COMP 1

A combined computational and NMR study of torsional motions and hydrogen bonding in ortho-substituted arylamides: Applications in molecular mechanics force fields parameterization and implications for the design of arylamide foldamers

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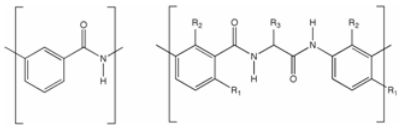
Foldamers, synthetic oligomers that adopt defined, stable secondary structures in solution, have been the focus of intense research efforts. The arylamide oligomer family of foldamers is characterized by a repetitive aromatic ring-amide bond pattern (Figure 1). The torsional motions around the $C_{aromatic}$-$C_{peptide}$ and/or $C_{aromatic}$-$N_{peptide}$ bonds, influenced by the nature and hydrogen bonding ability of the ortho substituents R_1 and R_2, greatly affect the backbone rigidity, and therefore folding of the oligomer. We will present ab initio study of the above torsions in ortho-methoxy-N-methylbenzamide and its analogs, the applications of ab initio torsional profiles in force fields parameterizations, as well as conformational distributions from MD simulations of the above compounds and related oligomers. Specifically, we have obtained surprising results regarding intramolecular H-bonding in aqueous and methanol solutions. To corroborate the computational results, gradient-enhanced 1D-NOESY spectroscopy has been performed on several model compounds and has confirmed our findings.



COMP 2

Coarse grain models for molecular dynamics simulation

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With recent advances in computational resources, all-atom (AA) molecular dynamics simulations have become a powerful tool for the investigation of biological and material systems. However, even with major increase in resources, there are many systems of interest that are still beyond the capability of AA representations. A popular solution to this problem is the use of reduced representations of the system via coarse grain (CG) models. One issue that still arises with CG models is the systematic and effective parameterization. Recently, we have developed a systematic method for the parameterization of CG models for biological and soft matter systems. This approach has been successfully applied to surfactants, lipids and amino acids allowing exploration of spatial and temporal scales far beyond the capabilities of AA methods. These applications include self assembly of surfactant and lipid systems and peptide aggregation.

COMP 3

Coarse grain molecular dynamics simulation of the bacterial chemotaxis system

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Molecular dynamics (MD) simulations provide a valuable approach to investigate structure and dynamics of membrane-protein systems. However, all-atom simulations are too expensive to explore the long time-scale biological processes. Coarse-grain (CG) models are utilized to explore millisecond scale mechanisms. The bacterial chemotaxis system is an important model system in the study of transmembrane signaling. In spite of the extensive experimental and theoretical studies on this system, a large portion of the signaling mechanism of the bacterial chemotaxis system is still missing. In this work, we develop new CG models and parameters for complex protein structures. We employed our novel coarse-grained molecular dynamics method to characterize the structural, conformational and dynamical properties of the bacterial chemotaxis system. This study further demonstrates the utility of CG molecular dynamics simulations to examine mechanisms governing membrane proteins and biological transmembrane systems.

COMP 4

Molecular mechanics modeling of the trans influence in organometallic complexes with application to asymmetric catalysis

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Efficient calculation of metal-containing complexes relevant to catalysis is of major interest for better characterizing and optimizing the catalysts. Based on an existing force field for organometallics (VALBOND), extensions to include electronic effects such as the trans influence of ligands on the bond lengths and energies are discussed. Parameters and results for model octahedral complexes of the platinum group metals are presented, as well as an application to the study of reactive intermediates involved in asymmetric hydrogenation catalyzed by iridium complexes with chiral phosphinooxazolines (PHOX) ligands. The new force field allows for the separation of electronic and steric effects on the stability of different geometric isomers and reproduces DFT results which are consistent with experimental observations.

COMP 5

Development and validation of OPLS-AA force field parameters for ionic liquid simulations

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OPLS–AA force field parameters have been developed and validated for use in the simulation of over 50 unique combinations of ionic liquids (IL) featuring 1–alkyl–3–methylimidazolium [RMIM] (R = Me, Et, Bu, Hex, Oct), N–alkylpyridinium [RPYR], and choline cations, along with Cl^-, PF_6^-, BF_4^-, NO_3^-, $AlCl_4^-$, $AlCl_7^-$, TfO^-, saccharinate, and acesulfamate anions. The new parameters were fit to reproduce experimental condensed–phase structural and thermodynamic properties, and experimental free–energies of hydration. Monte Carlo simulations of the ILs gave relative deviations from experimental densities and heats of vaporization of ca. 1–3% over a wide temperature range. Transferability of the cation parameters to multiple alkyl side chain lengths was tested and determined to give excellent agreement with potentials developed specific to desired alkyl chain lengths. The present force field has been systematically developed and thoroughly validated; the parameters presented have been shown to be highly accurate for a wide variety of cation/anion combinations.

COMP 6

Development of parameters for the CHARMM General Force Field

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Empirical force fields are presently the only computational methods fast enough to routinely perform molecular dynamics simulations of large molecular systems (such as proteins) on relevant time scales. The CHARMM set of force fields is widely used for simulating biomolecular systems, being capable of representing proteins, nucleic acids, lipids, and carbohydrates. Nevertheless, its usefulness for computer-aided drug design is limited because it does not support a wide range of drug-like molecules. The CHARMM General Force Field (CGenFF) aims to fill this void. It features force field parameters for moieties commonly encountered in drug-like molecules, as well as generic parameters for a wide range of functionalities and a charge assignment scheme for functional groups that are not explicitly covered in the force field.

COMP 7

Multiscale simulations of green solvents, from ab initio to physical properties modeling

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Ionic liquids have received considerable attention by the chemical industry in recent years, mostly towards the development of environmentally benign processes. In this work, microscopic structure, dynamic and thermodynamic properties of imidazolium‐based ionic liquids are calculated using theoretical models that cover a wide range of length and time scales, from *ab initio* density functional theory (DFT) calculations to atomistic molecular simulation and finally to a macroscopic equation of state based on perturbation theory. Model calculations are compared against literature experimental data and it is shown how carefully selected models can be used to reliably estimate properties, even in the absence of experimental measurements.

COMP 8

Calculation of anharmonic OH vibrations in the condensed phases

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Vibrational spectroscopy is one of the most powerful methods for characterization of OH groups and their surroundings in the condensed phases. Structure and bonding around such OH groups can be very complicated, however, and additional insight from theoretical calculations is often helpful. But also these are often complicated.

One such difficulty is the anharmonic nature of the OH bond. Already the gas-phase water molecule , and hydroxide ion are downshifted by almost 200 cm-1 due to anharmonicity, and the anharmonicty contribution usually increases with the strength of the intermolecular bonding. Anharmonicity thus needs to be included in the calculations.

Here we present plane-wave DFT calculations and anharmonic vibrational calculations for the IR and Raman active OH stretching modes in the layered lithium hydroxide (LiOH) crystal . We approach the anharmonic problem in three different ways: (1) A normal-mode following approach is used, where the 1-dimensional anharmonic vibrational Schrödinger equation is solved "along" each of the symmetric and antisymmetric normal modes. (2) A 2-dimensional vibrational Schrödinger equation is solved, allowing for the anharmonic coupling between the symmetric and anti-symmetric OH stretching modes in the crystal. (3) The 1-dimensional vibrational problem is solved for the OH vibration in an isotope-isolated LiOH crystal.

We find that Method (1) is inadequate for LiOH, because it underestimates the anharmonic contribution to the Raman mode by ~40% and gives a large anharmonic contribution in the wrong direction for the IR mode. Method (2), on the other hand, yields absolute frequencies and gas-to-solid frequency shifts in good agreement with experiment for both the Raman- and IR-active OH stretching modes. Also Method (3) gives a good frequency and frequency shift, and - just as in experiments - the isotope-isolation technique facilitates the chemical discussion of the crystal-induced frequency shifts.

COMP 9

Ab initio and direct dynamics studies of hyperthermal collisions of O(^{3}P) with CO_2

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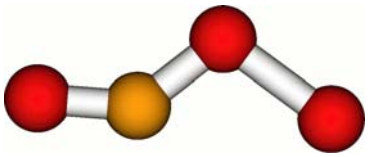
Hyperthermal collisions of $O(^3P)$ with small molecules occur in the vicinity of spacecraft as they travel in the Earth's upper atmosphere, and result in collisional energy transfer and chemical reactions. We report the results of direct dynamics-based simulations of hyperthermal collisions of $O(^3P)$ with CO_2, an important species in the upper atmosphere. Stationary points for this reaction on the lowest triplet potential-energy surface were characterized at levels of theory as high as CCSD(T)/aug-cc-pVTZ. The accuracy of a number of methods which are computationally practical for direct dynamics studies was evaluated by comparison to these CCSD(T) results. Based on the comparison, B3LYP/6-311G(d,p) and BMK/6-311G(d,p) were selected for the direct dynamics. Here we report the results of this study which involved the analysis of thousands of quasi-classical trajectories at collision energies between 1.0 and 6.5 eV. There are two important reaction channels at these energies. An exchange reaction ($O + CO_2 --> CO_2 + O$) can occur at relatively low energies ($\Delta E^{\ddagger}$ 28.9 kcal/mol) and involves the formation of a reaction complex (CO_3) which sometimes survives for several vibrational periods. The reaction $O + CO_2 --> O_2 + CO$ can only occur a higher collision energies ($\Delta E^{\ddagger}$ = 75.3 kcal/mol), and sometimes takes place by way of a stripping mechanism. However, more frequently, this reaction occurs by way of an interesting series of events that follow CO_3 formation.



COMP 10

An ab initio study of the electronic excited states, N_2 and O_2, using quantum Monte Carlo methods

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Quantum Monte Carlo (QMC) refers to a class of ab initio methods that use a stochastic simulation to solve the many-body Schrödinger equation. QMC differs from post-Hartree Fock methods in that it includes electron correlation explicitly. Diffusion Monte Carlo (DMC) and Variational Monte Carlo (VMC) are applied to elucidate the thermodynamic and electronic properties of reactions of that involve nitrogen and oxygen. In order to each that goal, excited states of the binary compounds for nitrogen and oxygen were estimated in order to illustrate the ability to accurately describe the range of reactions that may occur. Selected

excited states of the constituent elements were calculated in order to show the accuracy of various electronic structure techniques. These techniques include DMC, VMC, CASSCF and CISD. The basis set used was cc-pVTZ and all calculated values were compared against experiment.

COMP 11

Simulation of large-scale excited electron dynamics

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To study electron dynamics in large-scale highly excited systems, we have developed eFF, a molecular dynamics model which includes electrons. In eFF, electrons are represented by Gaussian wave packets whose size and position vary with time, and the nuclei are represented by point charges. The particles interact via an effective potential which is so simple that forces acting between thousands of nuclei and electrons can be computed in less than a second on a modern processor. Using eFF, we explore the thermodynamics of warm dense hydrogen, and find excellent agreement with path integral methods and diamond anvil and shock compression experiments over a temperature range of 0 to 100,000 K and densities up to 1 g/cm3. We also simulate the Auger process in a diamond nanoparticle (C196 H112), and discover direct and indirect pathways for the desorption of atomic fragments from the surface, in agreement with recent experiments.

COMP 12

Systematic fragmentation of clustered systems

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The Systematic Fragmentation Method (SFM) has been proposed for the study of large molecular systems. The SFM method has recently been extended to model liquid clusters. A brief introduction to both the SFM and the Fragment Molecular Orbital (FMO) method will be presented. The accuracy of water cluster

energies using SFM is compared to both FMO and ab initio results at the MP2 level of theory. SFM will be shown to give accurate results for a number of water clusters. Additionally, the effects of basis sets on SFM and FMO were investigated. Timing comparisons between different levels of SFM and FMO theory will be compared to ab initio results.

COMP 13

DFT treatment of excited potential surfaces: Combination of the restricted formalism for excitation energies with the broken-symmetry unrestricted approach to describe the diradical character of the ground state (rTD-uDFT)

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Thermal cycloreversion in Woodward-Hoffman symmetry-forbidden reactions proceeds via a transition state of strongly diradical character. In order to describe the minimal energy path (MEP) for photocyclization in these systems the computationally demanding multireference methods are usually applied. Here we propose a modified time dependent density functional theory treatment that combines the restricted formalism for the excitation energies calculation with the unrestricted formalism to describe the diradical character of the ground state energy surfaces (rTD-uDFT). We demonstrate that the fully restricted approach results in unphysical spikes on MEPs, which may have been the reason for the previous unsuccessful attempts to describe conical intersection regions at the TD-DFT theory level. The method is validated by comparison with the results obtained at higher theory levels, and is applied to the rational design of three-dimensional optical storage materials.

COMP 14

Monte Carlo methods in biological electrostatics

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Abstract: We will present a Monte Carlo method for solving boundary value problems (BVPs) involving the Poisson-Boltzmann equation (PBE). Such BVPs

arise in many situations where the calculation of electrostatic properties of solvated large molecules. The PBE is one of the implicit solvent models, and has accurately modeled electrostatics over a wide range of ionic solvent concentrations. With the new method we compare the algorithmic and computational properties of this algorithm to more commonly used, deterministic, techniques, and we present some computational results. This work is part of an ongoing collaboration with several FSU faculty members and students, and a collaborator at the Russian Academy of Sciences.

COMP 15

Computing the free energy profiles of protein conformational change using a reaction-path order parameter

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To compute the free energy profiles of complicated conformational changes of proteins and peptides, we developed a method that uses a transition pathway as the order parameter along which thermodynamic integration is performed. The input to this method is the two metastable states of interest of a molecular system. By replicating the system a number of times, a chain of states representing a path of transition is first formed. The mean forces perpendicular to the path are then minimized using a formulation motivated by the finite-temperature string method. The mean forces along the path are evaluated via constrained molecular dynamics (MD) simulations for each replica along the hyper plane perpendicular to the path, and mean forces are computed as the averaged displacement of each replica from the string in a MD simulation. Compared to the finite temperature string method, however, our new scheme uses holonomic constraints to maintain equal distances between replicas that enhances both the stability and efficiency of reaction path optimization. We also designed a kinetic energy potential to control the smoothness of a path in a systematic manner. The sampling on the hyper planes of a path is also implemented using holonomic constraints. A SHAKE like algorithm is employed to compute the required external forces to maintain the configurations of a molecular system on a hyper plane. This framework is applied to compute the minimum free energy paths and free energy profiles of the C7eq-to-αR transition of an alanine dipeptide, chair-to-boat transition of a glucopyranose ring, and the helix-to-hairpin transition of an alanine dodecapeptide in vacuum and in explicit water. The effects of solvation on minimum free energy pathways and free energy profiles are explained by hydrogen-bonding network, side-chain packing, and committor probability analysis.

COMP 16

New paradigm for binding free energy simulations: The simulated scaling based approaches

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Binding free energy simulation has been very challenging due to its generally low convergence. Although this general approach can ensure reliable predictions on drug binding affinities when adequate sampling and accurate potential are employed, fulfilling these inter-related requirements is not an easy task. Among many methods towards this target, the simulated scaling method shows promising efficiency, adaptability, and robustness. My talk will emphasize the simulated scaling (SS) based approaches, including the general SS method, the multi-resolution SS method, the native-guided SS method, the hybrid recursion SS method and their applications.

COMP 17

New computational algorithms for enhanced sampling and potential functions

***Jianpeng Ma**, Department of Biochemistry and Molecular Biology, Baylor Colllege of Medicine, One Baylor Plaza, BCM125, Houston, TX 77030*

We report recent progresses on algorithmic development on computational simulation and modeling of protein systems. Emphasis is given to those on multi-resolution and multi-length scale simulations. New methods for enhanced sampling and empirical potential functions will also be discussed

COMP 18

Replica exchange constant pH simulation of biomolecules

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Solution pH is an important thermodynamic variable in biophysics. Correct sampling of protonation state and conformation space is crucial when studying pH effects and predicting pKa. A constant pH replica exchange molecular dynamics (REMD) method based on discrete protonation state model is proposed to improve protonation state and conformation samplings. In our

method, two replicas having different protonation states and temperatures are allowed to exchange conformations and therefore avoid trapping in either protonation state or conformation space. Our constant pH REMD not only predicted pKa correctly for reference compounds but also converges faster than constant pH molecular dynamics (MD). We further tested our constant pH REMD by a heptapeptide from ovomucoid third domain (OMTKY3). The constant pH MD yielded completely wrong titration curves and structure information while the constant pH REMD demonstrated accurate results.

COMP 19

The generalized gradient-augmented Harmonic Fourier Beads: A practical method for accurate free energy calculations from multidimensional umbrella sampling

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We present a novel method, called generalized gradient-augmented Harmonic Fourier Beads (ggaHFB), for free energy calculations in multi-dimensional spaces. The ggaHFB method derives the free energy profiles or potentials of mean force from equilibrium umbrella sampling simulations in either Cartesian or nonlinear coordinates and presents a practical alternative to conventional weighted histogram analysis method (WHAM) without the limitations of the latter. Here, we benchmark the free-energy computed with the ggaHFB method against that from two conventional techniques, including WHAM. We then demonstrate the applicability of the ggaHFB method to a wide range of biophysical problems. In particular, we compute transition path ensembles and free energy profiles for an ion-ion separation in water; ion and water permeation through carbon nanotubes, lipid bilayers and ion channels; nontrivial conformational changes in peptides; and, finally, ligand binding to proteins.

COMP 20

A fragment-based computational protocol upon PDB to fragment library design, lead discovery and lead optimization

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Obtaining structural information on the fragment complexed to the protein target is a key factor and also a major limitation to the number and types of target that are amenable to fragment-based approaches. Therefore, computational methods are needed to mine efficiently all the available 3D structures of ligands complexed to proteins, both treated as a whole and as smaller fragments to increase the likelihood of fragment hopping from one target to another.

In this work, we used MED-SuMo[1,2] on a fragment database derived from the PDB: each pdb file is converted into one or more pdb files containing a single fragment as ligand. Fragments are defined as being a substructure of PDB ligand and an exact match of a molecule from a given fragment library (e.g. pubchem, MW inf 250 Da). Comparison with MED-SuMo of a query protein binding site (target) against the 3D structure of others proteins (potential analogs) in complex with a ligand enables ligand fragments from the analog complex to be transferred to 3D positions in the target site, so that the protein environments of the fragment and its image are similar. As we've achieved high efficiency and speed, the set of such fragments is derived upon the whole PDB (500,000 PDB fragments). Moreover a complete protein can be searched for the presence of an a priori unknown functional site.

In this talk, we will present the protocol and its main applications: fragment library design, lead discovery and lead optimization. Case studies from protein kinases, protein phosphatases and proteases will be detailed.

COMP 21

Druggability and chemical space in fragment docking

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Screens of fragment libraries have higher hit rates than do screens of lead-like or drug-like compounds. Because of the need for direct binding readout, libraries of only 1,000 to 10,000 fragments are typically screened, over an order of magnitude less than can be simply purchased. In principle, molecular docking can prioritize these untested molecules for testing. To test whether it can reliably identify fragments and predict their geometries, fragment libraries are being docked to both enclosed cavities and to solvent exposed enzyme sites. The hit rates for predicted fragments, their affinities and the correspondence of their poses to subsequent crystal structures are being determined. Results to date suggest that fragment hit rates are high to both sites, although the ligand efficiencies are much better for the cavities than the enzyme sites. Chemoinformatic considerations suggest bias towards biogenic chemistry in available fragments contributes to these high hit rates.

COMP 22

Computational methods for fragment linking

***Regine S. Bohacek**, Boston De Novo Design, 50 Commonwealth Ave., Boston, MA 02116*

A common motif in bioactive molecules is a central cyclic scaffold to which a number of side chains are attached. Examples range from penicillin to drugs which inhibit HIV protease to inhibitors of kinases.

The time line for discovery of these drugs varies but can be long. Often the starting point is a natural product. Sections of the lead are removed, retaining those features believed to be most important for activity. Then the fragments are reconnected with linkers designed to improve affinity and to acquire better pharmacokinetic properties.

The de novo program, AlleGrow(1), has been developed to hasten the discovery of cyclic scaffolds which connect and incorporate fragments already positioned in the target binding site.

To test AlleGrow, it has been applied to some past drug discovery projects including the discovery of ACE inhibitors, inhibitors of the SH2 domain of Src kinase, inhibitors of HIV protease and of kineases.

(1) AlleGrow is a second-generation program based on GrowMol (R.S. Bohacek, C. McMartin, JACS (1994) 116,5560-5571.)

COMP 23

Accurate prediction of structure-activity relationships by computational fragment mapping

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Computational solvent mapping (CS-Map) is applied to the estimation of structure-activity relationships (SAR) relevant for both lead optimization and focused library design. Previously we reported the application of CS-Map to the detection of hot spots, i.e. sub-sites of a binding region that contribute significantly to the binding free energy of ligands. Using an extended set of fragment-sized molecules (<150MW), we accurately predict the effects of functional group variations on binding affinity, in excellent agreement with published SAR data. CS-Map is then applied in conjunction with virtual screening (VS) to identify pharmacological chaperones for Uch-L1, a novel target for the treatment of Parkinson's disease. This study shows that a combined VS/fragment-based approach significantly increases the efficiency of experimental screening as compared to VS alone. Taken together, we provide a novel method for computational fragment screening that enhances both computational and experimental screening strategies.

COMP 24

Designing and analyzing a fragment collection

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Fragment-based screening approaches identify fragments that can be built or combined into active compounds with favorable pharmaceutical properties. A critical consideration for such methods is that the screening collection contains

fragments that sample bioactive space while remaining pharmaceutically acceptable. Sunesis' technology aids in discovering and combining fragments to yield inhibitors with sub-micromolar activity. This presentation focuses on how fragments compatible with our technology are selected and compares the evaluation of fragments alone or in the context of whole molecules. Topics will include computational approaches to defining fragment and whole-molecule bioactive spaces, ways to measure coverage of the respective spaces, and how such results have translated into efficient screening collections.

COMP 25

FFT-based fragment mapping for the identification of hot spots in the binding sites of drug target proteins

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Fragment mapping places molecular probes - small organic molecules containing various functional groups – around the protein surface, finds favorable positions, clusters the conformations, ranks the clusters, and determines their “consensus” sites [1]. X-ray and NMR data show that the most druggable “hot spots” of proteins also bind a variety of small organic molecules, and hence the “hit rate” in mapping is a good predictor of druggability. We present an efficient mapping algorithm based on the Fast Fourier Transform (FFT) correlation approach that generates billions of probe poses and evaluates an empirical energy function that account for van der Waals, electrostatics, desolvation, and hydrophobic enclosure terms. We show that the algorithm reproduces the experimental solvent mapping results for thermolysin and elastase, and describe the application of the method to a number of drug target proteins. [1] Landon MR, Lancia DR, Yu J, Thiel SC, and Vajda S. J. Med. Chem., 50:1231, 2007.

COMP 26

Exercising receptor-site similarity: From off-target identification to scaffold hopping

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For several years, researchers have leveraged protein sequence and structural similarity in numerous ways, including but not limited to target hypothesis, target

prioritization, ligand design, lead optimization, etc. With the rapidly growing body of over 50K publicly available apo- and co-complex structures, automated modeling and analysis methods are well positioned to continuously survey and relate physicochemical features across the structurally resolved and modelable proteome. Analyzing receptor-site similarity proteome-wide, for example, reveals that significant similarities exist not only within but also across target families. This observation not only helps to proactively identify potential off-target liabilities, but also further enables the design of novel matter by ligand hybridization or shuffling strategies.

COMP 27

Estrogen receptors as therapeutic targets in breast cancer

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The estrogen receptor α (ERα) has proven to be the single most important target in breast cancer. The use of the selective ER modulator (SERM) tamoxifen for the treatment and prevention of breast cancer has changed therapeutics. The study of tamoxifen metabolism has provided insights to aid structure function analysis, to understand tamoxifen-mediated rat liver carcinogenesis, and to identify tamoxifen's active metabolites. The SERM raloxifene, approved for treating osteoporosis, lacks tamoxifen's increased risk for endometrial cancer and is now used for the prevention of breast cancer in postmenopausal women. The antagonistic properties of tamoxifen and raloxifene are a result of their antiestrogenic side chains protruding from the ligand binding pocket, thereby preventing the receptor's helix 12 in the major transcriptional activation region AF-2 from sealing the pocket, and instead it occupies the coactivator recognition groove preventing coactivator recruitment. The agonist properties of these SERMs are likely due in part to their protruding antiestrogenic side chains recognizing Asp-351 on the surface of the receptor, which then participates in an occult transactivation function region AF-2b that allosterically interacts with ER's minor transactivation function region AF-1. Other SERMs include clomiphene, toremifene, idoxifene, droloxifene, ospemifene, GW5638, GW7604, lasofoxifene, levormeloxifene, CHF 4227, EM-800, acolbifene, arzoxifene, bazedoxifene, and HMR 3339. The pure antiestrogen fulvestrant is effective as a second line therapy following tamoxifen failure. The pure antiestrogen ICI 164,384 takes on an inverted conformation allowing the 7α-substituted side chain to exit the ligand binding pocket similarly to SERMs. The pure antiestrogen's side chain bends back towards the receptor's surface interacting at the coactivator recognition site and preventing helix 12 from doing so. Thus, pure antiestrogens induce an abnormal receptor structure that is in turn hyperubiquinated and shuttled to the proteasome for degradation. Additional pure antiestrogens under development include ZK-703, ZK-253, RU 58668, and TAS-108.

COMP 28

Localization, distribution, and pharmacology of G protein-coupled estrogen receptor GPR30

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GPR30 has been identified as a G protein-coupled estrogen receptor distinct from the nuclear estrogen receptors ERα and ERβ. Using intracellular injection vs. extracellular administration, and imaging techniques, we studied the effect of GPR30 ligands on rat central neurons, SKBR3 breast cancer cells, and human aortic endothelial cells (HAEC) in vitro. G-1, a selective GPR30 agonist, increased cytosolic Ca^{2+} concentrations $[Ca^{2+}]_i$ in rat central neurons. Intracellular injection of 17-β-estradiol (E2) or G-1 into SKBR3 cells evoked a rapid and robust increase of $[Ca^{2+}]_i$, which was attenuated by siRNA knock down of GPR30 expression. Extracellular administration of E2 or G-1 caused a small increase of $[Ca^{2+}]_i$. These observations demonstrated that functional GPR30 was primarily localized to the cytoplasm of SKBR3 cells. In HAEC, which express GPR30, G-1 and E2 mobilized calcium and hyperpolarized the membrane. G-1 was about 15-fold more effective than E2. Using an animal model of depression, G-1 or E2 administered to mice reduced the immobility time in the tail suspension test. Our result indicates that G-1 is a GPR30 selective agonist and supports a role of GPR30 in estrogen-mediated cellular and behavioral responses.

COMP 29

Opioid agonist-selective signaling.

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In the drug discovery process, the cellular location of the drug targets such as receptor is critical for the eventual efficacy of the drugs. Using opioid receptor and agonist activation of ERK phosphorylation as a model, we could demonstrate agonist-selective signaling. Such agonist-dependent signaling arises from the ability of various opioid agonists to induce the receptor to translocate from the lipid raft domains on plasma membrane, where the signaling molecules are clustered. The translocation of the receptor from the microdomains also affected the signals that the receptor could transduce, and also the consequence of the signal transduction, i.e., genes transcriptions. Thus, the ability of individual agonist to promote the drug target translocation will dictate the signals being transduced and subsequently the eventual cellular responses.

COMP 30

HTS and pharmacology of multiplexed small GTPase targets by flow cytometry

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We are multiplexing targets for HTS using the multi-parameter optical capabilities of the flow cytometer. Multiplexing is achieved with families of targets that are color-coded as suspension arrays. Several multiplexes have been screened against the NIH small molecule repository, a compound library of over 200,000 small molecules. We have screened a sixplex comprising small GTPases and a fluorescent GTP analog. One of the major advantages of multiplexing is that selectivity can be observed in the primary screen. The GTPase family screens reveal both activators and inhibitors. Among both classes of molecules are molecules with intracellular activities. Molecular insight into the mechanisms of action has been provided in a variety of novel assays including direct measures of GTPase activation, nucleotide exchange, and regulation of intracellular pathways in cell models of inflammatory response. Future opportunities for small molecule discovery include the development of HTS multiplexes that probe protein-protein interactions, such as those involving small GTPases and their regulatory partners.

COMP 31

Mechanisms of allostery and membrane attachment in Ras GTPases

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Ras GTPases are membrane anchored signaling mediators that control cell division and development. Despite their prominent role in many forms of cancer, the mechanism and thermodynamics of membrane insertion, the structure of the membrane bound Ras, and the allosteric modulation of lateral segregation by the catalytic domain remained elusive. Here, we establish the structural and dynamic link between the conserved active site switch regions and the membrane interacting C-terminal hypervariable region. We employed a variety of computational techniques, including classical and accelerated molecular dynamics simulations, structural bioinformatics, potential of mean force calculations, and other methods for the estimation of membrane insertion free energies. We will show that, upon GDP/GTP exchange, a coordinated network of interactions communicates information from switches I and II through a newly identified switch III to the membrane surface. The resulting differential interaction of the catalytic domain and/or the linker with membrane surfaces causes variations in the insertion depth and localized structural perturbation to the host lipid bilayer. We will discuss these findings in connection with previous and new collaborative experimental results.

COMP 32

Virtual screening provides a mechanism for finding a chemical tool from a biological messenger

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Historically, a primary means of probing the biological role of any given protein was with small molecules. Currently, this pharmacological approach has been surpassed by genetic techniques (knock-in, knock-out and small inhibitory RNA). Nevertheless, small molecules have the advantage that protein function can be altered in a rapid, selective, reversible and dose-dependent manner. Research into the biological role of the calcium-releasing second messenger NAADP

(nicotinic acid adenine dinucleotide phosphate) has been hampered by the lack of chemical tools. An attractive solution is to evaluate millions of molecules with virtual screening. We used a ligand-based virtual screen to progress from NAADP to an antagonist (Ned-14), which is potent at nanomolar concentrations, structurally unrelated to NAADP, cell permeant and fluorescent. Therefore, Ned-14 blocks NAADP signaling and labels NAADP receptors in intact cells. We conclude that virtual screening is now accessible, powerful and a largely untapped source of chemical tools.

COMP 33

Perspectives and learnings on *in silico* pharmacology and biological fingerprints

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Major challenges in the drug discovery process include the identification of new/relevant disease targets, the identification of tool and lead compounds for these targets and the selection of a development candidate that is differentiated from any other compounds with attrition risk minimised, or at least orthogonalized for multiple candidates. Major initiatives to systematically generate (e.g. Cerep BioPrint) and integrate (e.g. WOMBAT/GAUDI project & Pfizer “DrugStore” based on curated published data from Inpharmatica/BioFocusDPI StARLITe, BioPrint & in-house data)bioactivity data have enabled many new learnings and perspectives on drug-drug, drug-target, drug-antitarget, drug-property and target-target relationships and the analysis of concepts of molecular similarity vs biological similarity. These will be discussed, together with the use of relevant in silico chracterizations of ligands and protein targets (e.g. GRID-based FLAP pharmacophore fingerprints).

COMP 34

Using a network pharmacology approach to better understand adverse drug reactions

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Despite regulatory vigilance, unwanted toxicity and other especially adverse drug reactions (ADRs) of widely-used drugs remain a major public health concern. To avoid such cases and thereby improve the quality of life of patients it is without question highly desirable to identify and eliminate molecules with such anticipated problems during early phases of drug discovery.

In some cases the reason for an undesired effect can be found in the interaction of the compound with a certain target. These cases can then be identified by well-established in vitro-methods by determining the affinity to the target. Also, newly developed in silico-methods recognizing similar molecule structures can be used. However, often chemically diverse compounds cause similar problems. In some cases it happens when the compounds modulate two (or more) different targets in the same biological pathway. For this scenario, models solely based on compound-adverse event pairings can be established that predict certain adverse effects irrespective of target considerations. After computing these models a link through chemical space can be made to compute correlations with different target prediction models.2 Thereby it becomes possible to link certain phenotypic effects to the interaction between a molecule and a target.

To gain better pharmacological confidence in the predictions we introduced biological network information to establish firm links between side effects and the interference of a compound with a certain pathway. This way, the predictions can be validated by analyzing the data contained in well-known pathway tools and databases like GeneGo's MetaCore and Ingenuitys' IPA. In addition, new links between pathways and side effects can be established.

To summarize: The presentation will link Systems Chemical Biology approaches to the field of adverse side effects of drugs to better understand them in a pharmacological context..

COMP 35

All-atom and coarse-grained force fields for molecular mechanics

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Our original all-atom ECEPP force field (1) (Empirical Conformational Energy Program for Peptides) has undergone several modifications and improvements, the most recent being ECEPP-05 (2). Later, ECEPP-05 was implemented with a

surface area hydration model to discriminate computed native structures of proteins from decoys (3). The largest protein, whose folding was simulated (with the ECEPP/3 force field) was the 46-residue protein A (4). Concomitantly, a physics-based coarse-grained united-residue (UNRES) model (5) has been developed to treat larger proteins; subsequently the UNRES potential energy function was modified by inclusion of the temperature dependence of the effective energy function to compute folding trajectories and thermodynamic properties (6). The basis of these modifications of both the all-atom and coarse-grained force fields will be presented, and the performance of both of these force fields in simulations will be discussed.

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COMP 36

Development of a CHARMM pairwise-additive carbohydrate force field

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Carbohydrates play important biological roles not only as structural elements and energy storehouses, but also as direct participants in molecular recognition and signaling. So as to enable the modeling of biologically relevant carbohydrates, we have undertaken the development of a comprehensive pairwise-additive carbohydrate force field. The force field uses the same functional form and parametrization procedure as the existing CHARMM protein, nucleic acid, and lipid force fields, thereby allowing for the simulation of heterogeneous systems having carbohydrates as a component. Progress to date includes force field models for pyranose monosaccharides, glycosidic linkages, linear sugars, sugar alcohols, common chemical modifications, and furanose monosaccharides. Applications that will be presented include the thermodynamics and dynamics of pyranose monosaccharides, the conformational properties of oligosaccharides, and the simulation of a protein-oligosaccharide complex.

COMP 37

Classical force field development: What can we learn from carbohydrates?

***Robert J. Woods**, Complex Carbohydrate Research Center, University of Georgia, 315 Riverbend Road, Athens, GA 30602, Fax: 706-542-4412*

The development of the GLYCAM [1] force field for oligosaccharides is discussed with a focus on the factors that contribute to internal consistency as well as to accuracy when applied to biologically relevant systems. The relative importance of electrostatic, torsion and polarization terms is discussed. Pertinent issues associated with comparison with experiment are presented.

Oligosaccharides are remarkably flexible, often branched, polymers that are resistant to crystallization. Consequently most experimental 3D data come from NMR studies of free oligosaccharides, or occasionally from x-ray data of carbohydrate-protein complexes. Thus, carbohydrate force field validation inevitably requires the computation of NMR properties. Approaches to force field validation are illustrated with particular attention given to comparison with NMR data.

Many of the issues associated with modeling flexible carbohydrates are relevant for nucleic acids and peptides. New approaches to peptide force field validation are introduced, based on the lessons learned from carbohydrates.

1) Kirschner et al. *J. Comput. Chem.* (2008) 29, 622-655

COMP 38

Combining free energy perturbation and extensive conformation sampling in force field developments

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We propose a method which may allow data about the conformational equilibriums of peptides to enter the parameter calibration phase in force field developments. The method combines free energy perturbation with techniques for extensive sampling in the conformational space. It predicts shifts in computed conformational equilibriums in response to separate or combined perturbations of force field parameters. We present a Hamiltonian replica exchange approach for extensive sampling of the conformational equilibrium of peptides. In different replicas, biasing potentials of varying strengths are applied to all backbone (ö,ø) torsional angle pairs to overcome sampling barriers. A general form of constructing biasing potentials based on a reference free energy surface is employed to minimize sampling in physically irrelevant parts of the conformational space. An extension of the weighted histogram analysis formulation allows for conformational free energy surfaces to be computed using all replicas, including those with biased Hamiltonians. This approach can significantly reduce the statistical uncertainties in computed free energies.

COMP 39

Force-field development for computer simulation of biomolecular systems: The GROMOS case

***Wilfred F. van Gunsteren**, Department of Physical Chemistry, ETH Zentrum CAB, Swiss Federal Institute of Technology, ETH Zurich, Universitaetsstr. 6, Zurich 8092, Switzerland, Fax: 41-1-6321039*

Computer simulation of the dynamics of biomolecular systems by the molecular dynamics technique yields the possibility of describing structure-energy-function relationships of biomolecular processes in terms of interactions at the atomic level. These interactions are generally described using an energy function or force field. Since 1980, successive parametrisations of the GROMOS (GROningen Molecular Simulation) force field have been successfully used to simulate the behaviour of biomolecular systems, i.e. polypeptide folding, molecular complexation and partitioning. The basic philosophy of the GROMOS force field, its parametrisation procedure, and the problems met in force-field development will be discussed. Current developments and future trends, e.g. regarding inclusion of polarisability and derivation of coarse-grained model

parameters that are thermodynamically compatible with the corresponding fine-grained, atomic level ones, will be sketched.

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COMP 40

Information theory and measurement

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Measurement is a common denominator in all of molecular modeling and can be treated as a common phenomon. And yet it is not. This talk will suggest ways in which such a formalism may provide better communication and evaluation of computational procedures.

COMP 41

Progress and challenges in modeling organic and biomolecular systems

***William L Jorgensen**, Department of Chemistry, Yale University, New Haven, CT 06520-8107*

There has been much progress in the realistic modeling of organic and biomolecular systems over the last thirty years. My research group's contributions have focused on enhancing the evaluation of the energetics of molecular systems, simulations of reactions in condensed phases to elucidate mechanisms and solvent effects on reaction rates, computation of free energy changes for equilibria including host-guest binding, and de novo molecular design. Examples of the state-of-the-art in each area will be presented including our use of free-energy calculations to guide lead optimization in inhibitor design. Current challenges will also be discussed including the continuing need for polarizable force fields, improved fast quantum mechanical methods, better scoring functions for docking and molecular design, more prospective computational studies, and quality control for publications in computational chemistry.

