trans isomerases (PPIases) are ubiquitous enzymes in biology that catalyze the cis-trans isomerization of the proline imide peptide bond in many cell signaling pathways. The local change of the isomeric state of the prolyl peptide bond acts as a switching mechanism in altering the conformation of proteins. However, the timescale of cis-trans isomerization and even the timescale of the catalyzed process are beyond the sub-microsecond timescale of normal molecular dynamics. Therefore, a complete understanding of the mechanism of PPIases is still lacking, and current experimental techniques have not been able to provide a detailed atomistic picture. We have carried out several accelerated molecular dynamics simulations with explicit solvent, and we have provided a detailed description of cis-trans isomerization of the free and cyclophilin A catalyzed process.

COMP 48

Extended ensemble ligand binding affinities with OPLS-AA, AMBER99, and varying AM1-BCC charge sets

***Michael Shirts**, michael.shirts@virginia.edu, Department of Chemical Engineering, University of Virginia, P.O. Box 400741, Charlottesville, VA 22904-4741, Fax: 434-982-2658*

Recent developments in computational processing power and in theoretical methods are making simulations increasingly closer to predicting ligand binding affinities with pharmaceutical accuracy. However, significant improvements in computational efficiency are necessary in order to make these simulations useful in industry, and we do not yet understand how differences in force field parameters can affect such predictions. We compare extended ensemble simulations of ligand binding affinities and more standard ligand binding methods for the FKBP-12 system using large-scale distributed computing in order to understand how much more efficient such simulations may be. Additionally, we examine the free energies of ligand binding with ligand and protein parameters derived from both OPLS-AA and AMBER99. We also look at the differences in binding affinity using AM1-BCC charges obtained from different ligand configurations, observing variances of up to 0.5-1.0 kcal/mol, putting an upper bound on the accuracy of atomistic simulations using classical fixed charge force fields.

COMP 49

Homogeneous ice nucleation: A coarse grain approach

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Although water is one of the most well researched liquids, the mechanism through which homogeneous ice nucleation occurs is not yet understood. Further understanding of water's nucleation mechanism would lead to scientific advances in many fields, including meteorology, for better climate modeling, and biochemistry, for biopreservation of drugs and proteins.

Through molecular dynamics simulations using a newly developed coarse-grain model of water, mW , we investigate the mechanism of ice nucleation and its relationship to the local structure of supercooled metastable water. Cluster size, shape/compactness and local environment were explored as possible reaction coordinates for this complex process. For room pressure, at temperatures within 4K of the high density to low density transformation temperature, the critical cluster was determined to have a radius 0.7-1.0nm. This result is consistent with classical nucleation theory. Evidence of spinodal-like decomposition below the lowest temperature liquid water has been equilibrated is discussed.

COMP 50

Roles of Mg2+ in hammerhead ribozyme

***Tai-Sung Lee**, taisung@umn.edu, George Giambasu, GeorgeMGiambasu@umn.edu, and Darrin M. York, york@umn.edu, Department of Chemistry, University of Minnesota, Minneapolis, MN 55455*

Recent computational studies of the roles of Mg2+ ions in hammerhead ribozyme (HHR) will be summarized. Long-time molecular dynamics simulations suggested that HHR folds to form a negatively-charged pocket to recruit metal ion(s) in the its active site. The recruited ion(s), either a divalent ion or 2-3 monovalent ions, can help the HHR to form an active conformation and can assist the catalysis steps. However, divalent and monovalent ions exhibit slightly different mechanisms. Our simulation results are consistent with most available experimental evidence and provide a detailed insight view of the HHR self-cleavage reaction.

COMP 51

Thermostability of hydrogen bond network of cellulose

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Cellulose, an assembly of polymers of glucose, is an important renewable energy resource coming from plant and algae biomass. One critical problem encountered in the efficient depolymerization and biomass conversion is the unusual high thermal and mechanical stability of cellulose. The redundancy in hydrogen bonding pattern and the intertwinement of intra- and inter-molecular hydrogen bonds ensure this high stability. We performed calculations at both the atomistic level (replica exchange MD simulation) and the coarse-grained level (numerical transfer matrix calculation) to study the thermal responses of various hydrogen bond networks of cellulose. The disassembly process can be viewed as the transition from a state of low temperature with hydrogen bonds formed to a state of high temperature with the rupture of hydrogen bonds. Our calculations reveal the stability of different types of H-bonding as functions of temperature. It may provide useful clues on man-made procedure/design for the efficient degradation of cellulose.

COMP 52

TraPPE-UA force field for acrylates and Monte Carlo simulations for their mixtures with alkanes and alcohols

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Acrylate-based polymers are used in numerous industrial applications, such as films and adhesives, and their properties can be tailored through blending with additives, such as plasticizers. The transferable potentials for phase equilibria-united atom (TraPPE-UA) force field is extended here to acrylates and methacrylates. New parameters are fit to the liquid density, normal boiling point, and saturated vapor pressure using Gibbs ensemble Monte Carlo simulations of methyl acrylate and methyl methyacrylate. Excellent agreement with experiment was obtained for other monomers, with average errors in liquid density and normal boiling point of ~1%. The TraPPE-UA force field accurately predicts solubility parameters for monomers with up to eight carbon atoms in the alkyl side chain. In addition, simulations of binary vapor-liquid equilibria for the mixtures methyl acrylate/1-butanol and methyl acrylate/*n*-decane show that the TraPPE-UA acrylate force field performs well for mixtures with both polar and non-polar molecules. These mixture simulations exhibit structural microheterogeneity in the liquid phase.

COMP 53

Modeling conformation and toxicity of amyloid-forming peptides

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The aggregation of monomeric proteins/peptides to form ordered amyloid oligomers and fibrils is a pathogentic feature of many human degenerative diseases including Alzheimer's Parkinson's, Huntington's, and prion diseases. Despite of significant progress, the structure of the early oligomeric species on the aggregation pathways and the origin of their neurotoxicity remain unknown at an atomic level of detail. Knowledge of the structure of these oligomers is essential for understanding the process of pathology of the amyloidoses and for the rational design of drugs to against amyloid formation. A systemic analysis of preformed oligomeric structures is performed to examine their sequence and structural characteristics. We identify several stable oligomeric structures (A-beta, GNNQQNY, K3, and OspA) with different structural morphology, size, and sequences delineate several common features in amyloid organizations and amyloid structures, and illustrate aggregation driving forces that stabilize these oligomeric structures using computational simulations. The structural comparison among different oligomers suggests that the aggregation mechanism leading to distinct morphologies and the aggregation pathways is sequence specific due to differences in side-chain packing arrangements, intermolecular driving forces, sequence composition, and residue positions. Moreover, we are also modeling the stable A-beta oligomers in the DPPC lipid bilayer and illustrate the postulated mechanism of membrane damage associated with the amyloid toxicity.

COMP 54

Informatics for nanostructure discovery and design

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This presentation provides a discussion of how statistical learning and data mining techniques can be used to analyze crystallographic patterns in nanostructures. We show how by integrating electronic and crystal geometry information into both classification and predictive data mining techniques, one can extract complex rule based design strategies for materials; and specifically nanomaterials. In this presentation we also discuss how statistical learning techniques can be used to augment more classical approaches to computational

based design of materials. The role of data mining to identify dominant parameters influencing phase stability calculations is demonstrated. The use of such informatics based techniques to accelerate the computational approaches for first principle calculations is also discussed

COMP 55

Intelligent design of nanocomposites via informatics

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The explosion of computational and experimental methods able to glean detailed information about atomic and molecular structure, combined with control over organization at the nanoscale has led to an exponential increase in the complexity of the information space. These exciting developments have the potential to lead to true materials design. Using polymer nanocomposites as a model system, we are using informatics to develop a set of design rules based on a fundamental understanding of the filler/matrix interface enthalpy and entropy, the polymer structure and dynamics in the interfacial region, and the assembly or aggregation of nanofillers. In order to bridge the length-scale and time-scale gaps, we combine first principles calculations with heuristics and analytical modeling to predict the thermomechanical behavior of polymer nanocomposites. Experimental data is mined from the available literature for thermomechanical property changes as a function of constituent phases, and as available, nanoparticle aggregation.

COMP 56

Quantitative structure property relationships of nanotube structural and mechanical properties

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Intrinsic carbon nanotubes (CNTs) have extraordinary mechanical properties yet there is considerable variation in experimental measurements. During growth and post-growth stages, defects can be inadvertently or intentionally added to the CNTs. It is believed that the variation of the mechanical properties is due in part to the presence of these defects as well as other heterogeneities. Via a methodical exploration of the potential parameter space utilizing an MD level simulation for data generation, we will investigate the feasibility of deriving a quantitative structure property relationship (QSPR) between the structural features and mechanical properties of CNTs. We will evaluate the data set to derive an appropriate descriptor set, investigate a variety of linear and nonlinear methods to build the QSPR, exercise model validation and define a domain of applicability. The potential utilization of a QSPR will provide more visibility into the mechanical property space without having to execute lengthy MD calculations.

COMP 57

Finite element modeling of CNT-nanocomposite interlaminar shear strength

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Carbon nanotubes (CNTs) are being used in fiber - reinforced composites to increase mechanical properties such as modulus and stiffness. Multi-scale CNT composites can be analyzed using a simple methodology which combines analytical and finite element modeling. First, the enhanced matrix orthotropic elastic properties are computed by treating the CNTs as aligned inclusions of known dimensions and mechanical properties in the matrix. The shear strength of this enhanced matrix is computed from a shear lag model in which the interfacial strength of the CNT to matrix is specified. As needed, these orthotropic properties can also be reduced to equivalent isotropic properties computed from a quasi-isotropic laminate lay-up in which the individual plies are given the orthotropic properties. Next, and in either case, a progressive failure analysis is used to characterize the multi-scale structural properties. A finite element (f/e) model with progressive failure analysis of a three-point bend test was used to compute the interlaminar shear strength (ILSS) for a nanocomposite consisting of CNTs in a fiber-reinforced composite. The ILSS was computed versus CNT loading and interfacial strength (IFS): At 5% CNT loading, increasing the IFS by a factor of 4 increases the ILSS by a factor of 8.5, and at 10% CNT loading the ILSS increases by a factor of 11 for an increase in IFS of 4. And at 5% and 10% CNT loadings, the ILSS is a factor of 10 and 15 larger respectively than the matrix with no CNTs. These calculations show a substantial increase in ILSS as the CNT loading and IFS increase.

COMP 58

Interactions of epoxy-based polymers with carbon nanotubes studied by molecular modeling

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In this study initially molecular models of of epoxy-based cross linked polymers are built and investigated by molecular dynamics simulation. Properties like density, solubility parameters and elastic moduli are computed and compared against experimental results and also an idealized linear epoxy system. Then a mixed system of single walled carbon nanotubes and the polymer matrix is investigated, analyzing the impact of the CNT filler on the properties of the system. Finally the results from the atomistic simulations are used to parameterize a mesoscale Dissipative Particle Dynamics simulation (DPD) to investigate the impact of cross linking and chemical detail on the distribution of the carbon nanotubes in the polymer matrix.

COMP 59

Prediction and nanomechanics of interfacial strength between carbon nanotubes and resin

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Nano-particle's capability to improve neat resin properties is limited by the interfacial strength of the bond between the nano-particles and the resin material. Due to the nano-scale size, it is extremely difficult to conduct experiments (pull-out test) and to quantify (measure) the interfacial strength of the bond without having scatter in test data. In this paper, a high fidelity procedure that combines Progressive Failure Analysis (PFA) and Finite Element Method (FEM) is used. First, a CNT pull-out test is simulated using combined PFA and FEM approach and calibrated with limited average test data available in literature. Second, the combined PFA and FE approach is further integrated with probabilistic analysis to virtually simulate the scatter in the test data. The scatter in the simulated data comes from introducing variation in the aspect ratio (length/diameter) of the CNT, strength of the interface, matrix and the CNT. Using the proposed approach, a good correlation between the simulation and experimental data is established.

COMP 60

First-principles molecular dynamics on petascale computers: Algorithmic developments and applications

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Large-scale parallel computers offer a unique opportunity to extend the scale and accuracy of first-principles simulations. This however requires adapting and sometimes redesigning, numerical algorithms in order to achieve good scalability. We present recent progress in the development of parallel algorithms and implementations of First-Principles Molecular Dynamics (FPMD) for operation on large parallel platforms. Applications to the calculation of the electronic structure of nanoparticles are used to illustrate the challenges encountered when running large-scale FPMD simulations.

COMP 61

Large-scale quantum mechanical simulations of materials under extreme conditions

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The almost exponential increase in computer power over the last few decades has opened up the venue for increasingly more advanced and accurate computer simulations. As little as ten years ago, quantum mechanical calculations were restricted to predictions of static properties of systems containing tens of atoms, thus limiting first principles explorations to gas phase chemical and physical processes. With today's computers, quantum mechanical calculations can easily be performed for solids and liquids, thus opening up exploration into condensed phase physico-chemical processes. In this work, we demonstrate the ability of quantum mechanical approaches, in particular the density-functional method, to predict the response of condensed phase materials under extreme conditions. These simulations represent the leading edge of quantum mechanical density functional theory (DFT) simulation in both system size and simulation time with over 4000 atoms and ten thousand time steps utilizing as many as 512 processors per run. We will present three cases for which we are using these large scale simulations. First these are used to study the response of colliding nanodiamonds, proposed as additives to potentially enhance performance of

conventional explosive formulations. Second, simulations of shock waves in the novel energetic materials, polymeric nitrogen, will be shown. Finally simulations of pentaerythritol tetranitrate (PETN), a conventional high explosive, will be examined. All calculations are performed with the DFT code CP2K. Additionally we have used CP2K on a much smaller scale to calculate the pressure-energy curves for diamond, polymeric nitrogen, and PETN, the surface reconstruction of raw nano-diamonds and to extrapolate the internal pressure profile of the nano-diamond cluster.

COMP 62

NEMO 3-D and OMEN: Nanoelectronic modeling tools for advanced semiconductor device studies and their deployment on nanoHUB.org

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At the nanometer scale the concepts of device and material meet and a new device is a new material and vice versa. While atomistic device representations are novel to device physicists, the semiconductor materials modeling community usually treats infinitely periodic structures. NEMO 3-D bridges the gap and enables 52 million atom electronic structure simulations of quantum dots, quantum wells, nanowires, and impurities with relevant device dimensions. Two examples will illustrate the importance of atomistic representation in realistically large systems. Non-destructive metrology for depth and character of single impurities can be performed with NEMO 3D in realistic fin-FET devices. For InAs quantum dots embedded in an InGaAs strain reducing layer on top of a GaAs substrate NEMO 3-D can model the non-linear optical transition energy dependence as a function of In-concentration. Both simulation sets match experimental data without adjustment to the NEMO 3-D material parameters or device geometries. Electron and hole transport simulations through atomistically represented systems remain computationally and even conceptually challenging. We will show our results in disordered nanowires and FETs using OMEN. Transport through large cross section wires may be an opportunity to solve large cross section transport problems and we will show first results. Both tools scale extremely well on massively parallel compute platforms up to 8,196 and 59,904 core respectively.

Ultimately these simulation tools will have the most impact if they can leave the hands of computational scientists and be put into the hands of experimentalists and educators. nanoHUB.org provides a platform for such tool deployment and we will highlight our achievements and plans on tool deployment of OMEN and NEMO3D on the nanoHUB.

COMP 63

Scalable ab initio MD simulations for chemistry

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Many important problems in biochemistry, materials chemisty and physical chemistry can only be described via a first principles or ab initio based molecular modeling approach wherein atomic forces are derived from an energy function that explicitly considers the electronic degrees of freedom. The widely used, computationally intensive Car-Parrinello ab initio molecular dynamics method (CPAIMD) is typically applied to study complex systems containing hundreds to thousands of atoms. However, it has resisted attempts to achieve parallel scaling beyond processor numbers equal to a small multiple of the number of electronic states, particularly for small systems, until recent efforts by ourselves and others, thereby, limiting its potential scientific impact. CPAIMD involves a large number of phases with complex dependencies and high communication overhead. Using charm++ and the concept of processor virtualization, these phases are discretized into a large number of virtual processors which are, in turn, mapped flexibly onto physical processors. Here, several algorithmic and Blue Gene/L specific optimizations that enable CPAIMD to scale to 20000 nodes, about 8-times the number of electronic states in the largest benchmark system are presented. Application studies to technology using new materials chemistry, a new nanoscale memory design,

and biochemistry, proline's bioprotectant properties are then given.

COMP 64

Toward petaflop computing for electronic structure calculations

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At the atomic length scale, modern ab-initio electronic structure calculation techniques are capable of determining fundamental electronic and magnetic

properties. Despite their great success, recent development in materials science, especially in nanoscience and nanotechnology, places new demands on the capability of the ab-initio methods because the large numbers of atoms (1,000 – 1,000,000 atoms) are required in the simulation. In the past years, we have demonstrated that the locally self-consistent multiple scattering (LSMS) method is capable of performing the direct quantum mechanical simulation of the nano-structured materials of a length scale of several nanometers. However, it is clear that the computational challenges from the real world problems go much beyond the capability we have shown previously. Evidently, going from several nanometers to sub-hundred nanometers, an order of magnitude increase in length scale, increases the problem size from tens of thousands to millions of atoms, and consequently increases the computational cost by a factor of hundreds, even assuming the continued order-N scaling of our method, an assumption that will require considerable effort to realize. In this presentation, I will show our latest efforts to scale the LSMS code up to the full capacity on the state of art supercomputing systems available to us. A fully scalable full-potential LSMS code will allow us to take advantages of the future supercomputing systems to meet the computational challenges in materials science. I will demonstrate, as an example, the latest electronic and magnetic structure calculation for iron-based nanoparticles, and I will explain the potential challenges we will have in our efforts towards petascale computing for quantum mechanical simulation of real nano-structured materials.

COMP 65

Advances in density functionals for electronic structure calculations

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For most molecular systems, density functional theory (DFT) calculations provide the best balance between computational cost (feasibility) and the quality of the resulting relative energies (accuracy). However, widely used functionals are limited in accuracy by physical deficiencies. One major physical problem with most widely used functionals is self-interaction error, where an electron artificially sees itself. Another is the neglect of long-range dispersion (London) forces. In this talk I will discuss the formulation, calibration and testing of four new density functionals which significantly reduce these errors. As a consequence, the quality of chemical results that can be obtained is significantly improved, as will be demonstrated by a wide range of model applications.

COMP 66

Domain-specific languages for many-body molecular structure methods

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Domain-specific languages, defined as languages built for a particular purpose, are nearly ubiquitous in all aspects of computing. Yet their use in scientific computing is relatively limited due to the lack of expressiveness in the dominant general-purpose programming languages (Fortran77, C). Here I consider how a domain-specific language can be used to specify and solve the problem of computing multi-dimensional integrals in molecular structure computations. The domain-specific language compiler, Libint, was developed to reduce the high-level mathematical expressions for recurrence relations to optimized C++ computer code. I will discuss the performance of the code generated by Libint and demonstrate how Libint helps to experiment with new wave function ansatze by minimizing the cost of implementing new molecular integrals.

COMP 67

Generation of a database of hypothetical zeolite structures

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We present a computational approach to search through crystallographic space for frameworks that are zeolite-like. The search is performed by using Monte Carlo methods to sample a zeolite figure of merit. Refinements of these topologies are conducted using energy minimization methods. We discuss the creation of a database of hypothetical structures using this approach, and how the database may be used to search for new zeolite structures with specific material properties of interest in the future. To date, the computational search has identified over 3 million new hypothetical zeolite topologies, with over 400000 of these having framework energy in the range of known zeolite structures.

COMP 68

Predictive chemical computing in condensed phases

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An ideal problem for petascale computing is predictive simulations of solids based on hierarchical electronic and vibrational methods employing coupled-cluster and perturbation theories. These methods are not yet applicable to solids of any chemical compositions, but when particular classes of solids such as periodic insulators and molecular crystals are considered, one can apply these methods by exploiting known characteristics of their wave functions. We introduce two such schemes: one allowing the anharmonic phonon frequencies of polymers to be computed by electronic and vibrational perturbation theories and the other predicting the structures and phonons of molecular crystals. We discuss how these methods can straightforwardly be cast into processor-group parallel, fault-tolerant, restartable algorithms for future petascale applications.

COMP 69

Toward petascale applications with ACES III

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ACES III I the successor to the widely used ACES II program system which provides state-of-the-art coupled-cluster methods for application to molecules. Rather than making an attempt to upgrade serial ACES II for parallel applications, our group wrote an entirely new program, even with a new very fast integral and open-ended integral derivative program, to enable it to perform exceptionally well on tera- and petascale computers. This is accomplished with the new super-instruction assembler language (SIAL) procedure, which will be discussed in the contribution from Erik Deumens. ACESIII is shown to scale virtually perfectly through up to >1000 processors. In this talk, I will focus on several large scale applications of interest that can now be done with ACES III. These include coupled-cluster energies, analytical gradients, the equation-of-motion CC theory for excited states and others. Applications will include studies of water clusters, radical adducts of nucleic acid bases, and other applications of interest.

COMP 70

Multiscale modeling motivation, strategy, and approaches for nanoscale material and device design and development

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The multiscale modeling program at Lockheed Martin, with its academic and commercial collborators, emphasizes a value proposition based on performing factors of 100 or more fewer physical experiments, knowing and controlling the most powerful interface in the materials or devices under development, formulating new functionality from first principles, accelerated materials or device design convergence, and greatly reduced materials development, engineering, and integration costs. The program strives to exploit physics based models, component analyses, and design tools in conjunction with materials informatics to efficiently and rationally navigate the vast landscape between atomistic and bulk component length scales, and is a central effort that joins target materials and device development programs. In this talk we will describe the strategies and approaches toward bridging the modeling – experiment gap, define the key challenges, problems, and opportunities in multiscale modeling of nanoscale materials, and elaborate on our implementation of materials informatics to address these challenges.

COMP 71

New computational simulation techniques for nanosystems: Bridging the gap

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The ability to predict and control the density, position and orientation of nanoparticles in complex fluids and polymer matrices has far reaching applications in nanoscience and technology. For example, Whitesides has recently demonstrated how complex systems and devices may be “self-

assembled” by control of particle geometry, concentration and surface chemistry. Such methods may offer an extremely attractive route in manufacturing in that nanodevices might be assembled rapidly and cheaply using only wet chemistry techniques. However, in such systems it is by no means obvious how entropic and enthalpic interactions couple with a surface potential or external field to minimize a local free energy to produce a desired structure. It is one thing to observe an interesting nanostructure in the laboratory but it is quite another to understand the intermolecular and nanoparticulate forces with sufficient fidelity to design and predict the properties, phase behavior, and long term stability of this class of matter.

In this paper we report on the development of a new finite granular dynamics computer simulation technique that solves the equations of motion for systems of interacting nanoparticles of arbitrary size and shape. Phase diagrams and transport properties for mixtures of spheres and triangles on a two-dimensional substrate are presented. These systems form glasses readily and issues regarding thermodynamic stability in the mesoscopic regime will be discussed.

COMP 72

Investigation of multiwalled carbon nanotube nanocomposites at multiple scale

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Nanocomposites have multiscaled features that can impact the macroscaled mechanical properties. The multiscaled features have length scales that can vary from angstroms to millimeters. They include the morphology, the interfaces, and the interphase. The morphology is described by the distribution of the multiwalled carbon nanotubes (MWCNT) in the polymer matrix, the length and the diameter of the MWCNT, and the waviness and the mechanical entanglement characteristics of the MWCNT forest. Image processing of Scanning Electron Microscopy (SEM) and Transmission Electron Microscopy (TEM) images can be used to describe the morphology of the nanocomposite. The interfaces include the MWCNT to the polymer interface and the MWCNT to the fiber interface. Techniques such as Micro Raman, TEM of fractured surfaces and Near Field

Raman can provide information about the interfacial shear stress associated with these interfaces. The interphase is the region in the polymer in which the motion of polymer chains is constrained by the interface with the MWCNT or the fiber. One consequence is that the viscoelastic properties of the interphase are different from that of the bulk polymer. The change in the viscoelastic properties due to the interphase can be explored using Dynamic Mechanical Anaylsis (DMA). Information of the multiscaled features associated with nanocomposites can be used to build more accurate physics based multiscaled models and heuristics model.

COMP 73

Identification of critical parameters in continuum level modeling of nanocomposites through a multiscale study

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Carbon nanotubes (CNTs) have shown superior mechanical properties over the industry leading graphite fiber and experimentalists are getting closer to harnessing their full potential in composites. Estimation of mechanical properties would expedite the manufacturing optimization of nanocomposites. Traditional continuum modeling has overestimated mechanical properties of nanocomposites. The need for a multiscale or atomically informed continuum model is apparent. In this paper, we investigate a particular graphite epoxy laminate enhanced with CNTs synthesized from catalyst nanoparticles. We develop a modeling methodology that includes micromechanical parameters and atomistic information. Through this multiscale study, we will identify the critical modeling parameters necessary to incorporate into a continuum level finite element model. This model can be used to guide the optimization of nanocomposites.

COMP 74

Polymer nanophase multiscale modeling using CULGI

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The CULGI multiscale modeling library integrates a wide range of simulation techniques including atomistic molecular dynamics, both particle-based and field-based mesoscopic methods, novel hybrid particle-field methods and forward and backward mappers. We discuss ongoing work in applying multiscale modeling to typical industrial polymer nanophase materials, including: the dynamics of morphology formation in heterodisperse polymer blends, the rheology modeling of branched polymer distributions, prospects for the rational design of nanocomposite materials, the calculation of cohesive energy densities, and the modeling of polymer surfaces and surface energies. Such scientific development is a challenge, not only since the necessary theory and software is tough to make, but also since one changes language and wording, from forcefields to finite elements, from chemist to engineer, from fundamental science to everyday practical science.

COMP 75

Multiscale simulation study of nanotube composite mechanics

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The mechanical properties of nanocomposite materials are critically controlled by the failure initiation mechanisms at the interfaces between matrix and embedded fibers. In this paper, we investigate the detailed structural and mechanical properties of the interfaces between polymer and carbon fiber in the presence of carbon nanotubes (CNTs) grown from catalyst nanoparticles attached on the carbon fiber surface. Through a systematic multi-scale modeling study, we will investigate the detailed mechanisms controlling the critical failure of load transfer at the interface. Molecular dynamics (MD) simulations using the modified embedded atom method (MEAM) potential plays the central role of tracking detailed atomic structure evolution under the external loading conditions determined by continuum level analysis. We will report the MD study of CNTs and the Ni nanoparticle-CNT interface under diverse loading conditions. The findings of the multi-scale study will provide useful guidance to develop optimization strategy for the CNT reinforced polymer composite materials.

COMP 76

WITHDRAWN

COMP 77

Computational chemistry investigation of spin traps using hybrid solvation models

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The cyclic nitrone 5,5-dimethyl-1-pyrroline-N-oxide (DMPO), and the lesser known linear phenyl-N-tert-butylnitrone (PBN) and its phosphorylated analogues have been used as spin traps for the investigation of free radicals in biological systems. Theoretical work on these molecules suggests that there are significant differences in their properties between biological systems and isolated molecules in the gas phase, most likely resulting from intra and intermolecular hydrogen bonding. Most dielectric solvation models such as the polarized continuum model and COSMO are incapable of direct determination of solvent-spin trap chemical interactions. To examine this, hybrid models incorporating COSMO for long range effects and discrete solvent molecules for short range effects, at the DFT/B3LYP/6-31G* level of theory, have been used to study the stabilization and alteration of the spin trap molecules properties in protic and aprotic polar solvents.

COMP 78

Hypervalent vs. nonhypervalent carbon: Disk-between-balls model

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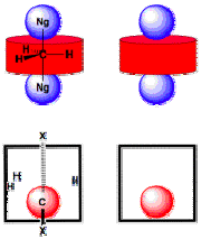
Silicon in $[Cl\text{-}SiH_3\text{-}Cl]^-$ is hypervalent whereas carbon in $[Cl\text{-}CH_3\text{-}Cl]^-$ is not. We have recently shown how this can be understood in terms of the ball-in-a-box

model according to which silicon fits perfectly into the box that is constituted by the five substituents, while carbon is too small and, in a sense, "drops to the bottom" of the box (see illustration, lower). But how does carbon acquire hypervalency in the isostructural and isoelectronic noble gas–methyl cation complexes $[Ng\text{-}CH_3\text{-}Ng]^+$, which feature a delocalized D_{3h} symmetric structure with two equivalent C–Ng bonds? That is, for Ng = He and Ne. From Ng = Ar, the $[Ng\text{-}CH_3\text{-}Ng]^+$ complex acquires again a propensity to localize one of its axial C–Ng bonds and to largely break the other one, and this propensity increases along Ng = Ar, Kr, Xe and Rn. The behavior of the helium and neon complexes violates the ball-in-a-box principle! Why does this happen? The purpose of this study is to answer these questions and to understand why carbon can become truly hypervalent under certain conditions (see illustration, upper).



COMP 79

Mechanism of efficient firefly bioluminescence via adiabatic transition state and seam of sloped conical intersection

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Firefly emission is a well-known efficient bioluminescence. However, the mystery of the efficient thermal generation of electronic excited states in firefly still remains unsolved, particularly at the atomic and molecular levels. We performed SA-CASSCF(12e,12o) and CASPT2(12e,12o)//SA-CASSCF(12e,12o) calculations to elucidate the reaction mechanism of bioluminescence from the firefly dioxetanone in the gas phase. Adiabatic transition state (TS) for the O-O bond cleavage and the minimum energy conical intersection (MECI) were located and characterized. The unique topology of MECI featuring a seam of sloped conical intersection for the firefly dioxetanone, which was uncovered for the first time, is emerged along the reaction pathway to provide a widely extended channel to diabatically access the excited state from the ground state.

COMP 80

Modeling reactions in proteins

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Using the still relatively new semiempirical procedure PM6, a method for modeling chemical reactions in proteins has been developed. This involved increasing the efficiency of solution of the SCF equations and of location of the approximate transition states, refining them, and finally characterizing them by evaluating vibrational frequencies and by use of the Intrinsic Reaction Coordinate. Some of the issues involved will be discussed, and an application to a hypothetical reaction involving the formation of the tetrahedral intermediate in Chymotrypsin catalyzed hydrolysis of a peptide bond will be described.

COMP 81

Molecular dynamics simulations of carbon tetrachloride properties using quantum chemistry calculated potentials

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We have calculated the carbon tetrachloride dimer interaction potentials using the supermolecule counterpoise corrected second-order Møller-Plesset (MP2) perturbation method with the basis set up to aug-cc-pVQZ. The MP2 binding curves display significant anisotropy with respect to the relative orientations of the dimer. The potential curves at the complete basis set (CBS) limit were estimated using well-established analytical extrapolation schemes. A six dimension ab initio potential energy surface (PES) has been constructed for molecular dynamics simulations of fluid properties. 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 82

Theoretical exploration of sensing mechanisms of nitroaromatics

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The fluorescence quenching of amplified fluorescence polymers (AFP) nitroaromatic compounds enables them to be used successfully for detection of trace quantities of explosive compounds. To understand more detailed structural information and the electronic characterization of these interactions, which would lead to better prediction and prioritization of the next generation of AFP materials, we used time dependent density functional theory (TD-DFT) and ZINDO methods to study ground and excited states of the target molecules as well their complexes with the AFP monomer. Calculations show that forming TNT-AFP complex causes significant decrease in the HOMO-LUMO energy gap of the free AFP. The results also predict the dynamic quenching of the AFP due to the low-lying dark charge transfer (CT) state in the presence of TNT and its derivatives such as DNT and NT. To examine the selectivity of the modeled polymer, toluene and benzene which are potential false positive compounds are also investigated and none of the aforementioned effects are observed in these complexes.

COMP 83

Using data mining algorithms to develop semi-empirical quantum chemical methods: Polarizable solvent models

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Semi-empirical quantum chemistry and molecular mechanics take advantage of molecular similarity, whereby molecular fragments behave similarly in different environments, to substantially reduce computational cost. Here, we explore the use of machine learning algorithms to take better advantage of molecular similarity. First, high level quantum chemistry is used to generate the molecular charge distribution of the solvent in external charge fields. Feature extraction algorithms are then used to identify the most important collective degrees of freedom for both the permanent and induced multipole moments, and the energy is written in terms of these features. This provides a systematic approach to polarizable molecular mechanics models, with well controlled and specifiable accuracy. The results also investigate the use of distributed multipoles as surrogates for the electron density, and the use of machine learning to generate results with the accuracy of high-level quantum chemistry (CCSD/6-311G(d,p)) from features generated by low-level theory (HF/STO-3G).

COMP 84

Massively parallel and multiscale simulations of strongly correlated electronic systems

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Complex phenomena, including superconductivity, magnetism, phase separation, and competing phases, emerge as many correlated atoms are collected together. Conventional theory has made limited progress towards a systematic and reliable way to study even the simplest models of these systems. We us massively parallel Quantum Monte Carlo methods, along with effective medium theories, to study these model systems. The main limitation of these methods is minus sign problem which makes the study of strongly correlated system NP hard. Supercomputer power alone cannot be used to overcome these problems. To circumvent this problem, we are developing multi-scale methods which separate the problem into different length scales, each with an appropriate approximation. Strong correlations at short length scales are treated explicitly, weaker correlations at intermediate length scales are treated with diagrammatic approximations such as the parquet, and the weakest correlations at long length scales are treated in a dynamical mean field. The parquet approximation, used for intermediate length correlations, scales algebraically with system complexity and scales efficiently to thousands of processors. Together, this multi-scale many body approach holds the promise of new discovery in and understand of strongly correlated systems.

COMP 85

Advances in quantum Monte Carlo: Topology of fermion nodes and pfaffian pairing wavefunctions

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Quantum Monte Carlo methods typically yield 90-95% of the electron-electron correlation energy for up to a few hundred electrons in molecules and solids. For fermion systems, the major remaining barrier is the fixed-node approximation. We explicitly prove that for d>1 the nondegenerate fermionic ground states have the minimal number of two nodal cells for any system size under rather general conditions. For systems with interactions the proof is based on exploring the properties of BCS wavefunctions. The same property is demonstrated for temperature density matrices in d>1. These proofs have inspired search for trial wave functions which have the correct topologies.

To this end, we propose and test pfaffian wavefunctions with both singlet and triplet pairing orbitals in a single and easy to evaluate form as an efficient way to capture the correct nodal topologies. The results show that a single pfaffian provides much better and more systematic accuracy than Hartree-Fock based

wavefunctions. Similarly, expansions in excited pfaffians converge much faster than corresponding expansions in determinants.

COMP 86

Applications of the quantum Monte Carlo method to challenging electron correlation problems

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The quantum Monte Carlo (QMC) method is used to examine the buckling of SiSi dimers on the Si(100) surface as described by cluster models and to calculate the binding of excess electrons to $(H_2O)_n$ clusters. For both problems, the sensitivity of the results to the choice to the trial function is explored. Where possible comparison is made with the predications of large basis set coupled-cluster calculations.

COMP 87

Optimal wave functions for diffusion Monte Carlo

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For many years the trial wave functions used for quantum Monte Carlo calculations were optimized by minimizing the variance of the local energy rather than the expectation value of the variational energy because a straightforward minimization of the energy requires orders of magnitude more Monte Carlo configurations than minimizing the variance of the local energy. However, in recent years methods have been developed for efficiently optimizing the variational energy. The wave functions so obtained yield much improved, but not optimal, fixed-node diffusion Monte Carlo (DMC) energies. In this talk we discuss the extension of these methods to optimizing the DMC energy or equivalently the nodal surface of the many-body wave functions.

COMP 88

Quantum Monte Carlo for the electronic structure of molecular systems

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The quantum Monte Carlo method has become recognized for its capability of describing the electronic structure of atomic, molecular, and condensed matter systems to high accuracy. This talk will summarize the approach and present recent developments connected with trial function construction and extension of the approach to a QM/MM (quantum mechanics/molecular mechanics) formulation in which QM is diffusion MC (DMC). This work was supported by the Director, Office of Science, Office of Basic Energy Sciences, Chemical Sciences Division of the Department of Energy under Contract No. DE-AC03-76SF00098, and by the National Science Foundation. Calculations were carried out at the National Energy Research Supercomputer Center (NERSC).

COMP 89

Recent advances in quantum Monte Carlo for quantum chemistry: Optimization of wave functions and calculation of observables

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We present a simple, robust and highly efficient method for optimizing the parameters of many-body wave functions by energy minimization in quantum Monte Carlo calculations. Using a strong zero-variance principle, the optimal parameters are determined by diagonalizing the Hamiltonian matrix in the space spanned by the wave function and its derivatives. We apply this method to obtain accurate multideterminant Jastrow-Slater wave functions for atomic and molecular systems, where the Jastrow parameters, the configuration state function coefficients, the orbital coefficients and the basis function exponents are simultaneously optimized. This allows us to reach near chemical accuracy on the dissociation energies of the first-row diatomic homonuclear molecules. We also illustrate the quality of the obtained wave functions by calculating accurate observables using improved statistical estimators.

COMP 90

Ab initio and hybrid QM/MM simulations on massively parallel supercomputers: Experience at ERDC

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With the announcement that RoadRunner supercomputer is the first system to reach the petaflop level, the HPC community is entering a realm of unprecedented computing power. More petascale computing systems will soon be available to the scientific community. Recent studies in the productivity of HPC platforms point to better software as a key enabler to science on these systems.

The combination of computationally demanding electronic structure methods with molecular dynamics is highly dependent on high-performance computing resources. The availability of such applications constitutes a big opportunity to evaluate both capabilities and limits of any HPC system and software application within the framework of a real-life feasibility study. The performance of benchmarks from the AIMD and hybrid QM/MM simulations on two high performance computing platforms will be discussed. Looking toward maximizing the computational time/performance ratio, we analyzed performance data for the Cray XT3/XT4 architectures available at ERDC.

COMP 91

A novel method for predicting ligand regioselectivity to metabolism by cyp p450 enzymes

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We have developed a computational model for rapidly predicting the susceptibility of sites on small drug-like molecules to oxidative metabolism by cytochrome P450 3A4, 2D6, and 2C9. In the present method, topologically

distinct regions of a ligand are identified and ranked as putative metabolic sites. Ranking is performed on the basis of 1) quantum mechanics-based electronic properties of each unique region and 2) spatial and steric scoring derived from a short constrained molecular dynamics simulation. The final combined method can be used as a reliable metric for evaluating metabolic susceptibility of lead compounds.

COMP 92

A QM/MM study of the cis-trans isomerism in peptide bonds

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Cis peptide bonds have been detected in up to 0.05% of the non-proline residues in structures deposited in the PDB, and up to 0.5% for small oligopeptides in solution.

The introduction of faster and more powerful computers has allowed for hybrid QM/MM calculations that use advanced sampling techniques such as replica exchange and umbrella sampling, and also include an ever growing number of atoms in the QM region. However, most of those calculations are still restricted to semi-empirical Hamiltonians for the QM region, by far the most used being MNDO, AM1 and PM3.

It is a well known fact that semi-empirical methods such as MNDO, AM1 and PM3 are incapable of correctly reproducing the cis-trans rotational barrier around the peptide bond, and correction terms have been developed that add a torsional restraint on the peptide bond. However, the vast majority of calculations to date that use those Hamiltonians do not employ any of these corrections.

We have explored the cis-trans isomerism of alanine dipeptide in explicit solvent by means of QM/MM calculations where the water solvent is treated as MM and the solute is treated with a variety of semi-empirical Hamiltonians, including MNDO, AM1, PM3 and the PDDG versions of PM3 and MNDO. We show the cis-trans populations obtained with different methods, and the influence of this distribution on various calculated properties.

COMP 93

Quantum mechanical/molecular mechanical studies of the reaction mechanism of human DNA polymerase λ with Mg^{2+} and Mn^{2+}

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DNA polymerases play a crucial role in the cell cycle due to their involvement in genome replication and repair. Understanding the reaction mechanism by which these polymerases carry out their function can provide insights into these processes. Recently, crystal structures of human DNA polymerase λ (Polλ) have been reported (Garcia-Diaz et al., DNA Repair, 3, 1333, 2007). We have employed the pre-catalytic complex as a starting structure for the determination of the catalytic mechanism of Polλ using *ab initio* quantum mechanical/molecular mechanical methods. Reaction paths have been calculated using Mg^{2+} and Mn^{2+} as the catalytic metals. In both cases the reaction proceeds through a two step mechanism where the 3'-OH of the primer sugar ring is deprotonated by one of the conserved Asp residues (D490) in the active site before the incorporation of the nucleotide to the nascent DNA chain. Significant charge transfer is observed between both metals and residues in the active site as the reaction takes place. The optimized reactant and product structures agree with the reported crystal structures. In addition, the calculated reaction barriers for both metals are close to experimentally estimated barriers. Energy decomposition analysis to explain individual residue contributions suggests that several amino acids surrounding the active site are important for catalysis. Some of these residues, including R420, R488 and E529, have been implicated in catalysis by previous mutagenesis experiments on the homologous residues on Polβ. Furthermore, Polλ residues R420 and E529, are homologous to residues R183 and E295 in Polβ, which have been linked to cancer. In addition, residues R386, E391, K422 and K472 appear to have an important role in catalysis and could be a potential target for mutagenesis experiments. These residues are conserved, or partially conserved, across the Pol X family of DNA polymerases.