COMP 42

Calculating the energetics of compounds that have more than one covalent structure, such as tautomers

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As modellers of many-atom systems, we frequently use programs that describe a molecule as atoms linked by covalent bonds. However, such programs fail if some of the covalent bonds participate in an equilibrium between different molecular structures: examples are bonds to protons in keto-enol or chain-ring tautomerizations and the movement of H+ along a water chain. Not only should our software recognize such equilibria, but it should provide an estimate of the relative energy of the alternative forms in non-polar environments and water. For modelling biomolecular complexes the software should calculate the 3D structure and interaction energy considering not only the tautomers of the ligands but also how changes in the tautomer of the ligand change the covalent structure of the binding site, including waters and co-factors. To accomplish this our software must abandon its focus on the construct of bonds and instead concentrate on the electrons and their associated nuclei.

COMP 43

Induced fit docking: Treating the intractable.

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The specific ligand-induced conformational changes in the binding pocket remain the key obstacle to predicting the ligand pose and assigning this pose the best binding score. Here we describe several recipes for handling the cases that were previously intractable with a single cross docking or a multiple receptor conformation approach. The first approach, nicknamed the SCARE algorithm (SCan pairs of Alanines and REfine), handles well the medium difficulty cases including the backbone deformations as demonstrated on a cross docking benchmark of diverse ligand-receptor pairs. However there is a class of cases in which the rearrangements of the backbone are too dramatic for the SCARE algorithm, for example, the loop restructuring upon binding of a type 2 inhibitor to an active conformation of a kinase, or binding of an antagonist to an agonist bound conformation of a nuclear receptor. We demonstrate that two new approaches, namely the “surgical” approach and the ligand-guided pocket building approach may overcome the previously insurmountable hurdle.

COMP 44

Calculating binding energies using molecular dynamics simulations and GB/SA: Application to protein-ligand docking in AMBERScore.

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Molecular docking computationally screens thousands to millions of organic molecules against protein structures, looking for those with complementary fits. Due to the formidable combinatorial complexity of modeling the interaction between a flexible protein and a flexible ligand, most of the current docking methods limit their search by approximating the receptor as a rigid structure. A fast and efficient framework to address the problem of docking a flexible ligand into a flexible receptor protein and calculate binding energies has been implemented in the program DOCK6. The AMBERScore in DOCK6 uses traditional all-atom AMBER force field for protein atoms and recently developed general AMBER force field (GAFF) for small molecules. The interaction between ligand and protein is represented by electrostatic and van der Waals energy terms and the solvation energy is calculated using Generalized Born solvation model as implemented in AMBER. In addition to ligand flexibility, this method

also allows a part of receptor flexible during minimization and Molecular Dynamics simulation, in order to reproduce the so-called “induced-fit”. The method has been applied to different protein targets, such as M102Q T4Lys, M102Q/L99A T4Lys, cytochrome c oxidase, amp C beta-lactamase, DHFR, and tested against a library of 5,000-10,000 small molecule ligands. AMBERScore better distinguished the known ligands for each cavity from known decoys, compared to the docking calculation alone. This encouraged us to test rescoring prospectively on molecules that ranked poorly by docking but that ranked well when re-scored by MM-GBSA. X-ray crystal structures were determined for some of the hits predicted by AMBERScore. In many cases, the geometry prediction by MM-GBSA closely resembled the crystallographic result; and yet in several cases, the rescored geometry failed to capture large conformational changes in the protein. Intriguingly, rescoring not only rescued docking false positives, but also introduced several new false positives into the top-ranking molecules.

COMP 45

How expert do we have to be

***Martha S Head**, MDR/CSC 3.4141B, GlaxoSmithKline Pharmaceuticals, 5 Moore Drive, Research Triangle Park, NC 27709*

Computer-aided drug design is seldom effective unless combined with expertise, and yet there have been few attempts to assess the relative importance on algorithm performance of expert input. Does the modeler make the method or the method the modeler? Presented here are some preliminary steps towards a rigorous analysis of the value of knowing both the tools and also the protein targets commonly faced in the pharmaceutical industry.

COMP 46

Designing kinase inhibitor prototypes

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Most medicinal chemistry projects in kinase target drug discovery start with a hit identified by massive or focused screening of collections of compounds. Structural biology and molecular modeling are then used to guide the optimization of the screening hits. However, because the structural determinants of kinase inhibition by small molecules binding to the ATP pocket (active or inactive conformations) are now well established, an alternative efficient approach to hit finding is possible. It involves the design by molecular modeling of prototype kinase inhibitors forming the key atomic interactions with the pocket

that are known to convey potency or selectivity. We will present examples of application of this approach to some oncology kinase targets. The application of the same principles to kinase scaffold morphing will also be discussed.

COMP 47

The DFG motif as a central conformational switch controlling drug binding

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In many protein kinases, a characteristic conformational change (the “DFG flip”) connects catalytically active and inactive conformations. Many kinase inhibitors—including the cancer drug imatinib—selectively target a specific DFG conformation, but the function and mechanism of the flip remain unclear. Using long molecular dynamics simulations of the Abl kinase, we visualized the DFG flip in atomic-level detail and formulated an energetic model predicting that the local electrostatics in the ATP-binding site controls the flip. Our model was experimentally validated using the imatinib binding to the kinase domain of c-Abl as a conformational probe of the DFG-out conformation. Our model suggests that the DFG motif may be conserved in part because the DFG flip allows the kinase to access flexible conformations facilitating nucleotide binding and release, thus facilitating the process of protein kinase catalysis. The set of intermediate conformations observed in our simulations of the DFG flip may present new opportunities for kinase inhibitor design.

COMP 48

Surveying ligand- and target-based similarities within the Kinome

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Several investigators have studied similarities and differences within the protein kinase complement of the human genome (the "kinome") from both sequence and ligand-based perspectives. We present a novel analysis of the human kinome using receptor-site similarity. Having clustered kinase domains by ATP binding-site similarity, we can identify kinases that may be selectively targetable as well as those that can be readily grouped and targeted together. We believe the same approach can be applied to the entire structure-resolvable/modelable

proteome, allowing receptor-site information from entire target families to be used in the rational design of compounds with desirable selectivity profiles.

COMP 49

Structure based design of irreversible kinase inhibitors

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Irreversible inhibition of protein kinases is emerging as an important strategy to achieve non-ATP competitive blockade of kinase mediated signaling. Because of their mode of action, irreversible inhibitors also offer distinct advantages to standard non-covalent ATP-site binders. Inhibitor potency is dependent on two factors: initial molecular recognition followed by a slow alkylation step where a covalent bond is formed to a free Cys in proximity to the inhibitor. Consequently, only kinases with available Cys residues in a suitable binding site can be targeted, thus affording greater control over the selectivity profile of the inhibitor. In addition to enhanced selectivity, irreversible inhibitors have emerged as a strategy to circumvent acquired resistance arising from mutations that reduce drug binding. We have applied a general strategy for the structure based design of irreversible kinase inhibitors that involves a structural bioinformatics analysis to identify kinases with accessible Cys residues in the ATP binding, ligand docking of suitable kinase specific scaffolds, and the incorporation of an alkylating group to target specific Cys residues. The design, characterization and properties for several example kinases will be discussed.

COMP 50

Reorganization energies and quantum corrections for a model electron self-exchange reaction: Comparison of polarizable and unpolarizable solvents

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The solvent contribution to the reorganization free energy for electron self-exchange in aqueous Ru(II)-Ru(III) is computed for two recently developed polarizable water models, AMOEBA and SWM4-NDP, and for the earlier POL3 model,

and compared to the reorganization energies of unpolarizable water models. We find that the solvent reorganization free energies for polarizable models, 0.94-1.10 eV, are within the range of values obtained for unpolarizable models, 0.95-1.23 eV, implying that solvent electronic polarizability does not significantly reduce solvent reorganization. Electronic polarization leads to a decrease of electronic reorganization energy by about 30\%, but also to an increase in orientational (ionic) reorganization. Both effects are of similar magnitude and effectively cancel one another. Rate enhancements due to quantum corrections are computed in the harmonic bath approximation and range between 3.6-10.9 in good agreement with the estimate obtained from experimental dispersion data of liquid water, 7.7. The rigid unpolarizable water models overestimate the quantum correction in the libration modes which effectively compensates for the neglect of quantum corrections in the absent stretching modes.

COMP 51

Thermodynamic and structural properties of methanol-water solutions using nonadditive interaction models

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Alcohol and water clusters in pure methanol, pure ethanol, and alcohol/water mixtures are investigated by analyzing extended time-scale molecular dynamics (MD) trajectories using polarizable force fields based on the charge equilibration formalism. Detailed results are reported for numerous concentrations of methanol and ethanol in water (Xalcohol = [0.1,0.9]). As a complete analysis of the clustering phenomenon in pure methanol, pure ethanol and their aqueous solutions at different concentrations, our results support the prediction of bi-percolation in alcohol/water mixtures as reported in recent experimental and modeling studies, and we find the appearance of large cyclic structures in such percolating networks. We observe that large water ring structures are present at low alcohol concentrations (where water percolation allows for the accommodation of extended cyclic structures), with a transition to conditions where small (mostly trimeric) water rings exist at higher alcohol concentrations. Furthermore, we discuss contrasting pictures of micro-structure in alcohol/water mixtures resulting from the use of two clustering criteria, one representing hydrogen bonding networks and the second representing both hydrogen bonding and hydrophobic packing networks; these analyses are within the context of discussing micro-scale immiscibility in such solutions as it relates to experimentally observed anomalous mixing entropies and other thermodynamic properties.

COMP 52

Development and implications of a distance dependant dielectric function for electronic polarization

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Macroscopic electrostatic approximations are used in force field models, which is reasonable at large distances. However at short distances, the microscopic version should be used to accommodate the atomistic nature of matter. The molecular scale version of Maxwell's 1st equation is compared to the macroscopic equation. The dielectric effect due to electronic polarization is formally separated into pairwise terms when polarization is linear with the electrostatic field. At vdW distance, the electrostatic field is the field obtained when the dielectric constant is one (D=1), consistent with charge model development. There are different perspectives regarding the equation for the long distance term resulting in epsilon or epsilon squared in the denominator (D=2 or D=4). The different equations are presented and discussed.

COMP 53

Effects of phase-dependent electrostatic polarizability on interfacial properties of aqueous liquid-vapor interfaces

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One of the largest shortcomings in modeling water has been the inability to accurately reproduce the liquid-vapor coexistence curve (density-temperature binodal) based on information from a single state point. Polarizable force fields allowing molecular charge distributions to respond to changes in local environment should afford, in theory, a better energetic description of anisotropic systems, e.g., aqueous liquid-vapor interfaces. Despite the success of several approaches to “engineer” polarizable force fields to reproduce the coexistence envelope an oft-neglected, critical component in such force fields is the phase dependence of molecular polarizability. Parameterization of polarizable models to date is fixed to reproduce either average condensed phase or vacuum polarizabilities. First principles, however, dictate that the intrinsic molecular polarizability of water is a function of cluster size, and more fundamentally of the thermodynamic phase. Therefore, parameterization based on condensed or gas phase properties cannot accurately represent properties of the liquid-vapor interface where the local environment is neither strictly considered bulk or

gaseous. In this work, we discuss an approach to explicitly account for a phase-dependent molecular polarizability associated with polarizble water force fields, employing the polarizable TIP4P-FQ water model. Molecular polarizabilities based on the Hirshfeld partitioning scheme are used to construct scaling functions allowing for smooth variation of the molecular polarizability from the vapor to condensed phase; analogous functions for the associated dipole moments are developed. The development and application of these mappings for use in modeling the liquid-vapor interfacial region of water will be discussed. For the water liquid-vapor interface at ambient conditions, we will discuss density profiles and interfacial thicknesses, surface tension, water structure (orientation), dynamics, and interfacial potential. We will discuss the differences relative to conventional non-polarizable models as well as the original TIP4P-FQ water model with static polarizability.

COMP 54

Polarizable force fields for carbohydrates: Application to protein-ligand binding

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Molecular recognition processes are critical in a variety of regulatory physiological processes. They are also exploited in the development of targeted therapeutics against a broad class of disease and genetic dysregulation. A theoretical understanding capable of allowing a quantitative description of the free energetics associated with such processes is thus critical on many levels. Current state-of-the-art methods for computing binding free energetics based on atomistic descriptions of protein-ligand complexes rely heavily on some model of the interactions between constituent species. From a molecular modeling perspective, the next generation of interaction models, or force fields, promises to incorporate environment dependent response of molecular electrostatics in order to provide a more physically realistic model that does not coarse-grain away the underlying subtle physics. As such, we present studies exploring the use of polarizable force fields in prediction of binding free energies of complexes of small carbohydrates such as N-acetyl glucosamine (NAG) to several receptor proteins. We will discuss the development of a polarizable force field for the carbohydrate functionality with NAG as the paradigmatic model compound. The parameterization will discuss ab initio (DFT and MP2) reference data to which the polarizable model was fit. The discussion will next focus on condensed phase properties of the NAG monomer as well as polymeric NAG species, all of which are relevant as ligands to naturally occurring receptors (hen egg white lysozyme, F17-AG lectin). These studies will present the first application of polarizable force

fields to such systems. Proceeding, we will discuss comparisons of binding free energy calculations using polarizable carbohydrate force fields in combination with several continuum approaches for electrostatic solvation free energy estimation. We will apply molecular dynamics trajectories generated using both non-polarizable and polarizable force fields in order to assess the effects of non-additive interactions on estimation of binding free energies.

COMP 55

Toward a polarizable force field for membrane simulations

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Integral membrane proteins such as G-protein coupled receptors and ion channels are now the subjects of intense theoretical and experimental study due to the prevalence of these molecules in normal human function. From a modeling perspective, molecular dynamics simulations have provided atomic-level information related to the structure-function in such systems. For accurate modeling of these systems, well-tuned, physics-based interaction models, or force fields, for proteins and lipid membranes are needed. The next generation of classical force fields strives to incorporate electrostatic polarization, and among the several approaches being pursued, the charge equilibration methods show promise as a viable, efficient approach for accounting for electrostatic non-additive effects. In this work, we present a revised CHARMM force field for lipids based on the charge equilibration model for incorporating polarization effects into molecular dynamics simulations. The model addresses deficiencies in the dihedral, electrostatic, and Lennard-Jones (van der Waals) parameters. The revised force field has been applied to molecular dynamics simulations of higher alkanes ranging from hexane to pentadecane. We will discuss calculated bulk liquid properties including enthalpy of vaporization, density, isothermal compressibility, constant pressure heat capacity, and self-diffusion coefficient. Finally, we will discuss extension of the alkane force field for application to lipid bilayer simulations. Specifically, the lipid molecule dimyristoylphosphatidylcholine (DMPC) has been modeled by smaller compounds, tetramethylammonium (TMA) and dimethylphosphate (DMP), which were used in the parametrization. Application of the revised polarizable force field to DMPC bilayers shows excellent performance with respect to predicted surface area per headgroup and local chain dynamics as represented by deuterium order parameters. We will discuss DMPC membrane properties using existing non-polarizable models contrasted with the newly developed polarizable force field.

COMP 56

DrugScoreFP: Profiling protein-ligand interactions using fingerprint simplicity paired with knowledge-based potential fields

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We present a vector-based extension of the DrugScoreCSD formalism to rescore docking results called DrugScore Fingerprints (DrugScoreFP). The DrugScore of a docked inhibitor is partitioned into per-atom scores resulting in a vector. Simple distance metrics allow the determination of similarities between fingerprints of docked compounds and reference fingerprints derived from crystal structures. Furthermore, DrugScoreFP allows the generation of family-based fingerprint profiles as implemented in SIFT and the knowledge-based interaction fingerprint scoring from Mpamhanga et al.

We have applied DrugScoreFP to handle the following three tasks of structure-based drug design:

First, the recognition of near-native docking-poses, which showed improved results compared to DrugScoreCSD and SIFT using the Wang dataset. Secondly, cross-validation studies on different consensus fingerprints were performed on a Trypsin dataset. In a leave-one-out experiment, DrugScoreFP showed better recognition rates of crystal over docked structures in 75% of the cases. At last, GOLD was used to dock 1800 compounds from the National Cancer Institute Diversity Set into Trypsin and 70 compounds into HIV-1 protease, respectively. DrugScoreFP shows superior ROC-AUCs of up to 99.9% compared to GOLD-Score (72%) and DrugScoreCSD (85%).

The results prove that DrugScoreFP can be used as a powerful filter identifying similar binding profiles. It could also be shown that DrugScoreFP is stable with respect to cross-validations, reliably discriminates near-native poses from widely spread decoys and recognizes active compounds merged into large databases almost perfectly.

COMP 57

Topologically-based multipolar reconstruction of electrostatic interactions in multiscale simulations of proteins

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We develop a new method to incorporate electrostatic interactions in coarse–grained representations of proteins. Our model is based on a topologically–reconstructed multipolar expansion of the all–atom centers of charge, in particular, of the backbone dipoles and of the dipolar or charged side chains. The reliability of our model is checked by studying different test cases, specifically: protein–cofactor/substrate interactions, protein large conformational changes and protein–protein complexes. In all cases, we find that the model performs quantitatively well. Our model is of general applicability, and can be used to improve both full coarse–grained simulations and all–atom/coarse–grained multiscale approaches.

COMP 58

Geometric models of uncertainty: Applications for robust target flexibility analysis and function prediction in computational chemistry

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Molecular structures or models have implicit imprecision in their coordinates, due to uncertainties and errors in measurement/representation of atomic coordinates, theoretical approximations, inconsistent experimental conditions, and intramolecular flexibility/motion. Geometric algorithms used in computational chemistry often ignore this underlying imprecision, and consequently risk drawing different conclusions from similar data, or failing to find patterns obscured by imprecision. We introduce a geometric framework, "almost-Delaunay simplices", to represent nearest-neighbor relationships amongst point coordinates with known imprecision. We describe two recent applications of our method relevant to drug discovery.

The first application aims to identify residues undergoing non-random non-rigid motion (hinge, shear, allostery and other complex motions) from two or more protein structures. These structures may comprise apo and ligand-bound crystal structures, different ligands/environments, NMR ensembles, and snapshots from MD simulations. We infer non-rigid motions from changes in the neighbor relationship captured by almost-Delaunay simplices. The inferred flexible residues are consistent across different datasets for the same protein, and also

match flexible residues from literature for motions categorized in the Molecular Movements Database(MolMovDB.org). Flexible residues are often crucial for protein function, and hence targeted by structure-based drug design efforts.

The second application, protein function prediction from structure, helps characterize new targets and discover off-target liabilities/opportunities. We use a graph representation of protein structure built using almost-Delaunay edges, which enables quick and robust mining for frequent patterns in large/diverse protein families compared to contact-graph and nearest-neighbor representations. We search within query structures for frequent patterns rare in the background(PDB), called family-specific fingerprints, and assign statistical significance to the function prediction. The method was validated by predicting new members of families, and distinguishing 20 sequence/structure-similar TIM-barrel enzymes. It was used to make predictions for the function of structural genomics proteins, corroborated by other computational methods or validated by subsequent functional characterization.

COMP 59

Let's meet somewhere in the middle: Combining computational macromolecular design with organic synthesis

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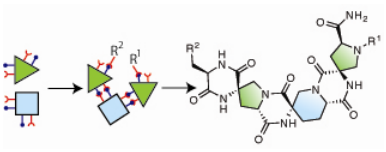
Oligomeric molecules such as peptides are highly disordered in solution and when they do demonstrate function, it is difficult to determine the structural basis or rationally optimize the function. My group has developed a new class of synthetically accessible oligomeric molecules called bis-peptides, together with a molecular mechanics based design methodology that enables the rational design of functional bis-peptides. We will describe our software package CANDO (Computer Aided Nanostructure Design and Optimization) that uses molecular mechanics to automatically assemble a structural database from a concise description of a small set of molecular building blocks, and then uses that database to search for large oligomers that can present functional groups in desired constellations. We will briefly describe our synthetic methodology in which we synthesize conformationally constrained, cyclic bis-amino acid monomers and couple them through pairs of amide bonds to create water-soluble, spiro-ladder oligomers. Finally, we will demonstrate applications that combine computer aided design with organic synthesis.



COMP 60

Graphical processing unit: A novel computational architecture for quantum chemistry

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We present a new massively parallel code for quantum chemistry calculations called TeraChem (standing for "Teraflop Chemistry") that performs all computationally intensive tasks, like the Fock matrix formation step in direct self-consistent-field calculations, entirely on Graphical Processing Unit (GPU). This code is different from existing solutions because it is optimized for the streaming-type architecture from the very beginning, keeping further multi-GPU parallelization in mind. In TeraChem, the data flow between different threads launched on distinct cores is completely eliminated, making it ideally suitable for execution on stream processing hardware such as the GPU. Ideally, this approach completely mitigates expensive inter-node communication once the code is parallelized over multiple GPUs, favoring linear problem scaling versus the number of computational units. We demonstrate that up to 100x speedup, compared to optimized quantum chemistry solutions, and over 100 GFLOP/sec performance are achievable on single GPU.

COMP 61

Quantum wavepacket ab initio molecular dynamics: Applications to hydrogen tunneling in biological enzymes and vibrational properties in hydrogen-bonded clusters

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This talk is arranged in three parts: The first part of the talk deals with the discussion of a novel computational methodology developed within our group. The approach combines quantum wavepacket dynamics with ab initio molecular dynamics and is potentially useful in studying problems where nuclear quantum effects can play a significant role. The approach is called quantum wavepacket ab initio molecular dynamics (QWAIMD). Computational bottlenecks and associated solutions are also discussed in some details. The second and third portions of the talk deal with applications of this approach that result in fascinating insights in hydrogen tunneling in biological enzymes, and (time-

permitting) solvation structure, dynamics, and simulation of vibrational spectroscopy in hydrogen-bonded clusters.

COMP 62

Molecular systems biology: Bridging the gap through multiscale modeling and high-performance computing

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We describe the application of a multiscale approach based on atomistic molecular dynamics, molecular docking, mesoscale stochastic dynamics on a coarse-grained system, and systems dynamics using a network model to signaling in the ErbB family receptors, in order to mechanistically describe how point-mutations in the ErbB receptors can profoundly alter signaling characteristics leading to the onset of oncogenic transformations. Erb family receptors (the epidermal growth factor receptor or EGFR/ErbB1/HER1, ErbB2/HER2, ErbB3, and ErbB4) signal by activating crucial pathways, in response to activation by ligands such as the EGF, and other peptide growth factors. The molecular context in which ErbB receptors activate and regulate signaling has not been fully recognized. In particular, the occurrence of somatic mutations in the ErbB1 kinase domain (L834R, del L723-P729 or del) as seen in non-small cell lung cancers renders the cell lines harboring such mutations more sensitive to treatment. To summarize, our results, our multiscale simulations on ErbB1 help rationalize and integrate the collective results emerging from structural, biochemical, cell biology, and clinical studies. At the molecular level, our results suggest that the clinically identified mutations of ErbB1 RTK induce network fragility in the stabilizing interactions of the inactive kinase conformation, thereby providing a persistent stimulus for kinase activation even in the absence of any growth factor. At a cellular level, parameter perturbations driving network hypersensitivity through the enhancement of phosphorylated ERK and Akt levels show a striking correlation with observed mutations of specific proteins in oncogenic cell lines as well as the observed mechanisms of drug resistance to ErbB1 inhibition. Therefore, subject to the well appreciated modeling limitations (i.e., uncertainty in network topology/parameters, neglect of molecular cross-talk, autocrine loops), we suggest that cascading mechanisms of network hypersensitivity/fragility at multiple scales enable molecular-level perturbations (clinical mutations) to induce oncogenic transformations and mechanisms of drug resistance.

COMP 63

Extensible environment for interfacing molecular modeling programs

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We present our recently developed environment for interfacing molecular modeling programs, PUPIL. Under this computational setup, the work of interfacing different programs falls to the interface and not to the user.

We have for instance, already included AMBER, GAUSSIAN, Siesta, DLPOLY and NWCHEM in the system, which means that every possible interconnect bewteen them is already included.

We will present some results using QM/MM advanced sampling of a N-N bond breaking process in water, using Amber and Gaussian, with both MP2 and B3LYP levels of theory.

This emerging technology allows the use to focus on his/her research and leave the computational details to the expert system.

COMP 64

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

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A new screening rule of structure parameters in Quantitative Structure-Activity Relationships (QSARs) models applying Artificial Neural Networks (ANN) is given. The new screening rule overcomes the problem, which some important nonlinear information between input nodes and output nodes may be omitted as screening input nodes in ANN-QSARs models. The structure parameters in multi-chlorophenol QSARs model can be screened fast and simply by using it. The results show that the structure parameters are cut down from 24 to 3, and the model quality and prediction ability in ANN are not reduced as the number of nodes in input layer is cut down, but are improved. In addition, the method expedites the convergence of networks model. So the method establishes the foundation for further developing the mechanism research of the toxicity of

organic chemicals on biology and may be popularized in the other fields using ANN.

COMP 65

New paradigms for improving dataflow and analysis of molecular dynamics simulations

***Thomas E. Cheatham III**, Departments of Medicinal Chemistry and of Pharmaceutics and Pharmaceutical Chemistry, University of Utah, 2000 East, 30 South, Skaggs Hall 201, Salt Lake City, UT 82117, Fax: 801-585-5366*

Biomolecular simulation methods are proving themselves to be immensely useful tools for understanding biomolecular structure, dynamics, and interactions in applications ranging from structure prediction to drug design. The emergence of petascale computing is fueling growth, promising the ability to simulate ever larger biomolecular assemblies for biologically relevant time scales. However as we push forward, our approach to the problem has not evolved at the same pace. Specifically and similar to the way simulation experiments were performed over a decade ago, molecular dynamics simulations are run as batch parallel jobs for weeks to months on both local and remote computational resources, and then the data is aggregated and moved locally for analysis. As the simulations become bigger and longer, this model breaks down as we spend more and more time manipulating and moving data then we spend trying to understand the bio-relevance. Moreover, the simulation experiment is moving away from one-off trajectories towards managing ensembles of loosely coupled simulations; this provides an added burden for managing the workflow and analysis. Over the past 16 years we have developed the "ptraj" program for MD trajectory analysis in AMBER; in this talk, we will discuss recent enhancements made to enable and facilitate the simulation workflow and analysis towards our goal of better documenting and annotating the process. Ultimately our emerging technology aims to provide the means for our scientific explorations by removing barriers to the simulation data management.

COMP 66

Method to evaluate the partition function from a computer simulation

***Richard H Henchman**, Manchester Interdisciplinary Biocentre, The University of Manchester, 131 Princess Street, Manchester M1 7DN, United Kingdom, Fax: +441613065201*

A method is presented to evaluate the partition function directly from a computer simulation. The full potential energy surface is approximated by a set of harmonic

potential functions of much lower-dimensionality that can be integrated analytically. The shape of each effective potential is determined from the forces measured in the simulation in the reference frame of each degree of freedom. The additional configuration space available to each degree of freedom is then integrated over three-dimensional space. The result is an explicit value for the system's entropy as well as an insightful decomposition of the entropy for each degree of freedom. The method has been applied to pure liquids including liquid water and argon, dilute solutions of noble-gas molecules, interfaces, and the binding of small molecules to proteins. This approach also makes it possible to account for the quantization of states, an essential feature for reproducing the thermodynamic properties of ice and supercooled water in the low-temperature limit.

COMP 67

CHARMMing: A new web based front-end to the CHARMM macromolecular modeling package

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CHARMMing (CHARMM interface and graphics, http://www.charmming.org), a new web based front-end to the CHARMM macromolecular modeling package, is presented. This tool provides a user friendly interface for the preparation, submission, monitoring, and visualization of molecular simulations (i.e., energy minimization, solvation, and dynamics (molecular, Langevin, and Self-guided Langevin). The infrastructure used to implement the web application is described. Two additional programs have been developed and integrated with CHARMMing: GENRTF, which is employed to define structural features not supported by the standard CHARMM force field, and a job broker, which is used to provide a portable method for using grid and cluster computing with CHARMMing. The use of the program is described with three proteins: 1YJP, 1O1O and 1UFY. Source code is provided allowing CHARMMing to be downloaded, installed, and used by supercomputing centers and research groups that have a CHARMM license. Although no software can replace a scientist's own judgment and experience,

CHARMMing eases the introduction of newcomers to the molecular modeling discipline by providing a graphical method for running simulations.

COMP 68

Improving constant pH simulation by replica exchange molecular dynamics

Yilin Meng *and Adrian E. Roitberg, Department of Chemistry, University of Florida, Gainesville, FL 32603*

Solution pH is an important thermodynamic variable in biophysics. Correct sampling of protonation state and conformation space is crucial when studying pH effects and predicting pKa. A constant pH replica exchange molecular dynamics (REMD) method based on discrete protonation state model is proposed to improve protonation state and conformation samplings. In our method, two replicas having different protonation states and temperatures are allowed to exchange conformations and therefore avoid trapping in either protonation state or conformation space. Our constant pH REMD not only predicted pKa correctly for reference compounds but also converges faster than constant pH molecular dynamics (MD). We further tested our constant pH REMD by a heptapeptide from ovomucoid third domain (OMTKY3). The constant pH MD yielded completely wrong titration curves and structure information while the constant pH REMD demonstrated accurate results.

COMP 69

Combined DFT/semiempirical approach, a tool for the multiscale modeling of conductive polymers

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A multiscale model able to predict and accurately describe a connection between the atomic and the continuum scale is a much needed tool to achieve a stage where macroscopic properties can be predicted from atomic information. The key aspect of the project described here is the parametric integration between well-defined single-scale approaches. To achieve that integration then, adapting and improving models at each of the involved scales must be done first. The progress towards improved models at the atomic and at the macroscopic level will be described. The atomic level is dealt with by using quantum mechanics calculations including semiempirical and DFT methods, and this will be the main focus of this talk. The macroscopic level is addressed with probabilistic models, based on the Monte Carlo Technique, to study the charge transport process.

Plans for the integration across scales, the final step to achieve multiscale modeling, will also be discussed.

COMP 70

Computational design of the prototype for a two-photon absorbing photoswitch

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Modern optical data storage uses a heat-mode recording. An alternative photon-mode recording has several advantages, such as reducing of the recording time and the laser power. Such devices are supposed to use photochromic materials (that contain photoswitching molecules), which can reversibly change their color upon illumination. In order to build a multi-layer optical disk, two-photon absorption (2PA) can be used. It reduces cross-talk between layers and realizes a none-destructive read-out in 3D geometry. Diarelethenes are known as promising one-photon photoswitches, but they do not possess large 2PA cross-sections. A single molecule possessing both a high 2PA cross-section and photochromism, could be easily doped into the polymer matrix. We developed a computational method, which allows predicting which molecule can serve as a two-photon absorbing photoswitch and used it to design a prototype.

COMP 71

High-accuracy ab initio studies of tetrasulfur energetics

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We apply the quantum Monte Carlo method to the problem of energetics of S4 conformers and dissociation. The results presented here estimate the energy gap between the C2V and D4h conformers of S4, an important species in interstellar chemistry using variational Monte Carlo (VMC) and diffusion Monte Carlo (DMC). In addition to the energy gap of the conformers, we also provide VMC and DMC estimates of atomization and bond energies of S4, as well as selected excited

states. The overall effectiveness and accuracy of the method is compared against other available theory and experiment.

COMP 72

DFT application in porous materials formation

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Despite the great efforts made, the principles governing the formation of porous materials are not yet well understood because of the complexity of the hydrothermal crystallizations. In this study, we used density functional theory (DFT) on periodic models of AlPO-5 at the generalized gradient approximation (GGA) level with the Hamprecht, Cohen, Tozer, and Handy (HCTH) exchange and correlation functional to calculate the interaction between the framework and four different organic templates.we show that computational calculations could give us better insights into host-guest interaction when supported by results from experimental techniques like XRD and FT-Raman spectroscopy.

COMP 73

Proton transport in zirconia at elevated temperature studied by density-functional based molecular dynamics

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In solid oxide fuel cells, the mechanism of hydrogen oxidation to produce water at the anode, typically composed of a nickel/yttria-stabilized zirconia (YSZ) cermet, is complex. In fact, proton diffusion in YSZ prior to the formation of water is thought to be significant. Notably, experiments suggest that a 6 nm-thick region of monoclinic zirconia is present near the YSZ surface. Accordingly, density-functional based computations are performed to understand better the mechanism of proton transport in pure zirconia. The methodology is extensively validated by computing selected physical properties of the ZrO molecule, yttria, and the three low pressure phases of zirconia. The predicted Murnaghan equations of state describing the crystalline materials are consistent with experimental findings, including the relative energies of the different zirconia polymorphs. Subsequently, results from molecular dynamics as well as from

constrained molecular dynamics simulations are related to the available experimental measurements of high-temperature proton diffusion in YSZ.

COMP 74

Density functional study of concave-convex π•••π interactions in supramolecular assemblies

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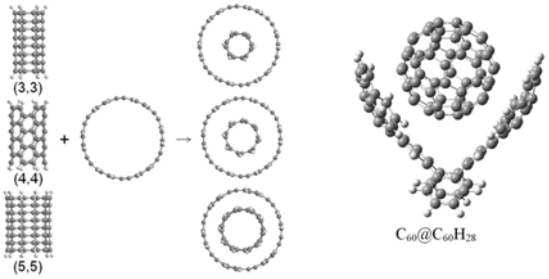
We employed two recently developed density functionals (M06-L and M06-2X) to characterize supramolecular interactions in a hydrocarbon nanoring and in buckyball tweezers. It is shown that the interactions in the nanoring are strong and size-selective. The pincer part of the C60H28 tweezers, corannulene, has a strong attractive interaction with C60. However, due to the entropy penalty, the calculated free energy of association of the C60@corannulene supramolecule is positive. The ability of new density functionals to analyze and accurately model attractive π•••π interactions opens new possibilities for computer-aided supramolecular design.



COMP 75

Revisiting the salt dependence of the association of charged ligands to nucleic acids

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Given the highly charged nature of nucleic acids it is not surprising that numerous kinetic and thermodynamic studies show that changes in salt concentration can greatly affect its association with charged ligands, from small drugs and peptides to proteins. Using different computational tools such as molecular mechanics, molecular dynamics and implicit solvent-based Poisson-Boltzmann algorithms we examined a variety of nucleic acids-charged ligand systems, to better understand the complex physical basis of the influence of salt on the binding energetics.

COMP 76

H3N2 Virus protein hemagglutinin binding with antibody: Free energy perturbation calculations

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In this paper, we calculated the binding affinity of H3N2 hemagglutinin (HA) protein (and its variants) with the monoclonical antibody fragment (Fab), using free energy perturbation method (FEP) with an all-atom explicit solvent model and an aggregate of 10+ μs molecular dynamics simulations. A single mutation of T131I in H3N2 HA is found to lower the binding affinity by 5.2 ±1.6 kcal/mol for the HA/Fab complex, thus introducing the escape of the antibody (Ab) neutralization. Our result confirms the recent experimental finding that the T131I mutation leads the dissociation constant Kd to increase by a factor of ~4000, but with a somewhat different molecular picture. Detailed analysis reveals that this large binding affinity decrease is related to the displacement of two bridge water molecules otherwise present in the wild-type HA/Fab interface, but not so much to the burial of the LYS156 carbonyl group as the experiment suggested. The loss of the binding affinity is also related to the large conformational distortion of one loop (residues 155-161) in the unbound state (w/o Fab) of the mutant. We then modeled all other possible mutations for this specific site T131, and predicted a few more mutations with even larger decrease in binding affinity, which might escape the antibody neutralization even better than the T131I mutation. As for further validation, we also modeled another experimentally designed mutation S157L and found again the calculated binding affinity agreeing with experimental affinity data very well. These large scale simulations provide new insights to the interaction and co-evolution relationship between viral protein HA and human antibodies.

COMP 77

Grand canonical competitive simulation of ligands and water

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Using the grand canonical paradigm we have implemented a simulation method that allows efficient simulation of free energies in the presence of explicit water molecules. In the grand canonical ensemble the system free energy is set, then the ligand and water molecules are inserted and deleted to create ensembles corresponding to the free energy level. The simulation is repeated for a series of energy levels. At each energy level the ligand and water compete for protein interactions as they are inserted and deleted and converge to equilibrated system. The method allows the concentration of ligand and water to be set separately for each simulation. The free energy of the water molecules involved in the simulation can thus be controlled to allow the ligand to compete with water at various energy levels ranging from the most tightly bound to bulk water. The use of explicit water is superior to using continuum models as water-mediated interactions between the ligand and protein can be reproduced. The basic properties and behaviors of the competitive simulation will be discussed. Examples of reproducing ligand-water-protein interactions observed in crystal structures will be presented. The crystallographically observed interactions of the ligand and water are sampled during the simulation without specification of the ligand and water poses beforehand.

COMP 78

Free-energy calculations for drug lead optimization

***William L Jorgensen**, Department of Chemistry, Yale University, New Haven, CT 06520-8107*

Efficient lead optimization is being guided by free-energy perturbation (FEP) calculations. Relative free energies of binding are computed for protein-inhibitor complexes using Monte Carlo simulations including ca. 1000 explicit water molecules. Starting with an inactive or weakly active core, typical modifications address optimization of substituents on an aromatic ring and choice of heterocycles. FEP “chlorine scans”, in which each hydrogen atom of the core is replaced by chlorine, are particularly attractive since they readily identify promising substitution sites and they are straightforward to perform. Successful application of the FEP-guided approach has been achieved in multiple inhibitor series for HIV reverse transcriptase and macrophage migration inhibitory factor (MIF); micromolar leads have been rapidly advanced to extraordinarily potent inhibitors in joint computational and experimental efforts. Some technical issues will also be covered including comparison of FEP calculations with double-wide or overlap sampling.