COMP 94

Theoretical insight into the nitroreductase mechanism

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The bacterial enzyme nitroxidoreductase (NTR) catalyzes the conversion of nitro group to hydroxylamine or amine. These enzymes reduce hazardous nitroaromatic compounds (NACs) and are of special interest due to their potential use in bioremediation and their activation of prodrugs in directed anticancer therapies. Although the major processes affecting the biodegradation of NACs have been investigated qualitatively, many issues regarding a reaction mechanism and enzymatic selectivity remain unsolved. In order to clarify the poorly understood mechanisms of two-electron reduction of NACs by flavoenzymes, we examined the NTR reactions by theoretical QM/MM calculations. We analyzed substrate's reduction and hydride-transfer potentials. The role of electronic and structural parameters of NACs in this process has been also discussed.

COMP 95

Tuning the acidity of organic acids, and investigating their dissociation mechanism: A QM/MM approach

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The dissociation mechanism of organic acids containing carboxyl (COOH), amino (NH2), and hydroxyl (OH) groups is investigated and compared with experimental data obtained by means of UV pumping/ IR probing of photoacids. The computational investigation relies on a methodological development whereby the inductive effect of a substituent is modeled by hydrogen capping in conjunction with an explicit modeling of the substituent's dipole moment. For exemple, CH3COOH is modeled as HCOOH plus a point dipole moment describing the dipole moment of the CH3 group. The method allows one to describe the series of acids F3C-COOH, H-COOH, and CH3-COOH by continuously changing the value of an appropriately located point dipole moment. We demonstrate that the point-dipole QM/MM approach predicts gas-phase and aqueous acidity constants in excellent agreement with full QM values. Subsequently, we tune the value of the point dipole moment for three organic acids containing carboxyl, amino and hydroxyl groups until the acid dissociation AND ion recombination reactions in water become sufficiently fast to be studied via UNBIASED ab initio molecular dynamics methods. Results are compared

with rates and mechanisms obtained from experimental investigations using the photoacid HPTS.

COMP 96

Will polarizable MM force field improve the QM/MM method: A test of solvation free energy simulations

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In past years significant efforts have been made to improve the performance of MM force fields and QM/MM methods. One important progress was the development of polarizable MM force fields, in particular the Drude model which was thought to be an efficient and accurate polarizable model for simulation of organic and biological molecules. It also seems very promising to combine QM with polarizable MM to improve the accuracy of QM/MM methods. However, critical tests for examining the performance of QM/(pol)MM were lacking. Here we report the QM/MM solvation free energy simulations with Drude model for the water molecules. The results, surprisingly to some extents, show no significant improvement upon conventional QM/MM methods. Therefore, improvement of the current polarizable MM force fields or development of new polarizable MM force fields becomes an important challenge for the future QM/MM methods.

COMP 97

Assessing the biological effects of nanoparticles using quantitative nanostructure – activity relationships

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Evaluation of various biological effects of Manufactured Nanoparticles (MNPs) is of critical importance for nanotechnology. Experimental studies (especially, toxicological) are time-consuming, costly, and impractical calling for the development of in silico approaches. We have begun to develop Quantitative Nanostructure – Activity Relationships models where

physical/chemical/geometrical properties of the MNPs such as composition, size, shape, aspect ratio, surface area, chemistry/morphology, zeta potential, chemical reactivity, etc. are used as MNPs' descriptors. Using data recently obtained from in-vitro cell viability assays (PNAS, 2008, 105, pp 7387-7392; Nat. Biotechnol., 2005, 23, pp 1418-1423) we have developed SVM-based classification and kNN-based regression models with strong external predictive power. Similar to conventional applications of QSAR modelling for the analysis of organic biomolecular datasets, these models can be used to predict activity profiles of newly designed nanomaterials and bias the design and manufacturing towards better and safer products.

COMP 98

QSAR Analysis of nanoparticle formulation performance for a diverse set of drug and polymer systems

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Using nanomaterials for improving drug delivery systems is a new and exciting field of scientific study. Many fundamental issues remain unsolved, with one focus centered on excipient formulation performance. Here, QSAR analysis was applied to data generated from a systematic evaluation of nanoparticle formulation performance for several saccharide-based polymers (excipients) and drug-like molecules. The ability of a drug/polymer mixture to form quality nanoparticle suspensions in an aqueous solution can be measured by observing the behavior of the system over time. The resultant formulation can be classified, e.g., as good, fair or poor. A mathematical link between drug/polymer structures and performance classification has been developed. Random forest (RF) models reveal that the descriptors appearing to be of high influence are largely polymer based. This implies that polymer characteristics are the main driver of formulation performance. Such models can be used to predict the performance of new polymers in future drug formulations.

COMP 99

Identification of possible sources of nanotoxicity from carbon nanotubes

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Possible sources of cellular toxicity due to the insertion of a carbon nanotube into a dimyristoylphosphatidylcholine (DMPC) membrane bilayer were explored using the membrane-interaction (MI-) QSAR methodology. Two large changes in the bilayer occur due to insertion of the carbon nanotube. First, there is an alteration in the packing of the DMPC bilayer molecules which extends at least 18 Å from the nanotube, and includes the creation of a relatively open, unoccupied cylindrical ring of 2 to 4 Å thickness directly around the nanotube. Secondly, the same bilayer structure which undergoes the change in structural organization also becomes much more rigid than when the nanotube is not inserted. Next, the affinities, expressed by log kb values, of 23 biologically active molecules to a carbon nanotube were estimated by molecular dynamics simulation, and then compared to the observed and estimated binding affinities of eight ligands to human serum albumin, HSA. The range of log kb values over the set of nanotube ligands is 0.25 to 7.14. Some ligands, like PGI2, bind in the log kb = 7 range which corresponds to the lower limit of known drugs. Such significant levels of binding of biologically relevant compounds to carbon nanotubes could lead to alterations in the normal pharmacodynamic profiles of these high affinity compounds and be a source of toxicity.

COMP 100

Modeling of multiblade molecular turbines

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Two- to six-bladed molecular turbines were designed and modeled in the computer. The structures are based on 10- and 12-vertex carboranes (C_2B_8, C_2B_{10}, CB_{11}^-) and mounted on molecular grids or in metallo-organic frameworks. Newton's laws and Universal Force Field were used to study the response of molecular turbines to external flows and electric fields. Simple properties such as rotation barriers, friction and turbine efficiencies were extracted from the simulations. The results suggest that for turbines with more than three blades the efficiency decreases with an increasing number of blades.

COMP 101

Optical absorption and EPR spectra of gold and silver nanoparticles

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Noble metal nanoparticles have been employed as biolabels for many years and have potential applications in sensing and photonics. However, numerous aspects of these systems remain unclear including the origins of their optical absorption spectra, ligand exchange reactions, and growth mechanisms. Recent crystal structure determination of small gold nanoparticles is currently enabling in-depth research into the properties and reactivity of these systems.

Small (< 2 nm) nanoparticles display multiple peaks in their optical absorption spectra rather than the strong plasmon resonance peak of larger nanoparticles. This characteristic is likely due in part to the structure of these systems. In this work, time-dependent density functional theory (TDDFT) is employed to calculate the optical absorption of the anionic Au25 nanoparticle and its silver and mixed metal analogs. The level of theory required to accurately compute the core structure and optical absorption spectrum of these systems is discussed. Precise core geometries are required in order to obtain good predictions for the splitting between the first two spectral peaks. The model potential used to compute the excitation spectrum is critical, but solvent effects play a relatively minor role.

The crystal structure of the neutral Au25 nanoparticle has also been solved recently, and experimental EPR data shows that the structure has a single unpaired electron. Density functional theory calculations predict the g tensor and hyperfine coupling elements in good agreement with experiment, and enable explanation of the axial nature of the EPR data.

COMP 102

Understanding the molecular mechanisms underlying the nucleation and growth of nanoparticles

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Understanding the nucleation and growth is of key importance for many applications e.g. for metal nanoparticles and catalysts. In particular, it is crucial to control the morphology as well as the structure of the crystallites formed during the crystallization process. When and how the selection of a specific structure (or polymorph) occurs remains a long-standing issue. This is a very complex problem, resulting from a subtle interplay between thermodynamics and kinetics. Solving this issue has remained elusive so far, even on simple model systems

composed of spherical particles. In this talk, we use molecular simulations to understand the molecular mechanisms underlying the formation of metal and semi-conductor nanoparticles. Using accurate many-body potential to model our systems, we carry out two different types of molecular simulations corresponding to the two steps of nucleation and growth. We first examine the formation of a nucleus of a critical size, which is an activated process, and therefore requires the use of sampling methods suited to study rare events. We then carefully study the subsequent evolution of the post-critical nucleus, both in terms of size and structure. Our simulation results shed light on the molecular mechanisms underlying the structure selection process during the crystallization process.

COMP 103

Dissipative particle dynamics simulation of the formation and stabilization of iron nanoparticle

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So far, there are not yet suitable methods for investigating the dynamic process of iron nanoparticle formation of ion atoms in liquid phase. In the present study, the Dissipative Particle Dynamics (DPD) method was employed to simulate the ion nanoparticles formation process of ion atoms in hexadecane solvent and in the presence of stabilizers. The initial state of iron nanoparticle formation was defined as the disorder situation of iron atoms produced by hydrogenation of acetylacetonate ion. It was found that the repulsive force between iron clusters and the solvent is the driving force to arose the aggregation of iron atoms, and that the adsorption of stabilizers on the iron nanoparticles could prevent the growth of nanoparticles. The box size and time scale in the simulation space were further investigated. The DPD simulation results of iron nanoparticle, hexadecane and stabilizers system agreed well with our experiment data.

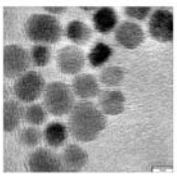

Figure 1. TEM bright field images of Iron Nanoparticle

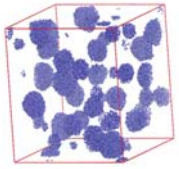

Figure 2. Simulation Result of Iron Nanoparticle (box size: 40×40×40)

COMP 104

Physical understanding through variational reasoning: Electron sharing and covalent bonding

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Energy minimization determines groundstates as the optimal compromise between the potential pull of the nuclear attractions and the localization-resisting kinetic pressure of the electron cloud. Groundstate changes resulting from parameter changes in the Hamiltonian can therefore be understood by examining this variational competition in terms of the physical attributes of the kinetic and potential energy functionals. Such a variational analysis of the exact hydrogen molecule ion wavefunction elucidates the origin of bond formation. Critical is that an orbital contracting simultaneously towards two nuclei can lower its potential energy while maintaining greater delocalization than an orbital contracting equally closely towards one nucleus. The former orbital has therefore a lower kinetic energy functional pressure so that the nuclear electrostatic pull can attach it more tightly to both nuclei. Covalent binding thus results from the softening of the kinetic pressure in the energy functional due to the delocalization caused by electron sharing.

COMP 105

Reading bond orders from the density matrix

***Michael W. Schmidt**, mike@si.msg.chem.iastate.edu and Klaus Ruedenberg, ruedenberg@iastate.edu, Department of Chemistry and Ames Laboratory USDOE, Iowa State University, Ames, IA 50011*

Quantum chemistry has made great progress in the accurate computation of energies and other properties, frequently to a level that rivals experimental measurement. However, this increase in numerical accuracy has not necessarily been accompanied by an increased understanding of electronic structure. This talk describes a method to extract qualitative information about bonding in molecules, from the first order density matrix expressed over atom-localized orthogonal MOs. A key step is the generation of ‘valence virtual orbitals' after construction of any type of SCF wavefunction, bringing the number of molecular orbitals up to the number of valence atomic orbitals. A CI-SD density matrix is obtained over the occupied and virtual valence orbitals, which are first transformed to atom-localized orbitals, and then automatically oriented into the appropriate bonding directions. The resultant density matrix is interpretable as Coulson's ‘charge and bond-order matrix'. A number of examples from main group chemistry will be presented.

COMP 106

Mechanisms of reactions of $C_4H_4^+$ with pyridine

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$C_4H_4^+$ reacts with pyridine (C_5H_5N) via the channels of proton transfer, charge transfer and condensation with H-elimination. The condensation reaction is the focus of the present study. By means of theoretical calculations and Fourier transform mass spectrometer experiments using deuterated pyridine and substituted pyridines, the structure of the product ion and the reaction mechanism are investigated. From the experimental results we find that an H atom is eliminated which can be originally from either pyridine or $C_4H_4^+$. Elimination of an H atom from $C_4H_4^+$ is preferred and there is an observable kinetic isotope effect. The experimental results also suggest possible steric blocking to the condensation by replacing H atoms with methyl groups in ortho positions of pyridine. Based on the experimental observations and results of theoretical calculations of several possible structures of intermediate and final product ions, a potential reaction mechanism for the condensation-H-elimination is proposed.

COMP 107

Polarizability effects and dispersion interactions in complexed molecules: Computational considerations

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Polarizability effects and dispersion interactions continue to be invoked as important structural determinants in a variety of natural and artificial molecules. Polar-pi interactions have been implicated as influencing the three-dimensional structures of important biomacromolecules such as proteins and nucleic acids. Investigation of polynuclear aromatic hydrocarbons have revealed weaknesses in commonly used computational theories regarding the treatment of delocalization and dispersion effects. Computational treatments of such systems is non-trivial and involves careful consideration of methodology. The challenges lie in the treatment of electron correlation, dispersion, polarization, and solvation, in a manner appropriate to the context of the application and within the limits of

available computational resources. This talk will describe our computational approaches, predictions made, and experimental comparisons for several large systems where such effects are dominant.

COMP 108

Calculation of molecular properties of proteins

Jan H. Jensen*, jhjensen@kemi.ku.dk, Department of Chemistry, University of Copenhagen, Universitetsparken 5, 2100 Copenhagen, Denmark*

In my talk I will present the PROPKA method (http://propka.ki.ku.dk) for the very rapid prediction and structural rationalization of protein pKa values. I will also discuss how the pKa values can be used to predict the electrostatic component of protein stability, activity, and binding. This component is pH-dependent and can be used of predict the pH of optimum stability, activity, and binding. Finally I will discuss implications for protein/enzyme design as well as validation for a family of enzymes called xylanases.

COMP 109

High performance computational chemistry

Theresa L. Windus*, theresa@fi.ameslab.gov, Department of Chemistry, Iowa State University, 1605 Gilman Hall, Ames, IA 50011-3111*

Mark Gordon has a long history of providing software to the chemistry community through the electronic structure code GAMESS. In honor of that contribution, I will discuss recent challenges (and, hopefully, some solutions!) to software development and the challenges of taking software - and science! - to the petascale. In particular, use of the Common Component Architecture (CCA), which allows several software codes to work together in a "plug-and-play" framework, and multi-level parallelism in the Dynamical Nucleation Theory Monte Carlo method will be presented.

COMP 110

Toward a comprehensive method for intermolecular interactions

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The effective fragment potential (EFP) method [1,2] has been developed with the ultimate goal of providing a general approach for accurately, efficiently, and generally treating intermolecular interactions. Among the many processes and properties of interest are the study of solvent effects on chemical reaction mechanisms, electronic spectroscopy, and solvent relaxation upon electronic excitation; properties of clusters and liquids; the details of ion solvation, and aggregation of polymers. The EFP method is a work in progress, with expanding capabilities to an ever broader range of problems. An overview of the method will be presented. This will be followed by a discussion of some of the most recent developments and applications.

[1] M.S. Gordon, M.A. Freitag, P.Bandyopadhyay, J.H. Jensen, V. Kairys, and W.J. Stevens, “The Effective Fragment Potential Method: A QM-Based MM Approach to Modelling Environmental Effects in Chemistry”, J. Phys. Chem. (Feature Article), A105, 293 (2001).

[2]M.S. Gordon, L. Slipchenko, H. Li, and J.H. Jensen, “The Effective Fragment Potential: A General Method for Predicting Intermolecular Forces”, Ann. Rep. Comp. Chem., 3, 177 (2007).

COMP 111

Accelerating density functional theory calculations using graphical processing units

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The graphical processing units (GPU) on a graphic card have quite computing power, which can be harvested for accelerating scientific computation. We have shown earlier that the resolution-of-the-identity Moller-Plesset second order perturbation theory (RI-MP2) can be sped significantly by carring computationally-intensive matrix-matrix multiplications on the GPU. Following the same spirit, we rewrite the exchange-correlation (XC) code within the Q-Chem quantum chemistry package such that the evaluation of the XC energy and matrix can be effectively done on the GPU, resulting significant increase in overall performance.

COMP 112

Biomolecular applications of graphics processors

***John E. Stone**, johns@ks.uiuc.edu, Theoretical Biophysics Group, University of Illinois and Beckman Institute, Urbana, IL 61801, James Phillips, Beckman Institute, University of Illinois, Urbana, IL 61801, and Klaus Schulten, Department of Physics and Beckman Institute, U. of Illinois at Urbana-Champaign, Urbana, IL 61801*

Highly parallel "many-core" processors are quickly evolving from specialized graphics accelerators to become a mainstream architecture for scientific computing. New programming languages for specifying the needed thousand-way parallelism have made many-core computing accessible to any scientist with a recent video card. This talk will discuss the current state of scientific computing on graphics processors, drawing examples from the acceleration of the molecular dynamics and visualization programs NAMD and VMD.

COMP 113

First principles molecular dynamics simulation of proteins on graphical processing units

***Ivan S. Ufimtsev**, iufimts2@uiuc.edu, Department of Chemistry, University of Illinois at Urbana-Champaign, 600 S. Mathews Ave. Box 72-6, Urbana, IL 61801, and Todd J. Martinez, tjm@spawn.scs.uiuc.edu, Department of Chemistry and the Beckman Institute, University of Illinois, Urbana, IL 61801*

Recent developments of force fields in classical molecular mechanics saw many successes, nevertheless, "truly" first principles calculations of biologically and pharmaceutically relevant molecules are highly desirable. We will present our experience with Hartree-Fock Born-Oppenheimer molecular dynamics simulation of large systems performed on a single workstation with three Nvidia GeForce 280GTX cards running in parallel. The systems of interest range from hundred-molecule water clusters and key protein structural elements such as alpha-helices and beta-sheets to the entire protein (BPTI). We are focusing on the effects produced by the choice of basis set and the presence of solution on resulting molecular structure and dynamics.

COMP 114

Quantum computation for chemistry

***Alán Aspuru-Guzik**, aspuru@chemistry.harvard.edu, Department of Chemistry and Chemical Biology, Harvard University, 12 Oxford St, Cambridge, MA 02138*

I will discuss two different applications of quantum computers to chemical problems. We have developed and characterized two quantum algorithms for the simulation of molecular systems. In the first algorithm, we obtain static properties such as energies, dipole moments and polarizabilities. As an application of this algorithm, I will talk about the first quantum computer simulation of a molecular system. The second quantum algorithm deals with dynamical proceses such as chemical reaction dynamics or electron dynamics. The two previous algorithms have an exponential speed-up over exact classical algorithms. The focus of the talk is to introduce the algorithms to a diverse audience of theoretical chemists, making emphasis on the open questions and challenges still lying ahead in the development of efficient and affordable quantum simulation algorithms and dedicated quantum simulation devices.

COMP 115

Meeting the challenge of petascale computing

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Chemistry has long been one of the research communities using the most advanced computers to further scientific discovery and the state-of-the-art. Within the next few years, petascale computers will be installed at several sites across the U.S. Although the opportunities associated with petascale computing are enormous—e.g., ab initio electronic structure calculations and molecular dynamics simulations will be feasible on far larger molecules than possible today—the challenges are equally daunting. Petascale computer will be built from multicore chips with 10,000s of chips and 100,000s of cores and will have 100s of terabytes of memory and 10,000s of disk drives. Petascale systems may also include accelerators, such as graphics processing units. The rise of these technologies has significant implications for the design of the next generation of chemistry applications.

COMP 116

Computational chemistry at the petascale using NWChem and MADNESS

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I shall describe our initial experiences (and hopefully some real applications!) with the two petascale Cray systems now being installed at ORNL and UT. Some of the numerous challenges in fielding software at this scale will be discussed with an emphasis on learning how the entire chemistry community can most effectively benefit from such resources. Lessons learned are already motivating preparations for exascale computers that are circa one decade away.

This work is funded by the U.S. Department of Energy, the divisions of Advanced Scientific Computing Research and Basic Energy Science, Office of Science, and was performed in part using resources of the National Center for Computational Sciences under contract DE-AC05-00OR22725 with Oak Ridge National Laboratory.

COMP 117

Controlling C60 self-assembly via tethering of a single PEO chain: A simulation study

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We have utilized coarse-grained molecular dynamics to investigate the controlled self-assembly of small, narrowly distributed C_{60} fullerene clusters via grafting of a single poly(ethylene oxide) (PEO) chain. We investigate the effect of both architecture (linear or star) and molecular weight in controlling the ability to promote the stabilization of small, stable fullerene clusters which resemble an inverted micelle phase, with the fullerene acting to form the micelle core. By using molecular weight and architecture as independent control variables, we demonstrate the ability to form clusters of varying size distributions and shape. We find that the tethered nanoparticles behave similarly to self-assembling lipid systems, with the particulate nature of the nanoparticle core causing quantitative variations in the observed behavior due to cluster packing constraints.

COMP 118

Morphology and rheology of the blend of amphiphilic ABA and AB block copolymers: DPD simulation study.

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Materials Directorate, U.S. Army Research Laboratory, Aberdeen Proving Ground, MD 21005-5069, Fax: 410-306-0676, (2) Department of Chemical Engineering, University of Texas at Austin, Austin, TX 78712

Gel systems based on self-assembled blend of amphiphilic ABA and AB block copolymers form the stable, spatially extended networks with a tunable viscoelastic behavior. The viscoelastic properties and morphology have been calculated employing a non-equilibrium oscillatory shear technique used with dissipative particle dynamics method (DPD), where the repulsion parameters were chosen according to the Flory-Huggins theory of polymer interactions. We have observed that addition of AB diblock copolymer increases relative number of bridgelike chains in the copolymer network with comparison of the pure ABA triblock. The addition of AB diblock also increases the micelle size for the low copolymer concentration and does not have significant effect on the micellar size for the higher concentrations. We have demonstrated that our simulation results are in good qualitative agreement with the experimental data.

COMP 119

Brownian dynamics modeling of charge mobility on single conjugated polymer chains in solution

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The high-frequency (GHz) mobility of charges on isolated conjugated polymers can now be measured in solution, providing detailed information on the intrinsic mobility of organic materials. Most current calculations of this mobility are based on propagation of the time-dependent Schroedinger equation on a disordered chain. Here, we assume instead that the wavepacket dephases rapidly in solution, and that the mobility reflects the tendency of a charge to self-localize on the chain and planarize the region upon which it is localized. Our model treats the polymer as a linear chain of sites with electronic couplings that vary with torsional angle, with the solvent included via Brownian dynamics. The parameters that determine the randomized force applied to the torsional angles are directly related to the rotational diffusion time of a single phenyl ring in solution. The results therefore provide an estimate for the polaron mobility as a function of rotational diffusion time.

COMP 120

Effect of a Stone-Wales defect on Li+ binding with (6,6) armchair single-walled carbon nanotube and graphene sheet

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Interactions of Li^+ on the external and internal surfaces of defect-free and Stone-Wales defective (6,6) armchair single-walled carbon nanotubes have been investigated using density functional theory. Comparisons of the structures and interaction energies were made between (6,6) SWNT and graphene sheet in order to examine the effect of curvature on Li^+ binding. The results indicate that the internal surface of nanotube has slightly stronger preference for Li^+ adsorption than the external surface in both defect-free and Stone-Wales defective tubes with few exceptions at the defect region. Binding of Li^+ affects the band gaps of nanotube as well as graphene sheet. The endohedral complexes possess higher values of HOMO-LUMO gap than exohedral complexes for both defect-free and defective tubes. Substantial electron charge transfer takes place from nanotube to Li^+ ion. The present study reveals that the diffusion of Li^+ inside the nanotube can take place more easily than outside the tube.

COMP 121

Architecture of transition metal monatomic strings on boron-doped carbon nanotubes: A density-functional theory study

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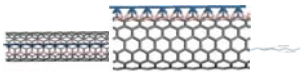
Further advancement of CNT-based nanoelectronics is impeded by constructing precisely-controlled interconnections. A central issue is how to achieve well-defined molecular interactions among the building blocks, which is of paramount importance to the molecular assembly and stability of future devices. As a counterpart to CNTs, metal nanowires have shown potential for microelectronic applications. The thinnest nanowires, i.e., monatomic chains, of several transition metals (TMs), including gold, platinum, and silver, have already been experimentally produced and observed by high-resolution transmission electron microscopy. Here, we report the first theoretical evidence for the molecular architecture of TM-string supported on boron-doped single-walled CNTs (B-SWCNTs), exhibiting high stability and unexpected electronic properties. The B-SWCNTs-templated TM strings demonstrate strong molecular recognition, leading to the self-assembly of TM atoms, with well-defined covalent bonds. The TM strings studied here include Au, Pt, Ru, Pd, Ag, Co, Ni, Cu, W, and Ti, which are well-known for their technical importance to nanoelectronics and nanocatalysis.



Pt-string/B-SWCNT(6, 6)

COMP 122

Ab initio and DFT studies of atomic hydrogen chemisorption on model graphite compounds

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Chemical adsorption of hydrogen atoms on graphite surfaces has attracted considerable interest due to its relevance for a broad range of areas including plasma/fusion physics, interstellar chemistry, and hydrogen storage. Remarkably, a rigorous benchmark of chemisorption barrier heights and potential wells predicted by widely applied density functionals such as GGA or B3LYP has not yet been reported. Obviously, molecular size represents a problem when attempting to compare DFT energetics to highly accurate ab initio levels of theory. Pyrene C16H10 and coronene C24H12 represent probably the smallest suitable compounds to model H attack on the graphite (0001) plane. Here, we show that the size effect is nearly negligible due to the surprisingly local character of the overall H-C interaction.

Our study presents counterpoise-corrected UGGA, UB3LYP, and ROMP2, ROCCSD, and ROCCSD(T) potential energy curves (PECs) based on relaxed-scan UB3LYP/cc-pVDZ geometries for the approach of atomic hydrogen head-on to one of the carbon atoms of the central carbon hexagon (site A), the midpoint of two neighbored central carbon atoms (site B), and the midpoint of a central hexagon (site C). Site A attack leads to the only global potential energy minimum corresponding to chemisorbed H (relative energy for CCSD(T) around -0.4 eV), and a barrier (CCSD(T): 0.5 eV) for the H approach. For site B attack, we found the existence of a shoulder in case of coronene + H, and a purely repulsive wall for pyrene + H. Site C is purely repulsive. Interestingly, ROCCSD(T)//UB3LYP PECs are close to that of straightforward UB3LYP, while commonly employed UGGA is much too attractive and does not possess a barrier for the H attack.

COMP 123

Calculation of protein-ligand binding free energy by a polarizable force field

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Specific recognition of ligands by proteins is the key of many crucial biological functions and systems. Binding affinity characterizes the strength of such recognition. All-atom molecular dynamics simulation with explicit solvent, coupled with efficient free energy sampling algorithms, can potentially offer accurate prediction of binding affinities of ligands to proteins. We report the calculation of the absolute and relative binding free energies of several charged ligands to trypsin from molecular dynamics simulations with a polarizable force field. The calculated absolute binding free energy of benzamidine to trypsin agrees with experiment measurement within 0.5 kcal/mol. We also found that electrostatics is the dominant force that drives binding and polarization exerts opposite effects upon solvation of ligand in water and in protein. Currently, we are focusing on relative binding free energies of a number of ligands, which have small structural variation from benzamidine, to trypsin. Again, the binding affinities we calculated are in great accordance with experimental data. The results indicate that chemical accuracy in predicting protein-ligand binding can be achieved using a polarizable force field.

COMP 124

Constant pH replica exchange molecular dynamics simulation in biomolecules

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Solution pH is a very important thermodynamic variable that affects protein structure and function. Both constant-pH molecular dynamics (MD) method and replica exchange molecular dynamics (REMD) methodology are necessary in modeling pH-dependent processes. In this work, replica exchange constant pH molecular dynamics method is applied to the study of hen egg white lysozyme (HEWL). Simulations are performed in acidic range and only aspartate and glutamate are selected to be titratable. Restraints on alpha carbons are put for each replica in order not to destroy secondary structures at high temperatures. pKa of aspartate and glutamate residues are calculated and compared with experimental values. Structural features such as hydrogen bonds are showed and compared to experiments. The coupling between conformation and protonation states is demonstrated in order to emphasize the importance of accurate sampling of the coupled conformations and protonation states. We also study the effect of restraint strength on pKa prediction and structures.

COMP 125

Estimating transition rate and free energy of Src kinase activation using Markov state model

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The activation of Src kinase is accompanied with complex conformational changes. Based on the activation pathway identified by the string method with swarms of trajectories, we build Markov state model to calculate the transition rate and free energy of Src kinase conformational activation. 51 states are conveniently defined by the 51 images along the pathway. A large number of short MD simulations are launched for each state. State-to-state transitions are counted and the transition matrix is built. The slowest relaxation time is found to be around 100 ns, very similar to the timescale observed in long MD simulations of c-Abl kinase. The free energy profile calculated from equilibrium probability distribution of each state is qualitatively in agreement with the one obtained from umbrella sampling free energy calculations. These results demonstrate Markov model along pathway can accurately probe Src kinase activation and further support the pathway determined from the string method.

COMP 126

Intramolecular electron transfer in two- and three-center mixed-valence triarylamines

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The intramolecular electron transfer (ET) processes and patterns of charge (de)localization in mixed-valence (MV) compounds depend on the interplay between the electronic and vibronic coupling. One can obtain both parameters from a Hush analysis of the intervalence band that arises upon optical ET, or from the activation barrier to thermal ET. Our recent study of two-center MV triarylamines showed that one can measure the thermal ET rate by means of variable-temperature ESR spectroscopy. Simulation of the ESR spectra based

on DFT calculation and comparison with optical spectra showed that the thermal ET in such systems occurs in the adiabatic regime. This presentation will show that one can observe a similar localized-to-delocalized ESR transition in three-center MV triarylamines and that the weak electronic coupling in these compounds pushes the thermal ET into the nonadiabatic regime.

COMP 127

Investigating the properties of new water models capable of polarization and intermolecular charge transfer

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Fluctuating-charge models have been used to model polarization effects in classical molecular dynamics simulations. In principle, they can also be used to model intermolecular charge transfer. However, existing models overestimate charge transfer and suffer from fractional charge separation for chemical species at dissociation. Our previously introduced QTPIE (charge transfer with polarization current equilibration) model is a fluctuating-charge model with correct asymptotic behavior. Here, we show that existing fluctuating-charge models do not have size-extensive electrostatic properties, and demonstrate how to obtain size-extensivity in QTPIE. We also report on the construction and parametrization of new water models that use QTPIE to model polarization and charge transfer. We are able to reproduce size-extensive dipoles and polarizabilities to quantitative agreement with MP2/aug-cc-pVTZ calculations. We also investigate the phase diagram of our new models, as well as the properties and energy orderings of small water clusters.

COMP 128

Practical many-body methods for computational thermochemistry, kinetics, and spectroscopy

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The basis set problem of the standard electronic structure methods, such as the coupled-cluster (CC) method, makes highly-accurate predictions of reaction enthalpies and barriers feasible for only very small systems. Here we will discuss our recent work on extending the explicitly-correlated R12 approach to the CC methods for ground and excited states. We developed a family of affordable and

simple CC-R12 methods that treat explicitly-correlated terms by perturbation theory. For the HEAT testset of small closed and open-shell molecules, the heats of formation computed with the novel CCSD(T)_R12 method have the basis set errors of only 2.8 kJ/mol in mean absolute sense, with a modest triple-zeta basis set. We will also discuss how the R12 approach can be applied to any electronic structure model (wave function or density-based). We aim to apply such universal correction in conjunction with multireference CC or CI models to systems with near-degenerate electronic structure.

COMP 129

A new generation of analytical tools for biomolecular electrostatics

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The current work horse of molecular simulations where efficiency is critical -- the generalized Born (GB) model which based on the implicit solvent framework -- appears to have reached its fundamental limitations.

To address the problem we have developed a set of analytical electrostatics models based on rigorous physics, avoiding heuristic steps at the early stages. The premise is that most of the key physics of the electrostatic interactions in complex biomolecular shapes can be captured at the level of simplified, basic shapes. We have shown how some of these solutions can be extended to realistic shapes while retaining the rigorous physical basis of the exact solutions. A new model based on a class of such solutions has important features completely missing from the GB model: continuous electrostatic potential can be computed everywhere in space. For large structures such as viral particles of 1,000,000+ atoms the traditional PB-based methodology will require hundreds or even thousands of CPU nodes to produce a low-resolution result, our approach based on an analytical formula computes the potential distribution at atomic resolution on a typical desktop PC. The immediate impact of the developed new model and the accompanying free software is that it makes calculation and visualization of electrostatic potential for available to researchers with the most modest computational resources.

COMP 130

Enhanced sampling methods for molecular systems far from equilibrium

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Many systems of interest in the chemical sciences take energy and matter from their surroundings by one means and return it by another; this exchange can drive them far from equilibrium. These include, but are not limited to, molecular motors, molecular electronics, polymers under shear, and regulatory modules of living cells. In the past decade or so, there have been dramatic advances in our ability to describe such systems quantitatively. Because few models of such complex systems are analytically tractable, simulations are essential for interpreting experimental data and for providing results that can be used to validate theories. Here, I will describe recent work to develop and apply umbrella-sampling-like algorithms for studying complex systems arbitrarily far from equilibrium.

COMP 131

Force-field development for heavy elements using ab initio data and the force matching method

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An algorithm has been developed for fitting classical force-fields, based upon the force matching method. It is interfaced with the electronic structure codes Gaussian03 and Crystal06 and the molecular dynamics codes DL_POLY, LAMMPS, and Amber. The quality of force-fields fit solely to the ab-initio data and PES (rather than experimental observables) has been examined with an emphasis upon the fitting of different functional forms with varying accuracy to the local minima vs. the entire dissociation curve for a given potential. The efficacy of different minimization methods has also been examined as a function of the analytic expression of the force-field. This method has been applied to the fitting of force-fields for trivalent lanthanides in aqueous solution that have relevance to both environmental remediation and nuclear fuel cycle processes.

COMP 132

A comparative study of B3LYP, X3LYP, and M06-class density functionals for predicting binding energies of neutral, protonated, and deprotonated water clusters

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We report a comparative study of B3LYP, X3LYP, and the newly developed M06-L, M06-2X, and M06 functionals for describing binding energies in a database of neutral ((H2O)n, n=2-8, 20), protonated (H3O+(H2O)n, n=1-6), and deprotonated (OH–(H2O)n, n=1-6) water clusters. The performance of each method is evaluated with three basis sets and the effect of including the basis set superposition error correction. M06-L and M06 methods show the overall best performance at the basis set limit. B3LYP/6-311++G(2d,2p) is tied for first with M06-L/aug-cc-pVTZ, if the data with the largest basis set (aug-cc-pV5Z) are not included. M06-L and M06 do a better job than B3LYP and X3LYP in reproducing relative energetics of isomeric structures. As a benchmark for determining the accuracy of DFT functionals, we used accurate binding energies at the complete basis set limit of the MP2 theory with the CCSD(T)/aug-cc-pVDZ corrections that were either compiled from the literature or calculated.

COMP 133

A single empirical expression for predicting protein-protein binding affinities and geometries

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Protein-protein and protein-peptide interactions are essential to life and also represent promising drug targets. Unfortunately, it is often difficult, costly and time consuming to obtain experimentally derived structural and energetic information about protein-protein and protein-peptide interactions. Hence, efficient in silico or computational methods for predicting and structurally rationalizing protein-protein and protein-peptide interactions are required to fill the gaps in our knowledge. Here we describe a single empirical expression that can be used to (1) predict experimental protein-protein and protein-peptide binding affinities; (2) accurately rank native and non-native protein-protein binding geometries; (3) predict the effects of interface mutations on protein-protein stability; and (4) correctly score and rank protein-peptide binding poses. Importantly, our empirical function can process an average-sized protein complex in a matter of seconds. Hence, the function is well-suited to solve a number of applied problems in protein engineering and drug design

COMP 134

An ab initio and DFT study of the effects of water molecules on sulfur oxide reactions

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Sulfur oxides are important species in atmospheric chemistry, particularly in the formation of acid rain. Many previous computational studies have demonstrated the importance of catalytic water molecules in reactions between sulfur trioxide and water to produce sulfuric acid. For example, one additional catalytic water molecule reduces the activation barrier for formation of sulfuric acid from 30 to 12 kcal/mol at the MP2/6-31+G(d) level. In this work, the effects of catalytic water molecules on other reactions involving sulfur oxides have been investigated. The reactions studied include the reactions of sulfur trioxide with hydrogen halides, as well as reactions of sulfur dioxide and sulfur trioxide with hydroxyl and hydroperoxy radicals. Both ab initio (MP2) and density functional (B3LYP) methods have been employed in the studies, along with basis sets ranging from 6-31+G(d) to aug-cc-pV(T+d)Z. The results obtained for structures, charge distributions, and activation energies have been compared with those obtained for the same reactions determined in the absence of catalytic water molecules. The calculations indicate that catalytic water molecules have a significant impact on most of the sulfur oxide reactions studied.

COMP 135

Benchmark calculations of ammonium and nitrate ions in aqueous solution

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The molar solubility of ammonium nitrate is very large compared to most other ionic compounds, to the point that it is quite easy to make solutions containing as many, or more, moles of solute ions as there are water molecules. This must be in part due to the ability of both the cation and anion in ammonium nitrate to form several hydrogen bonds each. What then is the structure of highly concentrated ammonium nitrate solutions, how does this structure differ from that of more dilute solutions, and what is the concentration at which this difference becomes manifest? In an effort to attack these questions with molecular modeling, benchmark calculations on ammonium and nitrate ions in various hydrogen bonding relationships have been performed as a first step in modeling this interesting system.

COMP 136

Binary QSAR model for classification of calpain inhibitors

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In this study we have focused on developing a binary quantitative structure-activity relationship model (QSAR) for Calpain I inhibitors. The model was designed to differentiate between inhibitors and non-inhibitors of this target. Calpain is an intracellular cysteine protease implicated in numerous diseases such as neurological disorders or muscular dystrophy with Calpain I being the predominant form activated during pathological conditions. Many reversible and irreversible inhibitors of Calpain have been reported. We collected a set of 300 inhibitors including those synthesized by our team, reported Calpain non-inhibitors, and a set of decoys and calculated their descriptors using E-Dragon software. The resulting dataset was used to explore various statistical and machine learning approaches to determine the best algorithm and a unique and optimal set of descriptors capable of differentiating between active and inactive molecules. Pairwise Correlation Analysis reduces the total number of descriptors by ~75% resulting in a unique, non-redundant set of descriptors. Optimal descriptors were then selected using Discrimination scores and Forward Selection algorithms. We observed that Forward Selection performs better than Discrimination scores approach. The optimal set of descriptors was then used to generate two decision tree models with threshold values at IC50 =1 and of 10 μM. Both models exhibit good predictive power suggesting that they can be used in virtual screening for inhibitors of Calpain 1. The procedure was validated with an external dataset published by Jorissen, R. N. and M. K. Gilson (2005). It was found that the statistical quality of our approach is comparable to that originally used for this dataset.

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COMP 137

BRICS: Breaking into retrosynthetically interesting chemical substructures

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Fragment-based approaches have become very popular within the lead finding phase of a drug design project. Different experimental techniques such as X-ray and NMR-supported protocols have been developed to detect and applied to successfully novel lead structures. In addition, in silico approaches considering either descriptor-, ligand- or structure-based information for navigating within chemical fragment spaces have been established. One open question still remains about the compilation and setup of fragment spaces. Therefore we have compiled a new and elaborate set of rules for the breaking into retrosynthetically interesting chem. substructures (BRICS) and used this for obtaining chemical fragments from biol. active compounds and vendor catalog sources.

Based on our studies three new fragment sets have been compiled, with different optimized performances in retrieving random sets of queries from different sources, which are available at http://www.zbh.uni-hamburg.de/BRICS . These sets can be used for further fragment-based searches to identify chemical probes for a given protein binding assay.