COMP 79

Computational docking and free energy calculations applied to carbohydrate-protein interactions

*Austin B. Yongye and **Robert J. Woods**, Complex Carbohydrate Research Center, University of Georgia, 315 Riverbend Road, Athens, GA 30602, Fax: 706-542-4412*

Direct experimental determination of the 3D structure of carbohydrate-protein complexes remains challenging, particularly for those involving complex oligo- and polysaccharides. For many complexes only indirect experimental data are available, such as Tr-NOE or STD-NMR intensities for the oligosaccharide or x-ray data for the unliganded protein. Computational methods can contribute significantly in the generation of accurate structural models for the complexes as well as in the prediction of affinities.

A study of the O-antigen carbohydrate from *Shigella flexneri* Y with a monoclonal antibody Fab fragment, which demonstrates the abilities of computational docking and binding-energy prediction methods is presented. Because it has been extensively studied experimentally the *S. flexneri* system serves as an ideal model for evaluating computational methods that target carbohydrate-protein interactions.

AutoDock is shown to be able to correctly align the oligosaccharide with respect to the antibody Fab surface in all cases. Deficiencies in the prediction of intermolecular hydrogen bonds are noted, and resolved by subjecting the docked complexes to molecular dynamics simulation with the GLYCAM/AMBER force field.

Relative binding energies for derivatives of the oligosaccharide are computed using Thermodynamic Integration and shown to be in quantitative agreement with experiment. The computed energies are decomposed into contributions from electrostatic, van der Waals and solvent effects, providing additional insight beyond that available from the experimental data.

COMP 80

Computational tools for successful fragment-based drug design

***Gianni Chessari**, Computational Chemistry, Astex Therapeutics, 436 Cambridge Science Park, Milton Road, Cambridge CB4 0QA, United Kingdom*

The field of fragment-based drug discovery (FBDD) has developed significantly over the past 10 years and is now recognised as a tangible alternative to more traditional methods of hit identification, such as high throughput screening. A variety of computational tools have been developed or adapted to support the different phases of FBDD programs and this is a rapidly developing area. Here, two case studies (Urokinase and HSP90) will be used to highlight specialised computational tools for FBDD that have been developed at Astex Therapeutics. In each case, the original fragment hit was successfully optimised into a lead compound; in particular the HSP90 program has delivered a lead molecule which is about to enter Phase I clinical trials.

COMP 81

Fragment-based tailoring of compound libraries for high-throughput docking and screening

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High-throughput docking is a computational tool frequently used to discover small-molecule inhibitors of enzymes or receptors of known three-dimensional structure. However, the large number of molecules in chemical databases make automatic procedures for pruning libraries before docking useful. We propose Anchor-based Library TAiloring (ALTA) as a strategy to focus chemical libraries by docking and prioritizing molecular fragments according to their binding energy. ALTA is able to identify compounds with optimal anchor fragments without any knowledge of known inhibitors.

We applied ALTA to the EphB4 receptor tyrosine kinase and docked 21418 molecules of a tailored library (obtained from an initial collection of about 730000), followed by ranking according to force-field-based energy including electrostatic solvation. Among 43 compounds tested in vitro, eight molecules originating from two different anchors show low-micromolar activity in a fluorescence-based enzymatic assay. Four of them are active in a cell-based assay and are potential anti-angiogenic compounds.

COMP 82

On modeling, selecting and using "drug-like" chemical matter: Toward optimized fragment collections

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We present a new approach for modeling, selecting and using ‘drug-like' chemical matter for virtual fragment-based searching and screening approaches. In an attempt to improve existing methods for the decomposition of molecules into fragments, we have compiled a new and more elaborate set of rules for the breaking of retrosynthetically interesting chemical substructures (BRICS) and used this for obtaining chemical fragments from biologically active compounds and vendor catalog sources. In addition, we incorporated more elaborate medicinal chemistry concepts and put considerable effort into compiling different sets of high-quality and high-performance fragments that are meant to serve as a possible basis for various molecular design objectives and screening techniques. When compared to existing methods, BRICS overall shows a significant increase in performance in retrieving compounds from various very large and diverse query sets. Furthermore, our analysis underlines that a high-performance set of fragments does not have to be derived solely from biologically active molecules. Based on our findings, we compiled three new fragment sets with optimized performances for different application scenarios. We also plan to make them publicly available in the near future. These can then be used in subsequent fragment-based searching and screening approaches to identify chemical probes for a given protein binding assay. The results of our case study highlight the capabilities of the BRICS fragment sets.

COMP 83

Putting together the pieces: A suite of computational tools for fragment-based drug discovery

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We have developed a set of tools geared toward fragment-based discovery. Applications will be presented for binding site analysis, hit identification, and lead optimization. These tools utilize a range of 3D structural information to perform fragment docking, joining, linking, and clustering. Additionally, we present our implementation of structural interaction fingerprints (SIFt) and show how SIFt profiles can be used to analyze and optimize fragment screening results. Finally, we address the challenges associated with fragment joining and discuss how

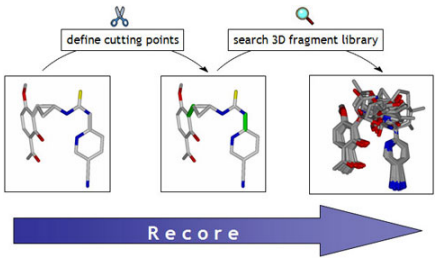
structural information can be used to increase the quality and quantity of active compounds returned when combining fragments.

COMP 84

Recore: Instant 3-D scaffold hopping using replacement fragments

***Christian Lemmen**, Carsten Detering, Marcus Gastreich, and Peter R. Oledzki, BioSolveIT GmbH, An der Ziegelei 75, 53757 Sankt Augustin, Germany, Fax: +49 2241 2525 525*

Recore, a 3D ligand scaffold replacement tool generates new ligand cores within a few seconds. It is an ideal solution for deriving new lead structures from existing ones which may be patent protected or otherwise unusable.Given a user-defined ‘core', Recore identifies the geometrically best possible replacement from a 3D fragment database. We used Recore to define 3D fragment sets based on either crystal structures or generated conformers of drug-like molecules. Recore identifies suitable fragments by shredding according to RECAP-type rules for high likelihood of synthetic accessibility. Recore was applied to pharmaceutically relevant targets using the bioactive conformations of known binders. Results show that Recore is able to replace a central unit and jump from one chemical series to another while preserving the position of the side-chains. Other known actives in their bioactive conformation were identified and additional pharmacophore-constraints further helped guide the search towards relevant solution sets.



COMP 85

Screening ligand binding site fragments

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Determining whether two proteins are likely to bind similar ligands is a task that becomes more difficult as the proteins' sequences diverge. Comparison of protein-ligand binding sites in 3D structures can highlight potential problems a ligand or drug candidate may have, including lack of specificity, and can provide insight on functional groups that are preferred for binding in subpockets. Using a discrete representation of preferred interaction sites in a query pocket or site, based on the distances and angles to neighboring protein atoms, SimSite3D (an implementation of our method) can rapidly search for and rank similar sites from structures in the Protein Data Bank. As shown by application to several protein families, our method allows the discovery of new and interesting similarities between proteins with low sequence similarity and can guide the design and evaluation of either selective or broad-spectrum inhibitors.

COMP 86

“Virtual Fragment Linking”: An approach to identify potent binders from low affinity fragment hits

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In this work we explore the possibilities of using fragment-based screening data to prioritize compounds from a full HTS library, a method we call Virtual Fragment Linking (VFL). The ability of VFL to identify compounds of nanomolar potency based on micromolar fragment binding data was tested on 75 target classes from the WOMBAT database and succeeded in 57 cases. Further, the method was demonstrated for seven drug targets from in-house screening programs that performed both fragment-based screening of 8800 fragments and screens of the full library. VFL captured between 28% and 67% of the hits (IC50<10μM) in the top 5% of the ranked library for four of the targets (enrichment between 5-fold and 13-fold). Our findings lead us to conclude that proper coverage of chemical space by the fragment library is crucial for both fragment hit finding itself and for prioritizing HTS libraries from fragment-based screening data.

COMP 87

Exploring the chemogenomic space

***Jordi Mestres**, Chemogenomics Laboratory, Research Unit on Biomedical Informatics, Municipal Institute of Medical Research and University Pompeu Fabra, Doctor Aiguader 88, 08003 Barcelona, Spain, Fax: +34 93 316 0550*

New trends in multitarget drug discovery seem to indicate that the design of a new generation of safer more efficient drugs may partly rely on our ability to anticipate the interconnectivity between small molecules and proteins at a large scale. This talk will focus on current efforts to exploring the chemogenomic space by expanding virtually the chemical space, estimating its interaction with the druggable target space, constructing ligand-target interaction networks, and navigating through all these data with novel integrative tools.

COMP 88

Quantitatively relating proteins by their ligands

***John J. Irwin**, MJ Keiser, Jérôme Hert, and Brian Shoichet, Department of Pharmaceutical Chemistry, University of California, San Francisco, 1700 4th Street, San Francisco, CA 94158*

The similarity of drug targets is typically measured using sequence or structural information. We have developed a chemo-centric approach that measures target similarity based on their ligands . We began with 65,000 ligands annotated into sets for hundreds of drug targets. The similarity score between each set was calculated using ligand topology. A statistical model was developed to rank the significance of the resulting similarity scores, which are expressed as a minimum spanning tree to map the sets together. Although these maps are connected solely by chemical similarity, biologically sensible clusters nevertheless emerged. Links among unexpected targets also emerged, among them that methadone, emetine and loperamide (Imodium) may antagonize muscarinic M3, &alpha2 adrenergic and neurokinin NK2 receptors, respectively. These predictions were subsequently confirmed experimentally. One question is how stable ligand networks are to changes in chemoinformatics metrics, and which network is the most reliable for prediction of pharmacology. Recent results using the Similarity Ensemble Approach will be presented.

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3. Web site. http://sea.docking.org/

COMP 89

Text analytics applied to large-scale pharmaceutical databases

***Stephen Boyer**, IBM Healthcare & Life Sciences, IBM Corporation, 18710 Vista de Almaden, San Jose, CA 95120*

IBM's Unstructured Information Management Architecture (UIMA) technology was used to identify chemical names and other entities in unstructured text for patented molecules. Names were converted to chemical structures using [name = structure] programs. SMILES and InChI (International Chemical Identifiers) strings of each chemical were generated, then used as input for other applications. Millions of patents and Medline abstracts were indexed in a scientific and patent literature chemical database. Proteins, genes, cell-lines, cell-types, disease codes and other domain-specific entities has been annotated as well. Data derived from the text analytics, combined with subsequent post processing operations are retained in a data warehouse to provide e-classification, visualization, and OLAP analysis capabilities. Using IBM's supercomputing (BlueGene) capabilities allows an unprecedented volume of simultaneous queries into the world's intellectual property and scientific literature, equivalent to ~240,000 simultaneous Google queries. The long-term vision is to build a database of every patented molecule for pharmaceutical use.

COMP 90

The trouble with translating information into medicines: Strategies for embracing serendipity and uncertainty

***Andew L. Hopkins**, Division of Biological Chemistry and Drug Discovery, University of Dundee, Dow Street, Dundee DD1 5EH, United Kingdom*

The paradox we face in the biomedical enterprize is that despite the fact that our accumulation of information is rapidly increasing, our rate to creating medical utility out of this information is apparently declining according to several measures of productivity, such the lowest number of drug approval in 2007 since 1983. This paradox is a challenge to the basic assumption that increasing knowledge linearly leads to an increase in useful applications of that knowledge. Thus there has been a call in recent years of the renewed need for a dedicated

"translational" mission. Here we will outline how drug discovery strategies can and must operate with uncertainty and limited knowledge and challenge some of the basic assumptions behind how modern science sometimes operates. We will explore the philosophy behind several of the most successful drug discovery strategies of all time and why they fell out of favour. We will illustrate how these strategies have inspired discovery informatics innovations that have successfully and cost effectively led to new clinical trials.

COMP 91

Drug informatics: Relating drug to target

Jean-Loup Faulon, *jfaulon@sandia.gov, Computational Systems Biology Department, Sandia National Laboratories and Joint BioEnergy Institute, Albuquerque, NM 87185, Fax: 505-284-1323, and Tudor I. Oprea, toprea@salud.unm.edu, Health Sciences Center, University of New Mexico, Albuquerque, NM 87131-0001*

We recently developed a kernel method coupled with support vector machines to predict drug-target interactions. Our kernel relies upon a representation of the chemical-protein complex using an extended connectivity fingerprint technique named molecular signature. These signatures are vectors of occurrence numbers of molecular fragments. Using a collection of over 1000 approved drugs and their corresponding targets extracted from DRUGBANK [http://www.drugbank.ca/] and WOMBAT-PK [http://sunsetmolecular.com/products/?id=5]. We use our kernel to expand upon the known network of drug-target interactions. New binding modes for existing targets as well as new targets for existing drugs can thus be mapped. Next, we probe the topology of the known and expanded drug-target networks as well as the distribution of fingerprint fragments for both drugs and targets. We further examine the fingerprints of high degree nodes (drugs and targets) and isolated nodes (drugs having only one target and vice versa). Finally, we use our kernel to evaluate the potential targets and off-target effects for a set of 258 small molecule drugs or candidate drugs undergoing Phase III clinical trials, extracted from Pharmaprojects [http://www.pharmaprojects.com/].

COMP 92

Force field development for metalloproteins

Kenneth M. Merz Jr., *Department of Chemistry and The Quantum Theory Project, University of Florida, 2328 New Physics Building, PO Box 118435, Gainesville, FL 32611-8435, Fax: 352-392-8722*

The routine simulation of metalloproteins continues to be a challenge given the difficulties of modeling their active sites. Dealing with long-range electrostatic interactions, incorporating active site structural dynamics and obtaining accurate structural and energetic information using high-level ab initio and DFT calculations are some of the major hurdles faced in developing metal ion force field models. Moreover, routinely prototyping metallo-centers is a significant software hurdle that has hindered development of metalloprotein force fields. In this talk we will discuss these issues, among others, and our solutions to these problems. In particular, the talk will focus on validation of DFT methods, software designed for routine metal center prototyping given a potential function form and examples of simulations of metalloproteins taken from work carried out in our laboratory.

COMP 93

Development of polarizable force field for ions

***Pengyu Ren**, Department of Biomedical Engineering, University of Texas at Austin, 1 University Station, C0800, Austin, TX 78712-0238, Fax: 512-471-0616*

Ions play a critical role in many chemical and biological systems. Modeling of ions with classical force field is challenging due to the presence of high charges and strong electronic polarization effect. Traditionally, ion parameters in the fixed-charge force field have been derived from single ion solvation free energy, which can be unreliable due to the assumptions used to decompose the experimental whole-salt data. We have successfully developed a classical potential that treat explicitly the electronic polarization via an atomic-dipole induction model. The necessary parameters, e.g. vdW radius and well-depth, in this model have been derived by comparing to ab initio quantum mechanical calculation of ion-water interaction in gas-phase. Condensed-phase simulations using the resulting parameters reproduce well the experimental ion-water cluster solvation enthalpy and experimental solvation free energy of whole salts. Water structure and dynamics around ion observed in our simulations are also in good agreement with experimental measurement and QM-based theoretical estimation. This approach has so far been tested on a series of mono- and divalent ions, including Cl-, K+, Na+, Ca++, Mg++, and Zn++. Our results demonstrate that inclusion of polarization effect enables us to derive a transferable classical potential based on ab initio QM calculations and make accurate prediction of bulk thermodynamic properties.

COMP 94

Charge transfer and local polarization effects on protein structure, mobility, and function

***Carmay Lim**, Academia Sinica, Institute of Biomedical Sciences, Taipei 115, Taiwan*

Nearly half of all proteins contain metal ions, which perform a wide variety of functions associated with life processes. However, insights into the local/global, structural and dynamical fluctuations in metalloproteins from molecular dynamics simulations have been hampered by the “conventional” potential energy function, which does not take into account the non-negligible charge transfer and polarization effects in many metal complexes.

In this talk, we will outline our strategy for deriving ion-water van der Waals (vdW) parameters that simultaneously reproduce the experimentally observed (i) relative hydration free energies, (ii) first-shell coordination numbers, and (iii) average ion-water distances of all the dications. We will also describe a novel potential energy function that incorporates the significant charge transfer and polarization effects in Zn complexes. Then, we will present the results of simulations of the central domain of human p53, which contains a Cys3His Zn-binding site, using both the “conventional” and new “CTPOL” force fields. The results show how a change in the metal coordination number affects the rest of the protein structure, the mobility of the protein, and its function.

COMP 95

Molecular dynamics simulations of RNA and the force field performance

***Jiri Sponer**, Institute of Biophysics, Academy od Sciences of the Czech Republic, Kralovopolska 135, 612 65 Brno, Czech Republic, Fax: 420-541212179*

RNA molecules represent a difficult task for molecular modeling. I will review our experience with force field performance from ~10 microseconds of fully analyzed and mostly published RNA simulation data for more than a dozen of distinct types of RNA systems, including recurrent RNA motifs (Kink-turns, Sarcin Ricin loop, Loop E), junctions, kissing-loop complexes and several ribozymes. Specific attention will be paid to the AMBER force field and its variants. I will also briefly comment on our latest QM benchmarks for base stacking, base pairing including all 12 non-Watson-Crick families of RNA base pairs, nonclassical H-bonds and the nucleic acids backbone. Some comments on DNA simulations will also be given. Ideas (and also some tests) where further tuning of the force field would be important will be presented.

COMP 96

Overcoming the lags in nucleic acid force field development

***Thomas E. Cheatham III**, Departments of Medicinal Chemistry and of Pharmaceutics and Pharmaceutical Chemistry, University of Utah, 2000 East, 30 South, Skaggs Hall 201, Salt Lake City, UT 82117, Fax: 801-585-5366*

Contrary to the situation with protein force fields, development of nucleic acid force fields have lagged. This is in part due to inherent difficulties in understanding the accessible conformational space of the nucleic acid poly-anion with its significant backbone conformational freedom and subtlety of interactions. To correctly model nucleic acid structure requires proper balance between base pairing, base stacking, backbone conformational freedom, and interactions with solvent and ions. We outline our approach to assess and validate the performance of nucleic acid force fields through large-scale simulations of RNA loop decoys, RNA NMR structures, and a myriad of DNA duplex systems. We show that to get the proper balance, ion parameters consistent with the simulation protocol and water model are required, as is omission of sub-state anomalies that lead to over-population of rarely accessed nucleic acid backbone conformations.

COMP 97

Making better drugs through improvements in computational methods

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The current state-of-the-art in drug discovery is largely dominated by incremental advances, with me-too drugs forming a very substantial fraction of the small molecule therapeutics market. Such drugs frequently yield no practical benefits in terms of therapy. Apart from drugs that target rapidly evolving organisms, justification for me-too design is problematic outside of narrow economic grounds. Coupled with a shifting regulatory environment that are changing the economic arguments, the need for truly novel drugs is increasingly apparent. This offers an opportunity for computational methods to have a larger impact than has been the historical norm. Strategies and methods will be discussed toward addressing the key bottlenecks in successful drug discovery through computational means.

COMP 98

Diverse reverse-turn and helix mimetics: Applications and limitations.

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Specific protein/protein interactions dominate biological recognition and control systems. Secondary structures, helices and reverse turns, often occur at the interface and provide most of the recognition motifs. A variety of privileged scaffolds have been suggested as helix and reverse-turn mimetics. A comprehensive study of such mimetics has discovered a number of limitations that impact their utility in the discovery and optimization of inhibitors of protein/protein interactions. One criteria is the degree of preorganization of the mimetic which impacts the loss of entropy upon binding. A second serious limitation is synthetic feasibility which determines the size and scope of chemical diversity available to probe recognition motifs. The third and unexpected limitation is a detailed understanding of the secondary structural motifs to be recognized. In the case of reverse turns, this is primarily the orientation of the four side chains at the i, i+1, i+2 and i+3 positions of the turn that is not specified by classical turn descriptors. In the case of helices, the torsional variables seen in high resolution protein helices are not those of the alpha helix or 310 helix, but rather an intermediate with bifurcated hydrogen bonds. Realization of these limitations for privileged scaffolds has led us to reconsider our own efforts to inhibit protein/protein interactions.

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COMP 99

How much computation is enough?

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One of the major challenges of predictive modeling is knowing when a given model or method will work, and to what extent. With the current explosion of computing power, there may be a tendency to utilize brute-force methods to extract the most "accurate" predictions possible for a given endpoint or physical

property, even when simpler approaches may be more robust. This creates a need for developing a rational scheme for establishing "best practice" evaluation processes for a variety of modeling scenarios. This talk will cover aspects of our work at RECCR in support of this goal.

COMP 100

Grand challenge force fields and beyond

***Thomas A. Halgren**, Schrödinger, Inc, 120 W 45th Street, New York, NY 10036, Fax: 646-366-9550*

Predicting ligand binding free energies to experimental accuracy is often considered the preeminent challenge of computational chemistry as applied to drug discovery. But while encouraging results have been obtained in many instances, few would argue that this objective has been achieved. This talk will place the objective in context by broadly discussing some of the elements needed to make such calculations possible, with a narrower focus on the development of force fields that combine impressive breadth of coverage with high accuracy. A force field with these properties should result in better predictions across a broad range of applications. Lessons learned from recent work in this research group directed toward developing such force fields will be cited.

COMP 101

Multitarget screening: Is cherry-picking scalable?

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With the growing performance of computer systems, most virtual screening methods tend at aiming to increase throughput and not improving prediction accuracy. This problem becomes even more relevant in case of activity profiling where the virtual screening process is reversed, i.e. a small number of molecules is screened versus a big number of targets. In this case current enrichment measures are not suitable to estimate the quality of a model, and "fine-tuning" of a scoring function becomes a more challenging task since selectivity and the

number of negative hits should be considered in a more differentiated way. We discuss the problem of multi-target screening using 3D pharmacophore based activity profiling and suggest protocols and visualization techniques to validate computational activity prediction model collections for virtual screening against multiple targets.

COMP 102

Looking for some good vibrations

***Robert D. Clark**, Tripos International, 1699 S. Hanley Rd., St. Louis, MO 63144*

There is wide-spread agreement that failure to adequately account for entropic effects in general is a major short-coming of available scoring approaches for estimating the free energy of binding between small molecules and proteins. There is also a general appreciation that binding site flexibility complicates things further, as does the fact that the free energy of binding often represents a small difference between two large numbers - the enthalpic and entropic components of free energy. This talk will examine how these three problems are interconnected at the level of molecular vibrations, and explore a route to potentially addressing them.

COMP 103

Computational tools in dynamic drug design workflows

***Norah MacCuish**, John MacCuish, and Mitch Chapman, Mesa Analytics & Computing, Inc, 212 Corona St., Santa Fe, NM 87501, Fax: 509-472-8131*

This study explores computational methods for drug design utilizing 2D and 3D descriptors to investigate targeted drug design for several kinase families. Applied exploratory data analysis, predictive modeling, and visualization tools, composed of FOSS and commercial software, will be described in this context and the utility of standalone applications and dynamic web application delivery systems will be also demonstrated.

COMP 104

Improving virtual screening by statistical modeling of interaction patterns

***Zhan Deng**, Lead Discovery Informatics, Novartis Institutes for Biomedical Research, 250 Massachusetts Avenue, Cambridge, MA 01890, Fax: 617-871-4088*

We will present a method for implementing knowledge-based filtering and enrichment of virtual screening results, using statistical modeling of the interaction patterns. We have thoroughly tested this method with a variety of target systems and stringent benchmark test sets, and in all cases, it showed consistent and significant improvement over traditional scoring function. Moreover, the enriched hit pools were structurally diverse, making it attractive for lead discovery or lead expansion. We will discuss two prospective case studies on a protein kinase and a non-kinase target respectively to illustrate the benefit of this strategy in early drug discovery.

COMP 105

From protein conformational change to lead hopping: An efficient core-fragment expansion method for computational design of kinase inhibitors

Jeffrey Jie-Lou Liao*, Department of Computer Modeling, TransTech Pharma Inc, 4170 Mendenhall Oaks Pkwy, High Point, NC 27265, Fax: (336) 841-0310*

Kinase enzymes switch functionally from one conformational state to another during the cell cycle. Binding a protein kinase into one such a conformation can trap the enzyme, either competing with ATP binding or shifting the equilibrium towards an inactive state, thereby, inhibiting the kinase activity. Multiple conformations of a protein kinase target offer an opportunity to design small-molecule inhibitors with distinct but clinically useful profiles. The rationale underlying this strategy is that in the different kinase conformations, the size, availability and topological distribution of the binding pockets are varied, molecular recognition of which can help to develop distinct kinase inhibitors. Currently, toxicity-related promiscuity and drug-resistant mutations are major issues in the anti-kinase therapy. A structure-based viewpoint will be provided in this talk for the correlation of selectivity and drug-resistant mutation profiles of protein kinase inhibitors. Targeting kinase multiple conformations offers an approach to optimize the selectivity and acquired resistance profiles of a kinase antagonist.

In this talk I will also discuss an efficient core-ragment expansion method along with computational prediction of flexible loop structures for the design of protein kinase inhibitors. In the method, a focused fragment library is applied.

COMP 106

Iterative kinase medium-throughput screening (ikMTS) with AutoShim and Profile-QSAR for kinase lead discovery

Eric Martin *and David Sullivan, Novartis Institute for Biomedical Research, 4560 Horton St, Emeryville, CA 94530, Fax: 510-923-2010*

High-throughput screening of our 1.5 million compound collection takes 6-9 months and costs $1,000,000. The virtual screening alternative of conventional docking suffers 3 significant limitations: 1) it requires a target protein structure, 2) it is slow, and 3) it predicts activity only poorly. Combining medium-throughput experimental activity data with docking, AutoShim creates highly predictive, target-specific, scoring functions by adding pharmacophoric features to the general-purpose scoring function, analogous to shims in an NMR magnet. For kinases, a “Universal Receptor”, made from an ensemble of 16 diverse kinase crystal structures, can be “shimmed” to reproduce experimental binding data for any new kinase. Pre-docking our 1.5 million member corporate screening archive into the 16 structures took months on a large cluster. But now, “shimming” and running highly predictive 3D virtual screenings of the archive takes hours instead of weeks, without a crystal structure, enabling efficient iterative screening for any of the >500 kinases.

COMP 107

A kinome wide view of inhibitor selectivity mining

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While kinase inhibitors are prevalent in oncology, they are not well represented in other therapeutic areas. One reason for this is that life threatening diseases accept a much larger efficacy/tolerance window than those less grave.

While the therapeutic window for kinase inhibitors may be directly related to the specificity profile of the compounds, cross reactivity cannot be predicted from the primary sequence of the kinase domain. In choosing particular kinases to target for drug discovery, it is necessary to consider data based on genetic validation. Since sequence information is unreliable for predicting cross reactivy for any given compound, it is necessary to establish a compound-based method for predicting cross reactivity between members of different kinase families.

The BI KGFS is a matrixed database describing the chemical sensitivity of 108 human kinases against a 10,207 compound library. This database has been used to develop a chemical based clustering of the kinase families. It has also been used to evaluate kinase drug discovery targets, allowing the prediction of drugability, selectivity and cross reactivity.

Analysis of the KGFS has demonstrated that compounds, standards, and benchmark compounds vary widely in the extent of selectivity displayed. Cross reactivity can be tightly linked to primary sequence, or entirely dissociated from it, in that this cross reactivity is seen between the target and other subfamilies in the kinome.

The value of the KGFS has been demonstrated in many discovery projects, and several examples are presented.

COMP 108

Simulations of drug molecules interaction with lipid bilayers

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The study of drug interaction with lipid bilayer is essentially for drug design, efficacy, and toxicology. For a detail molecular understanding, we have conducted investigations into the mechanism of drug binding to the lipid bilayer using molecular dynamics (MD) simulations Specifically, we investigate the interaction of the drug Dibucaine with that of the lipid bilayer POPC ((1-palmitoyl-2-oleoyl-sn-glycero-3-phosphatidylcholine). MD simulations are used to understand the molecular contribution of the binding energy, enthalpy, and entropy of the drug to the lipid bilayer. Preliminary data suggest that the increased entropy comes mainly from the tails of the lipids, while the enthalpy term is dominated by the head group-drug interaction. These investigations could leads to the rational drug design to improve efficacy, efficiency, and reduced toxicity of therapeutic agents.

COMP 109

Binding and release of cholesterol in the Osh4 protein of yeast

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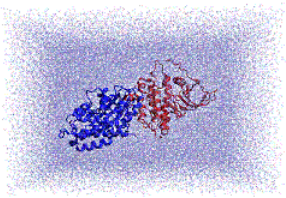
Sterols have been shown experimentally to bind to the *Osh*4 protein of Yeast within a binding tunnel. This and other *Osh* proteins are essential for intracellular transport of sterols and ultimately cell life. Molecular dynamics (MD) simulations are used to study the binding of cholesterol to *Osh*4. The conformational stability of cholesterol within the binding tunnel is the result of direct or water-mediated interactions between the 3-hydroxyl (3-OH) group of cholesterol and Trp^{46}, Gln^{96}, Tyr^{97}, Asn^{165}, and/or Gln^{181}. A MD simulation without the N-terminus lid resulted in similar binding conformations and binding energies compared to simulations with the full-length protein. Steered MD was used to determine details of the mechanism used by *Osh4* to release cholesterol to the cytoplasm. Gln^{96}, Asn^{165}, and Gln^{181} are found to direct the cholesterol as it exits the binding tunnel, as well as Lys^{109}. The mechanism of sterol release is conceptualized as a molecular ladder with the rungs being amino acids or water-mediated amino acids that interact with 3-OH.

COMP 110

Characterization of the allosteric activation mechanism of the HER2 tyrosine kinase domain using molecular dynamics simulations

Shannon E. Telesco*, Andrew Shih, and Ravi Radhakrishnan, Department of Bioengineering, University of Pennsylvania, 240 Skirkanich Hall, 210 South 33rd Street, Philadelphia, PA 19104*

Epidermal growth factor receptor (EGFR), HER2, and HER4 are receptor tyrosine kinases belonging to the ErbB family and are mutated in clinical malignancies such as lung and breast cancers. Since there is a growing effort to develop pharmacological inhibitors for the ErbB kinases, it is of great value to rationalize how specific mutations impact the molecular mechanism of receptor activation. In this work we perform molecular dynamics simulations of inactive and active HER2 structures and compare results to our earlier studies of EGFR and HER4. We highlight key differences in hydrogen bonding patterns and postulate an autoinhibitory mechanism whereby the inactive kinase is stabilized through sequestration of catalytic residues. We also predict a role for phosphorylated Y877 in bridging a network of bonds that fastens the A-loop in its active conformation, leading us to hypothesize that HER2 may be unique among the ErbB members in requiring A-loop tyrosine phosphorylation for functionality. Finally, we present results for a HER2/EGFR heterodimer and find that the dimeric interface disrupts key bonds, resulting in destabilization of the inactive structure. Our comparative analysis furthers insight into the mechanics of activation of ErbB kinases and enables us to predict the effect of an identified insertion mutation on HER2 activation.



COMP 111

COARSE: Enhanced sugar and lectin interaction scoring and energy function

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The ability to accurately evaluate the interaction between a carbohydrate and a protein is important in the design of novel drug candidates and engineered proteins. Building on the SLICK scoring and energy function of Kerzmann *et al*. (*JCIM* **46**:4, p1635-1642, 2006) the COARSE protein-receptor interaction scoring and energy function was constructed. The main component of COARSE is the CH-pi interaction with secondary stabilizing effects contributed by hydrogen bonding, electrostatics, and solvation effects. The COARSE scoring and energy function was trained on a set of high quality X-ray structures and validated on a separate Test Set collection. The validated COARSE scoring and energy functions were used to evaluate the results of docking monomer, dimers, trimers, tetramers, pentamers and hexamers to *Sm*Chi A and lysozyme.

COMP 112

Estimating binding free energies for large sets of protein-ligand complexes using the LIE method

Jens Carlsson *and Johan Åqvist, Department of Cell and Molecular Biology, Uppsala University, BMC, Box 596, SE-751 24 Uppsala, Sweden*

Recent development of the Linear Interaction Energy (LIE) method for estimating binding free energies from molecular dynamics (MD) simulations will be presented. Using automated generation of force field parameters and MD simulations, the LIE method can now be used to estimate binding affinities for thousands of potential ligands to a receptor. Recently, we have applied a combination of docking, MD, and LIE to large sets of protein-inhibitor complexes to evaluate the potential of this method in structure-based drug design.

COMP 113

Modeling the role of the solvent in protein-ligand binding

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Recently we have introduced a novel, computationally efficient, descriptor of the contribution of the solvent to the binding free energy of a small molecule and its associated receptor that captures the effects of the ligand displacing the solvent from the protein active site with atomic detail. Here we present the results of applying this technique to several pharmaceutically interesting test cases. The technique may elucidate physical properties of the active site solvent that appear to be missing in most continuum theories of hydration, and may be used to quantitatively predict the binding free energy differences between congeneric ligands.

COMP 114

Accelerating free energy estimates with accelerated dynamics

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In complex systems such as biological macromolecules, sampling all significant configurations is notoriously difficult. Although technological progress has enabled molecular dynamics simulations to observe motions in the sub-microsecond timescale, some biologically relevant conformational changes are known to occur on the order of seconds, hours, or even days. Even the longest trajectories can be kinetically trapped in local energy minima and fall far short of ergodicity. Here we present an accelerated dynamics approach that modifies the potential in a way that does not require as much foreknowledge in order to speed up the convergence of free energy estimates. We show that this approach samples the configuration space efficiently and that ensemble averages converge to the correct values.

COMP 115

Overcoming entropic barriers with coupled sampling at lower resolutions

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Enhanced sampling methods that couple a high-resolution model for accuracy and a low-resolution model for efficiency have gradually been adopted in protein simulations. These methods aim to overcome the entropic barrier found in the exponentially large protein conformational space when a high-resolution model, such as an all-atom molecular mechanics force field, is used. These methods can be designed to generate Boltzmann distributions in all sampling trajectories in both high and low resolutions. However, an issue in such coupled sampling methods is that low-resolution energy models are usually not perfect and such imperfectness does decrease the sampling efficiency of these models. Encouraged by these finding, we have initiated recent developments of low-resolution representations that are as consistent as possible to all-atom molecular mechanics force fields for coupled sampling to improve sampling efficiency. In our first effort, we have developed a new generation Amber united-atom force field for protein simulations. Tests with dipeptides and solvated proteins show that our goal is achieved quite successfully. The efficiency gain of the new united-atom force field in conformational sampling is demonstrated with several well-known toy protein folding systems, in both distance-dependent dielectric and generalized Born solvent treatments. The new united-atom force field was found to have an impressive gain over the tested all-atom force field for ab initio folding of the tested peptides.

COMP 116

Equilibrium sampling and free energy estimation using nondynamical sequential methods

Divesh Bhatt *and Daniel M. Zuckerman, Department of Computational Biology, University of Pittsburgh, 3088 Biomedical Sciences Tower 3, 3501 Fifth Ave, Pittsburgh, PA 15260*

In an effort to sidestep the intrinsic limitations of molecular dynamics and related simulation methods, we have explored variants of well-established polymer growth algorithms. These approaches grow molecular or liquid systems sequentially – one molecular fragment or solvent molecule at a time. They

provide equilibrium samples and free energy estimates simultaneously. We report on our progress using these approaches, which cannot readily be implemented using standard software packages. We note that, in principle, the ability to simulate explicit solvents in a sequential fashion permits the conversion of implicit-solvent ensembles to explicit solvent.

COMP 117

Determination of free energy profiles by repository based adaptive umbrella sampling: Bridging nonequilibrium and quasi-equilibrium simulations

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We propose a new adaptive sampling approach to determine free energy profiles with molecular dynamics simulations, called as ``repository based adaptive umbrella sampling'' (RBAUS). Its main idea is that a sampling repository is continuously updated based on the latest simulation data, and the accumulated knowledge and sampling history is then employed to determine whether and how to update the biasing umbrella potential for subsequent simulations. In comparison with other adaptive methods, a unique and attractive feature of the RBAUS approach is that the frequency for updating the biasing potential depends on the sampling history and is adaptively determined on-the-fly, which makes it possible to smoothly bridge non-equilibrium and quasi-equilibrium simulations.

COMP 118

Computing binding affinities using nonequilibrium unbinding simulations

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We compute absolute binding affinities (ΔG) using multiple non-equilibrium unbinding simulations. We compare this approach with equilibrium methodology using the FKBP protein bound to different ligands. The non-equilibrium methodology is straight-forward, requiring no modifications to most modern molecular simulation packages, and is trivially parallelizeable. The approach makes use of a physical pathway, eliminating the need for complicated alchemical decoupling schemes. For our systems, we estimate ΔG within less than 1.0 kcal/mol of experimental values. These results suggest that non-equilibrium simulation could provide a viable means to accurately estimate protein-ligand binding affinities.

COMP 119

Convergence metrics for generalized ensemble algorithms

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In response to the recently increase in the use of generalized ensemble algorithms for free-energy calculations, we apply a general mathematical metric to measure convergence of such simulations. Parallel generalized ensemble algorithms such as replica exchange have a unique characteristic in that they require simultaneous simulations (replicas) in various explicit ensembles. Convergence requires that all replicas equally sample the same space. We propose a measure for convergence based on this requirement and an estimator for time-to-convergence for systems that, by this method, are defined as diffusive. The method is general and valid for all systems that have at least partially sampled relevant regions of state-space.