COMP 138

Comparative ligand binding characteristics of indoleamine 2,3-dioxygenase and tryptophan 2,3-dioxygenase

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The first and rate-limiting step of the kynurenine pathway in which tryptophan (Trp) is converted to N-formylkynurenine can be catalyzed by two different heme-containing proteins, Indoleamine 2,3-dioxygenase (IDO) and Tryptophan 2,3-dioxygenase (TDO). Although both proteins catalyze the oxidative cleavage of the Trp indole ring, they are supposed to follow two distinct mechanisms, yet to be determined. IDO has become increasingly popular in pharmaceutical research as it has been found to have many physiological implications, including immune escape of cancer. This study utilized molecular docking methods to investigate possible binding conformations of L/D-Trp in IDO. Molecular dynamics (MD) simulations were performed on both free and substrate-bound forms of the two

enzymes. Key interactions useful for the future design of more potent IDO inhibitors as well as mechanistic implications for both enzymes are proposed.

COMP 139

Conformational studies of bridgehead disubstituted bicyclo[m.m.m]alkane and bridgehead disubstituted bicyclo[8.8.n]alkane systems

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Using a stochastic search, conformational analysis of disubstituted bicyclo[m.m.m]alkane and disubstituted bicyclo[8.8.n]alkanes were performed. Three parameters of interest were investigated: position of bridgehead substituents, bridgehead to bridgehead distances, and the “bite-angle” of the molecules. From these parameters, the ensemble population of in,in, in,out, and out,out isomers were found, the percent change of bridgehead-bridgehead distances indicating a theoretical elasticity of each bicyclo[m.m.m]alkane were tabulated, and the “bite-angle” showed an interesting even-odd effect within the bicyclo[8.8.n]alkane family. Computational results have been validated by the synthesis and characterization of two disubstituted bicyclo[8.8.8]hexacosanes.

COMP 140

Connecting experiment and principal mode analysis of QM/MM simulations to calculate vibrational frequency shifts for N-methylacetamide in water, a simple model for the peptide bond

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Principal component analysis is widely used in multivariate statistics, pattern recognition, signal processing, and informatics fields, but our adaptation to calculate molecular vibrational frequencies and modes, called “principal mode analysis” (PMA), shows that the method also gives optimal spectra in statistical mechanics. Numerical tests verify that PMA of QM/MM trajectories gives vibrational frequencies of N-methylacetamide, a simple model for the peptide bond, that are closer to experiment than those from conventional quantum chemical methods. In addition, PMA gives vibrational frequency shifts of N-methylacetamide in water. Strengths and limitations of the current implementation of method will be presented.

COMP 141

Crystalline structure of methyl 3-nitrosalicylate and properties comparison with methyl salicylate by experiments and calculations

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Methyl 3-nitrosalicylate (3-MNS) was synthesized and a single crystal was conducted to structure analysis. The infrared spectrum, proton nuclear magnetic resonance spectrum and photo fluorescent spectra of 3-MNS were determined and explained by comparison with methyl salicylate (MS) using both experiment and calculation results. The title compound crystallizes in Monoclinic P2(1)/c Space group, having lattice parameters a b c 7.6120(10), 11.716(2), 9.656(2) and â(deg), 101.830(10) respectively. Its layer structure is formed through the weak interactions, including the multi intermolecular weak hydrogen bonding within the layer and acyl-double bond interaction between nitroyl and phenolic ring between the adjacent layers. The calculation results showed that 3-MNS is more easily relaxed to the proton transfer configuration than MS by transferring the proton from the acid moiety to the basic moiety due to its stronger Intramolecular Hydrogen Bond and achieves more delocalized excited state arising from the electron-withdrawing nitro group.

COMP 142

Crystallization of charged nanoparticles in solution

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Recent experiments showed that negatively-charged nano-particles attract to each other and form highly-ordered clusters. In this study, we use Dressed Interaction Site Theory to get the effective short-range pair interaction potentials between components in a dilute solution composed of negatively-charged colloidal particles and small counter-ions in water. Based upon these effective potentials, molecular dynamics simulations are carried out and results show our effective potentials can give us crystallization of nano-particles under certain conditions, which is consistent with experimental observations.

COMP 143

Density functional theory and multiscale simulations combined with spectroscopic study of barium/strontium ferrate/cobaltate as a promising material for solid oxide fuel cell

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We are presenting combined experimental and theoretical study on $Ba_{0.5}Sr_{0.05}Co_{0.8}Fe_{0.2}O_{3-\delta}$ (BSCF) perovskite, a promising candidate for intermediate temperature solid oxide fuel cell. We apply multiscale technique to determine its vacancy diffusion coefficient. Density Functional theory (DFT) is used to calculate activation energy barriers for oxygen migration in different local cation distribution. Activation barriers are used in Arrhenius equation to predict the rates for elementary steps in diffusion processes. These rates are then input into Kinetic Monte Carlo at large scale simulations to obtain long time oxygen diffusivities and apparent activation energies. We use Micro-Raman spectroscopy to detect Jahn-Teller distortion in BSCF. We also use DFT to explain the Jahn-Teller distortion of octahedral coordination around Co4+ cations, and to confirm that Co4+ has intermediate spin state. Different cations and oxygen vacancies ordering are examined theoretically and brownmillerite type ordering was found to be energetically unfavorable, which explains remarkable phase stability BSCF.

COMP 144

Developing reweighting-based molecular dynamics with sights set on converged long-timescale biomolecular simulations

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Molecular dynamics is one of the most widely used techniques in computational chemistry due to its ability to accurately sample the energy landscape. For most biomolecules, there is a sub-microsecond timescale limitation; therefore, normal MD cannot explore portions of the landscape separated from the initial configuration by high barriers. We have proposed a method that eases the transition between energy basins by modifying the potential landscape in an efficient accelerated MD approach. In highlighting this method, we have studied a notoriously slow conformational transition in biology: the cis-trans isomerization of the peptide prolyl bond, and we have provided detailed atomistic picture of the catalytic mechanism by cyclophilin, an isomerase. Finally, we have addressed aspects of reweighted-based simulations that could affect the precision of the final results. We have provided a quantitative method to estimate the number of sampled points required in the crucial step of reweighting these advanced simulation methods.

COMP 145

Development of pharmacophore and CoMFA study for sigma 2 receptor ligands

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This study describes the development of a pharmacophore and CoMFA model for sigma 2 (σ2) receptor ligands. Derived from DISCOtech, the pharmacophore contains four points: nitrogen, two hydrophobic groups, and a lone pair of electrons. The CoMFA study contained 32 bioactive compounds calculated in three methods for geometry optimization and atomic charges: AM1, HF/3-21G*, and B3LYP/3-21G* in Gaussian 98. CoMFA maps consisted of 5 compounds in a test set and 27 compounds in the training set. The CoMFA model derived from HF/3-21G* calculations (q2 = 0.567, r2= 0.9923) used three optimal components with optimized geometries and atomic charges (steric contribution of 0.383; electrostatic contribution of 0.617) for more reliability in predicting bioactivities of σ2 receptor ligands. Using the HF/3-21G* analysis, new active σ2 receptor ligands were designed and pKi values predicted to conclude electron rich groups substituted on to cyclohexane and cyclohexanebenzene rings increase the σ2 bioactivity of ligands.

COMP 146

Effect of support, ZnO, on the structure and properties of Cu clusters

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The overall objective of this research is to explore new pathways for more efficient hydrogen production or synthesis of new energy carriers from coal gasification. This projects aims to find catalysts that maximize methanol formation and minimize the formation of methane from coal gasification. In this poster, we present the results of DFT calculations for the study of the adsorption of small copper clusters on the surface of zinc oxide. The calculations using PBE functionals were carried out using spin-polarized DFT method implemented in Vienna Ab-initio Simulation Package (VASP). In the calculations, Cu atoms as well as the first few layers of ZnO surface were fully relaxed to their ground state geometry. The structural and property changes of Cu clusters u¬¬¬pon their adsorption at different surface coverage on ZnO surface will be discussed.

COMP 147

Efficient methodologies for antibody homology modeling

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Antibodies are globular proteins composed of two heterodimers with each set containing a heavy chain (VH) and light chain (VL). The binding to an antigen is in most antibodies is facilitated by six loops, three originating from the VL domain, termed L1, L2 and L3, and three from the VH domain, termed H1, H2 and H3. Due to their modular composition and high target specificity antibodies have become increasingly attractive for using them as drugs. Antibody Homology Modeling techniques have often been applied in generating therapeutically more effective antibodies. Here, we demonstrate a collection of procedures as well as an interface to meet the demands of effective antibody homology modeling. The application has flexible components allowing the integration of various work-flows associated with this specific form of modeling. The routines account for the particular structural composition of antibodies when searching for template candidates and building models. A knowledge-based approach is applied with an underlying database of antibody structures originating from the Protein Data Bank (PDB), clustered by class, species, subclass and framework sequence identity. A especially designed loop grafting routine allows for generation of xenogeneic antibody models.

COMP 148

Empirical corrections to density functional theory highlight the importance of nonbonded intramolecular interactions in alkanes

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Energies of alkanes computed with many popular and even newer density functionals are flawed by systematic errors, which become considerable with larger molecules. The same energies, however, are well described by post Hartree-Fock methods. Similar DFT shortcomings are well documented for cases involving descriptions of intermolecular van der Waals complexes. One solution to the density functional problem is the addition of an empirical correction term, which more accurately models the known R^{-6} dependence of van der Waals energies. Here, we present the first empirical correction to DFT parameterized to reproduce experimental energies associated with *intra*molecular interactions in alkanes. Our training set used only three reactions involving simple linear and branched alkanes and provides a remarkable improvement over conventional DFT methods and empirical corrections optimized for *inter*molecular interactions. In contrast to many standard density functionals, the *intra*molecular empirical correction correctly predicts the lowest energy alkane isomer in addition to performing satisfactorily for describing the interaction energies of *inter*molecular complexes.

COMP 149

Evidence for multilayer active sites in enzymes

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Enzyme active sites have evolved distinct electrostatic and chemical properties that facilitate catalysis and substrate recognition. Do these properties arise solely from residues immediately surrounding the reacting substrate molecule, or do the next-nearest neighbors, the “second shell” residues located behind the first layer,

contribute also? Computational and bioinformatics evidence on a test set of enzymes, in addition to a limited set of previous experimental data from the literature, is presented to show the importance of remote residues in enzyme catalysis, particularly those in the “second shell” around the reacting substrate. In addition, our new experimental mutagenesis studies are reported for five “second shell” mutations that are predicted to be important for Nitrile hydratase from Ps. putida (ppNHase). THEMATICS, Evolutionary Trace (ET), and Consurf were used to study a test set of 37 proteins. For 32 of these enzymes, THEMATICS predicts at least one residue in the second shell of an annotated binding site. Furthermore, the predicted second- and third-shell residues on the average tend to be almost as well conserved as the first-shell residues. For all 37 proteins in the test set, the sites predicted by ET contain both second- and third-shell residues, in addition to first-shell residues. For the Nitrile hydratase experiments, conservative mutations were made for second shell residues predicted to be important. While the second- and third-shell mutations do not have much effect on KM, all five mutations have some effect on kcat. Values for the rate constants, expressed as the ratio kcat(mutant)/ kcat(WT), are: D164N = 1.4x10**-2; E168Q = 0.19; E56Q = 1.0x10**-2; H71L = 6.2x10**-2; Y213F = 0.54. The combination of computational and experimental evidence strongly suggests that second shell residues do play a role in catalysis and that enzyme active sites are in fact built in multiple layers.

COMP 150

Investigating the binding mode of ligand of bcl-xL by steered molecular dynamics simulation

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The b-cell lymphoma 2 (bcl-2) protein family, comprising of pro- and anti-apoptotic members, are important regulators of apoptosis. Over expression of anti-apoptotic bcl-2 family members, bcl-2 and bcl-xL, have been associated with the resistance development against standard chemotherapeutic agents and therefore considered as attractive targets of anti-cancer therapy. In the event of ligand binding in bcl-xL, significant backbone movement is observed particularly in the BH3 domain of the protein which is accompanied by large rotameric alterations of the residues near the binding site and result in the formation of a binding groove which is dependent on and unique to ligand binding to it. Here we studied the induced fit effects in the binding site of bcl-xl using nanosecond conventional and steered molecular dynamics simulations to reveal the specific

conformational states of the protein suitable for binding by bcl-xL inhibitors of different chemotypes for which ligand bound structures are not available.

COMP 151

Modeling nitrile-terminated polypropylene imine dendrimer fragmentation with DFT

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Dendrimers are regularly branched polymers with a treelike structure that can be tuned for size, shape, and functionality. This relatively new class of compound has shown potential for useful host-guest chemistries including site-specific drug delivery via molecular recognition, catalysis, and nonlinear optics. Gas-phase dissociation studies have been initiated to probe the structure and stability of the half and first generation polypropylene dendrimer complexes and to develop an analytical framework for their characterization. These dissociation studies result in fragmentation products of mass-to-charge ratios that can be assigned to multiple possible isomers formed by potentially competing mechanisms.

Since these reactions are under kinetic control we will present density functional results for modeling the dissociation mechanisms for the most abundantly produced fragments from the protonated dendrimers. The BMK functional in conjunction with a moderately-sized basis has been chosen for its utility in determining transition state energies and kinetic parameters.

COMP 152

Modeling of PXR ligands

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A set of structurally-diverse marketed drugs and structurally-similar in-house chemical entities were modeled into the PXR ligand-binding domain. Interactions between the ligands and the residues lining the PXR ligand-binding site were analyzed and compared with the experimental binding and induction data. The results from this study provide a molecular basis for addressing the PXR-dependent CYP 3A4 induction liability as part of our medicinal chemistry efforts.

COMP 153

Modeling the binding of CWAs to human AChE and BuChE compared to other species

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Traditional chemical weapon agents (CWAs) are known to bind acetylcholinesterase (AChE) and butyrylcholinesterase (BuChE). Their lethality is known to be different for different mammalian species. We have modeled the binding affinity of CWAs to human AChE and BuChE compared to homology models of three other species using molecular docking, MM-PBSA/GBSA, and free energy perturbation calculations. Through molecular docking we are able to predict the rank order of binding of the CWAs at the active site. However, a more accurate description of the binding is revealed with the free energy perturbation calculations. Through these calculations, we observe that recognition of the gorge is critical to binding, and there is a pathway from the gorge mouth to the active site.

COMP 154

Molecular dynamics and free energy calculations explain decreased inhibition of G-actin by oxalatrunculin B and semisynthetic analogs of latrunculin B

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Latrunculins, isolated from Negombata species, contain a distinctive macrocyclic lactone ring and 2-thiazolidinone moiety, and have been used as biochemical tools to inhibit actin polymerization. The stability of the actin cytoskeleton is intricately connected to the development of the tau hyperphosphorylated structures found in Alzheimer's disease. Hence, inhibiting G-actin from polymerizing into F-actin may prevent neurodegeneration. We carried out docking, molecular dynamics simulations and MM-PBSA binding free energy

(BFE) calculations of G-actin in complex with naturally occurring and semi-synthetic latrunculins. The BFE calculations agreed well with actin polymerization inhibition data demonstrating that the recently isolated oxalatrunculin B binds more weakly than latrunculins A and B to G-actin. The fit of the latrunculins into G-actin and details of the protein-ligand interactions explain the decrease in activity of oxalatrunculin B and semi-synthetic analogs, reduced inhibition which should be beneficial for avoiding general toxicity.

COMP 155

Molecular modeling of the dra snf2 intein for the investigation of the atypical splicing mechanism

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Intein-mediated protein splicing is a post-translational autocatalytic process where the embedded intein is removed from the precursor and the flanking polypeptides are ligated. Our recent studies on the Deinococcous radiodurans Snf2 intein, have outlined a novel protein splicing mechanism that utilizes a nucleophilic residue, Cysteine, in the intein. Cysteine has been implicated in in vivo studies to be crucial for the initial step of the reaction. The 3-dimensional structure of this intein is not known. In order to investigate the molecular mechanism of the Snf2 intein, we must know whether the Cysteine residue is close enough to the N-terminal splice junction. A molecular model of the Snf2 intein was constructed on the basis of sequence similarity with the Sce VMA intein, of known crystal structure, using Prime (Schrödinger, Inc). The structural features of the Dra Snf2 intein model will be discussed, including positioning conserved motifs with their catalytically important residues.

COMP 156

Moving domain QM/MM method to describe polarization effects in protein electrostatics

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In this study we utilize the Moving Domain QM/MM (MoD QM-MM) method to investigate the effect of polarization on the molecular electrostatic potential

(MEP) in an ion channel model. Further improvement of the method is achieved by exploring different QM/MM partitioning schemes, varying the size of QM domains, different charge scaling/fitting methods and incorporating delocalization of charges over neighboring domains.

Attempts are also made to investigate the effect of polarization on calculating activation energy barriers of enzymatic reactions and the geometry convergence properties by alternating polarizations with geometry optimizations. The reaction considered in the present study is a simple SN2 type methyl transfer in Glycine N-methyltransferase(GNMT).

COMP 157

MSMM-CoMFA, a novel 3-D-QSAR method for ligands with multiple species and multiple binding modes

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The existing methods for prediction of protein-ligand binding affinities from ligand structures assume that all ligands bind as one species in similar conformations. This common perception is being contradicted by the growing number of experimental structures showing multiple binding modes for flexible ligands. A novel ligand binding affinity prediction method is developed based on the rationale that, in the thermodynamic description of multi-species, multi-mode binding event, the overall association constant is equal to the weighed sum of the microscopic association constants of individual modes, with the weights given by the fractions of individual species. This approach is implemented in C programming language and is incorporated into CoMFA using Sybyl Programming Language. This robust method is validated using a published data for binding of 28 thyroxine analogs to transthyretin. The predictive ability of the obtained model establishes the significance of including multiple species and multiple modes for ionizable and flexible ligands.

COMP 158

New protocol for efficient and accurate ab initio prediction of thermodynamic parameters.

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High accuracy is crucially important in the determination of thermodynamic parameters of molecular species and chemical reactions when those species are involved. The available techniques represent various compromises between accuracy and computational cost. The most efficient technique includes calculations at the CCSD(T) level using extended basis sets or extrapolated to complete basis sets (CBSs), which according to definition should provide extremely accurate results. However, such an approach has a very serious disadvantage since it currently limits the size of the considered systems. In addition, the majority of available computational protocols are devoted to the prediction of the enthalpy of formation and Gibbs free energy of isolated molecules, ions, and radicals. In contrast, the related area of an ab initio prediction of the thermodynamic parameters of intermolecular interactions is not well represented. To fill this gap, we are proposing composite protocol for efficient and accurate determination of thermodynamic parameters of intermolecular complexes.

COMP 159

Optimization of pattern recognition and classification by combinatorial QSAR modeling of the carcinogenic potency database

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We report the optimization of pattern recognition and classification of chemical carcinogenicity based on combinatorial QSAR studies of compounds with available mutagenic and carcinogenic data from the Carcinogenic Potency Database. For 693 such compounds with MolconZ, Dragon and Frequent Sub-graph descriptors calculated, corresponding k-nearest-neighbor QSAR models were developed for (i) mutagens vs. non-mutagens, (ii) carcinogens vs. non-carcinogens, (iii) genotoxic carcinogens vs. non-genotoxic carcinogens, and (iv) genotoxic carcinogens vs. genotoxic non-carcinogens. Except for case (ii), models with predictive accuracy exceeding 80% each were obtained for training, test and external validation sets. Our results compare favorably with those generated with more common fragment-based approaches. Our method can reduce the rate of false positives/negative and strengthen the prediction

performance of the QSAR models. The patterns found would be helpful to identify alerts for non-genotoxic carcinogens and genotoxic non-carcinogens. They might also be helpful in understanding chemical mechanisms underlying mutagenicity, carcinogenicity and epigenicity. and external validation sets. Our results compare favorably with those generated with more common fragment-based approaches. Our method can reduce the rate of false positives/negative and strengthen the prediction performance of the QSAR models. The patterns found would be helpful to identify alerts for non-genotoxic carcinogens and genotoxic non-carcinogens. They might also be helpful in understanding chemical mechanisms underlying mutagenicity, carcinogenicity and epigenicity.

COMP 160

Pair-wise property-encoded shape distributions for comparing binding sites in proteins

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Detecting similarities in binding sites of proteins is of paramount importance in structure-based drug design and functional annotation of proteins. We have developed a novel method for alignment-free rapid automatic comparison of shape and property distributions on protein binding site surfaces by computing the pair-wise probability distribution functions of the surface shape and property. We compared the performance of our method against another method employing the well established geometric-hashing based similarity search in a virtual screening experiment with sites in bound conformations. Although the overall recall rates were comparable for the two methods, our method was able to identify several sites of similar or identical ligands not identified by the geometric-hashing based method and vice versa, demonstrating the complementarity between the methods. The results of the application to comparing bound and unbound binding sites will be presented in detail.

COMP 161

Prediction of thermal cycloreversion and fatigue-resistance

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The isomeric transition, due to irradiation, between open and closed forms of a photochromic comopunds, is a reversible process (photocyclization). The two isomeric forms differ in color and various physical and chemical propertie and they have prospective applications in optical switches and data storage applications. The study of the Structure/Activity realtionship of these chrmophores is an important component of rational design strategy. In this contribution we apply Density Functional Theory (DFT) to predict the equilibrium geometry and absorption spectra for a benchmark set of molecules. The accurate equilibrium geometry comparison was performed on the basis of bond length alternation (BLA1 and BLA2) values with the experimental X-ray geometry. Time Dependent-DFT (TD-DFT) absorption spectra evaluated under solvent conditions was compared to the experimental spectra. In addition we also employ DFT to predict kinetics of cycloreversion to estimate thermal stability, and the mechanism of byproduct formation in order to predict the fatigue resistance.

COMP 162

Predictive statistical model building for hERG liability based on pharmacophore fingerprint descriptors

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hERG liability is a major concern in drug design, given that potent hERG blockers have been connected with potentially fatal cardiac arrhythmias.1 Therefore predictive hERG models can be a valuable aid to guide the design and prioritize the synthesis of potent ligands with decreased hERG affinity. However, prediction of hERG inhibition (as determined experimentally by a PatchXpress functional assay) for one infectious disease project at GSK using QSAR models based on traditional physicochemical descriptors has been proved to be inaccurate. Therefore pharmacophore fingerprint descriptors2 and several

different statistical model building methods3-9 including partial least squares regression (PLS),3 support vector machine (SVM), and distanced-weighted discrimination (DWD), have been combined to identify predictive models for this challenging target. The statistical model building methodologies and prediction results will be compared and discussed in detail.

COMP 163

Q-Chem 3.2: Reaching higher ground

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Q-Chem is a high performance, comprehensive quantum chemistry package. The latest release Q-Chem 3.2 includes the following exciting new features: 1. constrained DFT; 2. long range corrected DFT functionals for better description of weak interactions; 3. MP2 model with better scaling property; 4. solvation model with gradient; 4. improved CCSD methods; 6. QM/MM frequency calculation and much more.

COMP 164

Qstr analysis of mixtures toxicity to Daphnia magna

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Hierarchical QSAR technology (HiT QSAR) has been employed for consensus QSTR (Quantitative Structure Toxicity Relationships) analysis of toxicity of ester sulphonates, phenols, aliphatic n-alcohols and their binary mixtures tested against *Daphnia magna*. The structure of a mixture was represented both using descriptors of individual compounds comprising the mixture as well as novel specific mixture parameters termed unbounded simplexes. The dataset included 15 single compounds and 20 mixtures. The logarithm of EC_{50} (mmole/l) has been used as a target function. The goals of this study included elucidating the structural determinants of mixture toxicity and developing rigorous HiT QSTR

models capable of accurate toxicity prediction of new compounds and mixtures from their structure and composition.

Successful consensus model based on forty best QSAR models (R^2 = 0.86-0.97; Q^2 = 0.74-0.96; R^2test = 0.86-0.99) have been obtained using different training and test sets. Molecular fragments both increasing and reducing toxicity were determined.

COMP 165

Quantitative predictions of protein-ligand binding affinities

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Computational methods have long been used to study protein-ligand interactions, partly with the promise that someday, computers would be able to take PDB structures of proteins of relevance to disease and design drugs based on those structures. This promise is, unfortunately, still largely unfulfilled. I discuss my recent work improving methods for accurate computation of binding free energies, their application in several different binding sites, and the insights gained from these studies. In particular, protein conformational change free energies, ligand orientational sampling, and solvation play key roles. A systematic approach to identifying and resolving sampling problems provides fundamental insight into the underlying thermodynamics and results in substantial improvements in results, even making predictions possible. I give an overview of my recent work in this area and discuss some future challenges.

COMP 166

Quantitative structure – activity relationship study of organophosphorus pesticides, nerve agents and their derivatives

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Organophosphorus compounds are often used as pesticides and warfare agents. These compounds exhibit their toxic behavior through the inhibition of acetylcholinesterase, a neurotransmitter. Organophosphates cause behavioral and psychological changes in humans which include irritability, nervousness, fatigue, insomnia, memory loss, impaired judgment, slurred speech, and depression. Many of them are acute toxins which irreversibly inhibit acetylcholinesterase. Current work is devoted to the investigation of structure – acute toxicity relationship for organophosphorus compounds, revealing of structural features responsible for toxic effect and development of new QSAR equations which will accurately predict toxicity for organophosphorus compounds. Therefore, the aim of this study is to find a relationship between structure and acute toxicity of organophosphates by application of quantum-chemical techniques and QSAR approach followed by subsequent validation of obtained results using broad spectrum of available experimentally determined data and the usage of QSAR models developed for virtual screening of toxicity for new compounds of interest.

COMP 167

Quantum calculations on the regioselectivity of nitration reaction of methyl salicylate with iron nitrate

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Nitration of organic compounds is an important reaction. Unfortunately, industrially nitration requires the use of corrosive nitric acid–sulfuric acid mixture and generates large amounts of diluted sulfuric acid waste, which is very energy consuming to separate and recycle. In this paper,methyl 3-nitrosalicylate and methyl 5-nitrosalicylate were obtained by the nitration reaction between methyl salicylate and iron (III) nitrate and separated by simple filtration and crystallization methods. The reaction regioselectivity were comparatively studied by experiment and theory calculations. The results show that C3 and C5 contain higher HOMO coefficients than C4, and the energy of the 3- or 5-susbtituted complex is lower than that of 4-susbtituted complex. Therefore, the interaction between NO2+ and methyl salicylate occurs mainly in the C3 and C5 positions. Furthermore, the intramocular hydrogen bond and the UV-Vis spectra of 3-MNS and 5-MNS are examined and illustrated by B3LYP/6-31+G* method.

COMP 168

Reactivity and stereospecificity in the Wittig reaction: A molecular modeling study of the Wittig reaction of 9-anthraldehyde with the benzyltriphenylphosphonium ylide

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The Wittig reaction is a well- established synthesis reaction used to prepare alkenes by treating an aldehyde or a ketone with a triphenylphosphonium ylide. For unsymmetrical triphenylphosphonium ylides, the reaction is stereoselective. It proceeds via two different four-center oxaphosphetane transition states to give a pair of diastereomeric alkenes in which either the cis- (Z-) or the trans- (E-) isomer predominates. The product distribution of the two alkenes formed depends on the relative energies of their transition states leading to their formation. When the Wittig reaction is carried out at room temperature in which 9-anthraldehyde and benzyltriphenylphosphonium ylide are allowed to react, the reaction is stereospecific. Only one product, trans-9-(2-Phenylethenyl)anthracene, is formed. To account for the stereospecificity of this reaction, molecular orbital calculations (Semi-Empirical/AM were carried out on both transition states. Molecular geometries, including steric strain (intramolecular distances), torsional strain, C-O and C-C bond lengths, and planar and dihedral bond angles in both transition states were measured; and transition state energies were compared. The report of this investigation: (1) presents these molecular parameters in the two respective transition states; (2) accounts for the unique stereospecificity of this reaction; and (3) offers evidence that the kinetic product and the thermodynamic product in this reaction are one and the same.

COMP 169

Relativistic calculations of the xenon – transition metal cation systems (XeM+, M=Ni, Pd, Pt, Cu, Ag, Au, Zn, Cd, Hg)

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Prior studies suggest that cation silver clusters in silver-exchanged zeolites are binding sites for xenon. In our other theoretical study, the xenon – ionic silver interaction is explained by the electron transfer from xenon to the virtual 5s orbital of silver. For a better understanding of this interaction, expanding to the XeM+ systems of other transition metals surrounding silver in the Periodic Table

is necessary. In this study, relativistic calculations on the XeM+ systems were performed using couple-cluster methods with both all-electron basis sets and model core potentials. Potential energy curves and molecular properties were investigated. The trend in XeM+ binding energies is metals in Group 10 > Group 11 > Group 12. The extra space in d orbitals of metals in Group 10 assists the charge transfer from xenon. Ni+ shows the strongest binding with xenon.

COMP 170

Residual reactive curves construction using spreadsheet and Aspen Properties® complement for Excel®

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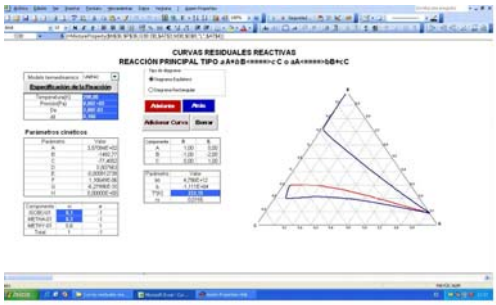
A general methodology for construction of reactive residual curves (RRC) in a spreadsheed using Aspen properties complement is presented. Two reactive systems, a ternary (methane-isobutane-methyl tert-butyl eter) and a quaternary (methanol-acetic acid-methyl acetate-water) are taken as study cases in order to illustrate the application of the methodology. Results obtained for these two reactive systems show good accuracy when compare to reported data available in the open literature. Implementation of this methodology in spreadsheet allows construction of RRC of any system in a flexible, fast and interactive way.



COMP 171

Scanning the potential energy surface of furanosyl oxocarbenium ions: Models for reactive intermediates in carbohydrate reactions

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A method for scanning the full potential energy surface (PES) of five-membered rings is presented. Graphs of the PES of oxocarbenium ions in five-membered rings are shown using the conformational description of furanoses by Altona and Sundaralingam [J. Am. Chem Soc. 1972, 94, 8205] and the PES is related to predictions made about the preferred conformation of attack of a neutral nucleophile [Lucero and Woerpel J. Org. Chem. 2006, 71, 2641]. The energy difference between diasteromeric intermediates is compared to the trajectories of attack of the neutral nucleophile from either face to determine which is the better predictor of preferred stereochemistry of addition.

COMP 172

Simulations of a tethered p53 peptide in aqueous salt solutions

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The capability to manipulate and control proteins/peptide fragments at the solid – liquid interface lead to many applications in material science and biotechnology. Understanding the detailed molecular structure of these molecules tethered to a surface is important for these applications which usually demand the retention of protein native structure and biological functionality at the desired material surface. We performed molecular dynamics simulations of a pentapeptide, RHSVV, an epitope of the tumor suppressor protein p53, tethered via a spacer on a functionalized silica surface and free in solution at different salt concentrations (0, 0.14, 0.5 ,1 M) to study the structural and conformational differences. Conformational similarities are found among major structural clusters of the tethered and free peptide. These calculations also allowed analyses of the kinetics of structural transitions, peptide-surface interactions and the sequence orientations to be performed.

COMP 173

Study of the active site of inosine monophosphate dehydrogenase

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Inosine monophosphate dehydrogenase (IMPDH) catalyzes the rate limiting step in guanine synthesis from an inosine precursor. IMPDH has arisen in recent years as a target for antiviral, anticancer, and immunosuppressive drugs. The intermediate in the reaction, xanthosine monophosphate (XMP), is covalently bound to the enzyme and is unique among nucleotide monophosphates because its pKa value hovers below physiological pH. An active site water molecule is believed to perform a hydrolysis, giving free XMP and enzyme. Some experimental studies have suggested the Arg418-Tyr419 dyad, or the Asp261-Arg418-Tyr419 triad, activate the water molecule. Using the Molaris software package, this work carefully looks at the protonation states of the active site residues and the intermediate, and attempts to understand how the active site water molecule can be activated by relatively basic sidechains.

COMP 174

Substrate induced population shifts and stochastic gating in the PBCV-1 mRNA capping enzyme

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The PBCV-1 mRNA capping enzyme catalyzes the transfer of GMP from GTP to the 5' diphosphate end of nascent mRNA. It is composed of two globular domains connected by a short flexible peptide linker. Based on crystal structure isomers, it has been suggested that domain motion mediates advancement through the catalytic cycle. In this work, we investigate domain motion in contexts of the induced fit and population shift models of substrate binding and explore how domain motion affects the rate of GTP binding. Additionally, we consider the influence of conformational flexibility from the perspective of polynucleotide specificity.

COMP 175

The gem-dimethyl effect revisited: Elucidation of rate acceleration for epoxidation reactions of chlorohydrins in water from QM/MM simulations

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QM/MM/MC simulations in water have been carried out for the cyclization reactions of three analogs of 2-chloroethoxide in order to investigate the experimentally observed rate enhancement resulting from increased methylation on C1 of the backbone. The transition states were identified using a novel two-

dimensional mapping technique, which projects the potentials of mean force (PMF) calculations onto a grid generated around a guess for the given transition state in a one-step process, allowing for a more accurate and computationally faster sampling of the regions of interest on the free energy surface. The QM/MM/MC, as well as ab initio Hartree-Fock (HF) simulations carried out in conjunction with polarizable continuum solvent model, reproduced the relative rate increase observed experimentally for these reactions. Analysis of the explicit solute–solvent interactions indicates that an enhanced formation of hydrogen bonds proceeding from the reactants to the transition states is largely responsible for the rate increase. This trend is due to the retention of the high C-O bond polarization in the substituted analogs of 2-chloroethoxide during the course of the reaction. Thus, we argue that the solvent effects are principally accountable for the observed differences in reaction rates, contradicting the previously dominating Thorpe-Ingold hypothesis.

COMP 176

Theoretical investigations on interactions between L-lactic acids and terpenoid mosquito repellents

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Recently a group of terpenoid mosquito repellents has been synthesized and shows the promising repellency capabilities from the preliminary bioassay, compared to the widely-used commercial product, N,N-diethyl-3-methylbenzamide or N,N-diethyl-m-toluamide (DEET or DETA). The subsequent QSAR studies were performed to supply the guidance to the future experimental work. Previous studies demonstrate that the pure repellent may be the attractant with the absence of L-lactic. The role of repellents is to prevent the detection of L-lactic acid by the chemoreceptor on mosquitoes, though the exact repelling mechanism is still not clear. In this study, the possible intermolecular interactions between L-lactic acid and terpenoid repellents are calculated at the HF and DFT level and the importance of such interactions in the relationship between structures of lactic acid-repellent complexes and their repellency capabilities are also investigated.

COMP 177

Weighted ensemble path sampling simulations of conformational transitions in lymphotactin

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We perform weighted ensemble (WE) path sampling simulations to determine the transition pathway(s) and intermediates during the conformation transition of lymphotactin, a 95 residue protein recently crystallized in two distinct folds. The WE method generates a transition path ensemble and is capable of finding multiple pathways when they exist. We study a "coarse-grained" model of lymphotactin with a fully atomistic backbone, which is much more realistic than models previously studied via the WE approach. Following initial studies on a purely structure-based (double Go) potential, we check the "robustness" of the paths by studying their sensitivity to the progressive addition of specific chemical interactions to the model.

COMP 178

Ligand conformational free energy change and its contribution toward improvement of binding affinity prediction between the XIAP BIR3 domain and its inhibitors.

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The X-linked inhibitor of apoptosis(XIAP) protein inhibits apoptosis by binding with several members of caspase proteins (such as caspase-3, 7, 8 and 9) to block the execution of apoptosis in cells. Endogenous inhibitor protein, Smac, antagonizes XIAP via a dimeric form. The primary interaction between Smac and XIAP is between the N-terminus four residues segment (AVPI) from Smac and a binding groove in the XIAP BIR3 domain. Several inhibitors, including those from our laboratory, targeting the XIAP BIR3 domain have been developed based on the structure of the four-residue scaffold from Smac. These inhibitors also bind to several members of IAP family proteins in cells. In this work, we combine molecular docking, molecular dynamics simulation and four different scoring functions, i.e. X-Score, Drugscore, M-Score, MM-GBSA, to predict the binding affinity of 31 compounds and the XIAP BIR3 domain. The correlation between

the calculated and experimentally determined binding affinities is analyzed. Our results show that the best effort by using snapshots of protein-ligand structures in scoring functions calculation can achieve a linear correlation coefficient of 0.6 for these compounds. However, by including differences of ligand conformational free energy changes upon binding, a greater improvement on the linear correlation coefficient can be achieved. Generalization and feasibility of such a strategy for improving the predictive power of computational estimate of binding affinity is discussed.

COMP 179

Molecular dynamics simulation of the interactions of Aß oligomers with lipid bilayers: Implication for toxicity of Alzheimer's disease

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Aß peptide, a major component found in the brain of patients who suffer from Alzheimer's disease (AD), is directly linked to the pathogenesis of AD. Accumulating evidences show that soluble Aß oligomer intermediates are more toxic than Aß mature fibrils. But, the molecular mechanisms of neurotoxicity remain elusive, primarily due to the lack of atomic details of oligomers. In this work, we first identified several stable Aß oligomers in solution with various structural topologies using molecular modeling and simulations. Then, these stable Aß oligomers were applied to interact with the lipid bilayers to exam how Aß oligomers could induce membrane damages. The effect of Aß location and orientation, lipid composition, ionic strength, and temperature on both conformation changes of Aß oligomers and lipid bilayers will be systematically examined. In parallel to simulation effects, we also performed in situ AFM study of Aß interactions with controlled polymer surfaces and cell membrane. The complementary results from simulations and experiments will provide valuable insights into the structures and the driving forces that are critical in illustrating the mechanism of neurotoxicity.

COMP 180

DFT study of the explosive tetraacetone tetraperoxide

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Peroxide-based explosives have been implicated in many acts of terrorism around the world. They remain a major cause of concern because of their ease of synthesis and difficulty in detection. In order to improve our understanding of this important class of molecules, theoretical calculations were performed on tetraacetone tetraperoxide (TeATeP) using density functional theory. The results predict the existence of many conformers, but only one, having pseudo-D_4 symmetry, should dominate the equilibrium properties of TeATeP. Thermochemical analysis suggests that it is not as thermodynamically stable as other peroxide-based explosives; the ring diameter is too small to accommodate fully trans O-O linkages but too large to permit gauche conformers. For this reason, synthesis of this compound may be more difficult than has previously been assumed. The computed ^{1}H and ^{13}C NMR spectra and harmonic vibrational frequencies show marked differences between TeATeP and the spectral properties of related peroxide-based explosives, which may assist in the detection of TeATeP. Preliminary experimental evidence on the synthesis of TeATeP will also be presented.

COMP 181

Peptide to potent compounds by structure-based design techniques

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Structure-based techniques can guide compound design and drug discovery efforts. These techniques include de novo ligand design, where compounds are constructed from an understanding of protein-ligand complementarity, ligand conformational profiles and other binding features. Computational techniques can be used to correlate binding predictions to experimental affinity and therefore be used to efficiently improve potency.

In this report, small, non-peptidic stromelysin (MMP-3) inhibitors were designed based on a known peptide substrate (substrate-based inhibitors) and the protein crystal structure of pro-stromelysin. In order to initially engage chemists, synthetically-simpler, similar compounds were designed as proof-of-concept compounds. Two simple compounds (MW 210-250) were synthesized and found to be modestly active (IC_{50}=40-150 μM) in biochemical assays. This proof-of-concept success encouraged further synthetic effort. After a few compounds were made, we found two scoring methods that were useful to rank compound designs. High-ranking designs were presented to the chemistry team and were

prioritized for synthesis against other targets. Increasingly more complex and potent compounds were synthesized, and the best compounds had a $K_{i,app}$ of about 12 nM, a >1000-fold increase in potency.

The strategies and computational methods used to design and enhance the potency of these compounds will be presented.

COMP 182

Development and characterization of cyclic analogs of apelin-13 through replica-exchange molecular dynamics and experimental validation

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The peptide apelin-13 (QRPRLSHKGPMPF) has recently been identified as the endogenous ligand of APJ, a G-Protein Coupled Receptor. The binding of this peptide causes a signal cascade that modulates many physiological responses, including vasoconstriction, HIV infection, and tumor neoangiogenesis [1]. The discovery of pharmacological probes of this receptor is vital to elucidate function but has been hampered by a lack of structural information. We present a ligand-based approach involving the design and characterization of cyclic analogues of apelin-13. These peptides provide insight into the binding requirements of APJ. Replica-exchange molecular dynamics as implemented in GROMACSv3.3.1 was used to explore the conformational space of these peptides incorporating NMR derived distance restraints from NOE measurements. The results provide insight into structural features necessary for binding. The computational data is supplemented with experimental validation through vasoconstrictor studies on endothelium denuded human saphenous vein.

[1] Sorli, SC, et. al. Drug Discovery Today, 1996: 11(23/24), 1100-1106.