COMP 120

Applying network to the structure analysis and modeling of helical membrane proteins

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Transmembrane (TM) proteins are estimated to account for ~20-30% of the human genome and serve as important drug targets. Despite the significant progress in experimental techniques, TM protein structure determination remains a challenge in general. Computational approaches, particularly de novo structure predictions, have played a significant role in structural and functional studies of membrane proteins, as well as in structure-based drug design efforts. A major challenge of membrane protein structure prediction is to assemble individual helices into high-quality tertiary structures. As network analysis have been shown to be a useful tool for soluble protein structure prediction, it is of interest to explore its application in TM proteins. Here, the application of network in structure analysis and prediction of helical membrane proteins will be presented. This work was supported by the Research Starter Grant in Informatics from the PhRMA Foundation.

COMP 121

Salt effects on the conformational preferences of alanine peptides

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The behavior of proteins in salt solutions constitutes a fundamental basis in the study of protein folding. Protein dynamics depends on the environment and the inclusion of salts in the simulation of folding/unfolding becomes extremely necessary when comparing energy barriers or reaction rates with experimental results. Recent experimental unfolding studies have been performed with helical peptides in solutions containing differing concentrations of sodium perchlorate $NaClO_4$. In this work we investigated the effects of $NaClO_4$ on helical peptide conformations, using molecular dynamics simulations of a mainly alanine based peptide (AP) immersed in $NaClO_4$, NaCl and TIP3P water. We compared the unfolding dynamics and found that $NaClO_4$ solution strongly stabilizes the peptide's α-helix like conformations while NaCl solution has a slight destabilizing effect. We investigated the possible (des) stabilizing mechanisms involved and found no direct ion binding processes or evidence of electrostatic screening between the arginine side-chains and the ions. Using a Kirkwood-Buff approach, preferential interaction parameters (Γ) were calculated and used to determine the change upon unfolding of the preferential interaction, $\Delta\Gamma^{(F\rightarrow U)}$. We found that $|\Delta\Gamma_{NaClO4}{}^{F\rightarrow U}| >> |\Delta\Gamma_{NaCl}{}^{F\rightarrow U}|$, representing a preferential water hydration favored by the folded peptide when immersed in $NaClO_4$ solution.

COMP 122

Water-mediated hydrophobic potential force field for protein structure prediction and refinement

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Computational methods for comparative modeling can consistently predict a protein's structure at medium resolution (~5Angstrom). However, solving the same problem at high resolution (~1-2Angstrom) still remains as a great challenge. Here we present a physical energy function that combines the AMBER99 protein force field, Generalized Born model for electrostatic components of aqueous solvation, and a potential of mean force for hydrophobic

interactions induced by the aqueous solvent. The force field has been tested on its ability to discriminate the native fold from other misfolds in which it outperforms other reported scoring functions in terms of correct native ranking and low Z-score for a variety of decoy sets, with demonstrable improvement for protein loop optimization over other biophysical or bioinformatics techniques. In this work we explore its ability to refine protein structures by a iterative process of selecting low-energy candidates along a molecular dynamics trajectory at a low temperature to improve comparative modeling refinement.

COMP 123

Origin of mutational effects at various positions on hammerhead ribozyme catalysis from molecular dynamics simulations

Tai-Sung Lee *and Darrin M. York, Department of Chemistry, University of Minnesota, Minneapolis, MN 55455*

A series of twenty four 100 ns (total 2.4 microseconds) molecular dynamics (MD) simulations of the native and mutated full length hammerhead ribozymes in the reactant state and in an activated precursor state (G8:2'OH deprotonated) are reported. Simulations include various single point mutants and double-mutant mutations at different key positions. The results provide critical details into the origin of the observed mutation effects, and support a mechanism where the 2'OH of G8 acts as a general acid catalyst that is held in position through several hydrogen bonding networks.

COMP 124

Energy and localization length of an electron hole in hydrated DNA

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First-principles, force-field, and lattice model calculations are used to address the electronic properties of an electron hole in duplex B-DNA in aqueous solution.

We provide with a statistical description of the energy deviations yielded across the DNA strands by the polar medium. We calculate the electron hole energy at uniform DNA segments embedded in hydrated DNA duplexes. Then, our results are used to infer information on the hole localization length and transfer dynamics. We find that the hole energy in DNA is governed by both solvation effects and polar medium fluctuations. The polar medium and the DNA sequence compete evenly to define the energy landscape of an electron hole in DNA. The medium-induced dynamical energy disorder leads to the occurrence of localized

hole states. Then, we show that the spatial correlations of the medium-induced energy disorder influence the hole transfer dynamics in DNA.

COMP 125

Dynamics-function relationships of the viral RNA-dependent RNA polymerase

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RNA viruses represent an existing and emerging threat to human health and include human pathogens like influenza virus, hepatitis C virus, SARS coronavirus, and West Nile virus.

The genome of RNA viruses are replicated by a virus-encoded enzyme, the RNA-dependent RNA polymerase (RdRp). By using poliovirus and its RdRp as a model system, it has become clear that polymerase error frequency, also referred to as fidelity, is optimized. The ability to define sites of the RdRp that control fidelity of the RdRp should define sites capable of attenuating viral pathogenesis, thereby enabling the rational design of vaccine strains. In this work, we employed the RdRp from poliovirus as our model systems. Molecular dynamics simulations are used to identify dynamical network(s); in-silico mutagenesis of the observed networks identify remote-site residues that may influence catalytic-site dynamics and function.

COMP 126

Computational study of the interaction of double-stranded RNA with Toll-like receptor 3

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Clinical trials of small interfering RNA (siRNA) targeting vascular endothelial growth factor-A (*VEGFA*) or its receptor *VEGFR1* for treatment of choroidal neovascularization (CNV) are premised on gene silencing by means of

intracellular RNA interference (RNAi). We show instead that CNV inhibition is a siRNA-class effect, and any 21-nucleotide or longer siRNAs independent of their sequence and target suppress CNV uniformly. Computational docking and molecular dynamics studies have been used to propose a dimer model for TLR3 and subsequently model the interaction between the TLR3 dimers and double-stranded RNAs, in an effort to understand the length requirement for TLR3 activation. Our results suggest that a minimum length of 21 nucleotides is necessary to span the distance between the functionally important residues on the receptor surface in a modeled 2:1 TLR3–RNA complex. This data was used to interpret results from recent experimental studies that showed that generic siRNAs, over a certain minimum length, can form a new class of anti-angiogenic drugs.

COMP 127

Ab Initio density-functional theory approach to evaluating electronic couplings in transition-metal systems: Application to the hexa-aquo $Fe^{2+/3+}$ redox couple.

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We present a density-functional theory (DFT) approach, with fractionally occupied orbitals, for studying the prototypical ferric-ferrous electron-transfer (ET) process in liquid water. We use a recently developed *ab initio* method to calculate the transfer integral (also named electronic-coupling or ET matrix element) between the solvated ions. The computed transfer integral is combined with previous *ab initio* valuations of the reorganization energy, within the framework of Marcus' theory, to estimate the rate of the electron self-exchange reaction. The self-interaction correction incorporated (through an appropriate treatment of the electronic correlation effects) into a Hubbard *U* extension to the DFT scheme leads to a theoretical value of the ET rate in good agreement with its experimental estimate from kinetic measurements. The use of fractional occupation numbers (FON) turned out to be crucial for the achievement of the convergence in most self-consistent calculations, because of the open-shell *d*-multiplet electronic structure of each iron and the near degeneracy of the involved redox groups. We provide the theoretical justification of the employed FON approach, which allows to describe the corresponding behavior of chemical potential and orbital relaxation, and extends to other transition-metal redox systems. Therefore, the methodology presented in this paper also proposes as a

fruitful approach for the quantitative description of ET reactions in biochemical systems.

COMP 128

Ab initio DFT + Hubbard U study of nonheme iron-dioxygen intermediates in superoxide reductase

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Transition-metal-containing enzymes are ubiquitous in biological processes, such as respiration, protein cleavage and toxic particles removal. While localized d-states of the transition-metal ions are central in these catalytic reactions, accurate descriptions of these states face great challenges when using density-functional theory (DFT) within local-density approximation (LDA) or general-gradient approximation (GGA). In this work, we employ a DFT + Hubbard U scheme in order to study the non-heme iron active site in superoxide reductase (SOR), with an appropriate description of the d-state electrons. This enzyme, found in several anaerobic bacteria and archaea, is important in toxic oxygen derivatives removal, by catalyzing the one-electron reduction of superoxide to hydrogen peroxide. We present the structure and energetics results of the iron-dioxygen intermediates at different stages of the reduction process. The effects of the Hubbard U correction are studied in detail, and significant improvements are found in the description of structures, reaction mechanism and spin state energetics. In particular, the role of each protonation step in the overall reduction process is highlighted. Our current results suggest that the implementation of DFT + Hubbard U into QM/MM can allow a reliable quantitative analysis of the enzymatic reaction mechanism, with negligible computational overhead.

COMP 129

Born-Oppenheimer molecular dynamics for the Cu(aq)+/Cu(aq)2+ redox couple: Deviations from linear response due to change in solvent coordination

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We have recently implemented a Born-Oppenheimer molecular dynamics/umbrella sampling method that allows us to compute full diabatic free energy curves for redox reactions. The system is transferred from the reduced to the oxidized state by coupling the ground state potential energy surfaces of the reduced and oxidized states. Both solute and solvent are treated at the same (GGA) density functional level of theory allowing to take into account bond breaking/making events between solute and solvent upon oxidation. In this contribution we present results for the half reaction Cu(aq)+ --> Cu(aq)2+ + e-. We find that the change in first shell solvent coordination number from 2 for Cu(aq)+ to 5 for Cu(aq)2+ leads to marked deviation from the linear response (or Gaussian) assumption that underlies Marcus theory of electron transfer. This is manifested in the redox potential of Cu(aq)+/Cu(aq)2+ relative to Ag(aq)+/Ag(aq)2+. A value of 1.5 eV was obtained from full umbrella sampling but a value of 1.1 eV when the linear response approximation was used (experiment: 1.83 eV). The deviation from linear response can be explained by the high stability of the five-fold coordination shell for Cu, which becomes the dominant coordination at an early stage of the oxidation reaction.

COMP 130

DFT study of unexpected reactivity of organic and organometallic compounds

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With the recent dramatic improvements in the available computational resources and in the accuracy of computational models, the use of theoretical studies has increased in recent years to become an indispensable tool in the design and understanding of molecular systems of interest in, inter alia, industrial catalysis, surface chemistry, materials design and pharmacology. Here I will present how such methods have be applied to the study of organic and organometallic systems whose behavior sharply contrasts that that one would have expected.

COMP 131

Computational studies of ion pair separation of organolithium compounds

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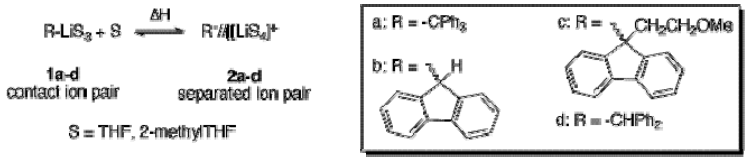
Aryl-substituted alkyllithiums undergo ion pair separation in ethereal solvents, but to date no computational studies of this process have been reported. ^{13}C NMR and UV-visible spectroscopic studies indicate that enthalpies for ion pair separation of **1a**-**1d** in THF and MeTHF range from -15 to -5 kcal/mol. To computationally estimate the enthalpy changes for these ion pair separations, the explicitly solvated contact ion pairs **1a-d** and separated ion pairs **2a-d** were located at B3LYP/6-31G*. Enthalpic corrections (298K) to the electronic energies were calculated from the B3LYP/6-31G* frequencies. Basis set superposition error was estimated by calculating single point energies at up to the 6-311+G** basis set, and by counterpoise correction. Our calculations reproduce the rank order of enthalpies of ion pair separation for **1a**-**1d**, but underestimate the exothermicities by 10-15 kcal/mol. Possible reasons for this divergence will be discussed.



COMP 132

Converging ligand binding calculations using Folding@Home: FKBP-12 and Factor Xa

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It usually requires sampling a large number of representative configurations to properly converge ligand binding affinity calculations. We present a comparison of absolute and relative ligand binding affinities for FKBP-12 using Folding@Home. Use of this distributed computing resource allows for many microseconds of total simulation time and significant sampling of all degrees of freedom for the majority of the ligands, resulting in binding affinities that are approximately 1 kcal/mol RMS error from experiment for those ligands that sample their configuration space well. We also present results from expanded ensemble simulations of relative binding affinities of more than 50 ligands to Factor Xa, and discuss the importance of using efficient free energy calculation methods to converge these results.

COMP 133

Free energy calculations in fragment-based drug design

*Jennifer L. Knight and **Charles L. Brooks III**, Department of Chemistry, University of Michigan, 930 North University Avenue, Ann Arbor, MI 48109, Fax: 734-647-1604*

Free energy calculations are fundamental to obtaining accurate theoretical estimates of hydration energies, protein-ligand binding affinities and energetics of conformational changes. Unlike traditional free energy perturbation and thermodynamic integration methods, we treat the conventional "lambda" as a dynamic variable in simulations and simultaneously evaluate the properties of multiple chemical moieties. Mimicking fragment-based drug design applications, we demonstrate how these lambda-dynamics simulations can efficiently and accurately compute binding affinities for a set of ligands to a common receptor. We have explored the impact of ligand parameterization on the quality of the free energy results and present an automated protocol for assigning and optimizing ligand partial charges. Biological systems to be examined include HIV-1 reverse transcriptase, indoleamine 2,3-dioxygenase and heat shock protein 90.

COMP 134

Monte Carlo/Free energy perturbation studies of MIF inhibitors as novel anticancer leads

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Macrophage migration inhibitory factor (MIF) is an immunoregulatory and proinflammatory cytokine that is released by T-cells and macrophages. MIF is implicated in multiple aspects of tumor growth and angiogenesis and is a promising target in anti-cancer research. Through a virtual screening of publicly available databases we identified 26 promising lead candidates, which were assayed *in vitro* for inhibition of human MIF binding to its receptor, CD74. Six leads were thus discovered to be active with half maximal inhibitory concentrations (IC50) in the 1.5μM – 65μM region. Substituent scans were applied for the active compounds with the BOMB program, which created analogs by adding substituents to a core directly in the MIF binding site. Free-energy perturbation (FEP) calculations using Monte Carlo (MC) statistical mechanics were then employed to guide lead optimization. Free energy changes

can be computed rigorously with FEP while converting a system with a molecule A to one with a molecule B over a series of non-physical intermediate states. The MC/FEP simulations were performed for each of the unbound ligands and protein-ligand complexes in the presence of ca. 1200 explicit water molecules. The resultant extensive structural information helps elucidate variations in binding affinities, provides further understanding of structure-activity relationships, and offers a basis for the design of novel ligands.

COMP 135

Integrated free energy simulations and X-ray refinement studies

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In this talk we will describe the use of molecular dynamics and free energy simulations to obtain insights into the active site characteristics and product distribution of Orf2 catalyzed prenylation reactions. In order to validate the computational results further the substrate orientations are confirmed using QM/MM based X-ray refinement methodologies. The value of this integrated approach for drug design and other applications will be discussed.

COMP 136

5-Membered heteroaromatic rings as building blocks for RNA-binding drugs

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5-membered heteroaromatic rings are used often as building blocks in drug molecules. The synthetic accessibility of these rings, together with the rigidity of their scaffolds, makes them common building blocks for lead generation in the drug design process. To be certain, the aromatic character of these rings can provide favorable stacking interactions with a receptor. Moreover, the presence of heteroatoms such as oxygen, nitrogen and sulfur allows these rings to act as H-bond acceptors and/or donors, leading to possible H-bond interactions in the final drug-receptor complex.

Here, we present a detailed comparative analysis of the stacking efficiency, stacking orientations and H-bond strengths formed by a series of 5-membered heteroaromatic rings in complex with model systems of an RNA-rich receptor.

Specifically, we employ methanol as a surrogate for sugar 2'-OH interactions, and we have constructed nucleotide host-guest systems to mimic heteroaromatic pockets that are plentiful in the 50S ribosome. Structural and energetic features of these systems, representing the drug-receptor complexes, are characterized and discussed in the context of a structure-based drug design approach (SBDD) targeting the 50S ribosomal subunit.

Ab initio and Density Functional Theory (DFT) calculations are performed and compared with those from Monte Carlo simulation employing the OPLS-AA and OPLS/CM1A force fields. The results of this study can provide guidance for the lead optimization process in SBDD in the case where ligands, including 5-membered heteroaromatic rings, make interactions with RNA-rich receptors.

COMP 137

Origins of drug resistance to the HIV entry inhibitor T20

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The first approved viral-host membrane fusion inhibitor called T20 inhibits viral entry by targeting the HIV protein gp41 during membrane fusion. No structures of T20 in complex with gp41 have been reported, thus the molecular mechanisms of resistance which occur from use of this peptide drug are not well-understood. Computational models of T20 bound with wild type gp41 and three point mutations have been constructed based on our prior studies of related C34 C-helix inhibitors. Results will be presented from explicit solvent and lipid molecular dynamics simulations, free energy calculations, and molecular footprinting at the binding interface which support the accuracy of the presented model. T20 is observed to interact with outer leaflet headgroups of the host cell lipid bilayer which could have important implications for the design of improved inhibitors.

COMP 138

From molecules to fragment spaces to focused libraries

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Chemical fragment spaces offer the promising possibility to model the chemical space in a combinatorial way. A Fragment space consists of molecular fragments and rules on how to recombine them. The possibility to encode both potential

biological activity as well as synthetic accessibility makes fragment spaces attractive for typical tasks in computer-aided drug design. In addition, their nature allows for using algorithms to tackle the problem of 'combinatorial explosion'. Here we present tools for a possible pipeline for generating fragment spaces by shredding molecules and enumerating them according to target derived physicochemical constraints. We used such a pipeline to generate and characterize focused fragment spaces for different target classes. We were able to enumerate the subspace for most of the targets on a standard workstation computer. The results indicate that the individual spaces and the underlying fragments have quite different and specific properties that should be taken care of in the early phases of a fragment based lead discovery scenario.

COMP 139

High throughput screening using pharmacophores generated from fragment based mapping

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Fragment mapping places molecular probes - small organic molecules containing various functional groups - around the protein surface, finds favorable positions, clusters the conformations, ranks the clusters, and determines their "consensus" sites [1]. Atomic denisites of these consensus sites can be used to create pharmacophore representations of hotspots in the binding site. These pharamcophore representations can then be used to screen against a database of known ligands and decoys. Here we present test cases, including HIV-1 protease, where we demonstrate that this screening technique can be used to discriminate between ligands and decoys and may therefore be an effective tool for high-throughput screening studies. [1] Landon MR, Lancia DR, Yu J, Thiel SC, and Vajda S. J. Med. Chem., 50:1231, 2007.

COMP 140

How ligand-based methods can further a fragment-based lead discovery project

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Computational support for the emerging FBLD strategy naturally reemphasizes receptor-based methodologies. Yet ligand-based methods can still play critical roles:

Filling the cavity. Pharmacophore-based searching, considering the unoccupied receptor volume, the vectors of potential ligand attachment bonds, and the dispositions of receptor pharmacophoric features, provides the appropriate “SAR by catalog” capability .

Novel R-groups and scaffolds. Many FBLD projects start by seeking binding of similar small pools of candidate ligand fragments to the same receptor structure. The resulting perhaps greater risks of IP conflict would be minimized by using ligand shape similarity to suggest as synthetic candidates the largest possible number of accessible R-groups and scaffolds.

pIC50 predictions. Perhaps surprisingly, local 3D-QSAR models provide more accurate pIC50 predictions than global physics-based models.

Off-target effects. Recent ligand shape similarity results suggest promise even for this challenging task.

COMP 141

Promiscuous patterns and perils in the NIH Molecular Libraries Initiative

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One challenge of high throughput screening is to avoid the costs and confusions which result from the class of false positives termed promiscuous or non-selective binders. One sub-class of non-selective binders is termed "aggregators" since their mechanism is to mimic the effects of binding via aggregation. Reactive molecules comprise another sub-class. In all cases the costs in time and resources of analysis and follow up on false positives and promiscuous compounds decrease the success rate of HTS and are hence highly undesirable. Thus in cases where compound promiscuity can be known a priori, globally or for specific assay classes, this knowledge is highly valuable to an HTS campaign. When this knowledge can be expressed in a rigorous and general way, such as a known substructure or scaffold which highly correlates with promiscuity, the value is even greater. This project describes some compounds and scaffolds found in PubChem which are indicated to be active in multiple biological assays, the

frequency of which suggests patterns of promiscuity. These findings emerged in the course of HTS projects at the New Mexico Molecular Libraries Screening Center, as part of the NIH Molecular Libraries Initiative.

COMP 142

Simulating molecular recognition through simultaneous multiple molecule docking

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Currently all existing docking methodologies simulate only a single ligand during docking process. In reality, the molecular recognition process always involves multiple molecular species, for example, substrate and cofactor in catalytic cycle; metal ion coordination together with ligand(s), ligand binding with water molecules in the binding interfaces. In order to simulate the real biochemical processes, I propose a novel multiple ligand docking strategy which can deal with all the above processes, vastly improving docking sampling and binding free energy scoring. The presentation will compare two search strategies: Lamarckian Genetic Algorithm and Particle Swarm Optimization, which have respective advantages and shortcomings depending on the molecular systems. The methodology proves robust through systematic testing against ten model systems. Besides the final correct docking poses and binding free energies, the simulations also capture the binding intermediates and reveal the binding kinetics/dynamics during the recognition processes. Two applications will be presented: a) peptide docking to deal with large number of torsions; b) multiple fragment searching for fragment-based drug design.

COMP 143

Substructural analysis of large chemical datasets for fragment based discovery

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Substructural analysis techniques have had a traditional, but limited place in chemoinformatics workflows. The approach is used to organize and retrieve information from chemical databases. In some areas of predictive drug design, most notably calculation of physicochemical and toxicological properties is predominant but multiple factors limit its use. A large number of substructures

that can be generated from a single chemical, more so, from a chemical collection can overwhelm data mining tools. An exhaustive enumeration of substructures in a dataset may not be the most productive when analyzing fragments in chemoinformatics. In this paper, we explore several factors that could be used to limit the number of substructures to keep under consideration and the way in which they affect the type and number of substructures collected. The analysis is carried out to develop rules to increase the efficiency of substructural analysis, given the importance of such techniques when designing libraries fro fragment based drug design. The types of substructures present in chemical collections is analyzed and correlated with those present in drugs.

COMP 144

Characterizing carbohydrate-protein interactions: Protein contact surface mapping employing hydroxyl radicals, mass spectrometry and MD simulations

*Olga Charvatova and **Robert J. Woods**, Complex Carbohydrate Research Center, University of Georgia, 315 Riverbend Rd, Athens, GA 30602, Fax: 706-542-4412*

For a large number of biomolecular complexes, it is not possible to apply traditional methods such as x-ray crystallography, particularly for oligosaccharide-protein interactions. While NMR methods such as STD-NMR can identify protons in the ligand that are close to the protein surface, these methods are not generally applicable to the protein. To address the lack of 3D information pertaining to the regions of the protein directly involved in the interaction with ligand, we are developing a surface mapping technique. Hydroxyl radicals react with the amino acid side chains and so can provide a generic labeling reagent, generated *in situ* by pulsed laser irradiation. Subsequent quantification of amino acid oxidation levels follows a proteomics approach employing MS/MS sequencing of tryptic peptides. We demonstrate that, for any given residue, the extent of surface modification is proportional to the side chain solvent accessibility. In order to interpret the experimental data, MD simulations of the complex are performed to provide theoretical values for the difference in solvent accessibility for the bound and free forms of the protein.

This experimental approach may be readily combined with theoretical docking methods to provide validation of the computational results, or potentially to guide the docking algorithm.

COMP 145

Geometric protein structure analysis approaches for designing inhibitors of protein-protein interactions

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Protein-protein interactions (PPI) were until recently considered difficult targets for small-molecule drug discovery, though with new developments and a new understanding of this field, that view is changing. We apply techniques from computational biology (particularly geometric analysis of protein structure) to describe and probe protein-protein interfaces, and describe how the resulting insights are valuable in a drug discovery setting. We have computed and categorized interfaces for a variety of protein-protein interaction targets, and are using the validated correspondence between deep/persistent parts of the interface surface and hotspot residues for structure-based design of PPI inhibitors. We find that functions computed on the interface give potent descriptors of protein-protein binding affinity, an important step forward in this field. Further, we apply and validate interface surface computation and analysis methods in the context of protein-small-molecule interaction, comparing them with established methods.

COMP 146

QUAPO: Quantitative analysis of pooling in high-throughput drug screening

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Pooling in high-throughput drug screening involves testing mixtures of compounds in a biochemical assay to minimize the number of tests required to screen a library for active compounds. In this talk, we will present recent work in our group for designing assay pooling schemes tailored for drug screening highlighting their resource savings, identification guarantees, error-correcting abilities and drug screening-specific modifications. Furthermore, we will present a biophysically relevant error-tolerant pooling strategy called Quantitative Analysis of Pooling (QUAPO). QUAPO utilizes state-of-the-art compression and decoding techniques from the field of compressed sensing, along with simple biochemical models, to obtain quantitative binding information from a primary drug screen while minimizing the number of tests needed and handling experimental error. We will present results from pooled in-silico experiments showcasing QUAPO's

ability to acquire robust quantitative binding information using data from a small competitive binding and a large competitive inhibition screen.

COMP 147

A technique for generating 3-D alignments of multiple ligands from 1-D alignments

***David J. Diller**, Molecular Modeling, Pharmacopeia, Box 5350, Princeton, NJ 08543-5350, Fax: 609-655-4187*

We describe and demonstrate a new method for the simultaneous, fully flexible alignment of multiple molecules with a common biological activity. The key aspect of the algorithm is that the alignment problem is first solved in a lower dimensional space, in this case using the one-dimensional representations of the molecules. The three-dimensional alignment is then guided by constraints derived from the one-dimensional alignment. We demonstrate the technique with a few test cases and compare to other commonly used alignment techniques.

COMP 148

Focused Library Design: An integration of knowledge-based information and multiple modern drug designing approaches

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In recent years, there has been increasing interest in smaller focused or targeted libraries against specific biological targets or gene families. Such target-family-oriented libraries are usually pursued with a variety of design approaches, including combinatorial libraries of privileged scaffolds, structure-based docking and 2D/3D pharmacophores or fingerprints. In this talk, we will present our recent works on GPCR focused library and how we combine knowledge-based information with multiple traditional/modern designing methodologies to further guide the design.

COMP 149

Molecular dynamics and binding studies on human paraoxonase 1: In silico optimization of activity against chemical nerve agents

***Toby T. Sanan**, Peng Tao, Sivaramakrishnan Muthukrishnan, Carrigan J. Hayes, and Christopher M. Hadad, Department of Chemistry, The Ohio State University, Columbus, OH 43210*

Human Paraoxonase 1 (huPON1) is an endogenous human protein which has been identified as having the ability to catalytically hydrolyze organophosphorous nerve agents, as well as a number of other substrates including aryl esters and lactones. At present, the mechanism of action of the enzyme is still under debate, and the majority of the available structural information comes from the crystal structure of a gene-shuffled protein with 86% sequence homology with the human enzyme, but with no substrate or inhibitor bound in the active site. Computational models have been prepared for both the human wild-type enzyme, as well as the gene-shuffled variant, and extensive (20 ns) molecular dynamics (MD) simulations were performed for these models. Mutant proteins were prepared in silico to rationalize experimental mutagenesis studies, and these models were also relaxed using MD techniques. Molecular docking simulations have been performed to explore the nature of substrate binding, and critical residues for binding and reactivity have been identified. Hybrid QM/MM simulations were performed to analyze potential reaction mechanisms in conjunction with the binding studies.

COMP 150

Protein loop modeling for structure-based drug design

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A key issue in protein modeling for structure-based drug design is the accurate modeling of loops, particularly when the loop in question is within interaction distance of the bound ligand. This study takes a critical look at modeled loops, evaluating them in terms of backbone and side-chain conformations with respect to the conformations found in the crystal structure. The computational protocols used for generating the loops include Monte Carlo searching, ab initio and knowledge-based methods. Even those loops that are well modeled with respect to the backbone atoms, however, may be poorly modeled with respect to side-chains and therefore may be unsuitable for ligand docking. With this concern in mind, we are specifically exploring the ability to accurately model the side-chains for those loops that show the best backbone RMSD using a variety of methods.

COMP 151

Subtype selectivity of the serotonin 5-HT2B receptor antagonists: Molecular modeling study

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Three 5-HT2 receptors (2A, 2B, 2C) are major drug targets such as schizophrenia, feeding disorders, perception, depression, migraines, hypertension, anxiety, hallucinogens, and gastrointestinal dysfunctions. The first 5HT2B/2C indol urea antagonist (SB-206553, pA2, 2B: 8.5, 2C: 8.3) exhibited >100-fold selectivity over the 2A. Conformational restriction within a six membered ring produced a 100-fold selectivity for the 5-HT2B receptors (pA2=7.27) over 2A/2C. To understand the subtype-selectivity, MembStruk and GenMSCDock were used to predict. The docking results show the sub-type selective key residues (2.53, 3.29, 4.60, 6.58). The simulations in a membrane environment reveal that the dissimilarity of water migration into the NPxxY motif (three times more waters in the agonist-bound structure) and the more fluctuation of agonist affect the conformational change upon activation differently. The refined 3D model would help the rational design of novel drugs for the 5-HT2B antagonists with higher subtype selectivity and lesser side effect.

COMP 152

Hologram QSAR studies on two types of PTP1B inhibitors

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In this research, two-dimensional quantitative structure-activity relationship (QSAR) studies for a set of protein tyrosine phosphatase 1B (PTP1B) inhibitors, which include 39 2-(oxalylamino) benzoic acid (OBA) and 60 benzofuran and benzothiophene biphenyls (BBB), were conducted using the hologram QSAR approach. The HQSAR models were systematically optimized by varying the molecular fragment sizes, the fragment sub-structural types, and the molecular hologram lengths to reduce the standard errors. The best HQSAR models were

statistically significant in the Leave-One-Out analysis: the correlation coefficient square (q2) are 0.751 and 0.715 for the OBA analogues and the BBB analogues, respectively. In comparison to the comparative molecular field analysis (CoMFA) models, the HQSAR models achieved a much better predictive ability. We believe that the two models are useful in high-throughput screening the promising inhibitors of PTP1B, given their high predictive ability and computational efficiency. The analysis of the key fragments identified by the HQSAR models can guide us to design more potent inhibitors.

COMP 153

Comparison of peptide simulations and NMR data: Effect of protein parameters, solvent model and salt

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Despite ongoing improvement in non-additive force fields, additive models remain an attractive alternative for simulation of long-time dynamics of biological systems. These models continue to evolve, and detailed validation of their accuracy remains a challenge. This presentation will focus on comparison of simulation and experimental data as a means to determine how the reliability of simulations is affected by choices such as protein parameter sets, solvent model and inclusion of salt effects.

COMP 154

Evaluating and improving molecular mechanics force fields by comparison of simulations with NMR experiments

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Molecular dynamics simulations and NMR spectroscopy provide complementary approaches to the study of protein structure and dynamics. We have carried out several long molecular dynamics simulations of globular proteins and compared the results to a range of NMR experiments that probe the structure and dynamics of these proteins. Such comparisons allow for the evaluation of the quality of the simulations and at the same time provide an atomistic interpretation of the NMR

experiments. Comparison of the results obtained using different commonly used molecular mechanics force fields show that recent modifications of these force fields significantly improve the agreement between simulation and experiments. The ability to perform long simulations of proteins in explicit solvent makes it possible to use such comparisons as part of the evaluation and development of force fields. Methods for how to use such comparisons in a direct improvement of force fields will be discussed.

COMP 155

Further development of a coarse-grained protein model coupled with a coarse-grained solvent model based on solvation properties of organic compounds

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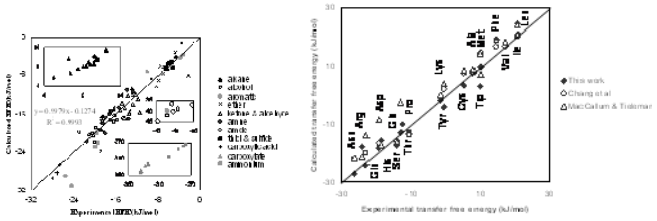
We have previously developed a coarse-grained (CG) protein model[1] for Ala, Gly, Leu and Val in tandem with a known CG water model,[2] and demonstrated its application to simulations of peptide secondary structures. We present here our further parametrization of the model that may enable us to study other amino acids and solvation of amino acids in different media. Bonded interactions were parameterized by comparison with conformational energies of organic compounds through quantum mechanics calculations. Non-bonded parameters were obtained by fitting experimental solvation free energies of pure organic liquid and organic compounds in water and n-octane through free energy perturbation calculation. In particular, 28 compounds including alkane, alcohol, aromatic, ether, ketone, aldehyde, amine, amide, thiol, sulfide, carboxylic acid and ammonium were used in parametrization by fitting solvation free energy in water. The average deviation from experimental values is about 0.6 kJ/mol. Moreover, the same parameters can reproduce the solvation free energy of another 76 compounds with a deviation of about 1.7 kJ/mol. We also calculated the transfer free energies of side chain analogues of 20 amino acids from water to cyclohexane with the optimized parameters. The average deviation from experiments is about 2.3 kJ/mol, which is slightly better than the results with all-atom force fields. It indicates that our current CG protein model may be useful to describe solvation change of amino acids which is associated with protein folding and protein-protein interactions.



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COMP 156

Toward a polarizable force field for membrane simulations

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We present a revised CHARMM force field for lipids based on the charge equilibration model for incorporating polarization effects into molecular dynamics simulations. The model addresses deficiencies in the dihedral, electrostatic, and Lennard-Jones (van der Waals) parameters. The revised force field has been applied to molecular dynamics simulations of higher alkanes ranging from hexane to pentadecane and bulk liquid properties including enthalpy of vaporization, density, isothermal compressibility, constant pressure heat capacity, and self-diffusion coefficient have been calculated. Extension to lipid bilayer simulations will be discussed using the lipid molecule dimyristoylphosphatidylcholine (DMPC), tetramethylammonium (TMA) and dimethylphosphate (DMP) as the model system. Application of the revised polarizable force field to DMPC bilayers demonstrates sound performance with respect to predicted surface area per headgroup and local chain dynamics as represented by deuterium order parameters. We will discuss the performance differences between the non-polarizable and the newly developed polarizable force field.

COMP 157

SAMPL-1: A true(r) test of modeling

A. Geoffrey Skillman*, OpenEye Scientific Software, 9D Bisbee Crt, Santa Fe, NM 87508*

SAMPL (Statistical Analysis of Modeling of Proteins and Ligands) was an attempt at a prospective, blind challenge using novel data from industry and academia.

Tested were virtual screening, pose prediction and affinity estimation for two systems, JNK3 kinase provided by Vertex Pharmaceuticals and Urokinase from Abbott Laboratories. In addition, sixty three vacuum to water transfer energies from Peter Guthrie of the University of Western Ontario were used as a test of solvation models. In total there were over two hundred submissions from academia, industry and software vendors. This presentation will cover the challenges faced in putting such an event together, what was learnt from the proceedings and the plans for SAMPL-2 in 2009.

COMP 158

Comprehensive analysis of hits from high-throughput and docking screens

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Quantitative high-throughput screens (qHTS) and molecular docking were used in parallel to discover novel inhibitors of the enzymes â-lactamase and cruzain. The mechanism of every active from a screen of 70,563 and 198,000 molecules, respectively, was determined, and the correspondence between the previous docking predictions and the true inhibitors determined. For this comparison it was critical to eliminate false-positive hits from the screen, including colloidal aggregators (90 to 95% of the initial hits), and promiscuous covalents (between 1 and 6% of the initial hits). Only with these eliminated could we compare the actives predicted by docking and measured by qHTS. Whereas docking had a high-false positive rate and, for cruzain, important false negatives, for both screens it correctly prioritized non-artifactual inhibitors among its top-ranked molecules. Structure-based methods may be useful to prioritize true ligands from HTS actives.

COMP 159

Validation using the RCSB: Good idea or bad idea?

***Paul Hawkins**, OpenEye Scientific Software, 9d Bisbee Court, Santa Fe, NM 87508, Fax: 505-473-0833*

Protein-ligand co-complexes from the RCSB database have been used in many studies on the quality of docking and conformer generation. However, due to the poor quality of some of the structures, many of their conclusions are invalid. This paper will discuss pitfalls associated with using structures from the RCSB for comparison or validation purposes. These pitfalls include local problems, such as poor quality fits to electron density (of ligand or protein), highly strained ligand structures and global issues such as lack of consideration of experimental error in the structural data. While nominal resolution has been frequently used for identifying good quality structures from the RCSB, much better assessments of quality can be obtained from global measures such as the diffraction-component precision index (DPI) and local measures including the real-space correlation coefficient. Consideration of these measures is mandatory when assembling a reliable set of structures for validation. Many of the problems associated with using ligand structures from the RCSB are eliminated when using small molecule crystal structures from the CCSD, as there is a much greater degree of precision in these structures.

With these issues in mind, datasets for validation of conformer generation applications derived from both the RCSB and the CCSD will be presented and the performance of a selection of methods on these datasets will be discussed using a number of different metrics.

COMP 160

Calculation of accurate protein geometries

James J P Stewart*, Stewart Computational Chemistry, 15210 Paddington Circle, Colorado Springs, CO 80921*

Because of technical difficulties associated with X-ray analysis of protein structures, most geometries deposited in the Protein Data Bank contain errors, for example hydrogen atoms are frequently omitted, or, if present, C-H and N-H bond lengths are often too short. Semiempirical methods have historically been of very limited usefulness in predicting polypeptide structures. However, the recently developed PM6 method has been demonstrated to of useful accuracy in predicting primary structure, and by use of a restraining function of the type proposed by Yu, Yennaway, and Merz, PM6 can now also generate accurate secondary and tertiary structures of proteins. The issues involved will be discussed and examples of improved protein structures given.

COMP 161

A high resolution view of protein, ligand and water interactions.