COMP 183

E-Novo automated workflow for structure-based lead optimization

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We have developed a computationally efficient automated workflow in Discovery Studio for structure-based lead optimization. Using the 3D coordinates of a protein docked ligand scaffold, docking efficiency is realized within a congeneric library for virtual screening. Data pipelining using Pipeline Pilot components facilitates flexibility and ease of use. A modified core-constrained CDOCKER protocol using CHARMm-based tools is a key component along with implicit solvation models using MM-GBSA for scoring the CDOCKER poses. Examples of protocol validation are presented.

COMP 184

Hepatitis B virus DNA polymerase inhibition: Computational insight into resistance development

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Hundreds of thousands of people are chronically infected with hepatitis B virus (HBV), a major cause of liver cirrhosis and cancer. There are 5 marketed nucleotide/nucleoside analogs for the treatment of HBV infections which target HBV DNA polymerase (HDP), but resistant HBV strains have developed in most cases. We built a three-dimensional comparative model of HDP based on an HIV-RT X-ray structure.

Conformational changes in amino acid side chains during a subsequent MD simulation led to the formation of a small pocket lined by hydrophobic residues including Met552 near the nucleotide binding site. The exocyclic alkene moiety of entecavir and the sulphur atom of lamivudine occupied this pocket, explaining the better binding affinity of the inhibitors compared to natural substrates. Furthermore, mutation of Met552 to a β-branched amino acid would cause steric hindrance, thus leading to the reduced activity of the inhibitors, as has been reported.

COMP 185

Good BREEDing, techniques for generating hybrid molecules

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This work presents a method for generating novel structures from aligned molecules, using the BREED methodology of Pierce et al (J Med Chem, 2004).

It automates the practice of joining fragments of two known structures to create new compounds, using tethered optimization to preserve the position and orientation of each fragment. To increase the structural diversity, the resulting molecules can be bred again to further exchange fragments.

BREED selects all proximate bonds when creating new molecules, which can lead to a combinatorial explosion when working with a large number of initial structures. This explosion can be reduced by restricting bond selection via retrosynthetic schemes such as Lewell et al's RECAP (J Chem Inf Comput Sci, 1998). This scheme labels bonds that are considered synthetically accessible using SMARTS patterns and unlabeled bonds are ignored, reducing the number of uninteresting structures. These patterns can be easily modified or extended to reflect the project's chemistry.

Finally, if protein/ligand cocrystal data is present, pseudo-docking is accomplished by relaxing the bred structures in the receptor site and scoring them with the MM/GBVI scoring function. Because the initial structures are aligned, the pose selection and placement steps are unnecessary.

COMP 186

Ro5.1: Pfizer rules revisited

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The "Rule of 5" (Ro5) guidelines [1] have been adopted by the drug discovery community as early filter considerations for lead discovery and development. The Ro5 analysis used 2245 USAN (US Adopted Names) compounds (Phase II or higher), and was intended for compounds other than natural products (NP). We analyzed 1037 clinically relevant drugs from WOMBAT-PK [2]: 738 have oral formulations, and 159 are injectable (no NPs). Of 736 drugs that do not violate Ro5 criteria (Ro5 ≤ 1), 70 are NPs, 155 are NP derivatives and 511 originate from medicinal chemistry ("medchem"); of the 48 drugs with Ro5 ≥ 2, only 13 are medchem, 20 NPs and 15 NP derivatives. Of the 101 drugs with oral bioavailability (Oral) below 10% that have Ro5 ≤ 1, 52 have oral formulation. Of the 26 drugs with Ro5 ≥ 2 that have Oral above 10%, only nine are of "medchem" origin, 11 are NPs and 6 are NP derivatives.

Based on 738 orally formulated, non-NP drugs, we propose the following “Ro5.1” criteria (observing the 90% distribution cut-off): MW ≤ 460, cLogP ≤ 5.25, H-bond donors (HDO) ≤ 4, and H-bond acceptors (HAC) ≤ 5. Of these, 90% have Oral > 14% (N = 609). From 159 injectable-formulated, non-NP drugs, the following Ro5.1 criteria (90% cut-off) are observed: MW ≤ 851.5, cLogP ≤ 3.7, HDO ≤ 7, HAC ≤ 10. Of these, 84% have Oral < 50% (N = 82). Thus, the original Ro5 criteria function well for "medchem" compounds as early filter for oral absorption, though they blend the property distributions from orally- and injectably-formulated drugs.

1. C.A. Lipinski et al. Adv. Drug Delivery Rev. 23:3-25, 1997.

2. WOMBAT-PK is available from Sunset Molecular Discovery LLC (www.sunsetmolecular.com)

COMP 187

Graph representation of molecular datasets: Applications to dataset visualization and comparison using graph indices.

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The representation of large chemical datasets in multidimensional chemistry spaces is a great challenge in cheminformatics. To this end, we have developed a novel approach, the Advanced Dataset Graph Analysis, which uses graph representations for ensembles of molecules-points. The dataset graph represents an ensemble of vertex-molecules connected by edges; the edge connects vertices that have the Euclidean distance between them in the original high dimensional descriptor space within a user-defined cutoff. In addition to the visualization, we have also implemented several simple graph indices for quantitative description and comparisons of dataset graphs. Results of three case studies suggest that some graph indices (such as the average vertex degree or Randic connectivity index) have the ability to discriminate similar vs. dissimilar pairs of datasets and address several other common issues in cheminformatics such as detection of outliers, finding shared regions in chemical and activity space.

COMP 188

Accurate prediction of logD and hERG liability by pharmacophore fingerprint QSAR (pFPQSAR) for drug discovery in GSK

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hERG (human ether-à-go-go related gene) K+-channel blockage is a major concern in drug design, as hERG blocking agents are implicated in decreased channel function and acquired long-QT syndrome.[1] One useful rule of thumb for designing compounds with decreased hERG liability is to increase hydrophilicity or lower logD, as hydrophilic molecules are less likely to access and bind within the hERG channel pore. For example, recent data obtained at GSK shows a correlation between measured logD and pIC_{50} as determined by patch clamp electrophysiology (PatchXpress). However, in one infectious disease project at GSK, accurate prediction of logD as well as prediction of hERG pIC_{50} by traditional QSAR methods has proved to be quite challenging. Based on a comparison of different methodologies, it was determined that models built using an in-house pharmacophore fingerprint[2] quantitative structure-activity relationship method (pFPQSAR)[3] were the most predictive. The pFPQSAR methodology, logD and hERG pIC50 prediction results, as well as the impact of both models on drug discovery efforts will be discussed.

1. Sanguinetti M.C., Jiang C., Curran M.E., and Keating M.T. "A mechanistic link between an inherited and an acquired cardiac arrhythmia: HERG encodes the IKr potassium channel". Cell (1995) 81 (2): 299–307.

2. Brady, P.G., Ligand-based Design at GSK via pFPs, 232nd American Chemical Society National Meeting, San Francisco, CA, USA., September 10-14, 2006.

3. Yang, Z., Application of Pharmacophore Fingerprint QSAR (pFPQSAR) to 7TM Drug Design

COMP 189

WITHDRAWN

COMP 190

A novel mehod for generating structure-based pharmacophores using energetic analysis

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We describe an innovated procedure to develop energetically optimized, structure-based pharmacophores for use in rapid in silico screening. The method utilizes a highly functional system for pharmacophore perception (Phase) in tandem with protein-ligand energetic terms, and specialized recognition motifs, computed by a novel scoring function (Glide XP). The method was used to generate pharmcophores for 30 pharmaceutically relevant examples, which were subsequently employed in virtual screening benchmarking studies to assess ligand enrichment. Database compounds were sourced from both our in-house datasets and the directory of universal decoys (DUD). In comparison to standard 2D ligand similarity, results show superior average enrichments and a yield greater diversity of actives. In addition, hits exhibit low RMSDs when compared to their relative bioactive conformations from x-ray crystal structures.

COMP 191

Alignment and overlay of protein surfaces using shape and chemical features: Application to detect local similarity among ligand binding sites

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We have developed a novel computational method that seeks to establish similarity between a pair of arbitrary size protein surfaces based on the alignment and overlay of their shape and chemical features. The algorithm represents the molecular surfaces by a Gaussian shape, which is derived from a collection of “colored” spheres with varying radii. The resulting Gaussian shapes are superimposed by maximizing their volume of intersection as well as their color overlap. Maximal superposition between two surfaces of arbitrary size is achieved by generating multiple initial alignments each of which are locally optimized. The method is capable of identifying and correctly overlaying locally similar surface patches even if the overall similarity between the two binding sites is weak. This has potential application in drug discovery as small molecule fragments retrieved from related binding sites can be used as a starting point for further ligand idea generation.

COMP 192

Automated QSAR modeling to guide drug design

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We will present an automatic model generation process for building QSAR models based on Gaussian Processes technique and describe the stages of the process that ensure models are built and validated within a rigorous framework. We will apply this automatic process to data sets of blood-brain barrier penetration and aqueous solubility and demonstrate that the performance of the automatic model generation process is robust and comparable to ‘manual' model building.

We will demonstrate a visualization tool, ‘Glowing Molecule™', which provides a link between compound structure and predicted property values and helps to understand SAR/SPR for a chemical series. We will present a case study illustrating how, an automatically built QSAR model of target activity can be used, in combination with the Glowing Molecule visualization and models of ADME properties, to guide the design of a new compound that is predicted to have a better balance of potency and ADME properties.

COMP 193

Combination of amide hydrogen/deuterium-exchange mass spectrometry and computational chemistry: Applications to study protein dynamics, protein-ligand interactions, and protein-protein interactions

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Amide hydrogen/deuterium exchange coupled with mass spectrometry (H/D-Ex) is an increasingly popular technique to study protein structure/dynamics, protein-ligand interaction, and protein-protein interaction. Upon incubated in a deuterated buffer, a backbone amide hydrogen of a protein exchanges with bulk deuterium at the rate depending on its physico-chemical environment. The deuterated protein is proteolyzed and the deuteration level of each digested fragment is determined by liquid chromatography-mass spectrometry (LC-MS). Protein molecular dynamic simulation (MDS) and protein-ligand / protein-protein docking are an essential tool in biochemistry / biophysics and drug discovery. Our attempt to combine H/D-Ex data and computational techniques will be discussed.

COMP 194

Detecting conserved patterns of shape and property distributions on ligand binding site surfaces of proteins using property-encoded shape distributions

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Often proteins showing selectivity towards a certain ligand have conserved atomic composition and orientation at the binding site, but not always. With illustrative examples we show how conservation of property distribution and shape at the binding site surface level with no significant conservation of atomic composition and orientation at the subsurface level can explain ligand selectivity, using our recently developed pair-wise Property-Encoded Shape Distributions (PESD), a signature capturing shape and property distributions on the Gauss-Connolly surface of a binding site. Identification of similarities in binding sites of ligands of low structural similarity can help in designing more specific drugs. Additionally, detection of subtle dissimilarities in binding sites of similar ligands can give us an opportunity to exploit the differences in order to design a more specific ligand. The PESD method is an effective algorithm for rapidly recognizing similarities in surface shape and property distributions of binding sites and overcomes the limitations of the state-of-the art 3D Zernike descriptors. The implications of the findings in predicting ligand cross-reactivity will be discussed.

COMP 195

Accurate calculation of explicit water molecule free energies: Applications to PDZ binding domains

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Peptides binding to most PDZ domains have the sequence [S/T]-W-[I/L/V]. While the preference for S/T and the terminal hydrophobic residue has been explained, the mechanism for Trp specificity at the second to last position has thus far remained unknown. Here, we use a new methodology to compute the free energies of explicit water molecules and show the presence of high energy water sites on the surface of several PDZ domains can explain the Trp specificity. The affinities of a series of peptides binding to the Erbin PDZ domain correlate very well with the computed free energy of displaced waters, suggesting a direct relationship between water displacement and peptide affinity. Finally, we show a correlation between the magnitude of the free energy of displaced water

molecules and the degree of Trp-sensitivity among subtypes of the HTRA PDZ family, indicating a water-mediated mechanism for specificity of peptide binding.

COMP 196

Statistics and physical origins of ionization state changes upon protein-ligand binding

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Quantitative understanding of the nature and physical causes of structural re-arrangements involved in protein-ligand binding is important for many areas of both fundamental and applied sciences, including rational drug design. Specifically, do significant changes in protein charge (ionization) state occur often upon ligand binding, or is this a rare effect that can be ignored in most cases, as is ``standard practice'' in today's all-atom modeling? Available experimental data points are too few to provide a definitive answer. We use continuum solvent methodology to analyze pK and ionization state changes upon ligand binding in a statistically significant set of protein-protein, protein-small molecule, and protein-DNA complexes. The vast majority of proteins analyzed have at least one amino acid that changes its ionization state upon ligand binding at pH=6.5: on average, about 10% of ionizable groups experience substantial pK changes. About 60% of these groups are located outside of the immediate protein-ligand interface. Physical and structural origins of the effect are discussed, along with errors that may result from ignoring it. We propose that the possibility of ionization state change must be considered in quantitative all-atom modeling of protein-ligand binding.

COMP 197

A solution structural model for human intrinsic blood coagulation tenase complex (fVIIIa:fIXa) derived from protein docking and MD simulations: Implications for factor X activation

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Human blood coagulation is a complex process of a series of activation-deactivation pathways that involve at least twenty proteins. Intrinsic Tenase pathway is one of key route to activating factor X zymogen by a complex between the cofactor VIIIa (fVIIIa) and the enzyme factor IXa (fIXa). Despite its central importance in blood clotting process, the full structural details of co-factor VIII/VIIIa and its complex with IXa are not clearly understood. In this

presentation, I will discuss our modeling efforts in building a full solution structural model of factor VIII/VIIIa and its complex with serine protenase fIXa by employing a combination of homology modeling, protein-protein docking and aqueous-phase MD refinement. The fVIII is a 2332-residue length single-chain inactive protein whose activation by thrombin leads to the loss of B-domain. The resulting fVIIIa is a non-covalent complex between A1-A2 and A3-C1-C2 chains. The full model of FVIIIa is built in several stages using the homologous templates of ceruloplasmin/bFVa structures and the resulting model was subsequently refined for over 100 nanoseconds in explicit water medium (a system size of 200K atoms). The resulting model was docking against the solution structure of human FIXa using ZDOCK. Due to complex nature of the multi-domain interactions and large number of docking possibilities, a systematic docking protocol was employed by incorporating key biological information that is relevant for Factor X zymogen binding to narrow down the likely complex between fVIIIa.fIXa. The best docked model between FVIIIa. FIXa is subsequently refined by MD simulations in explicit water (400K atoms). All MD simulations were performed based on AMBER-FF99SB force-field set and AMBER10 package. The modeling details, the nature of protein-protein interactions and implications for factor X zymogen activation will be discussed.

COMP 198

Definition of chemical reactivity parameter and its validation

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A new parameter is derived from quantum calculation. Specific gaussian orbital plays a decisive role in reaction due to orientational nature of chemical reaction. Influence from other parts is reflected on this peculiar site. Another factor to decide reactivity is the orbital populition weighted by its corresponding energy. It reasonably is assumed that the greater the population and the lower the energy contributes to a greater capacity of reaction, consequently a reactivity parameter is defined as R="(n2/e2), where the summation is over all the occupation orbitals.

This defination of paramer has been applied in several cases to show good promise:

A: OH radital adsorption on deffrent sites of Au surface. First an Au(111) surface with 13 Au atoms is made. The reaction(adsorption) energy at varying site is correlated with the defined parameter without exception, resulting in a quadratic curve.

B: Put carbon atoms increasingly to 20 in a line, and then let end carbon atom react respectively with a hydrogen energy. We find that the calculated energy and the parameter on the end cabon solely correlated fairly well, with an exception only when carbon atoms are 2 or 3. To further validate the modelling, nitrigen is put at the reaction end in place of carbon, following by carbon atoms as influencing species,likewise, the reaction energy between nitrigon and hydrogen coorelate well with the parameter on the nitrogen only, 2 or 3 carbon atom being as excepton.

C: As to typical aramotic system, like benzene, the established modelling strategy also holds fairly well. The second substitent ability of benzene substituted respectiviely by 16 group also fairly well (ca. 90 % is correct) correlats with the defined paramer value on the possible substituent site.

COMP 199

Cross Pharma High Performance Computing Forum: Collaboration to optimize HPC capabilities to accelerate drug discovery

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The world of high performance computing (HPC) has evolved quickly, as exemplified by recent developments in hardware (e.g. Intel Nehalem multi-core CPUs with integrated memory controller), software (e.g. Desmond, a highly scalable molecular dynamics program), computing services (e.g. cloud computing), and computing resource management. Such rapidly changing HPC technologies provide the pharmaceutical industry great opportunities to improve their capabilities to improve and speed up drug discovery efforts. However, now it is more challenging than ever for the pharmaceutical industry to evaluate relevant HPC technologies and come up with optimal solutions. To address this situation, the Cross Pharma HPC Forum was formed in late 2007 by group of large pharmaceutical companies and sponsored by Intel.* In this talk, the history, current status, and future directions of HPC in the pharmaceutical industry will be discussed. A case study of cloud computing will also be provided to illustrate the latest development within the area of computing services.

* Forum members include AstraZeneca, Bristol-Myers Squibb, Eli Lilly, GlaxoSmithKline, Johnson & Johnson, Merck, Novartis, Pfizer, Sanofi-Aventis, Schering-Plough, and Wyeth

COMP 200

Lemniscular phyrins as calibrants of electron correlation fidelity in hybrid DFT methods

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Dewar himself initiated interest in non-benzenoid aromaticity and its effect on geometry and reactivity. Handling electron correlation effects correctly has emerged as one essential pre-requisite to predicting the onset of bond length alternation in planar aromatic annulenes. That threshold is still controversial, starting as low as [14] annulene, but rarely exceeding [30]; whether [18] annulene bond-alternates is itself still controversial. Part of the difficulty is that crystal structures for simple symmetric annulenes are rare and ambiguous. The recent recognition that many lemniscular (Figure 8-shaped) phyrins exhibit highly characteristic aromatic (and antiaromatic) behavour in both their (X-ray) bond lengths and NMR shielding behaviour makes them ideal calibrants of standard and new generations of hybrid DFT methods. Those which do best reproduce bond-lengths in phyrins will be revealed, the results forming the basis for suggesting the threshold for non-alternation in lemniscular aromatics may exceed [30].

COMP 201

Acidity modeling of arsenic and arsenous oxide and sulfide acids using ab initio model chemistries

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A variety of quantum chemistry methods are used to model the acidities of a series of arsenic compounds found upon dissolution of H_3AsO_4, H_3AsO_3, H_3AsS_4, and H_3AsS_3 in water. Comparisons with available experimental results are conducted, and a linear extrapolation is presented which has an r^2=0.97 correlation between CBS-QB3 CPCM model results and experimental ones for the H_3AsO4 and H_3PO_4 systems. Extrapolated pK_as of pK_{a1}=1.7, pK_{a2}=7.3, and pK_{a3}=12.1 are shown for H_3AsO_4, and pK_{a1}=1.9, pK_{a2}=8.3, pK_{a3}=12.6 for H_3PO_4.

COMP 202

Red shift vs. blue shift of C-H stretching frequency of C-H…pi interactions in benzene dimer: Influence of counterpoise correction in the frequency calculations at the MP2 method

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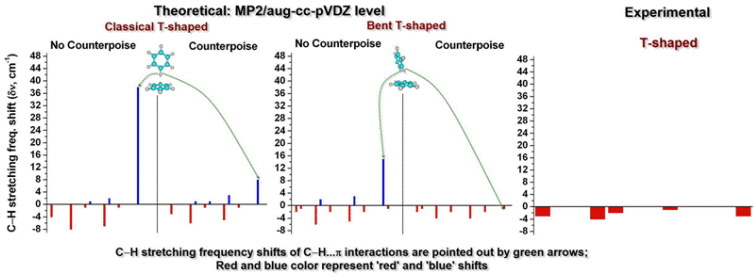
It has been considered for long time that benzene dimer exhibits “improper, blue shifting” H-bond rather than “classical, red shifting” H-bond for the C−H…π interactions based on the theoretical predictions. In agreement with the recent experimental results, we have obtained the small ‘red' shift of C−H stretching vibrational frequency for the bent-T shaped configuration of the benzene dimer using MP2 method with large basis set by the inclusion of counterpoise correction in the vibrational frequency calculation for the counterpoise corrected optimized geometry of the bent-T shaped configuration. The MP2/aug-cc-pVDZ level without counterpoise correction in the frequency calculation yields the 'blue' shift of 15 cm-1. The MP2 method is often employed for investigating the molecular assemblies involving π-π and C−H…π interactions. The present investigation reveals an important finding that counterpoise correction is vital for the correct prediction of vibrational frequency shifts as it is crucial for the binding energies. This study provides methodology for re-evaluation of vibrational spectra for simple and large complexes involving C−H…π interactions.



COMP 203

Density functional calculations of 15N chemical shielding in peptides and proteins

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We performed DFT calculations to examine the effects of solvation, hydrogen bonding, backbone conformation, side chain, and electrostatic interactions on 15N chemical shielding in proteins. We use a model dipeptide and fragments

from protein GB3. The conducting polarizable continuum model is employed to include solvent effects, while the charge-field perturbation theory is used to represent the electrostatic interaction within the protein. We describe a computationally efficient methodology to include all important effects in the calculation of chemical shieldings in proteins. The dipeptide calculations show that the difference in the isotropic chemical shift between the standard beta-sheet and alpha-helical conformations is in good agreement with the statistically averaged experimental chemical shifts in proteins. The orientation and anisotropy/asymmetry of the 15N chemical shielding tensor are also in the range of experimental values. Our results show that the net dipole moment along the alpha-helix can cause a significant deshielding of 15N.

COMP 204

Nonlinear dimensionality reduction for reaction path discovery in ab initio multiple spawning dynamics

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Traditional theories of chemical kinetics center on the identification of minima and transition states on the potential energy surface, and characterization of the least-energy pathways connecting these points. However, the true chemical dynamics may deviate significantly from these maximal friction paths, such as in systems with relatively flat potential energy surfaces, or on surfaces with barrierless pathways. In such systems, characterization of the reaction requires dynamical information. We have applied two non-linear dimensionality reduction techniques, diffusion maps and affinity propagation, to ab initio multiple spawning dynamics simulations, with data from both microcanonical and canonical ensembles. These techniques recover low dimensional reaction paths directly from simulation data, without a priori assumptions about the nature of the dynamics. The level of representation can be tuned to provide coarse- and fine-grained models of the reaction pathway.

COMP 205

Spin decoherence in carbon and boron-nitride nanoribbons

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Recent theoretical studies have shown that zigzag carbon and boron-nitride nanoribbons have spin polarized edges in the absence of electromagnetic field. This feature makes the zigzag nanoribbons one of the most perspective materials for building logical elements in spintronic devices. However, regular theoretical studies usually do not include relativistic corrections that can contribute to the electron spin decoherence and thus facilitate the destruction of the predicted alignment of electrons' spins. In this work we carefully assess magnitudes of electron spin-spin and hyperfine interactions for a series of zigzag carbon and boron-nitride nanoribbons within pure and hybrid density functional theory schemes. Obtained estimates have interesting implications for nanoelectronic applications and provide guidance for minimization of the electron spin decoherence.

COMP 206

Theoretical study of the anharmonicity of molecular vibrations of $Li^+–H_2$, $Na^+–H_2$, $B^+–H_2$ and $Al^+–H_2$ complexes

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In this work, we present a theoretical study of $Li^+–H_2$, $Na^+–H_2$, $B^+–H_2$, and $Al^+–H_2$ complexes through VSCF (vibrational self-consistenet field) calculations at the MP2/cc-pVTZ and CCSD((T)/cc-pVTZ levels of theory. The H–H stretching frequency in $Li^+–H_2$, $Na^+–H_2$, $B^+–H_2$, and $Al^+–H_2$ is red shifted by 111, 201, 75 and 65 cm^{-1}, respectively, from that of free H_2. The calculated red shifts are in good agreement with the available experimental data. The interaction energy of the metal hydrogen complexes is analyzed using symmetry-adapted perturbation theory (SAPT).

COMP 207

Calculation of quantum mechanical vibrational energy relaxation rates in liquids via semiclassical methods

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Time correlation functions can be calculated for relatively complex systems using classical molecular dynamics (MD) simulations; however quantum mechanical correlation functions are required for systems where quantum mechanical effects play a significant role. Unfortunately, calculating quantum mechanical time correlation functions is difficult due to the exponential scaling of the computational effort with the number of degrees of freedom. One strategy for tackling this challenge is to employ semiclassical approximations, where quantum mechanical properties are calculated from input that is obtained from classical MD simulations. One such method is based on the linearized-semiclassical (LSC) approximation, which can be obtained by linearizing the time correlation function (the linearization is with respect to the difference between forward and backward trajectories). The resulting approximation can be put in a classical-like form, where the classical quantities are replaced by their corresponding Wigner transforms and the time evolution is classical. We have developed LSC-based computational methodologies for calculating vibrational energy relaxation (VER) rates in liquids, with an emphasis put on developing more efficient algorithms that will allow us to apply LSC methods to polyatomic liquids. The VER rates of different model systems have been calculated using new LSC methods applied to both the symmetrized and Kubo transformed time correlation functions to compare the accuracy and efficiency of various LSC methods in cases where the force fields are well known.

COMP 208

eHiTS: Docking and scoring ligand/target interactions to give good score-rmsd and ic50 correlations in in silico high throughput screening.

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Adequate treatment of complex interactions, such as pi-cation, non-conventional hydrogen bonding, pi-stacking in ligand -protein/receptor recognition can be crucial to accurate pose prediction in in silico virtual screening of compounds for diverse endpoints such as drug-discovery, predictive metabolism, and toxicity prediction. The ability of this docking/scoring approach to provide good score-based low RMSD discrimination of (correct) biochemically/pharmacologically relevant poses and IC50 correlations is shown with illustrations from several systems: nicotinic acetylcholine receptors and their surrogate binding proteins, kinases, and cytochrome P450s. The use of customized family training to improved pose prediction accuracy and lnKd/ln(IC50) correlations for specific user problems will be discussed as an method to improve discrimination of ligand-target recognition. A critical analysis is presented examining the merits of docking scoring functions as compared to quantum mechanical (QM) and

molecular mechanics Poisson-Boltzmann free energy scoring of pharmacologically relevant poses.

COMP 209

Mining public databases for structure-activity relationships

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Recent years have seen huge efforts in creating databases that store chemical structures with their biological activities for the public domain. PubChem, one of the richest sources of information on structures and activities, stores more than 19-million compound records and biological data from over 1300 biological assays. Mining databases this size requires fast, robust, effective workflows, and to be useful for rational design of potent, selective lead structures it's necessary to extract structure-activity-relationships from this wealth of information. We've developed a new method, quantitative series enrichment analysis (QSEA), enabling fully-automated 3D-QSAR model creation and prediction. SAR-tables, lists of structures with associated activities used as input, are constructed from shape similarity searches using a collection of 57 marketed drugs as queries. Visual output reveals crucial information about the applicability domain of each series within a SAR-table with insights where and how structural changes in the series might affect the biological activity. Results from prospective and retrospective studies will be reported.

COMP 210

Protein ensemble generation for improved ligand-protein docking

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Using a single rigid protein structure for docking a variety of ligands often leads to unsatisfactory binding poses because the positioning of the side-chains in the binding pocket precludes anything but the endogeneous ligand (or small variants) from binding. In such cases, it is necessary to generate multiple models for the binding site based on generous conformational sampling of the side-chains in

order to allow for diverse ligands to adequately sample the binding site. The benefits and caveats of cross docking versus ensemble docking are considered with numerous examples, followed by a discussion of when the use of ensemble docking is warranted.

COMP 211

Screening tools and results for inhibitors of human tyrosyl DNA phosphodiesterase (Tdp1)

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Tdp1 inhibitors have become a major area of drug research and structure-based design since they have been shown to work synergistically and selectively in cancer cells. The goal of in silico drug design is usually to find small molecules with desired geometric and chemical properties that dock in a receptor cavity of a specific protein, with the typical tools of virtual screening being docking/scoring, and ADME/Tox property prediction. We have applied these methods to find novel chemical structures of Tdp1 inhibitors. The goal of our study was also to determine how known inhibitors may be binding at the active site of Tdp1. Screening of the ChemNavigator Library of about 25 million purchasable (unique) samples yielded a final selection of 46 samples. They were purchased and tested in vitro, and yielded a number of promising hits. We will also discuss the nature of the activity in the assay, as well as our docking results for a second, large set of ~300,000 compounds assayed in HTS.

COMP 212

Structure-based discovery and biological evaluation of novel selective TRAF6 inhibitors

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The binding of RANKL to its receptor RANK results in the recruitment of TRAF6, which activates NF-êB, JNK, and MAP kinase pathways. TRAF6 is a critical adaptor molecule, and therefore targeting this protein is advantageous for the treatment of osteoporosis, multiple myeloma, and other diseases. To discover novel TRAF6 inhibitors, we employed our structure-based method HiPCDock to

screen 5.4 million compounds and selected 100 of them. These hits were further evaluated in silico against TRAF2 for specificity, followed by biological testing with GST-RANK pull down as well as fluorescence polarization assays. We found that several hits bound strongly to TRAF6, and effectively inhibited its functions. Further testing showed that none of the selected compounds had effect on TRAF2. These data demonstrate that it is feasible to use virtual screening methods for the identification of selective TRAF6 inhibitors, and our active compounds shall be optimized to improve their potency.

COMP 213

Understanding the potential role of hydrogen bonding in drug discovery

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A hydrogen bond acceptor (HBA) calculation tool has been developed and implemented in Roche Palo Alto. The acceptor values (logkb) were calculated through a computational model using an experimental database of measured values and molecular electrostatic potentials. Application of this tool to chemical targets of therapeutic interest has been investigated. Relationships between biological activity and strength of HBA values will be discussed.

COMP 214

Computational approaches to antibacterial and antimalarial hit finding

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Malaria and tuberculosis are major causes of mortality in developing countries, a situation exacerbated by the emergence of species resistant to current therapies. Structure based approaches have been applied to the design of inhibitors of the essential enzymes (a) dihydroorotate dehydrogenase from P. falciparum and (b) bacterial RNA polymerase, the target of tuberculosis therapy using analogues of rifamycin. De novo design (SPROUT) and virtual high throughput screening (eHITS) led to a series of ligand structures, a small number of which were synthesised or purchased as appropriate and subjected to biological assay which

identified several low micromolecular inhibitors. Structure based hit optimisation (using SPROUT LeadOpt) provided compounds with increased inhibitory activity. The higher than usual success rate achieved in the virtual high throughput screening approach is attributed to the accuracy and conservatism of the eHITS scoring function. Details of the computational and experimental techniques and results will be presented.

COMP 215

Computer-aided design of [(biphenyloxy)propyl]isoxazoles – agents against coxsackievirus B3

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The objectives of this study are (a) the QSAR analysis of antiviral activity of various [(biphenyloxy)propyl]isoxazole derivatives to determine/identify structural factors responsible for antiviral action and (b) design of novel antiviral compounds based on QSAR models

Hierarchic QSAR Technology (HiT QSAR) was used as a main tool of investigation. Thorough analysis of the relationship between antiviral activity against the clinical CVB3 isolate 97927 ($\log 10IC_{50}$, μM) and selectivity index and the structure of 21 [(biphenyloxy)propyl]isoxazole derivatives were carried out.

The resulting PLS QSAR models are quite satisfactory (R^2=0.91–0.97, Q^2=0.78–0.94, R^2test=0.65–0.90). Oxadiazole and p-fluorophenyl fragments were found to promote antiviral activity. High impact of atom identity and electrostatic factors was found for both properties.

The models were used for designing new potential antivirals. One highly active designed compound was synthesized and tested. Experimental results indicate good concurrence with predicted values.

COMP 216

Docking and 3-D-QSAR studies on isatin sulfonamide analogs as caspase-3 inhibitors

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To provide insight of their inhibition mechanism and facilitate the design of more potent ligands, a series of 41 isatin sulfonamide analogues made previously in our research group (Chu, W. et al. J Med Chem 2005, 48, 7637-7647; Chu, W. et al. J Med Chem 2007, 50, 3751-3755.) were docked to the X-ray structure of caspase-3, one of the important cysteine aspartyl-specific execution proteases in apoptosis, and their binding conformations were analyzed by 3D-QSAR studies. Comparative Molecular Field Analysis (CoMFA) and Comparative Molecular Similarity Index Analysis (CoMSIA) studies suggest that both steric and electrostatic interactions contribute to the compounds' binding affinity, with the major contribution coming from hydrophobicity as well as hydrogen bonding of these series of ligands. The statistically best CoMSIA model shows excellent correlation (r2 = 0.95, q2 = 0.79, test set r2test = 0.79) and high predictive power even evaluated by the most stringent criteria for a QSAR model. The results of this work demonstrate that structure-based design methods (such as docking) cultivate the development of reliable QSAR models, they also illustrate the utility of this procedure in design of new potent caspase-3 ligands.

COMP 217

Prediction of cytochrome P450 mediated oxidation using induced fit docking

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Structure-based methods have great potential for predicting sites of oxidation by specific isoforms of cytochrome P450(CYP). However, there are two primary factors that hinder the success of traditional rigid-receptor docking approaches: (a) sites of oxidation do not correlate well with the most stable binding mode of a substrate, and (b) in order to accommodate structurally diverse substrates, CYP active sites are highly flexible. We describe a new method for predicting sites of oxidation based on analysis of ensembles of structures generated by Induced Fit Docking combined with empirically derived rules that define the intrinsic reactivity

of a given site. The method is highly successful in predicting sites of oxidation for a dataset of known CYP2D6 substrates.

COMP 218

Protein modeling and virtual screening to discover novel GSK-3 inhibitors

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Glycogen synthase kinase-3 (GSK-3) is a serine-threonine kinase which phosphorylates glycogen synthase, the rate-limiting enzyme in glycogen biosynthesis. Inhibition of GSK-3 is seen as a potential target for treating diabetes, Alzheimer's disease, stroke, bipolar disorder, malaria and cancer. There could be great value in development of selective inhibitors of α and β isoforms. We have used various computational procedures to compare the isoforms, to study the requirements for GSK-3 inhibition, and to obtain novel inhibitors for GSK-3. We prepared a homology model for GSK-3α based on a GSK-3β X-ray structure. We examined docking poses of maleimides to GSK-3β, and showed that for maleimide binding the difference between isoforms was insignificant. GSK-3β virtual screening of a variety of databases has yielded promising structures which are being tested for GSK-3 inhibition.

COMP 219

Targeting the acetylcholine binding protein: A relaxed-complex approach to virtual screening

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The ligand-gated ion channels are of great importance in many neurological processes. One such channel protein is the nicotinic acetlycholine receptor (nAChR). Unfortunately, being a large membrane protein, the receptor is difficult to crystallize and study for structure-based drug design. Instead, one can examine the surrogate structure of the receptor's extra-cellular domain, the acetylcholine binding protein (AChBP). AChBP has been crystallized several times and binds the ligands of nAChR in a common fashion. It has been proposed that any small molecule drugs that bind to AChBP may in turn become useful pharmacological agents against nAChR. Here, we present a virtual screening study targeting AChBP, using a diversity set of compounds from the National Cancer Institute. We utilized the relaxed-complex approach, in which the flexibility of the target protein is achieved first via molecular dynamics simulations. Potential binders against AChBP are identified from the diversity set.

COMP 220

First-principles studies of octacyclopropylcubane: A novel high-energy density material

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The ongoing quest for novel high-energy density materials (HEDMs) is clearly motivated by both a fundamental interest in molecular science as well as a search for new propellants and explosives. Recently de Meijere *et al.* have synthesized a new HEDM, octacyclopropylcubane ($C_{32}H_{40}$), in which the eight hydrogen atoms of cubane were replaced by cyclopropyl groups. The existence of $C_{32}H_{40}$ was confirmed by x-ray diffraction and mass spectroscopy and it was found to have a half-life of about three hours at 250^{o}C and a strain energy of 390 kcal mol^{-1}. In this work we report the results of a first-principles density-functional theory (DFT) calculation using the suite of codes known as NRLMOL (Naval Research Laboratory Molecular Orbital Library) to compute the structural, electronic, and vibrational properties of octacyclopropylcubane. We have calculated the infrared and Raman active frequencies and intensities for this novel HEDM and compare our results with experiment. We have also employed a DFT-based tight-binding scheme to compute the vibrational density of states for octacyclopropylcubane and compare these results with our full DFT-based results. Interesting enough, the geometry of the cyclopropyl groups in octacyclopropylcubane does not allow for the quartic-concerted torsional mode

(QCTM) that we and other workers have previously seen in octanitrocubane using DFT and other *ab initio* quantum chemical approaches.

COMP 221

Mechanism of thermal decomposition of carbamoyl phosphate and its stabilization by aspartate and ornithine transcarbamoylases

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Carbamoyl phosphate (CP) has a half-life for thermal decomposition of less than 2 sec at 100°C, yet this critical metabolic intermediate is found even in organisms that grow at 95-100 °C. We show here that the binding of CP to the enzymes aspartate and ornithine transcarbamoylase reduces the rate of thermal decomposition of CP by a factor of more than 5000. In order to understand how the enzyme•CP complex is able to stabilize CP we investigated the mechanism of the thermal decomposition of CP in aqueous solution in the absence and presence of enzyme. Using a combination of density functional theory, quantum mechanics/molecular mechanics calculations and molecular dynamics simulations we show that the critical step in the thermal decomposition of CP in aqueous solution, in the absence of enzyme, involves the breaking of the C-O bond facilitated by the intramolecular proton transfer from the amine to the phosphate. Furthermore, we demonstrate that the binding of CP to the active sites of these enzymes significantly inhibits this process by restricting the accessible conformations of the bound ligand to those disfavoring the reactive geometry. These results not only provide new insight into the reaction pathways for the thermal decomposition of free CP in an aqueous solution, but also show why these reaction pathways are not accessible when the metabolite is bound to the active sites of these transcarbamoylases.

COMP 222

Theoretical studies of uranyl complexes

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Advances in the past 70 years in nuclear technology have come at a significant environmental cost. Effective strategies for waste disposal, storage, and remediation necessitate an understanding of actinide chemistry. To facilitate this, complexes of the uranyl dication are investigated using Density Functional Theory. The complexes studied contain carbonyl and nitrile ligands (e.g. $[UO_2(RCO)_n]^{2+}$ and $[UO_2(RCN)_n]^{2+}$ with $n < 6$). Additional systems of interest include complexes containing both water and nitrile ligands (e.g. $[UO_2(H_2O)_n(RCN)_m]^{2+}$ with $n + m < 6$). The Stuttgart SC-ECP accounts for the relativistic effects of uranium and triple-ζ basis sets are used for all other atoms.

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Theoretical study on the interaction between xenon and positive silver clusters in the gas phase and on the (001) chabazite surface

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Silver-exchanged zeolites are promising materials for extracting xenon from air; therefore, understanding the interaction of xenon with such materials is important. This interaction was investigated by using DFT calculations on xenon and silver clusters Agn (n=1-4) in the gas phase and on a chabazite surface. Xenon does not bind neutral but ionic silver clusters. Unlike previous studies, our results show that xenon – ionic silver interaction cannot be explained by the dpi-dpi back-donation but by the sigma donation from xenon's 5p orbital to the virtual 5s orbital of ionic silver. In the gas phase and on the chabazite surface, the Ag+ cation is the strongest binding site with binding energies of 73.91 and 14.53 kJ/mol, respectively; increasing the size of the clusters weakens the binding; and the binding energy and the amount of electron transfer correlate closely. Our results also explain the negative chemical shifts observed in previous NMR experimental studies.

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Interfacing the effective fragment potential with the reactive force field

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There is a need to have faster methods that maintain reasonable chemical accuracy (within 2 kcal/mol error) in the analysis of silica systems. The focus here is on taking advantage of an accurate molecular mechanics (MM) method, which would then be combined with both electronic structure theory and a method that can model solvent effects. The Reactive Force Field (ReaxFF) is the target MM method, since it is able to treat bond breaking and bond formation. The Effective Fragment Potential (EFP) method is chosen to model solvents, since it has proven to be very accurate for modeling aqueous solvent effects. The ReaxFF method is interfaced with EFP and with electronic structure theory to study catalysis in silica pores. This interface is implemented in the GAMESS computational program package.

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Using pseudo atoms to model silicon and silicon oxide surface chemistries with electronic structure theory

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A first principles treatment of reactions at surfaces continues to be a significant challenge facing the computational chemistry community due primarily to the sheer size of the systems being studied. Despite algorithmic and technological advancements, practitioners are often limited to using cluster models where dangling bonds are terminated with hydrogen atoms. However, hydrogen terminated clusters can suffer from a poor description of the electronic structure at the cluster boundary, an effect also observed in many QM:MM and QM:QM schemes where hydrogen termination is also commonly employed. We have developed pseudo-atoms for termination in silicon and silicon oxide clusters that can more appropriately model surface chemistry. In contrast to other developments in this area, our pseudo-atoms are capable of occupying divalent termination sites and saturating polar bonds, both of which are essential properties for accurate applications. Our development approach and present results from initial applications in silicon and silicon oxide surface chemistry studies will be described.