***Colin McMartin**, Thistlesoft, 603 Colebrook Rd., Colebrook, CT 06021*

I have been studying potency since 1964; the greatest limitation to progress remains lack of reliable information about structure and affinity.

This talk explores the use of structural information found in high resolution X-ray experiments.

Large amounts of reflection data are observed when a significant part of the unit cell is well-ordered. Even at high resolution, reliable coordinates are only obtained for parts of the structure which are well-ordered. These regions have low B-factors and full occupancy.

Values of bond angles, torsions, hydrogen bond and Van der Waals contacts were calculated for 730 PDB

(< 1.2 Angstrom resolution) and 9,000 small molecule structures. The B-factor filter gave values with variances which indicate an error of less than 0.05 Angstrom. The variation in core residues in 12 HIV structures shows an even lower error of < 0.01 Angstrom.

This data provides precise answers to many structural questions e.g.

Which motifs have well-defined values?

What is the range/average value of hydrogen bond lengths? How does water behave?

Are ligand-protein and protein-protein interactions similar?

COMP 162

Challenging the concept of protein folding units with in vitro folding data

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Trifonov's hypothesis that the basic protein folding unit is a closed loop of about 25 amino acid residues. is attractive because it elucidates the concept of a funnel, an elegant solution to the Levinthal paradox. Consequently, this hypothesis has been challenged against two of the most prominent experimental techniques used to study in vitro protein folding, namely phi value analysis, which can be used to infer the nature of the folding transition structure, and kinetics, which can be related to metrics calculated from the protein structure. From phi value analysis we note that the ends of the ~25 mer folding units tend to be

structured in the folding transition state. From the kinetics we note that the folding rate correlates with contact metrics evaluated only over residues associated with the ends of the ~25mer folding unit. Together, these results suggest that the residues that form the closed loops play an important role in determining the folding kinetics.

COMP 163

Kinase bioprints: Understanding, modeling and exploring kinase selectivity

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The problem of predicting kinase selectivity for specific kinase inhibitors or chemotypes requires either a traditional small molecule approach or a novel combination of bio- and chemo-informatic methods.

We have observed that kinase selectivity profiles can be understood from the fragment composition of active ligands. We have endeavored to predict the selectivity of compound sets by traditional small molecule QSAR approaches, using descriptors that denote molecular composition and substructures. Cheminformatics-based molecular descriptors are supplemented with sequence similarities, given the predictive value of sequence-derived information for understanding selectivity. The reliable prediction of potency and selectivity could allow for denovo-design of new compounds with desired profiles.

Using selectivity date from our chemogenomics database, statistical random forest models were developed for predicting potency and selectivity from sequence similarity and small molecule descriptors, and compared to more traditional models using only small molecule descriptors. These approaches are compared to Bayesian models of kinase selectivity based on frequencies of fragments. The models have been statistically validated using standard random splits of the data as well as prospective evaluation of new data. We have found that some cross-validation methods give over-optimistic expectations for prospective testing, while chronologically aware cross-validation tends to give the most accurate predictions. Prospective validation tests on 6 kinase targets yielded hit rates ranging from 20% to 100% depending on modeling method, novelty of the tested sets and kinase target. In the presentation we demonstrate the details of the sequence, small molecule based modeling approach, validation and specific statistical metrics we have introduced to properly evaluate the approach. We will also show an example of utilization of the validated and

qualified models and how one can utilize the available data to design a screening paradigm for related targets.

COMP 164

Gini coefficient: A new way to express selectivity of kinase inhibitors against a family of kinases

***Piotr P. Graczyk**, Department of Medicinal Chemistry, Eisai London Research Laboratories Limited, University College London, Gower Street, London WC1E 6BT, United Kingdom, Fax: +44 (0) 20 7413 1121*

Gini coefficient can provide a useful tool to quickly estimate the selectivity of kinase inhibitors against a large set of kinases. Nonselective inhibitors are characterized by Gini values close to zero (Staurosporine, Gini 0.150). Highly selective compounds exhibit Gini values close to 1 (PD184352 Gini 0.905). The method works for ATP-competitive and noncompetitive inhibitors. It uses single-point experimental data generated economically at the same, single ATP concentration for all kinases. It is population-independent so that, for instance, the Gini coefficient generated with a 50 kinase panel can be compared with the Gini coefficient obtained by screening against the panel of 100 kinases. Low selectivity, as determined by the Gini coefficient, can lead to increased toxicity observed in in vivo studies.

COMP 165

Seeking knowledge through the fog of information

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In the past decade, drug discovery efforts to kinases as targets have proliferated. Because of their importance to biological function and their amenity to structure-based design techniques, they continue to be appealing targets. However, these remain challenging targets, especially if trying to prospectively model compounds into their plastic binding sites, improving selectivity, or identifying opportunities for

chemical novelty. To augment our target-based drug discovery approaches, we have recently begun to derive ligand-based structure-activity, structure-property, and structure-patent knowledge. We have obtained access to a database of 2.9 million curated drug-like compounds, of which approximately 484,000 were associated with kinase patents and publications. For many of these, some measure of biological activity was included. We have begun the process of testing our accumulated experience of kinase drug design against this database, in an effort to separate the general from the anecdotal.

COMP 166

Selectivity in structure-based drug design: Tools for identifying similar sites in diverse proteins and pinpointing selectivity determinants

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We have developed two tools to guide selective ligand design, by identifying and comparing positions where ligand atoms can interact favorably with a protein. SimSite3D was designed to screen protein structures to identify binding sites with significantly similar shape and chemistry to a query, regardless of protein homology. CompSite then can analyze the pair of aligned structures to identify subsites that differ in chemistry, based on clustering. The significance of chemical differences is assessed by using DrugScore to score interactions with neighboring protein atoms. The result is identification of a set of interaction sites and steric volumes (formatted for molecular graphics visualization) that differ significantly between the proteins, as potential selectivity determinants. Interaction sites that are similar between proteins or conformations are also identified. Applications will be shown for identifying similar sites and specificity determinants for diverse ATP binding proteins, including protein kinases.

COMP 167

QSAR models for predicting the similarity in binding profiles for pairs of protein kinases

***Robert P. Sheridan**, Kiyean Nam, Vladimir N. Maiorov, Daniel R. McMasters, and Wendy D. Cornell, Molecular Systems, Merck Research Laboratories, P.O. Box 2000, RY50SW-100, Rahway, NJ 07065*

We propose a direct QSAR methodology to predict how similar the inhibitor-binding profiles of two protein kinases are likely to be based on the similarity of the properties of the residues surrounding the ATP-binding site. A model is produced for two sets of data: Kd's published by Karaman et al (Nature Biotechnology 2008, 26, 127-132) for 38 compounds on 200 kinases, and percent inhibition data on up to 900 in-house compounds tested on 30 to 51 kinases by the Dundee University DSTT Consortium. Each model is self-consistent by cross-validation and both models point to only a few residues in the active site of kinase controlling the binding profiles, however they do not agree on which residue is most important. We apply each model to predict the similarity in binding profile to all pairs in a set of 411 kinases from the human genome. While we do not believe either model is definitive, the approach is promising and can be applied to larger and better datasets when they become available.

COMP 168

A theoretical investigation of the absorption spectra of 1-methyl-4-phenyl-1H-tetrazole-5(4H)-thiones

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UV irradiation of tetrazolethiones results in the formation of a variety of products including isothiocyanates, azides, carbodiimides and diazridinethiones. However, the mechanism of the photodecomposition of tetrazolethiones or "tetrazolic" compounds in general, is poorly understood. In order to study potential energy surface involved in the photodecomposition of tetrazolethiones and determine the excited states that give rise to products, the electronic properties of these compounds needs to be fully investigated. Our experimental studies have revealed that the UV spectra of 1-methyl-4-phenyl-1H-tetrazole-5(4H)-thiones exhibit two bands λ_1 and λ_2. We have carried out the TDDFT calculations to determine the nature of transitions that give rise to these bands and our results indicate that the former is the result of π to π* excitation while the latter corresponds to an intramolecular charge transfer. We conclude that as the acceptor strength increases in the order: p-C_6H_4OMe < C_6H_5 < p-C_6H_4Cl < p-$C_6H_4NO_2$, the HOMO/HOMO-1 to LUMO gaps decrease and the CT increases.

COMP 169

Computational studies of unbridged dizinc compounds

Steven S. Hepperle *and Yan Alexander Wang, Department of Chemistry, University of British Columbia, 2036 Main Mall, Vancouver, BC V6T1Z1, Canada*

It has been four years since the first synthesis of the dizinc compound $Zn_2(\eta_5\text{-}C_5(CH_3)_5)_2$ from $Zn(\eta_5\text{-}C_5(CH_3)_5)(\eta_1\text{-}C_5(CH_3)_5)$ and $Zn(C_2H_5)_2$, and since then numerous theoretical papers have been published regarding the properties of this molecule. However, the mechanism of this reaction has yet to be elucidated. We have used Kohn-Sham computational methods to study a variety of different mechanistic possibilities for the formation of $Zn_2(\eta_5\text{-}C_5(CH_3)_5)_2$. In order to understand the plausibilities of each of these mechanisms, they will be further compared with pseudo-mechanisms for the synthesis of $Zn_2(\eta_5\text{-}C_5H_5)_2$ (which does not form experimentally). From these comparisons, a suitable rationalization of the role the methyl groups play in the formation of $Zn_2(\eta_5\text{-}C_5(CH_3)_5)_2$ can be inferred. Also, it has been found that only certain ZnR_2 reagents (R= C_2H_5, C_6H_5) react to form $Zn_2(\eta_5\text{-}C_5(CH_3)_5)_2$, and an analysis of this experimental data will also be included in this work.

COMP 170

High level ab initio calculations for glycyl and alanyl dipeptides

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We present the results of high level *ab initio* molecular orbital calculations on hydrogen-blocked or methyl-blocked glycyl and alanyl dipeptides. Fully relaxed 15 degree grids of the conventionally defined conformational space variables φ and ψ have been evaluated for the four molecules at the MP2/6-31G(d) level. Finding out the lowest energy path for φ (or ψ) to change from -180 to 180 degrees in the contour map we performed the MP4/6-311G(d,p)//MP2/6-31G(d) level calculation to get energy profiles for φ and ψ. The results were compared with higher level calculations by MP4/6-311++G(d,p)//MP2/6-31+G(d). The final profiles will be compared with the profiles obtained by the molecular mechanics with AMBER96 and AMBER99 force field.

COMP 171

First principles Monte Carlo simulations of fluid phase equilibria at extreme conditions

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We present a simulation framework in which a combination of modern Monte Carlo sampling methods are used in concert with standard electronic structure codes (CPMD and NWChem) to perform liquid-vapor and liquid-liquid coexistence calculations from first principles. The use of an approximate pre-sampling potential to generate large moves with a high probability of acceptance is critical to the method. Issues of system size, efficiency, correctness and load-balancing arising from the use of iterative density functional theory potentials are addressed both directly and through analysis of model systems. The method is applied to phase coexistence and (P,V,T) data in simple metals including lithium and sodium, as well as to other systems. The prospects for extension of this technique to more complex systems, solid-solid and solid-liquid phase equilibria is also discussed.

COMP 172

Interfacing ab initio quantum mechanical method with classical Drude oscillatorpolarizable model for molecular dynamics simulation of chemical reactions

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In order to further improve the accuracy and applicability of combined quantum mechanical/molecular mechanical (QM/MM) methods, we have interfaced ab initio QM method with the classical Drude oscillator polarizable MM force field (ai-QM/MM-Drude). Three coupling approaches have been employed: 1. the direct self-consistent-field (SCF) scheme, in which QM densities and MM Drude positions are converged simultaneously; 2. the micro-iterative SCF scheme, in which the Drude positions of the polarizable model are fully converged during each self-consistent field (SCF) step of QM calculations; 3. the one-step-Drude-update scheme, in which the MM Drude positions are updated only once instead of fully converged during each molecular dynamics (MD) step. All three coupling approaches are found to be efficient and can achieve the desired convergence in a similar number of QM SCF steps comparing with the corresponding QM method coupled to a non-polarizable force field. Our results indicate that the ai-QM/MM-Drude approach is very promising, which provides a better description of QM/MM interactions while can achieve quite similar computational efficiency in comparison with the corresponding conventional ab initio QM/MM method.

COMP 173

First principles study of ion transport across air/water interface

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Using first principles molecular dynamics (FPMD) simulations based on density functional theory, the molecular mechanism of ion (F^- and ClO_4^-) transport across the air/water interface was investigated. Surface enhancement of ClO_4^- near the Gibbs dividing surface (GDS) at the air/water interface was confirmed by computing the potential of mean force via FPMD. In addition, perturbation of interfacial properties (structural, dynamical, and electronic) in the presence of F^- or ClO_4^- will be discussed in detail.

COMP 174

A computational study of the coordination of nickel atoms to the surface of a single-walled carbon nanotube

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In order to investigate the role of metal atoms used as catalysts in growing single-walled carbon naontubes (SWNT's), the coordination of nickel atoms to a model tube have been studied. The tube is composed of 100 carbon atoms comprising an end-cap and the growing section of a tube in the armchair configuration. Optimization of a nickel atom on the surface of the tube was carried out using a mixed basis-set approach with the B3LYP level of theory and a basis set of m6-31G(d) for the nickel atom, 6-31G(d) for the six carbon atoms closest to the coordination site, and 3-21G for the remaining carbon atoms, and the hydrogen atoms used to terminate the tube. It was determined that the nickel atom is most thermodynamically stable at the point where the tube bends to terminate, and prefers to be in an η^2 coordination environment.

COMP 175

A density functional theory study of gas and condensed phase behavior of intermolecular complexes of sulfur oxides

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Intermolecular donor-acceptor complexes of sulfur oxides exhibit significant structural and property differences in the gas and condensed phases. Some of these complexes, including SO_3-H_2O and SO_3-NH_3, also are thought to be important species in atmospheric chemistry. Gas and condensed phase density functional calculations of donor-acceptor complexes formed between sulfur oxides and oxygen- and nitrogen-containing donor molecules have been performed in which the condensed phase was modeled using the Polarizable Continuum Model. Systematic studies of the differences between the gas and condensed phase geometries and other properties of the complexes are reported. The Natural Bond Orbital and Natural Resonance Theory methods have been employed in order to investigate the bonding of the complexes in the gas and condensed phases. The calculated bond orders exhibit significant differences in the gas and condensed phases, in some cases increasing by more than a factor of two in the condensed phase relative to the gas phase value.

COMP 176

A free web application for sharing resources about cyclodextrin/ligand complexes

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In most research fields, computer sciences and molecular modeling are invaluable tools to guide the design and help the interpretation of experimental determinations. This is not often verified for cyclodextrin related studies, which to date have often been performed without the support of any computational aid. To fill this gap we designed and implemented a software tool, based on web technologies, consisting in a free web application (CDLig, freely accessible at https://kdd.di.unito.it/casmedchem) and a Wiki site (= a software that allows users to create, edit, and link web pages easily, http://cyclodextrins.pbwiki.com/). The web application enables the search and the deposition of data of complexes between native/substituted cyclodextrins (CDs) with various ligands (L), whereas the Wiki site favors the sharing of information among scientists working in CDs research fields. In the first version of the application two kinds of data are supported: log K (K is the association constant of a CD/L complex in [M-1]) obtained by experimental measurements, and 3D structures in mol2 format resulting either from experimental data (e.g. NMR, X-ray) or from theoretical

studies. To participate to this initiative no particular computer science related skill/resource is required, apart from an Internet connection and a Web browser (e.g. Miscrosoft Explorer, Mozilla Firefox, etc.). After registration, any user can access the CDLig Wiki to gain some insights about the usage of the application and then can start searching the database and enter his own data to help the initiative to grow up. The high scientific level of the entries is guaranteed by the validation performed by an expert board of scientists affiliated with the Associazione Italiana Chimica e Tecnologia delle Ciclodestrine (http://www.cdtec.unito.it).

COMP 177

A Kirkwood-Buff derived force field for small amino acids in water by molecular dynamics simulations

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We describe molecular dynamics simulations of aqueous amino acid solutions based on the force field of fragmented salts corresponding to the ammonium group and the carbonyl group of each amino acid of different concentrations. These models are developed specifically to reproduce the experimentally determined Kirkwood-Buff integrals and solution activities as a function of solute concentration. In addition, experimental basic known properties are reproduced by these models.

COMP 178

A soft-sensor model of paper tensile strength

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In the all-physical properties of paper, the tensile strength is the most important one. At present the test method for sheet tensile strength is touching and breaking method that must be carried out off-line, the test results are behind the real process and it can't suitable to the modern high run speed paper machine.

A novel soft-sensor model was established to predict the sheet tensile strength which based on the function relations between the fiber geometry characteristics parameters and fiber bonding characteristics parameters aided with modern mathematics tools as well as the dynamics theory, Kubelka-Munk light scattering principles and PAGE equation theory. The results showed that the model had

good precision which standard error mean was about 8% and offered a strong theory support to realize real-time measuring the sheet tensile strength.

COMP 179

A theoretical study of hydrolysis of SO3 using a combined discrete-continuum model

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A theoretical study of hydrolysis of SO_3 using a combined discrete-continuum model

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The hydrolysis reaction of sulfur trioxide to form sulfuric acid is investigated using a mixed discrete-continuum model, in which the solute and a limited number of solvent molecules are treated quantum chemically and the remaining solvent is simulated by the polarizable continuum model (PCM) method. The results show that the discrete-continuum model can predict the solvation free energies of charged species within the chemical accuracy. We further explore the hydrolysis reaction of SO_3 in aqueous solution. Analyses reveal that the long-range solvation effects play a very important role. Compared to four water molecules in the pure cluster model [1], two explicit water molecules in the combined discrete-continuum model are enough to simulate the solvation effects accurately, which simplifies the study of the reaction mechanism.

[1] Larson, L. J.; Kuno, M.; Tao, F. M. Hydrolysis of sulfur trioxide to form sulfuric acid in small water clusters, *J. Chem. Phys.*, **2000**, 112(20): 8830.

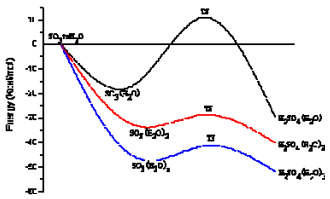

Fig. 1 Potential energy profiles in the continuum IEFPCM model

COMP 180

A virtual screen for diverse ligands: Discovery of selective G protein-coupled receptor antagonists

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Virtual screening has become a major focus of bioactive small molecule lead identification and reports of agonists and antagonists discovered via virtual methods are becoming more frequent. G protein-coupled receptors (GPCRs) are the one class of protein targets for which success with this approach has been limited. This is likely due to the paucity of detailed experimental information describing GPCR structure and the intrinsic function-associated structural flexibility of GPCRs which present major challenges in the application of receptor-based virtual screening. Here we describe an in silico methodology that diminishes the effects of structural uncertainty, allowing for more inclusive representation of a potential docking interaction with exogenous ligands. Using this approach, we screened one million compounds from a virtual database, and a diverse subgroup of one hundred compounds was selected leading to experimental identification of five structurally diverse antagonists of the thyrotropin-releasing hormone receptors (TRH-R1 and TRH-R2). The chirality of most potent chemotype was demonstrated to be important in its binding affinity to TRH receptors; the most potent stereoisomer was noted to have a 13-fold selectivity for TRH-R1 over TRH-R2. A comprehensive mutational analysis of key amino acid residues that form the putative binding pocket of TRH receptors further verified the binding modality of these small molecule antagonists. The described virtual screening approach may prove applicable in the search for novel small molecules agonists and antagonists of other GPCRs.

COMP 181

All-atom additive CHARMM force field for furanose carbohydrates

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We present the parametrization of monosaccharide furanoses for the CHARMM force field. Carbohydrates are one of the four major building blocks in living things and participate in many biological mechanisms, by utilizing the process of molecular recognition performed by glycoproteins. Previously, several force fields have been developed for carbohydrates, but these force fields lack the ability to describe the structure and dynamics necessary for the simulation of large carbohydrate-containing biological systems. The internal parameters are fit to reproduce vibrational spectra and gas-phase quantum mechanical (QM) conformational energies at the MP2/cc-pVTZ//MP2/6-31g(d) level. The non-bonded parameters are fit to reproduce heats of vaporization, condensed-phase molecular volumes, water and rare gas interactions and crystal simulation results. The dihedral energies are parametrized to reproduce QM energies of 1900 conformations using a Monte Carlo simulated-annealing formalism developed by Guvench and MacKerell. This force field will allow investigations of the structure-function relationship of glycoproteins and glycolipids.

COMP 182

An efficient search protocol for mapping potential energy landscapes and conformations of alpha-helix- and beta-sheet-rich polypeptides

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We recently developed new molecular dynamics protocols for protein folding simulations called disrupted velocity (DIVE) search simulations. The simulations can explore a diverse set of conformations on the potential energy surface of a peptide. We illustrate the new MD simulations by investigating the global and local potential energy minima of several alpha-helix- and beta-sheet-rich polypeptides. Results demonstrate that DIVE simulations can efficiently sample widely different regions of conformational space.

COMP 183

Analysis of biological fingerprint data using molecular equivalence indices

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Molecular Equivalence Indices (MEQI) are a class of 2-D descriptors which describes molecular aspects at various resolutions. The program parses a chemical structure into five major categories: complete 2D-structure, cyclic system, rings, side chains and functional groups. Each chemotype is identified by a code that uniquely identifies that chemotype. Searching using MEQI provides a variety of information regarding the structural and topological features contained in the molecules such as cyclic systems, ring systems and functional groups. This study analyzes published affinity data of several compounds profiled in different gene families and will focus on chemical features that are important for selectivity and polypharmacology.

COMP 184

Applying computational titration to selective nitration of tyrosines

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Computational Titration is a tool for optimizing hydrogen placement in molecular models, including adjusting ionization states of acidic/basic residues and functional groups. It is based on the HINT program that calculates the free energies of non-covalent interactions between organic and biological molecules. HINT uses experimentally-obtained octanol/water partition coefficients of small molecules to quantify hydrophobic and hydrophilic interactions, implicitly taking desolvation and entropic effects into account. We are studying selective nitration of tyrosines in proteins using HINT and Computational Titration. In biological systems tyrosines can get nitrated in response to many factors. Some get nitrated and denitrated very specifically, participating in cell signaling. Gaining an insight into which tyrosines get nitrated and under what conditions is important for the understanding of the biological significance of these events. Our computational analysis reveals some of the structural and chemical conditions leading to tyrosine nitration within proteins.

COMP 185

Atomic detail investigation of the denaturation of RNA by urea via molecular dynamics simulations

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Urea titration experiments are helpful in deriving the unfolding/folding free energies and in obtaining information about the pathway of unfolding of proteins and nucleic acids. MD simulations of a 22-nt RNA hairpin in aqueous solution and in several concentrations of urea (1-8M) were performed to elucidate the structural and energetic basis of the denaturation of RNA by urea. At higher concentrations of urea, the hairpin undergoes denaturation consistent with experimental studies. Surprisingly, at lower concentrations (1 and 2M), the hairpin was observed to be more stable than in aqueous solution. Various structural, energetic and solvation properties were analyzed to understand the mechanism of the interaction of urea with the hairpin. It was observed that urea does not directly facilitate the opening of the base pairs, but stabilizes the open states via direct hydrogen bonding and stacking interactions thereby stabilizing the denatured form of RNA.

COMP 186

Avogadro: A framework for quantum chemistry simulation and visualization

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The Avogadro project is an open source approach to building chemical structures. It uses external simulation packages in addition to integrated analysis and visualization. The work presented here illustrates a new approach to working with the results of quantum mechanical simulations by rapidly displaying all possible molecular orbitals and allowing the user to select orbitals of interest.

Other aspects of the Avogadro program allow the user to prepare new jobs for various quantum packages such as GAMESS-US, GAMESS-UK, Gaussian and Molpro. Due to the plugin based nature of the Avogadro project many specialized options can be added for a large range of applications, such as molecular

docking. Specific results will include electronic structure and molecule/surface binding.

COMP 187

Bioinformatics analysis and molecular modeling of the enoyl-acyl carrier protein reductase (ENR) of Staphylococcus aureus

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Frequent outbreaks of the super-bacteria such as methicillin-resistant Staphylococcus aureus (MRSA) have been a major public health problem. Recently, in the United States, MRSA infections tend to attribute more deaths than HIV/AIDS. For treatment against MRSA, Tuberculosis and Malaria, three of major infectious problems of the world, there have been extensive research about selective antibacterial action of bacterial enoyl-acyl carrier protein reductase (ENR) inhibitor. This protein has been considered as an attractive potential drug target due to a low homology with a related mammalian enzyme. Here, we constructed a homology model structure of ENR from MRSA sequence using multiple templates of the ENR's of Helicobacter pylori, Escherichia coli and Mycobacterium Tuberculosis. Docking simulations of the refined structure with several known ENR inhibitors were carried out and the ligand binding affinity were evaluated using the molecular mechanics Generalized-Born surface area (MM-GBSA) method using the several snapshots of the molecular dynamic simulations. The calculated binding free energy of inhibitors showed good correlation with available experimental inhibition activities. The contribution of each of the residues to the total binding free energy was estimated with residue decomposition analysis. Based on this result, we investigate the characteristics of interaction features of the model protein with its inhibitors and recognize the important binding residues in its active site. This information would be useful for rational structure-based design toward the finding of new ENR-inhibitors and hence discovery of new Staphylococcus aureus antibiotics.

COMP 188

Block copolymers fluid-fluid phase separation: A coarse grained molecular dynamics study.

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The diblock copolymers have been widely seen in experiments to self-assemble in water giving a variety of morphologies. Our interest are focused in a system consisting of a mixture of neutral and charged diblock copolymer in a lamellar phase. We have employed coarse grained molecular dynamics simulation to study a system composed by a binary mixture of two dissimilar diblock copolymers having a common hydrophobic block but containing, at the hydrophilic region, sites with different interaction parameters which mimic the charged group. We observed phase separation of the two hydrophilic block yielding patchy assemblages. The structure and distribution of the obtained patches were related with the length of the hydrophobic tails and the interaction strength of the different block with water and between them as well as the hydrophilic versus hydrophobic composition.

COMP 189

Building aromatic oligoamide foldamers: Applications in computational chemistry

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Abstract text not available.

COMP 190

Calculation of ligand conformational free energy change upon binding

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Upon binding to the receptor, the conformation that a ligand adopts may differ from its lowest-energy conformation in unbound state. Besides, bound ligand is restricted in certain configuration, which will result a configurational entropy loss. The conformational free energy loss due to these effects is either neglected or treated inaccurately in most docking program. Here we present a new method to

analysis this free energy loss. The method starts with a low energy well identification by conformational search protocol. Free energy of each well is then calculated by free energy perturbation (FEP) using a quasiharmonic (QH) reference system. Comparing free energy between all possible wells in unbound state and bound state well, we can estimate the conformational energy loss upon binding. This method was applied to a set of 260 protein-ligand complexes. Whether this correction term improves current docking score was also examined.

COMP 191

Characterization of structural and dynamic properties of the SHP-2 tyrosine phosphatase via molecular dynamics simulation study

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Non-receptor protein tyrosine phosphatase SHP-2 participates in intracellular signal transduction and plays an important role in variety of cellular processes. Low-molecular weight compounds can bind to the catalytic site and specifically inhibit SHP-2 enzymatic activity. We used molecular dynamics (MD) simulations to better understand structural and dynamic properties that contribute to the biochemical activity of the SHP-2 protein as well as identify novel binding sites for small drug-like inhibitors of SHP-2 protein. These molecules may have the potential to serve as research tools in identifying therapeutic agents for the diseases like Noonan syndrome and childhood leukemia thus leading to the rational drug design.

COMP 192

Characterization of the membrane-bound structure of the Influenza HA2 fusion peptide from MD simulations

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The fusion peptide is the only part of the Influenza hemagglutinin A directly in contact with the endosomal membrane during the infection process. Its structure at the fusogenic pH presents two helices with a kink angle [Han et al., Nat. Struct. Biol. 8, p. 715 (2001)]. Site-directed spin-label EPR spectroscopy indicate that the plan formed by the two helices lies along the bilayer's normal, with the residue N12 at the phosphate groups level and the extremities deeply inserted in the bilayer. Many studies demonstrated that this particular shape is essential for fusogenic activities. However, recent MD simulations suggest a single-helix structure is adopted at the membrane interface. Extended MD simulations were

produced to elucidate the structure of the fusion domain in lipid bilayers. Our results show that the kink is conserved, but the plane of the peptide lies in the bilayer's plane. A complete analysis of the fusion peptide structure will be presented, with the emphasis on the interactions promoting the kinked structure.

COMP 193

CHARMM Polarizable Force Field for sulfur containing compounds based on the classical Drude oscillator

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The advantage of a polarizable empirical force field over an additive model is that it allows for an electronic response to the local environment. Towards development of a polarizable force field for biological molecules parameters for a series of sulfur-containing molecules were optimized. Optimization was performed to reproduce ab initio and experimental values for geometries, conformational energies, vibrational spectra, molecular volumes, dipole moments, heats of vaporization, and free energies of hydration. The training set includes methanethiol, ethanethiol, propanethiol, ethylmethylsulfide, and dimethyldisulfide. The molecular volumes and heats of vaporization are in good accordance with experimental values. The new force field paves the way for more accurate simulation studies of sulfur-containing molecules as well as cysteine and methionine residues in proteins.

COMP 194

Coarse-grain molecular dynamics of increasingly complex protein systems: Tetrapeptides, rhodopsin, and bacterial chemotaxis

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Coarse-grain molecular dynamics (CGMD) is a reduced model approach that expands existing all-atom (AA) MD techniques. Temporal and spatial scales can

be extended by a factor of 1000 at the expense of atomistic details. CG parameters are derived using tetrapeptides as a model protein system. Physicochemical information from AAMD simulations, such as bond lengths, bond angles, and torsions, is used to derive CG parameters. CGMD simulations of tetrapeptides using the derived parameters, as well as parameters derived from PDB structures of proteins are carried out where comparisons are made. CGMD is performed on two transmembrane systems: the photosensing GPCR rhodopsin and the bacterial chemotaxis system. Comparisons of the translational and rotational orientation of each helix in the membrane between CGMD and AAMD simulations are made in which the resulting forcefield will be further refined and ultimately validated. The CG forcefield is also further developed (in bacterial chemotaxis) to understand how ligand binding to the periplasmic domain of the chemoreceptor sends the signal to modulate kinase activity inside the cell via a piston-type displacement of a single α-helix in the periplasmic and transmembrane domains.

COMP 195

Combinatorial QSAR analysis of 5HT-7 receptor agonists and its application to virtual screening

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5HT-7 receptor is involved in the pathogenesis of neuropsychiatric and other diseases. In this connection, selective agonists of 5HT-7 receptor are promising to the treatment of schizophrenia and other emotional and psychic disturbances. We have applied a combinatorial QSAR modeling approach to 63 chemically diverse 5HT-7 receptor agonists. MolConnZ and DRAGON based descriptors were combined with kNN and DWD approaches independently to achieve models with the highest external predictive power. In addition, we have also built classification kNN QSAR models using 63 5HT-7 receptor agonists and 70 non-binders. Validated QSAR models were then used to mine the World Drug Index database totaling over 54,000 compounds. Virtual screening identified 19 consensus hits and the experimental validations are currently underway.

COMP 196

Combined property clustering and GC+ techniques for molecular synthesis

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Identifying the molecular structures that satisfy a given set of property constraints is a typical problem in chemical industry. Numerous works have already been done to extend the property integration framework to include group contribution (GC)methods for solving the molecular design problem. But, there are molecular groups whose property contributions are not estimated in group contribution methods. Recently, techniques have been developed to create such missing groups and their property contributions through a set of zero order and first order connectivity indices (GC+ approach). In this contribution, a methodology has been introduced to combine property clustering techniques and GC+ approach to generate molecular structures which satisfy a given set of property constraints. The advantage of this method is we are not limited to the molecular groups whose GC properties are known. This contribution will illustrate the developed methods and highlight their use through a case study.

COMP 197

Combining docking, molecular dynamics and the linear interaction energy method to predict binding modes and affinities for nonnucleoside inhibitors to HIV-1 reverse transcriptase

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HIV reverse transcriptase (HIV-RT) is one of the promising targets in the development of drugs against AIDS. Several drugs are already used in AIDS therapy, but a major problem is that drug resistant mutants arise quickly after treatment is initiated. In the case of HIV-RT, where a large amount of crystallographic data is available, computational structure-based drug design is a promising approach to identify possible drug candidates. In this work, docking, molecular dynamics (MD) and the linear interaction energy (LIE) method are used to predict binding modes and estimate binding free energies for HIV-1 RT inhibitors. Using the LIE method, the experimental binding free energies are reproduced with a correlation coefficient of 0.7 and an unsigned average error of 0.8 kcal/mol. The calculations illustrate that a combination of docking, MD, and LIE can be a powerful tool in computational inhibitor design.

COMP 198

Comparing maximum common substructure search methods

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The assessment of molecular similarity and diversity is widely used in various steps of the drug discovery process. Traditionally, molecular similarity is evaluated by the rapid comparisons of fingerprints. Fingerprints effectively encode local structural features; however, they fall short in describing more than local similarities, since they are unable to express the relative position of the encoded functional groups. Maximum common substructure (MCS) search provides an alternative method to quantify molecular similarity, in which the full molecular connectivity is taken into account. Additionally, the atom mapping calculated by the MCS search can be used to solve important cheminformatics problems such as automatic reaction mapping.

OEChem provides two methods to detect maximum common substructures. The exhaustive method is based on a back-tracking algorithm in which the atom mapping of two structures is systematically extended and evaluated by using either one of the built-in or a user-defined scoring function. Due to the computational complexity of the MCS problem, applying the exhaustive search to a large set of complex structures is not practical. In order to reduce the computational cost, a rapid approximate MCS search method was also devised. The approximate method is based on traversing through predefined paths of a query structure and trying to map the visited atoms onto target atoms.

Comparing the two methods for thousands of structures revealed that the approximate method provides a good trade-off between speed and accuracy. The poster will give details of the two search methods and their comparisons along with possible applications such as automatic R-group decomposition.

COMP 199

Computational model for predicting chemical substituent effects on passive drug permeability across parallel artificial membranes

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Permeability is often a limiting step in drug action. In this work the effect of chemical substituents on passive permeability across parallel artificial membranes was studied for the congeneric series of benzoic acid, pyridine and quinoline. Computational models were built to explain the permeability of these

series based on molecular descriptors. The relevant descriptors for the benzoic acids with neutral acid groups were also important for the pyridines and quinolines. Considering that the permeability of the benzoic acids is about two orders of magnitude lower than the pyridines and quinolines and that a change of pKa of about 2 units of the acid group of benzoic acid will make the neutral species dominant at the experimental pH (6.5), the results suggest that the additional energy barrier for the permeation of the benzoic acids is associated with the need to protonate the acid group which may then cross the hydrophobic membrane.

COMP 200

Computational tools for the prediction of ligand efficacy in the ß$_2$-adrenergic receptor

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G protein-coupled receptors (GPCRs) form the largest superfamily of cell surface receptors in nature and represent very attractive drug targets for a variety of conditions. The crystal structures of rhodopsin and the ß$_2$-adrenergic receptor - the only two members of the superfamily for which high resolution 3D information exists - argue in favor of the existence of a conserved 7TM core among GPCRs. The exact mechanism of GPCR agonist-induced activation has not been fully elucidated and there is no straightforward way to predict the efficacy of ligands. Here, the ß$_2$-adrenergic receptor and a training set of compounds with known efficacy are used as a model GPCR system for the identification of parameters that correlate with ligand efficacy. This model can then possibly be used for the development of in silico tools for the discrimination between agonists, antagonists, and inverse agonists.

COMP 201

Computer-assisted discovery of small molecule inhibitors of the uPAR/uPA interaction: A target in tumor invasion and metastasis

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The urokinase receptor (uPAR) is a GPI-anchored cell surface receptor that focuses proteolysis at the cell surface through its association with the serine protease urokinase. uPAR has also been found to associate with various cell surface receptors that include integrins, receptor tyrosine kinases and G-coupled protein receptors (GPCRs). We have targeted these protein-protein interactions with small molecules identified through computational screening of libraries of compounds. This screening was guided by our web-based target-specific customizable scoring function tools. Top compounds from virtual screening were obtained and tested in the lab using fluorescence polarization binding assay. Active compounds from binding assay were further tested with cell based assay. We found several that inhibited MDA-MB-231 breast tumor cell proliferation, migration, invasion and adhesion. Inhibition of tumor cell migration and adhesion in particular suggested that these compounds also inhibit the interaction between uPAR and integrins at the cell surface, despite the distal nature of the integrin and uPA binding sites on uPAR. This suggests that inhibition of the protein-protein interaction occurs through an allosteric mechanism. Extensive molecular dynamics simulations of uPAR complexes in the presence of various ligands bound to the uPA binding site revealed that uPAR is a highly dynamic macromolecule whose interactions can be allosterically modulated. Consistent with experimental observations, the results show that the uPA binding site of uPAR can be exploited to modulate distal interactions of the receptor with other proteins

COMP 202

Concept of druggability and active site properties

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We evaluated a recently published method of druggability prediction (Cheng et al., Nature Biotechnology 2007, 8, 71) using an expanded set of Protein Data Bank entries. The set included 50 entries from the Cheng et al. paper and 40 additional entries compiled from the literature. We found that "druggability" is too vague a concept and that Cheng's approach seems to predict active site "bindability." We also developed a complementary approach to quantify druggability by exploration of the correlation of physical properties between

active sites and their ligands in terms of total volume, area, percent hydrophobicity and solvent exposure. We showed that in general hydrophobic and deep active sites are associated with better ligand binding. A protocol was developed to quantitatively characterize binding pockets of any protein 3D structure in the context of data available for the known targets. These characteristics of potential active sites seem to be useful during the search for new targets.

COMP 203

Condensed phase testing of force fields using crystal simulations

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The all-atom additive CHARMM force fields have been successfully used to simulate a variety of biological systems. In an effort to implement a model which can respond to dynamic biological environments, a polarizable force field based on classical Drude oscillator has recently been introduced. To facilitate optimization and evaluation of the polarizable force field, crystal calculations are of particular utility due to their ability to monitor individual atomic interactions in a condensed phase environment. We have carried out crystal simulations using both the CHARMM additive force field and the new polarizable force fields on crystal structures of N-methylacetamide, dipeptides, cyclic peptides, and peptidic mu-opioid ligands. Results from those calculations will be presented.

COMP 204

Deciphering membrane permeabilizing function of purothionins with molecular dynamics simulations

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We utilized high precision molecular dynamics (MD) simulations to study molecular motions and conformational changes of wheat â1-purothionin in the presence of anions to investigate membrane permeabilizing activity. Several hypotheses have been proposed, yet the mechanism of membrane permeabilizing activity remains to be solved. Using MD simulations, we found the

evidence pointing to the mechanism of membrane permeabilizing activity for â1-purothionin. Anions triggered dynamic and conformational changes in á1 and á2 helices. Interaction of anions with L1 loop caused series of 2- to 5-ps-long unfolding of the á1 C-end. An increase of anion density at the R5-R30-G42 hydrogen-bonding network triggered series of 2-ps-long unfolding of the á2 C-end. Simultaneous increase of anion density at the á1 C-end and á2 N-end triggered the largest conformational changes with a predominantly unfolded á2 C-end and formation of two new cavities. One cavity was formed by the unfolded á2 C-end, and another cavity appeared in a middle of the large hydrophobic area between á1 and á2 helices. Persisting water molecules formed strong hydrogen bonds with the peptide in both cavities. The former cavity was periodically reaching Y13, which is situated in the peptide core, protruding inside of the peptide toward the second cavity. These data point to formation of a water-permeable channel in the peptide starting at the positively charged outer corner and ending in the middle of hydrophobic region, triggered by a negative charge. We will present a hypothetical scheme of the mechanism of membrane permeabilization for â1-purothionin.8-->

COMP 205

Developing a Kirkwood-Buff force field for methanethiol

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A molecular mechanics force field for methanethiol will be presented. The force field was developed from experimental activity coefficients of a methanethiol/methanol mixture, and molecular dynamics simulations, and it is based on the Kirkwood-Buff theory of solutions. Possible applications on the modeling of sulfur-containing peptides and on the separation of sulfur-containing compounds from petroleum will be discussed.

COMP 206

Development of AM1 specific reaction parameters for aldehyde dehydrogenase enzymatic chemistry

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We will describe our strategy for re-parameterizing the AM1 method to calculate, with considerably improved accuracy, various intermolecular interactions and reactions important to Aldehyde Dehydrogenase (ALDH) chemistry. The “fitness” of a particular AM1 parameter set was evaluated by comparison to properties collected from either published experimental results or high-level Quantum Mechanical (QM) calculations. This reference data includes geometries, dipole moments, ionization potentials, heats of formation and reaction energies. Various non-linear search algorithms were then employed to search for parameter sets that best reproduce the reference data using a modified version of the DYNAMO library (www.pdynamo.org). Finally, the use of these parameters in QM/MM simulations of ALDH reactions will be presented.

COMP 207

Development of linear scaling semiempirical quantum models

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Methods for the rapid calculation of semiempirical models is discussed with emphasis on linear scaling techniques. A new advancement in the divide-and-conquer method is explored which involves the reduction of the buffer region through the use of charge dependent nonbonded effective potentials. The new method is applied to large biomolecules, and the timing profiles are compared with traditional linear scaling methods.

COMP 208

DNA pol λ R517 mutant simulations indicate 517's crucial role in ternary complex stability and suggest DNA slippage origin

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DNA polymerase λ (pol λ) utilizes DNA motion and active-site residue rearrangements to transition between its active and inactive states. Pol λ also generates many deletions resulting from DNA template-strand slippage. An understanding of these features requires connecting the atomic-level structural changes to the observed biochemical functions. Our simulations of pol λ ternary complexes of 517 mutants (Lys, Glu, His, Met, Gln, Ala) reveal discrete

orientations of the 517 residue with respect to the DNA and associated interactions that explain the wide range of mutant-dependent DNA motion observed: (WT < [R517K ~ R517H ~ R517Q] < [R517E ~ R517A ~ R517M]). This motion critically impacts the stability of the ternary complex. The close connection between DNA movement and active-site residue changes suggests that pol λ's architecture facilitates deletions because small variations in the active-site (e.g., orientation of 517) can have large effects on the dynamics of the ternary complex.

COMP 209

Drug discovery of dihydroorotase using virtual high throughput screening system

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Dihydroorotase (DHOase), which catalyzes the third step reaction in pyrimidine nucleotide biosynthesis, has become a target for the development of anti-proliferation drugs. Here we used a virtual high-throughput screening (vHTS) system developed in our lab to identify inhibitors of the enzyme which may become lead compounds as potential drug candidates. In particular, we first combined this system with SURFLEX to screen about 3,000,000 compounds from the ZINC database. The top five hundred compounds were then docked and re-evaluated using four docking tools: AUTODOCK3, DOCK5, SURFLEX and GOLD. Among the top fifty hits selected by these four programs, purchasable compounds were examined by enzyme assays and the best inhibitor identified so far has an IC50 of ~14μM.

COMP 210

Effect of hydrogen-bonding strengths in various foldamer building blocks on the conformational distribution of aromatic oligomers

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Hydrogen bonding is known to play an important role in biological secondary structures, such as alpha-helices and beta-sheets. In synthetic foldamers, which

mimic naturally occurring polymers, the same principles that govern the conformations of biofoldamers are used. In this study, we investigate the intramolecular hydrogen-bonding ability of model aromatic amides with varying H-bonded ring size, i.e. 5-membered, 6-membered and 7-membered H-bonded ring systems, and its effect on the conformational distributions of the aromatic oligomers. We have developed a systematic scheme using a combination of quantum mechanics and molecular dynamics simulations to estimate the strengths of hydrogen bonds and their effect on the conformational distributions of the aromatic oligomers. In addition, we modified the GAFF (general AMBER force field) parameters for this class of compounds and applied them in the molecular dynamics simulations. This study is aimed to provide further insights in the design of aromatic foldamers.

COMP 211

Efficient calculation of absolute solvation free energies from quasi-chemical theory

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Quasi-chemical theory, introduced by Pratt and coworkers, exactly partitions molecular solvation free energies into inner-shell and outer-shell contributions. The inner-shell portion represents the direct chemical interactions of the solvent with the solute. The outer-shell free energy includes both packing and long-ranged components. The packing part is the free energy of solvation for a hard sphere whose radius is that of the inner/outer- shell partitioning. The long-ranged contribution represents the difference between the solvation free energy of a hard sphere and that of a solute- occupied hard sphere. As the size of the hard sphere radius is increased, the distribution of interaction energies for the long-ranged term approaches a Gaussian form. Here we exploit this observation to develop an efficient method to calculate that long-ranged contribution to the free energy from a molecular dynamics simulation. A repulsive but continuous model potential is employed for the sampling, and we find that the averages of two bounding mean-field terms yield accurate estimates of the free energy, due to the near-cancellation of fluctuation terms. Thus the absolute solvation free energies can be obtained from relatively short simulations. These techniques are applied to nonpolar and polar molecule solvation.

COMP 212

Electronic structure and vibrational analysis of calcium and zinc cluster anions: A hybrid density functional approach

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The structure, electronic states with their vibrational analysis of cluster anions and neutral clusters containing up to 19 calcium atoms and up to 9 zinc atoms were optimized within the hybrid density functional approach. Based on these results, the electron affinities (EA) for all these cluster sizes were calculated and compared with published experimental work. This comparison is excellent displaying the EA experimental kink observed in calcium. This kink occurs because the neutral 10-atom cluster is very stable whereas the anion cluster of the same size is not very stable. Additionally, the theoretical electron detachment binding energies (BE) were calculated for calcium and zinc cluster anions containing up to six atoms. These calculations are in excellent agreement with photoelectron detachment experimental results. For several cluster sizes the theoretical predictions of the BE display additional peaks that are not present in the published experimental data.

COMP 213

Energy analysis of paper mill based on three-link model

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According to the paper mill characteristics, the energy system of the paper mill was classified into three-system (three-links): energy-conversion link, energy-use link and energy-recovery link. The physical three-link model and mathematical three-link model for a paper mill in South China was established and the three-link models in 2005 and 2007 were compared. The analysis results showed the energy efficiency was enhanced through equipments update, and the mill wide energy optimization system was point out to improve energy efficiency and reduce exergy loss.

COMP 214

Evaluation of density functionals, semiempirical methods, and new parameter sets for zinc bio- and nanocenters

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We present relativistic benchmark parameter databases, obtained by coupled cluster calculations, of Zn-ligand bond distances, dipole moments and bond dissociation energies in Zn coordination compounds with O, S, NH3, H2O, SCH3, OH, H, halogen, methyl and ethyl ligands. These benchmarks are used to test the predictions of four density functionals and six semiempirical methods, including neglect of differential overlap (NDO) calculations incorporating new PM3 parameter sets developed especially for Zn. We examine the efficacy of these new parameter sets compared to established DFT and WFT methods, and we specify the most accurate methods for our test data, toward the development of new semiempirical methods that will be especially accurate for Zn coordination centers and for simulations of zinc macromolecules.

COMP 215

Explicit molecular dynamics simulations of kissing loop motif formed between TAR-RNA element of HIV-1 and aptamer

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Kissing loops(KL) found in nature have significant role in viral transcription and building block for nano-devices. The molecular architecture of RNA culminates in kissing loops that are hydrogen bonded motifs comprising of at least two hairpins. Molecular dynamics using Amber 9, investigates the fundamental study of the formation of kissing loops in terms of the directional hydrogen bonding and ionic environment which allows hairpin molecules to conform to the minimum energy states. Individual components of the KL were simulated separately under identical conditions. The stabilized single chains were subjected to the targeted molecular dynamics technique that reveals the development of KL from the individual components. The self assembled stable structure with estimated molecular dynamics parameters was used as a reference for the simulations. This study has impact on health and nanotechnology.

COMP 216

Exploring L1 Ligase intrinsic flexibility and its impact for catalysis

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L1 Ligase aptazyme 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 known ribozyme ligases that make non-canonical base pairs with their substrate at the ligation site. L1 Ligaze is organized in three stems (A,B and C) joined by a three-way junction.Two conformers of the ligation product of the I1x6c construct were resolved in the same crystal structure [Robertson and Scott, Science 315 (2007) 1549] – one of them thought to be in an active form (stems A and C are docked) and the other in an inactive conformation (stems A and C undocked). We investigate the solution structures obtained from more than 500 ns of large-scale explicit solvent Molecular Dynamics simulations starting from the two product conformations found in crystal and several modeled reactant states. In the undocked conformation Stem C shows a large degree of intrinsic flexibility (with deviations of up to 15 A with respect to crystal structure) making specific contacts with Stem B. These contacts are intermediated by the 95% conserved U19 base and are not revealed by the crystal structure. The non-canonically base-paired ligation site shows a high degree of variability observed in visting several states characterized by specific hydrogen bond networks that are sometimes intermediated by water molecules and/or magnesium ions. We correlate these different states with the in-line attack fitness of the ligation site.

COMP 217

Field induced partial charges for ligands: Impact on molecular dynamics simulations and estimated interaction energies

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Impact of ligand polarization on interaction energies and MD simulations has been explored in this study. To estimate the contribution of ligand polarization (electronic) to the interaction energies, partial atomic charges for a series of HIV-1 protease ligands was derived by fitting to the ESP (RESP) calculated in the presence of the protein environment represented as a static field. The study also aims to discuss the impact of the charging process on molecular dynamics trajectories and estimated interaction energies. Further, the interaction energy is decomposed to estimate the percent of the polarization contribution accounted for by this protocol.

COMP 218

High incidence of ubiquitin-like domains in human ubiquitin-specific proteases

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Ubiquitin-specific proteases (USPs) emerge as key regulators of numerous cellular processes and account for the bulk of human deubiquitinating enzymes (DUBs). Their modular structure, mostly annotated by sequence homology, is believed to determine substrate recognition and subcellular localization. Currently, a large proportion of known human USP sequences are annotated neither structurally nor functionally, including regions both within and flanking their catalytic cores. To extend the current understanding of human USPs, we applied consensus fold recognition to the unannotated content of the human USP family. The most interesting discovery was the marked presence of reliably predicted ubiquitin-like (UBL) domains in this family of enzymes. The presence of multiple UBL domains per USP protein, as well as of UBL domains embedded in the USP catalytic core, add to the structural complexity currently recognized for many DUBs.

COMP 219

High performance cheminformatics: Squeezing performance out of chemical file I/O

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There are many chemical information file formats in common use today. They all have their own unique strengths and weaknesses. However, few can support the throughput necessary for high throughput virtual screening on compute clusters. This is further complicated by the fact that databases are growing in size to the point where they can only be stored on slow network-attached-storage devices. In this poster we will describe the use of multi-threading techniques to alleviate the high I/O overhead of chemical file formats. Performance will be compared to on-the-fly compression methods alone and in combination with multi-threading. We will present data assessing the costs and benefits of each method in common cheminformatics computing environments ranging from multi-core personal desktops to high performance compute clusters.

COMP 220

Hydration free energy calculations: Testing force fields and identifying systematic errors

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Hydration free energies are valuable as a test of the accuracy of force fields, and a tool for identifying systematic errors. We discuss recent work calculating hydration free energies in implicit and explicit solvent for a set of 504 small molecules with known hydration free energies, using the general Amber force field (GAFF). We discuss the separation of the explicit solvent results into nonpolar and electrostatic components and find that the correlation with surface area is nearly zero, and we discuss the explanation. We use the explicit solvent results to identify some systematic errors in GAFF and suggest some fixes, notably for alkynes. We also discuss the application of free energy methods to predict hydration free energies in a blind test.

COMP 221

Identification of privileged fragments using in-silico molecules fragmentation methods: The case for CNS penetrant molecules

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The in-silico molecular fragmentation is being proposed as an effective and efficient way to extract useful information from specific sets of molecules. Examples reported in literature describe the identification of privileged fragments occurring more frequently within molecules active at particular targets -or target class- compared to fragments present within inactive ones. Such privileged fragments can then be “translated” into appropriate reagents to be used for synthesizing focused arrays of molecules. During our research work both retro-synthetic, and rings/linkers based fragmentation methods were used for fragmenting appropriate sets of molecules with the aim to identify core fragments

(fragments with multiple attachment points). Both standard and ad-hoc computational implementation were used for this part of the process. Such cores were then evaluated in light of their potential use in the synthesis of CNS penetrant molecules where “novelty”, developability criteria and physicochemical properties are the important ranking factors. The objective of this paper is to highlight the pros and cons of such general approach as well as critically review the results obtained.

COMP 222

Impact of mutation on the proton-coupled electron transfer reaction catalyzed by soybean lipoxygenase

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The hydrogen abstraction catalyzed by soybean lipoxygenase (SLO) occurs by a proton coupled-electron transfer (PCET) mechanism. Experimental kinetic studies indicate that the deuterium kinetic isotope effect (KIE) for this reaction is ~80 at room temperature and exhibits weak temperature dependence. Kinetic studies also show that mutation of Ile 553 in SLO can significantly alter the magnitude and the temperature dependence of the KIE for this reaction. We have studied the wild-type and mutant SLO with a vibronically nonadiabatic theory of PCET that includes quantum effects of the electrons and transferring proton. The reorganization energy and the proton donor-acceptor distance and vibrational frequency are determined from molecular dynamics simulations that include the entire solvated protein. The vibronic couplings are calculated with quantum mechanical methods for a model system. The calculations illustrate the impact of mutation on the various quantities in the PCET rate constant expression. This theoretical treatment indicates that the magnitude and temperature dependence of the KIE depend on the proton donor-acceptor distance and vibrational frequency, as well as the overlap between the reactant and product proton vibrational wavefunctions.

COMP 223

Influence of charge models on binding free energy calculations using the linear interaction energy method

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Electrostatic interactions are important in ligand binding, and they are often the key to explaining relative binding free energies among chemically related ligands. Here, a number of quantum chemical charge models, both ab initio and semi-empirical, are evaluated with regard to their usefulness in binding free energy calculations with the linear interaction energy (LIE) method. The LIE method has previously been successfully applied in combination with molecular dynamics (MD) simulations to a series of HIV-1 reverse transcriptase inhibitors. Ten such inhibitors have been selected as test compounds to monitor the effect of varying the partial charges on the binding free energy estimates. Nine different charge derivation methods, and one continuum polarization model, are used to obtain 23 different partial charge sets. These charge sets are compared to each other and their applicability in MD simulations are discussed. To estimate binding free energies for the ten ligands using the different charge sets, over 800 ns of MD simulation is conducted in total. The results from these extensive simulations highlight the usefulness of semiempirical charge models as valid alternatives for deriving charges. The semiempirical charge models have the benefit of being fast and may hence be used to assign partial charges in large compound libraries for screening with the LIE method.

COMP 224

Insights into the association and interaction of cohesin-dockerin complex in cellulosome assembly

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The organization and assembly of cellulosome, an extracellular multi-enzyme complex produced by anaerobic bacteria, is mediated by the high-affinity interaction of cohesin domains from scaffolding proteins with dockerins of cellulosomal enzymes. We have performed molecular dynamics simulations on both the wild type (WT) and D39N mutant of the C. thermocellum cohesin-dockerin complex. The simulations reveal significant differences in their conformations and protein flexibility. The simulations indicate that D39N mutation likely causes a change of the hydrogen-bonding network in the recognition strips, the conserved loop regions previously proposed to be involved in binding, presumably through the electrostatic or salt-bridge interactions between the loops and the helix-3 of the dockerin. Such alteration triggers significant flexibility of the recognition strips. Results of the root-mean-square fluctuation analysis and principal component analysis corroborate the above findings. Additional free energy perturbation estimate for the D39N point mutation yields a 4.8 kcal/mol difference in binding energy, in reasonable agreement with the values determined experimentally. The free energy profile of cohesin-dockerin association in bulk was also estimated using adaptive biasing force approach.

The preliminary results show an overall 12 kcal/mol barrier and also reveal two critical steps of cohesin-dockerin association.

COMP 225

Investigations into mechanism of drug interaction with lipid bilayer

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

COMP 226

Hamiltonian replica exchange molecular dynamics and its application to biologically relevant protein motions

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Replica exchange molecular dynamics is gaining popularity as a computational method which enhances conformational sampling. However, limitations to this

method are also becoming evident. In order to cover a desired temperature range, an increase in the number of replicas proportional to the square root of the number of atoms is necessary, and temperature fluctuations can cause instability in the protein and also do not necessarily accelerate sampling of motions of interest. To overcome these limitations and sample specific protein motions, we have implemented Hamiltonian replica exchange molecular dynamics in AMBER to enhance sampling of conformational changes in proteins. A scaled biasing potential is added to the force field to enhance sampling along a replica coordinate. The results and sensitivity to parameters will be discussed.

COMP 227

Mapping protein binding domain and small molecule interactions

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A well-defined paradigm exists for predicting the ability of small molecules to interact with a protein surface, yet current computational methods for small molecule docking have both theoretical and computational limitations. Advancements in algorithms continue to reduce computational complexity and optimize the scoring of posed molecules, yet studies show that differing methods produce accurate results for only a small set of problems (i.e., no docking methodology or scoring functions can be universally and successfully applied). To address this challenge, we combine evolutionary analysis of protein binding sites with cheminformatics obtained from petascale computational docking experiments to create libraries of protein-ligand interaction data. We present results applying this analysis to identify inhibitors for pathogenic targets solved at the Midwest Center for Structural Genomics.

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COMP 228

Molecular dynamics of proteins embedded in lipid bilayers

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Membranes and their embedded ion channels play a crucial role in numerous cell processes such as signaling, energy conversion, and ion conductance. In particular, ion channels regulate the ionic concentration by selectively allowing certain ionic species, such as Na+, Ca2+, and K+, to be transported down their electrochemical gradient and across the membrane. They are pore-forming proteins that are ubiquitous in basic cell function as well as intercellular communications. In order to understand the structural and dynamical aspects of peptide assembly within lipid bilayers in large temporal and spatial scales, a series of coarse grain (CG) molecular dynamics (MD) simulations of four synthetic transmembrane peptides were performed. From these simulations, it can be concluded that the formation of ion channels are both enthalphically and entropically driven. By understanding the assembly of peptides in membranes, it will help facilitate the design of antimicrobial, antiviral, and other pharmaceutical agents which will target ion channels. Also, it will provide a detailed description of the biophysical properties of membranes.

COMP 229

Molecular dynamics simulations of potential antimicrobial peptides in their membrane-bound state

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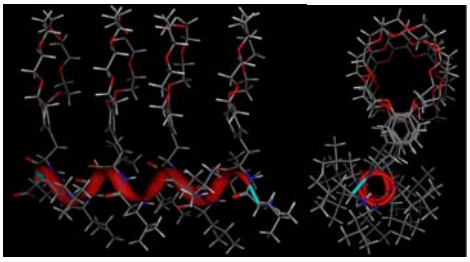

Since bacterial resistance is a public health concern, two potential antimicrobial compounds have been developed and recently characterized [Ouellet M., Otis F., Voyer N. and Auger M., Biochimica et Biophysica Acta 1758 (2006) 1235]. Those are small peptides composed of 14 and 21 amino acids, leucines and

phenylalanines modified by addition of crown ethers (see Figures). Experimental results demonstrated that these macromolecules have a strong antimicrobial potential and, on the basis on NMR studies, mechanisms of action have been proposed. However, despite rigorous experimental protocols, the accurate descriptions of peptide-membranes interactions are difficult to obtain and proposed mechanisms remain hypothetic. So, to shed light on the membrane insertion of these novel peptides, we performed molecular dynamics simulations in both implicit and explicit environments. We present our exhaustive investigations and the resulting analysis compared with experiment.

COMP 230

Multicomponent nucleation: From mechanisms to applications

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This poster will showcase our research output regarding both fundamental and applied aspects of nucleation research. Using the AVUS-HR approach, we found that binary mixtures (n-nonane / 1-alcohol series) could nucleate via several unique mechanisms, namely, mutual nucleation, multichannel/reluctant conucleation, and independent nucleation. We have also performed pioneering investigations of ternary nucleation to examine the unusual mixing behavior for these systems. We noticed that increasing the aliphatic chain of the surfactant/amphiphile (alcohol) could effectively increase the miscibility of two immiscible compounds such as water (polar) and n-nonane (nonpolar). Lastly, interesting application involving extraterrestrial atmospheric profiling was done.

COMP 231

Native-state guided method to overcome the diffusion sampling problem in generalized ensemble simulations

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Generalized ensemble based simulation methods are becoming increasingly popular in computational physics, because they can accelerate canonical sampling by smoothing ragged energy surfaces. Even though the flattened energy surfaces allow faster barriers crossings, spatially unspecific surface smoothing can increase the volumes of diffusion spaces dramatically, particularly

in the systems of high dimensionalities. Therefore, in the generalized ensemble based simulations, the energy barrier crossing problem, in which the essential transitions are blocked by energy barriers, is converted to the diffusion sampling problem, in which essential transitions become rare events in the enlarged diffusion spaces. To overcome such diffusion-sampling problem, we develop a native-state guided Langevin dynamics (NSGLD) strategy. As demonstrated in our model studies, this NSGLD strategy can greatly improve the sampling efficiencies in generalized ensemble simulations so as to possibly play an essential role in dealing with the present bottleneck of generalized ensemble method developments: the system size limitations.

COMP 232

New anticancer agents: De novo design from HINT complementary maps

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A new algorithm for the de novo generation of small molecules within the binding site of a protein is described. The algorithm is based on HINT paradigm for identifying binding sites using 3D hydropathic complementary maps, which indicate the hydropathic “field” of an “ideally” interacting ligand for the binding site. Molecular fragments, selected from a library are docked into the binding site as isolated units. All the possible fragment additions are evaluated according to the HINT force field and the best scoring fragments are chosen. The best-scoring fragments are then connected using a scaffold library to form molecules. The HINT score for the interaction between the ligand and protein is then optimized by translations and rotations. The libraries used in this presentation were gleaned from a series of tubulin-binding small molecules that are presumed to bind in the colchicine site and disrupt polymerization. These molecules are based on a pyrrole scaffold that has very high synthetic flexibility.

COMP 233

Optimizing models for protein-ligand interactions using a hydrophobic force field: Application to design of novel probes for ERK2

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Although docking methods have been extremely helpful in identifying molecules that might bind to predefined binding pockets on proteins, better models could be developed by optimizing the protein-ligand interactions – particularly hydrophobic interactions. An algorithm has been developed that utilizes the HINT (Hydropathic INTeraction) force field and finds optimum conformations for side chains of amino acid residues in close proximity to a docked ligand. Extracellular signal-Regulated Kinase 2 (ERK2) is a Mitogen-Activated Protein Kinase (MAP Kinase) involved in the activation of several nuclear transcription factors and cytosolic enzymes. Molecules have been designed to bind to the ‘CD domain' of ERK2. A molecular modeling study has been conducted, wherein the designed ligands have been docked into the CD domain and scored using the HINT force field. An application of the new algorithm in optimizing models in the docking study shall be discussed herein.

COMP 234

Phase behavior and diffusional dynamics of driven nonequilibrium liquid crystals

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The liquid crystal phase behavior of a liquid comprised of hard spherocylindrical particles is probed via molecular dynamics. Hard spherocylindrical particles are known to exhibit liquid crystal phases when the particles are geometrically anisotropic [McGrother, Williams and Jackson, J. Chem. Phys, 104 (1996) 6755]. Spherocylindrical particles are modeled as cylinders capped by hemispheres. Their properties depend strongly on the ratio of the length of the principal axis of the cylinder to the diameter of the hemispheres. Larger aspect ratios give rise to richer liquid crystal phase behavior. Nematogens in the fluid are driven by an external rotating electric eld. The frequency of the rotation of the fi eld is varied and the resulting frequency-dependent phase behavior of the fluid along with dynamical properties are elucidated. The phase of the resulting fluid is determined using the nematic order parameter as well as higher order radial distribution functions. From these simulations, a better understanding of driven liquid crystal systems can be ascertained.

COMP 235

Polarizable empirical force field parameters for nitrogen containing heteroaromatic compounds

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The polarizable empirical CHARMM force field based on the classical Drude oscillator has been extended to heteroaromatic compounds that are take part in

the structure of biologically significant molecules. The compounds considered are: pyridine, pyrimidine, pyrrole, imidazole, indole and purine. Optimization of all parameters was performed against quantum mechanical and experimental data. Ab initio data was used for determination of the electrostatic parameters, the vibrational analysis, and in the optimization of the relative magnitudes of the Lennard-Jones parameters, through computations of the interactions of rare gases with model compounds. The absolute values of the Lennard-Jones parameters were determined by comparing computed and experimental heats of vaporization, molecular volumes, free energies of hydration and dielectric constants. The newly developed parameters were extensively tested against additional experimental data such as diffusion constants, heat capacities at constant pressure and isothermal compressibilities including data as a function of temperature, whenever experimental data was available.

COMP 236

Pose scaling: Geometrical assessment of ligand binding poses

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In virtual database screening compounds that are predicted to bind outside of the putative binding site may receive favorable energy scores leading to their selection as hits for experimental studies. However, such compounds may not have the desired biological activity due to their not being located in the targeted binding site. A descriptor, the pose scaling factor, is proposed to quantitatively evaluate ligand binding poses with respect to their geometrical match with the targeted binding site. In addition, the pose scaling factor can be used to rescale other scoring functions and quantitatively describe the location of a ligand without viewing the structure. This provides a convenient way to monitor the docking results of a huge compound database and will be of utility to refine docking algorithms and scoring functions.

COMP 237

Prediction of ionization constants for complex multicenter electrolytes utilizing proprietary "in-house" data

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The methodology of ionization constants prediction, utilizing a sophisticated procedure of deriving the baseline pKa values and the subsequent application of the ‘Trainable Model' concept is presented. Data set of 18,000 compounds with experimental pKa measurements, a database of 4,600 ionization centers (including environment) and a set of ca. 500 various interaction constants are used to derive the initial set of ionization micro- and macroconstants for all possible ionization centers. Predicted baseline values are further corrected according to experimental data for similar compounds in the dataset, yielding final pKa predictions that allow the simulation of complete distribution plot of all protonation states of the molecule at different pH conditions. In addition, this methodology allows prediction reliability estimation (evaluation of the Model Applicability Domain) and provides industrial users with a unique possibility to expand the Model Applicability Domain with the help of any user-defined proprietary ‘in-house' databases of experimental pKa values.

COMP 238

Probing the effects of heterogeneity on delocalized π π interaction energies

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Dimers composed of benzene (Bz), 1,3,5-triazine (Tz), cyanogen (Cy) and diacetylene (Di) are used to examine the effects of heterogeneity at the molecular level and at the cluster level on pi...pi stacking energies. The MP2 complete basis set (CBS) limits for the interaction energies (E_{int}) of these model systems were determined with extrapolation techniques designed for correlation consistent basis sets. CCSD(T) calculations were used to correct for higher-order correlation effects which are as large as +2.81 kcal mol^{-1}. The introduction of nitrogen atoms into the parallel-slipped dimers of the aforementioned molecules causes significant changes to E_{int}. Symmetry-adapted perturbation theory

calculations reveal a correlation between the electrostatic component of E_{int} and the large increase in the interaction energy for the mixed dimers. However, all components (exchange, inductions, dispersion) must be considered to rationalize the observed trend.

COMP 239

Proton transfer reactions in Ketosteroid Isomerase

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A hybrid quantum/classical molecular dynamics approach was used to investigate the mechanisms of proton transfer reactions in Δ^5-3-ketosteroid isomerase (KSI). KSI catalyzes the allylic isomerization reaction of 3-oxo-Δ^5-steroids to their conjugate Δ^4-isomers at a rate approaching the diffusion limit. The reaction follows a two-step mechanism involving the formation of a dienolate intermediate stabilized by hydrogen bonds. Free energy profiles were obtained along a collective reaction coordinate for both proton transfer steps. The electrostatic potential of the enzyme was analyzed along the reaction coordinate. Thermally averaged distances between the substrate and key residues in the active site were calculated along the collective reaction coordinate to identify conformational changes that facilitate the proton transfer reactions. This analysis illustrates the impact of hydrogen bonding interactions on the conformational changes coupled to proton transfer. These calculations provide insight into the roles of enzyme motion and hydrogen bonding interactions in enzyme catalysis.

COMP 240

QM/MM solvation using the Poisson-Boltzmann equation

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A method of solving the mixed quantum mechanical/molecular mechanical (QM/MM) Hamiltonian in solution, using the Poisson-Boltzmann (PB) equation to calculate partial charges and solvation free energies is presented. This method combines a linear scaling divide and conquer semi-empirical algorithm with the PB equation in a QM/MM framework, allowing only a specified region's charges to be polarized by the solvent while using fixed charges from a MM force field for the remaining system. The solvation free energy of several pentapeptides capped with an acetyl group (ACE) at the N-terminus and an N-methylamine

group at the C-terminus (NME) were used to study the accuracy of this method as well as three small protein systems. The solvation free energies for the QM/MM implementation compare well with a full QM treatment of the same system, giving reasonable representations of the solvation free energy of the entire system. Possible applications for this method include protein-ligand binding and reaction mechanism studies.

COMP 241

QSAR study of insect repellents from terpenoids

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Low-toxicity mosquito repellent and aphid antifeedant can smooth the corresponding concerns regarding to human health and food safety. A new kind of insect repellents (both mosquito repellent and aphid antifeedant) is synthesized from α- and β-pinene in natural terpenoid compounds. Preliminary biological tests show the promising results. In this study, statistic modeling is built using Codessa in order to reveal the quantitative relationship between the chemical structures and the biological activities. From QSAR modeling, chemical insights toward how to improve the biolgical activities may supply the guidance for the further synthetic work.

COMP 242

Quantum chemistry study of single molecule conductivity on silicon surfaces

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First-principles simulations of STM images have been used to understand the factors that influence molecular conductance. In styrene lines on H-covered Si(100), the rings at chain ends are found to be fluxional, favoring structures with rings that are arranged perpendicularly. Simulated STM images show that the molecular conductivity is highly dependent on conformation, and bright spots at the end of styrene lines indicate the perpendicular conformation. The model

reproduces the experimental observed variation in conductance with distance from a negatively charged dangling bond.

Comparing styrene, phenyl acetylene and benzaldehyde on H-covered Si(111) shows that the attachment chemistry has a great impact on conductance. A new STM scanning protocol was used to obtain chemical contrast among these molecules.

COMP 243

Reactivation via water removal of OH- inhibited [Fe-Fe]-hydrogenase H-cluster

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This poster provides reaction enthalpies, entropies, and free energies for the elementary reaction steps of reactivation pathway I and II in both gas and aqueous enzyme phase. For the gas phase, reactivation pathway I undergoes reduction, protonation, and water removal. In spite of the observed spontaneity for protonation and water removal, the overall pathway I is nevertheless hindered from being completed due to the endergonic reductive step. Reactivation pathway II (for gas phase) proceeds by proton transfer, water removal, and reduction. As opposed to pathway I, the reactivation of pathway II proceeds exergonically. For the aqueous enzyme phase, reactivation pathway I shows that only the protonation step occurs spontaneously, hence the overall reaction does not proceed to completion. The same overall nonspontaneity is found to occur for reactivation pathway II. For the aqueous enzyme phase, the results for the overall nonspontaneous reactivation pathway I and II do make sense in that they agrees with the observed behavior of [Fe-Fe]-hydrogenase H-cluster in the presence of air.

COMP 244

Refined homology model of human monoacylglycerol lipase: Toward a selective inhibitor

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The serine esterase monoacylglycerol lipase (MGL) is primarily responsible for the metabolism of the signaling lipid 2-arachidonoylglycerol (2-AG), an endocannabinoid with full agonist activity at both cannabinoid receptors. MGL is

considered to have therapeutic potential in the treatment of pain, inflammation and neurodegenerative and immune disorders. However, the lack of structural information has hindered the development of MGL-selective inhibitors. Here, we describe a fully refined homology model of MGL. Molecular dynamics simulations of the proposed structure were performed and key modes identified. Docked poses of both the natural substrate and known inhibitors were also explored. A comparison of the MGL binding site to that of fatty acid amide hydrolase (FAAH) highlights essential differences, which can provide crucial insight toward the design of selective MGL inhibitors as potential drugs.

COMP 245

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

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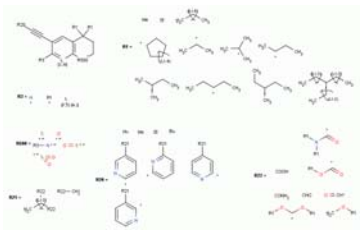
Cheminformatics systems usually focus primarily on handling specific molecules and reactions. However, generic (Markush) structures are also indispensable in various areas, like combinatorial library design or chemical patent applications for the description of compound classes. The presentation will discuss how an existing molecule drawing tool (Marvin) and chemical database engine (JChem Base/Cartridge) are extended to handle generic features (R-group definitions, atom and bond lists and link nodes). Markush structures can be drawn and visualized in the Marvin sketcher and viewer, registered in the database and their library space is searchable without the enumeration of library members. Different enumeration methods allow the analysis of Markush structures and their enumerated libraries. These methods include full, partial and random enumerations as well as calculation of the library size with arbitrary precision. Patent documents often involve further generic features, for example position and homology variation and bridged R-group definitions. The representation of these features will be discussed, as well as a future extension of the system towards full patent handling. The figure below shows an example Markush structure containing atom lists, R-groups and link nodes. This generic structure represents 4.1×10^{11} molecules.



COMP 246

Simulation study of RNA-binding protein by fragment molecular orbital (FMO) method

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RNA-binding protein (RBP) is one of protein group, which manages the quality of RNA molecules in living cell. RBPs, binding the target RNA by sequence or structure specific manner, are involved in RNA stabilization/destabilization, localization, translational control, splicing etc.

Biochemical studies have revealed the target sequence and the function of each RBP. In addition, structural biology shows the architecture of protein-RNA binding. These structural studies offer qualitative view of RNA recognition mechanism of RBP but not quantitative one, so physico-chemical studies on RBPs are required for deeper understanding of RBP function.

In this study, we employ fragment molecular orbital (FMO) method to perform quantum chemical calculation of Protein-RNA complex and analyze inter- and intra-molecule interaction based on its electronic state, and then refer quantitatively the properties of RBP from the aspect of physical chemistry.

COMP 247

Stabilities of the secondary structures of point mutated miniprotein Trp-cage via molecular dynamics study

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Molecular dynamics provides detailed images and trajectories of peptide/protein structures and movements, which can be used to investigate the properties of peptide/protein in a molecular level. Trp-cage, a mimiprotein containing 20 amino

acid, has attract much attention these days. Studying on this short protein has provided valuable information on protein folding mechanism since small size and fast folding nature make it fall into the capable scope for both experiments and computer simulation. Using MD simulation with explicit solvent, we here investigate the thermodynamic properties, such as free energy difference, of various mutated Trp-cage mimiprotein to reveal how point mutation affects the stability of protein secondary structures. By looking at the atomic resolution of the equilibrated structure, we will also trace the chemical driving force that causes the stability changes in the protein component mutation.

COMP 248

Study of [Fe-Fe]-hydrogenase H-cluster by means of polarizable continuum model

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Hydrogenases (such as Desulfovibrio desulfuricans hydrogenase) are enzymes that reduce protons to hydrogen (contributing to physiological energy storage). The eventual elucidation of the catalytic mechanism of hydrogen synthesis may be helpful in production of clean hydrogen fuel for the future using certain anaerobic prokaryotes or green algae. The H-cluster (Fe6S6 cluster) is the [Fe-Fe]-hydrogenase active site. To date, many gas phase studies have been performed on native and synthetic H-clusters using computational methods, such as density functional theory; however, little is known about the influence of solvent on H-cluster reactivity. Therefore, the polarizable continuum model is utilized to study the solvated H-cluster undergoing oxygen poisoning. The free energy difference between gas and aqueous phase essentially results form the solvation free energy, which is rather small for neutral clusters. However, for charged clusters the phase free energy difference is about five times larger.

COMP 249

The effect of substituents on conformational preference in a model arylamide compound

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Synthetic oligomers have been of great interest within the past decade. We investigate synthetic oligomers comprising of benzene rings connected by peptide bonds, which can be designed to have medical functions. The torsions around the backbone bonds of these molecules control their shape, which in turn controls their biological function. Therefore, our focus is on the torsions around the backbone bonds and how the nature of substituents influences these internal motions.

Presented here is a study of ortho-methoxy benzamide derivatives with side chains on the amide nitrogen systematically grown. Using a combination of QM, MD and NMR methods, we studies the influence of the charge and size of the substituent on the amide N atom, on the torsion around the $C_{aromatic}$-$C_{peptide}$ bond. The implications on the flexibility of the related oligomers in aqueous solution will be presented.

COMP 250

The transition between the closed and semi-open form of apo HIV-1 protease through the rearrangement of hydrophobic cores

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Abstract Anti-viral treatment has made a dramatic increase in the survival of AIDS patients; however, the success of conventional long-treatment therapies has been limited due to the emergence of drug-resistant mutants of HIV-1. Therefore, complete understanding of the structure and molecular dynamics associated with the conformational changes of HIV-1 protease is crucial in rational design of more effective treatment regimes. The flap regions of the protease, which exhibit much higher flexibility than other regions in apo HIV-1 protease, are believed to control the access to the active site; therefore a prime target of anti-AIDS drugs. We previously reported a series of simulations in implicit solvent that provide a model for flap dynamics, with spontaneous conversions between the bound and unbound crystal forms upon addition or removal of an inhibitor. In this work, one microsecond, unrestrained, all-atom molecular dynamics simulations with an explicit solvent model were performed on a wild type HIV-1 protease using the Amberff99SB force field. The flaps showed complex dynamics and various flap conformations (closed, semi-open, open and curled) during the simulations. Significantly, we observed not only multiple conversions among different states of the flaps, but also well reproduced

the two major crystallographic forms of HIV-protease with flap Root-mean-square deviations (RMSD) less than 2Å from two crystal structures. The global dynamics obtained from these explicit solvent MD simulations agree very well with those from X-ray and NMR observations and our previous implicit solvent simulations. Our simulations gain insights into the flap conformational changes that are associated with the function of this enzyme. We propose that the rearrangement of intra- and inter- monomer hydrophobic clusters triggers the transition of the flap conformations.

COMP 251

Theoretical calculations based on Brueckner method for geometrical structures and barrier heights of methylamine

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Accurate electronic energies and structural parameters of the staggered, eclipsed and planar conformers of methylamine were determined using Brueckner Double method including triples and quadruples contribution with the correlation-consistent polarized-valence double, triple and quadruple basis sets. Also we compared the computed barrier heights for torsion and inversion with available experimental observation and previous coupled cluster calculations with doubles and triples contribution.

COMP 252

Theoretical identification of adsorption products of multifunctional organic molecules on Si(001): Energetics and simulated STM images

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Organic functionalization of Si (001) surface has potential for realizing novel applications of hybrid semiconductor materials, such as electronic devices and chemical sensor. Recently, the reaction of a family of molecules relatede to acetyl acetone, RCOCH2COR (R=H, CF3, C(CH3)3) on Si(001) surface, have been experimentally studied. Some of these molecules are used as ligands for the deposition of metals or metal oxides. These molecules all have the same functional groups as acetyl acetone (R=H), but differ by non-reactive substituents. The multiple functional groups make their surface chemistry quite complex. This paper describes DFT calculations of the structure and energetics

for all possible surface species. STM simulations based on these calculations are compared to the features observed in STM experiments and the specific structures are assigned to each feature. The effect of the substituents on adsorption energy and molecular conductivity are discussed.

COMP 253

Theoretical studies of static field enhanced SFG spectroscopy at aqueous interfaces

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The primary goal of spectroscopy is to obtain molecularly detailed information about the system under study. Sum frequency generation (SFG) vibrational spectroscopy is a nonlinear optical technique that is highly interface specific, and is therefore a powerful tool for probing interface structure and dynamics. SFG is a second order, electronically nonresonant, polarization experiment and is therefore dipole forbidden in isotropic media such as a bulk liquid. Interfaces however, serve to break the symmetry and produce a signal. The alignment of the interfacial molecules in the presence of a charged species gives rise to a noticeable enhancement in intensity of the O-H stretching region of the SFG spectra. Theoretical approximations to the SFG spectrum of O-H stretching at charged interfaces are constructed using time correlation function methods. Detailed comparisons of theoretical spectra are made with those obtained experimentally. This work builds on our success in understanding the SFG spectra of aqueous interfaces.

COMP 254

Theoretical study of quinol oxidation via proton-coupled electron transfer

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The magnitudes and temperature dependences of the kinetic isotope effects (KIEs) are examined for quinol oxidation by a photoactivated ruthenium complex. This reaction occurs by a proton-coupled electron transfer mechanism, in which the quinol simultaneously transfers an electron to the ruthenium and a proton to the pyridyl-benzimidazolate ligand. The oxidation of two similar quinol species, a ubiquinol analogue and a plastoquinol analogue, has been studied experimentally. The experiments indicate that the magnitudes and temperature

dependences of the KIEs for these two quinols are qualitatively different. We use a multistate continuum theory for proton-coupled electron transfer to calculate the KIEs for these reactions. This theory includes the quantum mechanical effects of the electrons and the transferring proton, as well as the reorganization of the solvent environment. Our calculations provide insight into the underlying physical principles dictating the experimentally observed differences for the oxidation of the two quinols.

COMP 255

Topomer CoMFA directed Topomer search

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Topomer CoMFA®-directed topomer search provides a capability to screen for active R-groups based on 3D-QSAR potency predictions as well as shape similarity. For a given Topomer CoMFA model the number of fragments identified by the search increases both with increasing topomeric distance cutoff, as well as with decreasing the minimum number of heavy atoms required for fragmentation. The effect of changes in both of these parameters on the number of hits and the highest predicted potencies of R-groups found from a large subset of the ZINC database will be presented. Performance benchmarks for these changes, as well as improvements from not including all of the training set molecules in the query will also be presented.

COMP 256

Uncover the mechanism of synthesized drug candidates for Alzheimer's disease using MD simulations

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The deposition of the amyloid fibrils which have a particular cross β-pattern structure is the major character of Alzheimer's Disease. Using the all-atom molecular dynamics we studied four recently developed drug candidates for AD. Our simulations show that the active compound, LRL22, stabilizes the hydrophobic core (residues 18-23) and part of the turn (residues 26-27) of the $A\beta_{1-42}$ monomer to their α-helical conformations. While the non-active compound, LRL27, fails to do so. The other two compounds, K162 (EC_{50} = 0.85 nM) and K182 (EC_{50} > 1000 nM), show the similar stabilization effect, but K182 is less effective than K162. And all compounds can destabilize the cross β structure. These results indicate that stabilizing α conformation of the monomer can reverse the formation of amyloid fibrils and the hydrophobic core of $A\beta_{1-42}$ peptide is important in forming the amyloid fibrils, which shines lights on developing new drugs against AD.

COMP 257

Understanding self-assembly of RNA motifs into nanostructures

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RNA molecules can be engineered into novel nanostructutures using the straightforward molecular recognition properties of base pairing. However, the structures are not determined by base pairing alone and unpaired residues play a critical role in nanodesign and superassembly. Yet there is a limited understanding of the rules of formation of RNA superstructures. For successful design we need to understand and control the intermolecular associations, natural tendency, favorability and various physical components. We use molecular modeling to understand self-assembly processes of natural and synthetic RNA. We discovered that in most organisms the loop-loop assembly process depends on the presence of electronegative and hydration pocket. The size of this pocket and RNA sequence determines the stability, the hydrogen bonding interactions and the angle of the distinct kink between stems. Using these angles we can engineer the assembly of RNA building blocks via kissing loops motifs into nanostructures of a predefined geometry.

COMP 258

Unraveling the enzymatic mechanism of the protein farnesyltransferase: A QM/MM study

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The protein farnesyltransferase (FTase) is a Zinc-metalloenzyme that catalyzes the farnesylation reaction, which is the transfer of the 15-carbon farnesyl group from the farnesyl diphosphate (FPP) to one cysteine of protein substrates. It has been reported that oncogenic Ras proteins, which are among the FTase substrates, were observed in ~30% of human cancer cells. Therefore, FTase has become a promising target for anti-cancer drug design. Here, we present a classical force field-based and quantum mechanics/molecular mechanics computational study of the FTase reaction mechanism. Our findings offer a detailed picture of the FTase catalytic pathway, describing structural characteristic and energetic of its saddle points.

COMP 259

Using a computational serotonin transporter model to identify likely binding pocket residues

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The serotonin transporter (SERT), which belongs to the Neurotransmitter Sodium Symporter family is responsible for the reuptake of serotonin from the synaptic cleft and has been proposed as an important target in the treatment of anxiety and depression. Recent crystal structures of a homologous leucine transporter ($LeuT_{Aa}$) with and without tricyclic antidepressants (TCAs) suggest a pocket distinct from that identified for the substrate leucine. Using our LeuT-based homology model of SERT we have developed a docking protocol to study the binding of structurally diverse SERT ligands. The SERT binding pocket for antidepressants is not well defined. Consequently, a computational investigation has been employed in order to identify key binding pocket residues.

COMP 260

Using data mining algorithms to extract polarizable solvent models from quantum chemical data

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An accurate and efficient description of intermolecular interactions is of great importance in biochemical and materials simulations. To make large simulations computationally feasible, current molecular mechanics models often use highly simplified descriptions of the charge distributions and polarizabilities. This project explores a new approach to the development of polarizable models, beginning with simple solvent molecules such as water and carbon dioxide. The approach uses high level quantum chemical methods to generate information on the molecular charge distribution and its response to external charge fields. Feature extraction algorithms, such as principal component analysis, are then used to discover the most important collective degrees of freedom for both the permanent and induced multipole moments. This provides a systematic approach to development of polarizable electrostatic models, with well controlled and specifiable accuracy.

COMP 261

Analysis of residue packing in helical membrane proteins and its application in membrane protein structure prediction using network approach

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De novo protein structure prediction plays an important role in studies of helical membrane proteins as well as structure-based drug design efforts. Developing an accurate scoring function for protein structure discrimination and validation remains a current challenge. Network approaches based on overall network patterns of residue packing have proven useful in soluble protein structure discrimination. It is thus of interest to apply similar approaches to the studies of residue packing in membrane proteins. In this work, we first carried out such analysis on a set of diverse, non-redundant and high-resolution membrane protein structures. Next, we applied the same approach to three test sets. The first set includes nine structures of membrane proteins with the resolution worse than 2.5 Å; the other two sets include a total of 101 G-protein coupled receptor models, constructed using either de novo or homology modeling techniques. Results of analyses indicate the two criteria derived from studying high-resolution

membrane protein structures are good indicators of a high-quality native fold and the approach is very effective for discriminating native membrane protein folds from less-native ones. These findings should be of help for the investigation of the fundamental problem of membrane protein structure prediction.

COMP 262

Ensemble-based virtual screening reveals potential novel antiviral compounds for avian influenza neuraminidase

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Avian influenza virus H5N1 is a potential pandemic threat with human-adapted strains resistant to antiviral drugs. Although virtual screening (VS) against a crystal or relaxed receptor structure is an established method to identify potential inhibitors, dynamic changes within binding sites are routinely neglected. To accommodate full receptor flexibility, we use AutoDock4 to screen the NCI diversity set against representative receptor ensembles extracted from explicitly solvated molecular dynamics simulations of the neuraminidase system. The top hits are re-docked to the entire non-redundant receptor ensemble and rescored using the relaxed complex scheme (RCS). Of the 27 top hits reported, half ranked very poorly if only crystal structures are used. These compounds target the catalytic cavity as well as the newly identified 150- and 430-cavities, which exhibit dynamic properties in electrostatic surface and geometric shape. This ensemble-based VS and RCS approach may offer improvement over existing strategies for structure based drug discovery.

COMP 263

Identification of ligand binding site of urotensin-II receptor by site-directed mutagenesis and molecular modeling

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Urotensin II (UII) is a cyclic peptide hormone that was originally identified in fish, has prompted some substantial interests in the field of cardiovascular medicine. Its actions are mediated by a specific G-protein coupled receptor, GPR14, now designated the UT receptor. Small molecule UT receptor antagonists have been developed and were shown to be effective in animal models of heart failure and restenosis. In order to understand the SAR of UT receptor antagonists, it is necessary to identify the UII binding site of the UT receptor. For this purpose, a homology model for the rat UT receptor has been constructed and five mutants have been designed based on this model. Stable HEK 293 cells overexpressing these mutants were generated. Immunostaining detected plasma membrane expression of these mutants. Radiolabeled UII binding and UII-induced Ca2+ mobilization were subsequently performed. Site-directed mutagenesis study of five mutants Tyr71Ala, Trp76Ala, Phe87Ala, Asp90Ala and Trp158Ala, confirmed that Asp90 in TM-4 helix is the key reside for UII binding and the UT receptor activation. Trp76 in ET-2 loop also plays an important role for UII binding and the UT receptor activation. These data supported the binding site model proposed by the modeling study and can be applied to elucidate a binding mode and explain the SAR for the UT receptor antagonists.

COMP 264

Unraveling the mechanism of antagonism for human C5a receptor: Comparison of three structurally different antagonists

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C5a (74 aminoacid peptide) is a major chemotaxin responsible for recruiting human immune cells to sites of infection and cellular/tissue damage. The C-terminus of C5a is responsible for agonist activity, and compounds derived from the C-terminus can potentially antagonize C5a action. Among potent antagonists of C5aR are the insurmountable cyclic peptide antagonists Ac-cyclo-(2,6)-F[OP(D-Cha)WR] and the acyclic hexapeptide (N-methyl)FKP(D-Cha)Wr, as well as a range of a reversible competitive nonpeptide antagonists such as W54011. These were modelled and docked as flexible ligands into the transmembrane region of a homology model of C5aR, enabling predictions of interactions with receptor residues. We have defined ligand-binding sites for such antagonists and compared the binding sites with antagonists of other GPCRs. These predictions are being tested through effects of receptor mutagenesis on ligand binding and

activity. Such refined models of antagonist binding can facilitate a better understanding of C5aR and other GPCRs.

COMP 265

Validating the network-based scoring function for helical membrane protein structure prediction

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Computational structure prediction, including de novo and homology modeling, is an important tool for membrane protein studies. Developing an accurate scoring function that can be used for structure discrimination and evaluation remains a challenge.In our previous work, we have analyzed a set of high-resolution membrane protein structures using the network approach developed in our lab and proposed such a scoring function. Here, we aimed to validate this function from two aspects. First, we applied it to a diverse set of 139 homology models using four widely adopted network approaches. The models included in this dataset represent ten unique membrane protein superfamilies and have 20-100% sequence identity to their respective templates. The four chosen network approaches work by transforming a protein's structure into a network according to different criteria for defining connectivity. Network connectivity could be defined by specific inter-residue interactions detected or by the distance between atoms of two residues. Next, the discrimination capability of the proposed scoring function was tested using the HOMEP benchmark dataset of 92 membrane protein models and compared with the AMBER/GBSA energy function. Finally, the ability of the proposed network measure working as an independent packing quality indicator was further confirmed by detailed analysis of the results for models in the first dataset. Results of these analyses indicated the proposed scoring function, based on the network approach defined by inter-residue interactions, is a good indicator of high-quality models and can be applied to a variety of membrane protein models.

COMP 266

The performance of 3-D shape-based virtual screening is not necessarily related to the quality of the query conformation

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The accurate representation of the bioactive conformation is considered an essential precondition for 3D virtual screening methods.

Recent studies prove that state-of-the-art conformational model generators are able to represent the bioactive conformation in a quality that is suitable for screening most of the times. However, further investigations show that high computational efforts for conformational space sub sampling do not necessarily lead to superior predictive power of virtual screening. It seems that with increasing number of conformers per ensemble the chance that known inactive compounds are retrieved by such methods increase steeper than the chance that active compounds are correctly being identified (i.e., selectivity drops faster than sensitivity increases). This successive study provides evidence that 3D shape-based virtual screening does not heavily rely on query input conformation. In fact, our results point out that any reasonable query conformation is suitable for virtual screening and leads to comparable results. We have examined the performance of ROCS using input conformations of different origin in combination with the DUD database as a comprehensive testing environment. The ROCS screening results are illustrated using ROC (Receiver Operating Characteristic) curves. Our data shows that on average ROCS obtains comparable - or better - predictive power than docking protocols. Moreover, these results highlight the usefulness of such methods in cases where the bioactive conformation is unknown.

COMP 267

RESP charge derivation and force field topology database generation for complex bio-molecular systems and analogs

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We report on the development of new force field (FF) topology databases (FFTPDB) for coenzymes and analogs, natural and chemically engineered nucleic acids, calix[n]arenes used as potential metal chelators, amino-acid derivatives and Fe-III based hemes. Data were generated using the R.E.D.-IV program, which allows the execution of complex charge derivation and the generation of FFTPDB in the Tripos mol2 file format. These FF related information were deposited in the R.E.DD.B. database. MEP computation has been carried out using various QM theory levels for a compatibility with the most recent AMBER FF. The implementation of multiple orientation, multiple conformation, multiple molecule and multiple multiplicity RESP fit, and the use of effective core potentials in MEP computation and of specific constraints during the fit are fully justified. To the best of our knowledge this represents the largest set of FFTPDB ever released on the Internet. These FFTPDB are freely available from the http://q4md-forcefieldtools.org/ web site.

COMP 268

Derivation and implementation of the pairwise spin-contamination correction and application to study potential energy curves for 3-D transition metal hydrides from BS-DFT

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Chemical bond between transition metal atom and hydrogen is important in surface chemistry and nanoparticle cluster catalysis. The studies of Transition Metal (TM) systems present a challenge for theoretical description due to the presence of several electronic states close in energy which results in strong electron correlation. Density functional theory (DFT) is the method of choice to study large systems, due to relatively low computational cost.A clear advantage of unrestricted DFT is qualitatively correct description of bond dissociation process, but its disadvantage is that spin-polarized Slater determinant is no longer a pure spin state, which is called spin contamination. We propose a new approach to eliminate the spin-contamination, based on canonical Natural Orbitals (NO), and apply it to study potential energy curves for 3-d TM hydrides. The equilibrium bond lengths and dissociation energies were found in good agreement with published ab initio results.

COMP 269

Mechanism of electronic stabilization of the 3MR and divalent carbon of cyclopropenylidene by amino-substitution: Comparison of topology of the electron density and orbital analysis methods

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Mechanisms of electronic stabilization of singlet cyclopropenylidene by amino substitution are presented. Topology of the electron density of an abbreviated model of the known, stable bis(diisopropylamino)cyclopropenylidene reveals operating mechanisms of induction/back-polarization (not back-donation), σ-aromaticity, and σ-π polarization. Validation of this premise is found in integrated atomic basin and interatomic surface properties, bond path ellipticities, and diamagnetic/paramagnetic components of NMR shielding tensors. These actual, physical mechanisms based upon the quantum theory of atoms in molecules (QTAIM) are at odds with the stabilizing π-conjugation and -hyperconjugation interactions suggested by the necessarily arbitrary constructs of natural bond orbital and molecular orbital calculations. Discrepancies between orbital-based and topological methods are revealed through analysis of the σ- and π-orbital contributions to atomic overlap matrices, electron localization and delocalization indices, and nucleus-independent chemical shifts (NICS)—gauges of delocalization/aromaticity. Graphical visualizations of QTAIM properties mapped onto orbital isosurfaces also expose the disparity between the two theoretical approaches.

COMP 270

Determination of alkali and halide monovalent ion parameters for use in explicitly solvated biomolecular simulations

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Alkali (Li^+, Na^+, K^+, Rb^+, and Cs^+) and halide (F^-, Cl^-, Br^-, and I^-) ions play an important role in many biological phenomena. This suggests that an accurate model or representation is critically necessary. The previous models of the ions, within the context of a pair-wise additive Coulombic and 6-12 Lennard-Jones force field framework, lack the appropriate balance between ion-ion interactions, although their interactions with water molecules are reasonable. This mis-

balance leads to non-realistic precipitation even at low concentrations. Thus, we re-optimized the Lennard-Jones parameters for the monovalent ions. To validate and optimize the parameters, we calculated lattice constant and lattice energy as well as hydration free energies of the solvated ions across the Lennard-Jones space (well depth and radius). The key idea of the parameterization was using the pair properties along with the properties of the single ions. This reduces otherwise serious deviations that may occur when targeting properties of the ions individually.

COMP 271

The binding affinity awarded for hydrophobic bonding in scoring functions needs to be context dependent

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Previously we designed and synthesized a series of thrombin inhibitors to probe the possibility that ligand side chains may cooperatively enhance each other's contribution to the overall ligand binding affinity. The binding affinities were measured experimentally and the hydrophobic contact surface areas for the series were analyzed using Sybyl and with representative thrombin-inhibitor crystal structures. The data obtained showed that the free energy of hydrophobic binding per sq. angstrom of contact surface area doubled in presence of an additional H-bond between the ligand and the protein. Herein we further analyze this observed phenomenon with molecular dynamics (MD) simulations of representative thrombin inhibitor complexes from the series. The results obtained suggest that the strength of the hydrophobic binding was increases due to a residual motion restriction of the inhibitor hydrophobic side chains within the thrombin hydrophobic pocket which increased the average amount of time the hydrophobic surfaces spend in close contact with each other. Interestingly, whereas the hydrogen bonding side chain doubled the strength of the hydrophobic bond, increasing the size of the hydrophobic side chain did not conversely increase the strength of the hydrogen bond.

COMP 272

Systematic development of OPLS-AA force field parameters for ionic liquid simulations

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OPLS-AA force field parameters have been developed and validated for use in the simulation of over 50 unique combinations of ionic liquids (IL) featuring 1-alkyl-3-methylimidazolium [RMIM] (R = Me, Et, Bu, Hex, Oct), N-alkylpyridinium [RPYR], and choline cations, along with Cl^-, PF_6^-, BF_4^-, NO_3^-, $AlCl_4^-$, $AlCl_7^-$, TfO^-, saccharinate, and acesulfamate anions. Torsional free-energy profiles and electrostatic charges were obtained at the LMP2/cc-pVTZ(-f)//HF/6-31G(d) level. The new parameters were fit to reproduce experimental condensed-phase structural and thermodynamic properties, and experimental free-energies of hydration. Monte Carlo simulations of the ILs gave relative deviations from experimental densities and heats of vaporization of ca. 1-3%. Transferability of the cations was tested by comparing the new parameters to potentials specific to alkyl chain length. Both parameter sets gave nearly identical values over a wide temperature range regardless of the anion chosen. The highly accurate parameters should be of considerable interest to the IL modeling community

COMP 273

Atomistic simulations of a two-domain protein switch: Mechanically-induced unfolding of one domain by the other

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A novel, two-domain protein switch has been designed by inserting ubiquitin into a surface loop of barnase. The domain insertion provides a means of allosteric regulation by imposing a significant degree of mechanical stress on the system such that the folding of one domain is coupled to unfolding of the other. The objective of our study was to understand the structural basis for this “mutually exclusive folding” mechanism by employing unforced, all-atom Langevin dynamics simulations. Our simulations support the hypothesis that the degree of unfolding depends on the length of interdomain peptide linkers as well as the inherent plasticity of the individual domains. We propose a mechanism for the mechanically-induced unfolding, which will be further tested by NMR spectroscopy experiments.

COMP 274

Development of polarizable force field for ions

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Ions play a critical role in many chemical and biological systems. Modeling of ions with classical force field is challenging due to the presence of high charges and strong electronic polarization effect. Traditionally, ion parameters in the fixed-charge force field have been derived from single ion solvation free energy, which can be unreliable due to the assumptions used to decompose the experimental whole-salt data. We have successfully developed a classical potential that treat explicitly the electronic polarization via an atomic-dipole induction model. The necessary parameters, e.g. vdW radius and well-depth, in this model have been derived by comparing to ab initio quantum mechanical calculation of ion-water interaction in gas-phase. Condensed-phase simulations using the resulting parameters reproduce well the experimental ion-water cluster solvation enthalpy and experimental solvation free energy of whole salts. Water structure and dynamics around ion observed in our simulations are also in good agreement with experimental measurement and QM-based theoretical estimation. This approach has so far been tested on a series of mono- and divalent ions, including Cl-, K+, Na+, Ca++, Mg++, and Zn++. Our results demonstrate that inclusion of polarization effect enables us to derive a transferable classical potential based on ab initio QM calculations and make accurate prediction of bulk thermodynamic properties.

COMP 275

Dynamic coupling machinery in DNA polymerases

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We present a theoretical and computational approach to dissect at a sub-atomic detail the molecular machinery associated with single molecule function in DNA polymerases. The new paradigm we propose is the coupling between long-range (or global) and short-range (or local) motions in utilized during the chemical reaction associated with DNA replication and the molecular context within which such a dynamical coupling is operational. Through computer simulations of the dynamics of a polymerase DNA complex at atomic resolution we suggest that an

intriguing dynamical coupling between the cooperative motion of polymerase and DNA atoms may play a significant role in aiding and abetting the chemical reaction (chemical step) that leads to nucleotide incorporation during DNA replication. We also suggest that the coupling is disrupted to varying extents in a context-specific fashion, i.e., when the inserted nucleotide is not complementary to the template base (mispair) or when the template base in the DNA is oxidatively damaged. Using an elastic response formalism, we also show that as a direct consequence of the dynamical coupling, the rate of the chemical step is dependent on the applied force on the DNA (template) strand, and that the force-dependence is also context-specific. Our results challenge the status quo, i.e. the existing paradigm which attributes the force-response to elasticity changes between single and double-stranded DNA and hence does not predict a context specific force-response. Our predictions can be tested directly through single-molecule experiments. More broadly, our work relates to error-free and error-prone DNA replication with significance to cancer, neurological aberrations, and premature aging.

COMP 276

Comparison of sum over states (SOS) and coupled electronic oscillator (CEO) formalisms used for computational design of two-photon absorbing materials with time-dependent density functional theory

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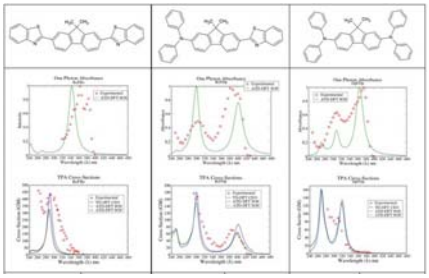
Two-photon absorption (2PA) and subsequent processes may be localized in space with a tightly focused laser beam. This property is used in a wide range of applications, including three dimensional data storage. We report theoretical studies of 3 conjugated chromophores experimentally shown to have large 2PA cross-sections. We use Time Dependent Density Functional Theory (TD-DFT) to describe the electronic structure. A third order coupled electronic oscillator (CEO) formalism is applied to calculate the frequency-dependent third order polarizability. Alternatively, sum over states (SOS) formalism using permanent and state-to-state transition dipoles provided by a posteriory Tamm-Dancoff approximation (ATDA) is employed. SOS and CEO results are in quantitative agreement with each other, which validates ATDA/SOS method. Predicted 2PA profiles also agree well with experimental ones. It provides new venues for

qualitative interpretation and rational design strategies directed toward improved Two-Photon absorbing materials.



COMP 277

Ensemble of transition state structures for the cis-trans isomerization of *N*-methylacetamide

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The cis-trans isomerization of a model peptidic fragment is studied using a recently introduced theoretical method to search nonlocally for different (folding) pathways in complex molecular systems at finite temperature, implemented within an empirical force field description [D. Branduardi, F. L. Gervasio, and M. Parrinello, *J. Chem. Phys.* **126**, 054103 (2007)]. Transition state structures of *N*-methylacetamide in vacuo and in explicit water solvent are identified by computing committor distribution functions for both systems. The functions of *N*-methylacetamide in vacuo are computed both without velocity randomization in the standard way as well as with periodic velocity randomization, as a substitute for molecular collisions, for comparison to those of solvated *N*-methylacetamide. The description of the most relevant saddle point in the gas phase is very similar to that in aqueous solution. However, for the latter, solvent degrees of freedom must technically be included. Also of importance, an additional feature of the theoretical method is illustrated here for the first time, namely, the capacity to increase the subspace of nonlocal pathways considered in a systematic fashion.

COMP 278

Interfacial and dynamic properties of polydimethylsiloxane-water systems

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Polydimethylsiloxane (PDMS) is a main constituent of silicone adhesives, and are often used as sealants; its interaction with water is of fundamental importance. To improve our understanding at the molecular level, we have performed molecular dynamics simulations of PDMS in the presence of water, with the long-term goal of studying how water molecules effect debonding at the surface. Knowledge of the basic interfacial properties of a multicomponent system, such as surface tension, contact angle, and diffusion constant, are essential to obtain the proper dynamic behavior in simulations of adhesion and wetting processes. Explicit-atom simulations of 10^5 or more atoms were used to determine liquid-vapor surface tension and the contact angle for water on the surface of PDMS. We present results for the dependence of the surface tension on chain length and end-group functionality. We also demonstrate how alternative routes for calculating interfacial properties lead to consistent results.

COMP 279

Mesoscale simulation of viscoelastic behavior of ABA triblock copolymers

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Amphiphilic block copolymers have been widely used in many practical applications and are well-known to undergo microphase separation in a selective solvent into a variety of periodic microstructures. The main interest of this study is to control morphology of a gel formed by association of ABA copolymer in B selective solvent in order to achieve the desirable mechanical properties. This challenging problem necessitates the use of advanced mesoscale modeling and requires significant computer resources. We explored the viscoelastic properties of solution of triblock copolymers by means of the (DPD) simulation method with the non-equilibrium time dependent Lees-Edwards boundary conditions. We showed principally different viscoelastic behavior of microstructures formed by ABA copolymer in A and B selective solvents. We obtained good agreement with other theoretical and experimental results and extended this novel approach to predict viscoelastic properties of the block copolymers for different block architecture, concentration, solvent selectivity and temperature.

COMP 280

Modeling linear and three-arm triblock SIBS copolymers

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Copolymers built from polystyrene and polyisobutylene (SIBS) components are good candidates for textile applications, where breathable yet protective clothing is required. Relative permeability of water and a warfare agent simulant (dimethylmethylphosphonate, DMMP), increases with sulfonation level and also in the presence of metal ions. Recently, we have studied linear triblock copolymer, using a multiscale approach to predict morphology and atomistic structure of polymer solution in water and mixture of water and DMMP. We have found a strong tendency of water to bind to sulfonated groups, unlike DMMP that prefers hydrophobic groups. This may explain a striking difference in observed permeability of the water and DMMP at low sulfonation level. The effect of metal ions on sulfonated groups was measured via infra-red-spectroscopy (FTIR). We will compare these data with simulations explaining the IR frequency shifts at the atomistic level. We will present computational results of morphology and atomistic structure of water and DMMP solutions with the sulfonated three-arm star SIBS copolymers.

COMP 281

Predicting the viscosity of supercooled liquids

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We present an atomistic description of the viscosity of supercooled liquids capturing the highly non-Arrhenius temperature variation for which no previous calculation has been given. A temperature dependent activation energy for structural relaxation is derived by mapping the potential energy surface and extracting saddle-point configurations and associated atomic coordinates. This essential information is combined with the temperature variation of an effective local energy minimum (inherent structure) to describe shear relaxation by thermal activation. For both the binary Lennard-Jones and modified Born–Mayer–Huggins SiO2 model systems, the calculated viscosity shows characteristic crossover from strong (Arrhenius) to fragile (highly non-Arrhenius) behavior upon appreciable undercooling, followed by a second crossover from fragile back to

strong behavior on approaching the glass transition temperature, both features we believe to be generic. Analysis of atomic displacements associated with barrier crossing in the fragile regime suggests a scenario of correlated motions along a chain of particles as the underlying mechanism for slow viscous relaxation in glassy states.

COMP 282

Predictive computational methods for the design and discovery of asymmetric catalysts

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Predicting stereochemical outcome of asymmetric reactions in a timely fashion would be of great interest for the synthetic chemistry community. We have developed and validated a computational method (ACE) that evaluates the enantio/diastereo induction of asymmetric catalysts or auxiliaries within minutes. The last developments in this area will be presented.

COMP 283

Theoretical investigation of the interaction of H_2O, H_2, O_2, OH species with the alpha-Al_2O_3 (0001) surface

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αAl_2O_3 is a technologically important material as a catalytic support as well as for microelectronics. However, a complete model of how the surface termination affects its interaction with the environment has been lacking. In this paper, we employ DFT/GGA calculations to clarify the reaction mechanism for hydrogen combustion on the Al terminated (0001) αAl_2O_3. We provide barrier calculations and reaction pathways for both the molecular and dissociative adsorption of H_2O, H_2, O_2, OH and their ability to recombine or further dissociate after the initial adsorption event. In addition, we performed a detailed analysis of how the surface reconstructs in the vicinity of the dissociation products and how this

influences the barriers for diffusion across the αAl_2O_3 surface. Our results confirm that water can either adsorb molecularly on the αAl_2O_3 surface or spontaneously dissociate into 1-2 and 1-4 configurations. The barrier for dissociation from molecular adsorbed H_2O into 1-4 dissociation products is lower than for 1-2. Since the energy released due to spontaneous dissociation from free water is well in excess of the barriers for dissociation from molecular water, our results suggest that if molecular water exists on the surface, it is unlikely to have a long lifetime. These results will be compared with the results from other theoretical and experimental investigations of the αAl_2O_3 surface.

COMP 284

An electron density study of the mechanism of peptide bond formation in the ribosome

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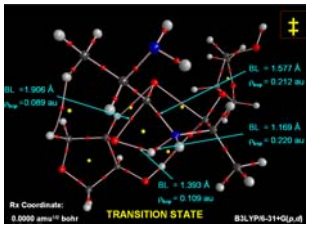
Using quantum mechanics and exploiting known crystallographic coordinates we have investigated the mechanism for peptide-bond formation in the ribosome. The calculation is based on a choice of 50 atoms assumed to be important in the mechanism. We used density functional theory to optimize the geometry and energy of the transition state (TS) for peptide-bond formation. The calculated TS activation energy, Ea, is 35.5 kcal/mol, and the increase in hydrogen bonding between the rotating A-site tRNA and ribosome nucleotides as the TS forms appears to stabilize it to a value qualitatively estimated to be 18 kcal/mol. The optimized geometry corresponds to a structure in which the peptide bond is being formed as other bonds are being broken, in such a manner as to release the P-site tRNA so that it may exit as a free molecule and be replaced by the translocating A-site tRNA. At TS formation the 2' OH group of the P-site tRNA forms a hydrogen bond with the oxygen atom of the carboxyl group of the amino acid attached to the A-site tRNA, which may be indicative of its catalytic role, consistent with recent biochemical experiments. An electron density study illuminates the role of the bonds which participate in the mechanism of formation of the TS.



COMP 285

Sequence effects on the electronic structure of nucleic acids

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The effect of DNA sequence on its charge transfer (CT) characteristics is studied using a combination of molecular dynamics simulations and quantum mechanical computations. The energy and localization of a hole in a DNA radical cation is calculated for several DNA sequences, in which the hole donor and acceptor, composed of several GC base pairs, are separated by a bridge of several AT base pairs. The calculations employ thermal ensembles of the DNA structures obtained in the course of molecular dynamics simulations. The hole delocalization onto the AT bridge is found to be significant in all studied DNA segments, and strongly dependent on the sequence and size of the donor, acceptor, and the bridge. It is suggested that a thermally-induced hopping mechanism may contribute significantly to the DNA CT rate, even at short donor-acceptor distances. The modulation of the CT properties by the DNA sequence is discussed.

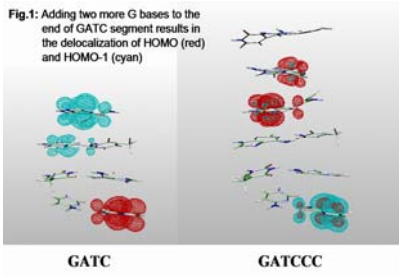

Fig.1: Adding two more G bases to the end of GATC segment results in the delocalization of HOMO (red) and HOMO-1 (cyan)

COMP 286

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

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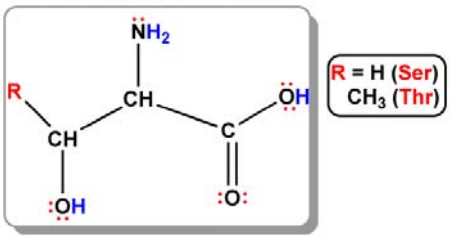
A method for scanning the full potential energy surface (PES) of five-membered rings is presented. Graphs of the PES of oxocarbenium ions in five-membered rings are shown using the conformational description of furanoses by Altona and Sundaralingam [J. Am. Chem Soc. 1972, 94, 8205] and the PES is related 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 287

Strength vs. strain: An exploration of chameleonic hydrogen bonds of serine and threonine in different pHs

***Mihaela D. Bojin**, Department of Chemistry, Queensborough Community College, City University of New York, 222-05 56th Avenue, Science, S-445, Bayside, NY 11364*

The development of efficient computational methods and amino acids' small sizes, along with their remarkable role in our lives, renders them as suitable candidates for theoretical investigations. However, it is difficult to understand their flexibility, and hence the multiple conformations that stem from the vast possibilities for intra- and intermolecular hydrogen bonding interactions. These control secondary and tertiary structures of proteins and significantly affect enzymatic activity. We analyze various conformers of serine (Ser) and threonine (Thr), and three dimers: Ser-Ser, Thr-Thr, Ser-Thr, while varying the pH, using DFT methods. We also compute chemical shifts, and compare them to experimental data. The strength of hydrogen bonds together with the strain imposed on these systems are strongly influenced by pH, but essential in determining the stability of these systems. By examining these intrinsic bonding elements in Ser and Thr, we aim to identify similar hydrogen bonding motifs in complex biological systems.



COMP 288

Unraveling the origin of substituent effects in pi-stacking interactions

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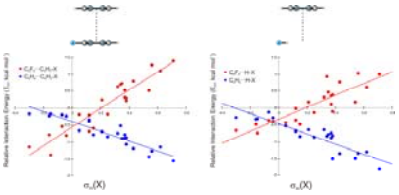
The prevailing view of substituent effects in the benzene dimer is flawed. In the Hunter-Sanders model (*J. Am. Chem. Soc.* **1990**, 112, 5525), electron withdrawing substituents enhance the binding of the benzene dimer by withdrawing electron density from the π-cloud of the substituted ring, reducing the repulsive electrostatic interaction with the non-substituted benzene. Conversely, electron donating substituents donate excess electrons into the π-system and diminish the π-stacking interaction. We present computed interaction energies for the sandwich configuration of the benzene dimer and 25 substituted dimers, as well as sandwich complexes of substituted benzenes with perfluorobenzene. While the computed interaction energies correlate well with σ_m values for the substituents, in accord with the recent experimental results of Hunter and co-workers (*Org. Biomol. Chem.* **2007**, 5, 1062), interaction energies for related model systems demonstrate that this trend is completely independent of the π-system of the substituted ring. Instead, the observed trends are due completely to the direct interaction of the substituents with the unsubstituted ring. For the interaction of substituted benzenes with perfluorobenzene, there is some involvement of the π-system of the substituted ring, but the dominant cause of observed trends is direct interactions of the substituents with the perfluorobenzene.



COMP 289

Accurate calculations of binding and folding free energies by a scaled generalized Born method

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The Poisson-Boltzmann equation is widely used for modeling solvation effects. The computational cost of PB has largely restricted its applications to single-conformation calculations. The generalized Born model provides an approximation at substantially reduced cost. Currently the best GB methods reproduce PB results for electrostatic solvation energies with errors at > 5 to 10 kcal/mol. When two proteins form a complex, the net electrostatic contributions to

the binding free energy are typically of the order of 5 to 10 kcal/mol. Similarly, the net contributions of individual residues to protein folding free energy are < 5 kcal/mol. Clearly in these applications the accuracy of current GB methods is insufficient. Here we present a simple scaling scheme that allows our GB method, GBr6, to reproduce PB results for binding and folding free energies with high accuracy. From an ensemble of conformations sampled from molecular dynamics simulations, five were judiciously selected for PB calculations. These PB results were used for scaling GBr6. Tests on protein binding and folding show that effects of point mutations calculated by scaled GBr6 are accurate to within 0.5 kcal/mol or less. This method makes it possible to incorporate conformational sampling in electrostatic modeling without loss of accuracy.

COMP 290

Free energy of hydration in the protein interior

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Computer simulation methods to quantify the thermodynamics of hydration in the protein interior will be discussed. Water in the interior of proteins can serve both structural and functional roles, for instance as mediator in the transfer of protons. In a number of proteins, the interior water appears to be absent in the resting state, but enters transiently in the active state. Examples of such transient filling by water include cytochrome c oxidase and bacteriorhodopsin, enzymes that convert chemical and light energy into an electrochemical proton gradient, respectively. With proton transfer involving the transient water molecules, understanding the function of these and other enzymes thus requires a quantitative analysis of the thermodynamics of interior hydration. However, residence times of interior water are normally longer than the time scales of typical molecular simulations. Thus, equilibrium between the interior and exterior hydration has to be established virtually. As a complicating factor, many of the interesting cavities can be filled with multiple water molecules. To calculate the free energy of hydration and decompose it into enthalpy and entropy contributions, we have developed a grand-canonical formalism. A semi-grand-canonical partition function is constructed from a series of conventional canonical simulations with N=0, 1, 2, etc. water molecules in the cavity of interest. From these canonical simulations, one can construct the equilibrium probability p(N) of finding exactly N water molecules in the cavity by using test-particle insertion and particle-removal techniques. From p(N) and the observed binding energies we calculate the free energy, enthalpy, and entropy of the interior water. The

formalism is general and can be used in other cases of multiple binding, including small ligands. The method will be illustrated with applications to several proteins, including lysozyme, tetrabrachion, and interleukin 1beta.

COMP 291

A double mutation can alter receptor specificity of the avian H5N1 hemagglutinin: A free energy simulation approach

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Earlier influenza pandemics have been caused by human-adapted H1N1 and H3N2 viruses, in which a specificity switch of the avian hemagglutinin (HA) is believed to occur from the avian-like (α-2,3-linked) to the human-like (α-2,6-linked) sialylated glycan receptors. We provide a computational framework that combines molecular modeling with extensive free energy simulations to define mutations with ability to alter receptor specificity of a currently circulating avian H5N1 HA. Our results show that the simulated binding affinities of few avian H5N1 HA mutants are in excellent agreement with experimental data. In addition, we predict one double mutation that dramatically enhances human-like receptor recognition of the avian H5N1 HA. This double mutation enables the avian H5N1 HA to bind a human receptor analog in a similar manner to what was observed in the human-adapted H1N1 HA. Therefore, this double mutant may represent a step toward human adaptation of the avian H5N1 virus.

COMP 292

Free energies of ions and ionizable side chains in membranes.

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Biological membranes present free energy barriers to polar and charged molecules as a result of segregating their hydrocarbon cores into slab-like geometries that are highly unfavorable to all polar species. Yet, this view has been challenged by biological translocon-based experiments that report small apparent free energies to insert charged side chains in the center of a transmembrane helix. We provide a renewed theoretical picture of the movement

of ions and ionizable protein side chains across membranes with fully atomistic molecular dynamics simulations to provide free energy and pKa profiles. We reveal that the membrane is very different to the traditional picture of a uniform slab of low dielectric hydrocarbon because the membrane undergoes deformations to maintain solvation of the charged groups. We compare to available experimental partitioning and permeability data, and carry out quantum mechanical calculations and polarizable membrane simulations to demonstrate surprisingly high accuracy of these models. These studies help us understand the ability of different ions and amino acids to carry charge in the membrane, with implications for many biological processes, including the gating mechanisms of voltage gated ion channels.

COMP 293

Computational mutagenesis of protein and estimation of protein/peptide configurational entropy

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Alanine-scanning at protein-protein interface is a very important process for identifying the binding “hot spot” and rational drug design. We have revisited the classical model system of alanine scanning, 1:1 human growth hormone–receptor complex. A multi-nanosecond trajectory and new parameters have improved the performance of computational alanine scanning.

Estimation of configurational entropy is another difficult task closely related to free energy calculation. A multi-macrosecond trajectory was collected for a peptide, and the “counting method” was used to obtain the relative free energies and configurational entropies. These entropies are used to evaluate different entropy estimators. It is found that the quasi-harmonic entropy estimator operating in dihedral angle space performs better than the one using Cartesian coordinates. A recent generalization of the quasi-harmonic approach that computes Shannon entropies of probability distributions obtained by projecting the conformers along the eigenvectors of the covariance matrix performs similarly well. For the best entropy estimators, a linear correlation coefficient between 0.92 and 0.97 is found. Unexpectedly, when correlations between dihedral angles are neglected, the agreement with the reference entropies improved.

COMP 294

Free energy of peptide – carbon nanotube interactions: The single amino acid approach

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Non-covalent functionalization of single walled carbon nanotubes (SWNTs) using bio-molecules, such as proteins or DNA, has been proposed to enable their biological applications. Unfortunately, most current imaging techniques require dried samples which make it difficult to infer the bio-molecule/SWNT structure in aqueous solution. In this study, we apply the idea of component analysis of the free energy by breaking down the total free energy of the peptide – SWNT interaction into single amino acid – SWNT contributions. We test this method on a known nanotube binder, B1, a non-binder, NB1, and on nano-1, a designed helical peptide which uses its aromatic sidechains to interact with the SWNT sidewall. Based on these studies, we suggest when the method is applicable. Such a method could be very powerful in predicting and understanding peptide – SWNT interactions at the molecular level.

COMP 295

Dynamics of recognition between tRNA and elongation factor Tu

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Elongation factor Tu (EF-Tu) binds to all the standard aminoacyl-transferRNAs (aa-tRNAs) and transports them to the ribosome while protecting the ester linkage between the tRNA and its cognate amino acid. We use molecular dynamics simulations to investigate the dynamics of the EF-Tu·GTP·aa-tRNACys complex and the roles played by Mg^{2+} ions and modified nucleosides on the free energy of protein·RNA binding. Combined energetic and evolutionary analyses identify the coevolution of residues in EF-Tu and aa-tRNAs at the binding interface. Protein residues responsible for both attractive and repulsive interactions with aa-tRNAs are highly conserved across all three domains of life. In addition to the 3' CCA end, nucleotides, conserved within tRNA specificities, appear to be responsible for tuning aa-tRNA binding to EF-Tu. The trend in EF-Tu·CystRNACys binding energies observed as the result of mutating the tRNA agrees with experimental observation. We also predict variations in binding free energies upon misacylation of tRNACys with D-cysteine or O-phosphoserine and upon changing the protonation state of L-cysteine. Principal components analysis in each case reveals changes in the communication network across the protein·tRNA interface and is the basis for the entropy calculations.

COMP 296

Feature analysis of functional sites in proteins: Specificity and mechanistic determinants of function

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Sequence and structural genomics projects have identified large numbers of proteins and putative proteins. Methods have been developed to predict the molecular functions of these proteins, but development of specific inhibitors requires identification of mechanistic or specificity determinants at those functional sites. Here we present methods for identification of functional sites in proteins and compare the results of those methods in both crystal structures and structures from large scale modeling projects. Functional site profiling of these sites is then used to compare and cluster protein family members based on the structure and sequence information at the functional site. This information can be used for comparison of substrate or inhibitor specificity in computational drug discovery.

COMP 297

Modeling amyloid conformations and toxic ion channels

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Calcium exchange through cellular membrane in amyloid-related neurodegenerative diseases is believed to underlie neuronal cell death. Yet, the mechanism through which calcium permeates cellular membranes is controversial. One proposed mechanism involves membrane thinning through medium-to-large soluble particles ‘sitting' on the membrane surface, leading to leakiness. Another involves channels made of smaller particles. We shall present molecular dynamics simulations of channels consisting of the U-shaped beta-strand-turn-beta-strand Alzheimer Abeta. The results appear to reconcile the apparent conflicting data and provide atomic scale-resolution channel models. The channels can conduct calcium and obtain shapes and dimensions consistent with Atomic Force Microscopy (AFM) images. Interestingly, all channels break into mobile subunits suggesting that membranes do not support intact beta-sheet channels. We shall further present results of modeling PG-1 antimicrobial

channels, presenting a consistent general picture of toxic beta-sheet based channels.

COMP 298

How do antimicrobial peptides work? Simulations of the pore structure of Protegrin-1 and its mutants

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We performed over 150ns of simulation of a protegrin-1 pore in a lipid bilayer bacterial cell mimic composed of POPE and POPG lipids (Langham et al. JACS 2008). The simulation improves on a model of an octameric pore proposed from NMR experiments. We explore the movement of ions and water through the pore in detail. We use the results of the simulations as input to a continuum electrodiffusion model of ion permeation (Poisson-Nernst-Planck theory). Through homology modeling, we predict structures of protegrin-mutant pores and test the stability of these pores to determine if pore stability is a requirement for activity. With this multifaceted approach a clear picture emerges of the timeline of events that result in bacterial lysis.

This work was supported by a grant from NIH (GM 070989). Computational support from the Minnesota Supercomputing Institute is gratefully acknowledged. This work was also partially supported by National Computational Science Alliance.

COMP 299

Evolution of enzyme fold: Linking protein dynamics and catalysis

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Enzymes are dynamic molecules. In the past, enzymes have been viewed as static entities and their high catalytic power has been explained on the basis of direct structural interactions between the enzyme and the substrate. Recent evidence has linked protein dynamics to catalytic efficiency of enzymes. Further,

motions in hydration-shell/bulk solvent have been shown to impact protein motions, therefore, function.

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

COMP 300

A comparative study of human beta-2 adrenergic GPCR theoretical models and crystal structure: The applicability for virtual screening

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The recently determined crystal structures of human beta2-adrenergic receptor (beta2AR) make it possible to conduct a retrospective study on the theoretical modeling of beta2AR, and GPCRs in a broad sense, with the reference to crystal structures. Theoretical models from five group (i.e. Vriend, Sali, Skolnick, Lybrand and Goddard), together with two GPCRs crystal structures (beta2AR and rhodopsin), have been employed to conduct a systematic study on the structural similarity and capacity for virtual screening. As expected, homology models are dissimilar to b2AR crystal structure (TMs backbone RMSD 2.25Å ~ 3.19Å) but proximate to bovine rhodopsin. In comparison, de novo models are more divergent from both b2AR and rhodopsin (TMs backbone RMSD > 3.0Å). In the virtual screening of known b2AR ligands from WDI database using Glide, AutoDock4 and eHiTS, Lybrand's de novo models perform better than crystal structure in recovering 13 agonists and have comparable capacity for 13 antagonists.

COMP 301

Discovery of novel human histamine H4 receptor ligands by large-scale structure-based virtual screening

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A structure-based virtual screening (SBVS) was conducted on a ligand-supported homology model of the human histamine H4 receptor (hH4R). More than 8.7 million 3D structures derived from different vendor databases were investigated by docking to the hH4R binding site using FlexX. A total of 255 selected compounds were tested by radioligand binding assay, and 16 of them possessed significant [3H]histamine displacement. Several novel scaffolds were identified that can be used to develop selective H4 ligands in future. As far as we know, this is the first SBVS reported on H4R representing one of the largest virtual screens validated by the biological evaluation of the virtual hits.

COMP 302

Coupling ligand-steered homology modeling and structure-based virtual screening: Discovery of novel antagonist chemotypes to the melanin concentrating hormone receptor, a class A GPCR

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The advances of the structural genomics initiatives have rendered comparative or homology modeling more important than ever, since it constitutes a bridge between the sequence and the structural realms. The *ligand-steered homology modeling* method in presented, in which the knowledge of existing ligands is explicitly used to model the binding site through a docking-based stochastic global energy optimization procedure. The structural modeling approach was applied to the Class A GPCR Melanin Concentrating Hormone Receptor 1 (MCH-R1), a protein known to be linked to obesity. The models thus generated were used in a structure-based virtual screening followed by biological evaluation. Top-ranking molecules were experimentally evaluated, and six out of 129 compounds were found to be active with K_i values in the low micromolar range, showing a hit enrichment rate of more than 10-fold compared to high-throughput screening.

COMP 303

Novel scoring metric for enhancing the prediction of ligand binding mode

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Our goal is to improve prediction of ligand binding modes in virtual screening, which is essential to accurately define the interactions used to predict binding affinity. For training, a set of poses was generated with known ligand docking RMSD values relative to the crystallographic pose, for a set of diverse complexes. A scoring function was formed by selecting a linear combination of protein-ligand interaction terms, then training the terms' weights to fit -1/RMSD. This metric provides large-magnitude scores for nearly correct poses, while assigning small scores to poses offset by >2 Å RMSD. This creates a funnel-like scoring landscape and new insights into the terms most useful for predicting binding mode. Using this scoring function, SLIDE selected dockings within 2 Å RMSD of the crystallographic position for 61% of the ligands in 100 protein complexes; quick energy minimization resulted in refining 53% of these dockings to ≤ 1 Å RMSD.

COMP 304

Can quantum mechanical energies be used as scoring for protein docking?

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In protein docking, scoring is one of the fundamental ingredients. Along with search algorithms, it is the other half of the essential parts of docking that generates predictions for binding mode of protein-ligand complexes. Various scoring functions for docking have been developed and implemented in a number of programs over the years. Most of the scoring functions are based on physical/chemical energy functions, but incorporate some empirical/experimental parameters, which are often fine-tuned with “training sets”. Furthermore, some programs adopt motif-based scoring components, which are modeled through elaborate molecular dynamics or quantum mechanical calculations. Although it is generally accepted that quantum level calculations give us the most detailed description of protein-ligand binding, aforementioned scoring schemes were concocted to reduce the computational demand so that the program can be used in fast docking environment. In this talk, we discuss development of a protocol which utilizes quantum mechanical energy as scoring for docking. We then present the test of this idea on a number of examples grouped in several categories. The results suggest that for certain classes of proteins such idea can be useful.

COMP 305

Novel detection strategy for drug discovery using Shape Signatures and the subtype selective engineered nuclear hormone biosensors

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The superfamily of nuclear receptors (NR) contains a wide variety of proteins which are linked to the development of common diseases including cancer, obesity and neurodegenerative disorders. Their rapid drug-enzyme complex analysis is crucial in development of novel pharmaceuticals. This presentation shows a unique strategy for fast study of large databases of potential therapeutical compounds by joining computer aided drug design methods including Shape Signatures, a ray-tracing based screening method, docking as well as novel nuclear hormone biosensors developed in-house. The subtype selective engineered chimeric enzymes acting essentially as highly sensitive switches were used for detection of agonist's and antagonist's binding including weak van der Waals interactions. The case study will be discussed here including a comparison of the results to mammalian cell-based assays.

COMP 306

Virtual screening strategies toward the design of novel anthrax toxin lethal factor inhibitors

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Anthrax is an acute infectious disease caused by the spore-forming bacterium Bacillus anthracis. The lethal factor (LF) enzyme is secreted by B. anthracis as part of a tripartite exotoxin and is chiefly responsible for anthrax-related

cytotoxicity. As LF can remain in the system for weeks after antibiotics have eradicated B. anthracis from the body, the preferred therapeutic modality is the administration of antibiotics together with an effective LF inhibitor. Such inhibitors must not only bind strongly to the receptor but must also possess excellent ADMET profiles. Published crystal structures of LF with bound inhibitors provide valuable insight into binding modes. In addition, extensive research carried out in academic and industrial laboratories yields many useful rules-of-thumb for ADMET profiling. In this work, all the above resources are applied to create binding filters based on molecular modeling techniques such as docking, pharmacophore mapping and topomeric searching. In addition, common ADMET filters such as reactive group filtering, Lipinski's and Veber's rules, etc., together with modern in silico ADMET-related property prediction techniques, are applied to facilitate compound profiling and prioritization. Together with experimental high-throughput screening of compound libraries at the University of Minnesota's Institute for Therapeutics Discovery and Development (ITDD), the binding and ADMET filters are used to narrow the search space of novel anthrax lethal factor inhibitors from millions of compounds in our databases to dozens of potential leads.

COMP 307

Virtual screening to identify novel Dengue virus inhbitors

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Dengue fever, a neglected disease, is a viral infection found in tropical and sub-tropical regions which can cause fever, severe joint pain, hemorrhage and shock, and, in the worst cases, death. Being endemic in more than 100 countries on five continents, Dengue is becoming a major international public health concern. To identify new potential drug leads, a database of 6 million purchasable compounds was screened using the Glide Virtual Screening Workflow on a mixture of cluster and grid computing resources. Further post-processing and selection yielded a list of 200 compounds to assay, of which 24 were active with IC50s ranging from 2 to 25 uM. Prior to this work, very few ligands were known, with none having IC50s better than 50 uM. Details of the workflow and further work involving Phase pharmacophore searching and Canvas similarity-based searching to identify additional potential leads will be presented.

COMP 308

Development of a general molecular mechanics force field for organic molecules

***Richard A. Friesner**, Department of Chemistry, Columbia University, 116th and Broadway, New York, NY 10027, Fax: 212-854-7454*

We will describe the development of a new molecular mechanics force field aimed at broad coverage of chemical space, with a particular focus on compounds of interest in medicinal chemistry. In contrast to previous force fields such as MMFF, the present force field employs a large number of torsional parameters (more than 12,000, vs. 200 for MMFF)derived from high level quantum chemistry as a starting point for building an accurate potential energy surface for rotatable bonds in general organic molecules. Automated tools have been developed to facilitate the process of fitting novel torsions as they appear in molecules of interest. Various tests of the force field, as well as performance on the training set, will be presented.

COMP 309

Developing a fast polarizable force field: Small molecules and alanine peptides

***George A. Kaminski**, Department of Chemistry, Central Michigan University, Mount Pleasant, MI 48859, Fax: 989-774-3883*

We have previously developed a fast approximation for explicitly treating electrostatic polarization. It permits to speed up polarizable calculations by ca. an order of magnitude without any loss of accuracy. This formalism is now being used to produce a new fast polarizable force field for proteins and other biologically relevant molecules. In this presentation, parameters for small model molecules and alanine peptides will be discussed. Quantum mechanical data has been used extensively to provide target data for the parameter fitting. Strengths, weaknesses and challenges related to this approach will be addressed with the NMA molecule used as a biologically important example. -13-2008-->

COMP 310

Kirkwood-Buff theory as a guide to parameter development

***Paul E. Smith**, Department of Chemistry, Kansas State University, 111 Willard Hall, Manhattan, KS 66506-3701, Fax: 785-532-6666*

Kirkwood-Buff (KB) theory is an exact theory of solutions that can be applied to mixtures of any number of components of any type. KB theory relates thermodynamic properties of the solution to intermolecular distributions observed between the different components within the solution. We have been using KB theory to help guide the parameter determination process for a simple nonpolarizable force field being developed for peptides and proteins. In particular, this approach allows for a correct balance between self association and solvation in solution. Here we review our current progress in this area to date.

COMP 311

Polarizable force fields for continuum solvent models

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We have explored the feasibility for a continuum treatment of electronic polarization in molecular mechanics simulations with implicit solvents based on the Poisson-Boltzmann theory. Our tests show that the charging model can be used consistently in different dielectric environments and different molecular conformations, and it transfers well from training monomers to tested dimers. Comparison with experiment shows that the new continuum polarizable model is reasonable, with similar accuracy as B3LYP/cc-pVTZ in reproduction of dipole moments of selected organic molecules in the gas phase. We have further tested the validity of interchanging the Amber van der Waals parameters between the explicit and continuum polarizable force fields with a series of dimers. It can be found that the continuum polarizable model agrees with MP2/cc-pVTZ very well, with deviations in dimer binding energies less than 0.9kcal/mol in the aqueous dielectric environment. Finally we have optimized atomic cavity radii with respect to experimental solvation free energies of 353 training/testing molecules. Overall a root-mean-squared deviation of 1.30kcal/mol, unsigned average error of 1.07kacl/mol, and correlation coefficient of 92% are achieved for all molecules. Given the development documented here, the next natural step is the construction of a full protein/nucleic acid force field within the new continuum polarization framework.

COMP 312

Browsing chemogenomic space with protein-ligand fingerprints

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Predicting the selectivity profile of bioactive compounds towards numerous targets can be addressed either by considering ligand-based similarity to biologically-annotated ligands or by serially docking a ligand to multiple ligand-binding sites. Combining both ligand-based and target-based searches in a same query should enable a more exhaustive search of chemogenomic space but requires designing generic protein-ligand descriptors. We herewith present a novel descriptor of protein-ligand complexes generated by concatenating ligand and protein cavity fingerprints.

Starting from 23,000 non-peptides ligands of 160 human G Protein-coupled receptors (GPCRs), several machine learning algorithms were tested for their ability to discriminate true from false GPCR-ligand complexes using specifically designed GPCR-ligand 1-D fingerprints. The protein-ligand fingerprints were interestingly superior to simple ligand fingerprints in predicting the true target of GPCR ligands and could be used to predict ligands for orphan GPCRs close to liganded receptors.

The first generation of target descriptors can only be applied to a single gene target family but novel directions to encode any protein cavity with a unique 1-D fingerprint will be outlined. The second generation of cavity descriptor should enable browsing the entire target-ligand chemogenomic space with true predictve power.

COMP 313

Optimizing drug classification by feature selection: To bind or not to bind that is the question

*Henning Riedesel and **E. W. Knapp**, Department of Biology, Chemistry, Pharmacy, Freie Universität Berlin, Fabeckstrasse 36A, Berlin 14195, Germany, Fax: **49 30 838-3464*

The classification samples of the 2006 COEPRA [http://www.coepra.org/] contest comprise small training and test sets of nonapeptides described by 5787 component feature vectors. A scoring function linear in parameter and quadratic in feature space that defines a quadratic hyper-surface in feature space was used for classification. Parameters of the scoring function were determined by least square optimization. Since the dimension of feature space was much too large, feature selection was necessary, which was performed with a genetic algorithm. The resulting small optimized feature sets are among the best obtained by all groups in the COEPRA contest. The prediction performance was optimized furthermore, deriving for each pair of molecules from training and test

set weights that are based on molecular similarity. These weights were used for learning. Thus, the parameters of the scoring function were tuned individually for each molecule of the prediction set resulting in additional improvements of prediction performance.

COMP 314

Modeling of complex chemical genomics databases

***Alexander Tropsha**, Laboratory for Molecular Modeling, School of Pharmacy, University of North Carolina, CB # 7360, Beard Hall, School of Pharmacy, Chapel Hill, NC 27599-7360, Fax: 919-966-0204*

Modern experimental drug discovery efforts are increasingly focusing on the development of multi-target directed ligands that produce the desired pharmacological and pharmaceutical effects. Recent advances in high-throughput screening and multi-target testing of compound libraries coupled with the establishing publicly available databases of biologically tested compounds call for the development of sophisticated computational tools and models of complex chemical genomics data. We define a dataset as complex if multiple measures of biological activity/property are reported for all (or most of) compounds in the entire chemical library. The examples of complex datasets include Pubchem, PDSP, DSS-Tox and others. We shall consider emerging methodologies for analyzing complex chemogenomics datasets such as subspace clustering, Distance Weighted Discrimination, database graph analysis, and others. We shall present models that relate compound structure to their multi-target profiles (as opposed to more traditional single target specific models). Modeling of complex chemogenomics databases present new challenges and new frontiers in molecular modeling.

COMP 315

Fragment based de novo design

***Regine S. Bohacek**, Boston De Novo Design, 50 Commonwealth Ave., Boston, MA, MA 02116*

An ideal de novo design program would generate all possible molecules that bind to a target and have specific properties such as high affinity, synthetic accessibility and good pharmacokinetics. To achieve this goal, our initial strategy was to first generate all molecules that are spatially and chemically compatible to a binding site and then evaluate and rank them using scoring functions. This strategy proved to be impractical because the number of unique molecules that

can fill a binding site was extremely large(1) and the scoring functions could not reliably filter the output.

Our new strategy narrows the search by using fragments already positioned in the target binding site. The fragments and their coordinates can come from X-ray structures or docking studies of know ligands or small molecules. The user can select fragments already known to possess desirable chemical properties or fragments known to form important interactions with binding site atoms.

The de novo program, AlleGrow, links the fragments using both linear linkers as well as an extensive library of simple and complex cyclic scaffolds. The scaffold libraries contain 3-dimensional coordinates for all low energy ring conformers. To ensure accurate geometry, AlleGrow reproduces these 3-dimensional structures.

This talk will give examples which show how AlleGrow can use fragments and “regrow” known inhibitors of ACE, HIV protease, CDK2 and the SH2 domain of SRC kinase.

This work leaves open the question of how to identify a larger ensemble of desirable starting fragments which can be used to generate a more complete set of desirable molecules.

(1) R.S. Bohacek, C. McMartin, JACS (1994) 116, 5560-5571.

COMP 316

High-throughput MD simulations for predicting ligand binding affinities and thermodynamic parameters

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MD simulations have traditionally been viewed as too time consuming for practical use in drug discovery applications and free energy calculation techniques may also have failed in delivering sufficiently reliable results. With modern large-scale computational resources it is, however, becoming possible to explore the actual limits of these methods for problems related to ligand binding. We will discuss the use of MD simulation techniques for binding affinity prediction on larger compound sets (>1000) and present examples of this approach. Another topic that will be discussed is whether it is possible to obtained sufficiently accurate thermodynamic parameters from “brute force” MD simulations of protein-ligand complexes. It this context it is important to bear in mind that the connection to experiments is via the total enthalpy and entropy changes that involve both ligand, protein and solvent contributions.

COMP 317

Moiety-based design of ligands: Impact of low free energy, tightly-bound waters

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Waters bound with low free energy to a target molecule play an important role in ligand binding, but characterizing this role remains a challenge. We have developed new methods for ranking bound water sites by free energy, sampling 3-way protein-water-ligand interactions, and finding multi-body water configurations. The approach described here is a substantial elaboration of the method of annealing of chemical potential in GC Monte Carlo simulations (Guarnieri, et al). First, more complete sampling and rapid convergence is achieved using a novel adaptive, multivariate, multiple-resolution annealing scheme. Second, a charge factoring algorithm for electrostatics provides a more efficient and reliable energy calculation. Third, mixed-species (water + fragment) MC sampling models 3-way effects. Three case studies of ligand designs, including comparisons to experiments for P38, Cox-2, and cAbl, will be reported. The results will be contrasted to methods that do not adequately account for entropy or multi-body water configurations.

COMP 318

Cross-docking to cdk2: A virtual screening study

Johannes Voigt*, Vincent S. Madison, and Jose S. Duca, Department of Drug Design, Schering-Plough Research Institute, 2015 Galloping Hill Road, Kenilworth, NJ 07033, Fax: 908-740-4640*

We recently published a comprehensive cross docking study on CDK2 covering the analysis of docking accuracy and score/affinity correlations for a uniform set of 150 CDK2 crystal structures (Duca, Voigt, J. Chem. Inf. Model. 2008, 48, 659-668 and 669-678).

In agreement with previous docking/scoring evaluations, the docking accuracy of Gold and Glide was good, while the score/affinity correlations were not satisfactory.

In this study virtual screening for this unique data set was investigated. The following questions were addressed: A) Does virtual screening for this data set work? B) If yes, does it work for the correct reasons? Here it is valuable to have the experimentally determined binding modes of the active ligands. C) What is the best choice of the decoy set, what really is a decoy, and is a decoy set only valid in the context of the active molecules? In comparison to our in-house ligands, the DUD CDK2 data set was used ("Benchmarking Sets for Molecular Docking" Huang, N., Shoichet, B.K., Irwin, J.J., J. Med. Chem. 2006, 49, 23, 6789 - 6801.) D) Does combing of docking results from multiple protein structures enhance the performance? E) How do Gold and Glide compare?

COMP 319

Predicting kinase selectivity profile using Free-Wilson QSAR analysis

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Kinases are involved in a variety of diseases such as cancer, diabetes, and arthritis. In recent years, many kinase small molecule inhibitors have been developed as potential disease treatments.

Despite the recent advances, selectivity remains one of the most challenging aspects in kinase inhibitor design. To interrogate kinase selectivity, a panel of 45 kinase assays has been developed in-house at Pfizer.

Here we present an application of in-silico quantitative structure activity relationship (QSAR) models to extract rules from this experimental screening data and make reliable selectivity profile predictions for all compounds enumerated from virtual libraries.

We also propose the construction of R-group selectivity profiles by deriving their activity contribution against each kinase using QSAR models. Such selectivity

profiles can be used to provide better understanding of subtle structure selectivity relationships during kinase inhibitor design.

COMP 320

Use of multiple kinase crystal structures in lead discovery

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A set of five crystal structures of the catalytic domain of the same kinase in complex with five different chemotypes was used in virtual screening (VS). The five structures were chosen from a larger set of available co-crystal structures and exhibited significant movements in the ATP-binding site. The five structures were used both in prospective and retrospective virtual screening using Glide docking.

The prospective VS studies were performed using HTVS Glide followed by Glide in SP mode. Re-ranking with MMGBSA was performed after Glide SP docking. Both the in-house compound collection and commercially available compound libraries were used to find novel leads. Top-scoring lists from each of the five receptors were assessed visually and chemically before submission for experimental testing.

The retrospective VS studies were performed using a lead-like subset of compounds tested in HTS. The ability of each of the five structures to enrich for confirmed HTS hits will be assessed.

For both the prospective and retrospective VS studies hit rates will be presented as well as chemical overlap between the top-scoring compounds. Enrichment factors for individual receptors and consensus enrichment across the set will be presented as well.

COMP 321

Obtaining chemistry ideas from computational de novo design

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In-silico virtual screening is routinely conducted for selecting candidate compounds from general compound collection or reaction-based virtual compound libraries based on either target receptor structures or known drug/lead compounds. While looking for viable ligand candidates from available compounds can quickly follow-up through biological testing, the difficulty in achieving structural novelty is its intrinsic weakness. Screening a novel chemical reaction-based virtual compound library may resolve the novelty deficiency, but many reaction ideas are not necessarily related to the current drug target. Computational de novo design can also be based on receptor structures or drug molecules, and it helps to create novel chemistry ideas that are enriched with feasible drug candidates. Here, we propose a practical approach with its application in a kinase target.

COMP 322

Atomic details of the Mg2+-dependent ADP release from the catalytic subunit of the cyclic-AMP-dependent protein kinase

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Protein kinases comprise an important class of enzymes that is involved in regulation of diverse biological processes in eukaryotic cells by means of phosphorylation. The cyclic-AMP-dependent kinase - PKA - is among the best studied. The catalytic C-subunit of PKA is conserved within the family, and transfers the phosphate group from ATP to its protein targets. Kinetics studies indicate that subsequent release of the product ADP by the C-subunit could limit the enzyme turnover rate and also involves an unknown conformational transition. Importantly, the ADP release strongly depends on the presence of Mg2+ ions within the active site that can accommodate up to two ions. However, the mechanism of the Mg2+-dependent ADP release is poorly understood. Here we use a novel transition path ensemble technique – the generalized gradient-augmented Harmonic Fourier Beads method - to explore the atomic details of how the Mg2+ ions regulate release of the ADP.

COMP 323

Sensitivity in alchemical free energy calculations: What matters?

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Often, choices of parameters, algorithms, or decisions made in setting up a system for alchemical free energy calculations can greatly affect the potential energies but may or may not have a significant impact on the computed free energies. We examine a number of such choices in comparison with "gold standard reference" calculations, examining the impact on both hydration free energies of small molecules and small-molecule binding free energies to a model protein system in an effort to practically gauge the sensitivity of the computed free energy to a number of these choices.

COMP 324

Improving efficiency and accuracy in relative free energy calculations

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Relative free energy calculations continue to hold great promise for rational drug design and molecular engineering applications. Yet their daily application requires improvements in efficiency and accuracy to enable a prediction for measurement that is reasonably bounded and capable of being interpreted in the right context. In this talk the emphasis will be on approaches to speed up the relative free energy calculation and to perform these calculations with an understanding of the errors, so that results from a calculation can be fairly presented to the experimental community.

COMP 325

Solvation free energies of small molecules: Comparison of the nonpolar and electrostatic contributions from different charge methods, force fields and free energy protocols.

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Accurate determination of solvation free energy plays important roles in numerous areas of drug discovery. For example, ligand and receptor desolvation is a vital component of current docking tools. Also, partitioning of the drug between various solvents governs its pharmacokinetics properties.

Here we describe a methodology based on state-of-the-art Free Energy Perturbation calculation with explicit water model TIP3P to accurately determine the solvation free energy for a set of 244 ligands with diverse chemical functional groups commonly found in drugs and drug-like candidates. The free energy of solvation for these ligands were calculated using three coupling (staging) parameters, s, ξ, and λ , using the PERT module of the program CHARMM to separate the free energy into its components - electrostatic, dispersive and attractive parts. The resulting trajectories from MD simulations were processed by the weighted histogram analysis method (WHAM). To increase the computational efficiency, all free energies were calculated with only 400 explicit TIP3P water molecules, with the influence of the remaining bulk being incorporated via the spherical solvent boundary potential (SSBP). As a comparison, we also calculate the solvation free energies of the test set using Generalized Born model of solvation (GBSA in AMBER and GBSW in CHARMm). We use two fixed-charge force fields designed for small molecules - General AMBER force field (GAFF), and CHARMm MSI. Since electrostatics plays a crucial role in free energy calculations, we also compare the results from various commonly used charge generation models based on semi-empirical (AM1-BCC) and quantum chemical calculations [charge fitting using ChelpG and RESP]. The results from these free energy calculations will be discussed. While running these FEP calculations, the emphasis has been given on automating them so that it can be used on larger database of ligands in a user friendly way with minimum user intervention.

COMP 326

Inclusion of free energies of solvation during force field optimization

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Empirical force field parameters for biological systems need to accurately treat interactions of the solute portion of the model with the surrounding environment. Of these interactions, those with aqueous solution are among the most important. Accordingly, accurate treatment of solute-solvent interactions by an empirical force field represents an essential component of the model. To achieve this goal

during our ongoing optimization of a polarizable force field based on a classical Drude oscillator free energies of solvation have been considered during parameter optimization. Careful evaluation of the free energies showed systematic differences between calculated and experimental free energies of solvation when nonbond parameters optimized for pure solvents (i.e. neat liquids) were applied. Corrections for these systematic differences have been developed and implemented.

COMP 327

Comprehensive comparison and assessment of force fields for pharmaceutical applications by computation of hydration free energy

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The use of force fields for molecular simulations by the pharmaceutical industry has been somewhat hampered by the lack of a thorough and consistent comparison of statisticaly well converged simulation results for properties where adequate experimental data is available. We are engaged in a joint effort to assess three of the most popular force fields (AMBER, CHARMM and OPLS-AA) with respect to their ability to accurately compute hydration free energies for a set of approximately 300 molecules possessing various amounts of drug-like chemical functionality. Early results showing the differences in hydration free energies computed using the force fields and from experiment will be presented. The simulations are being performed on the BlueGene supercomputer at IBM using specially developed software. Extreme care was taken to verify that support for each force field was correctly implemented in the software and that consistent methodology was employed.

COMP 328

Predictive calculations of absolute binding free energies

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Accurate and reliable calculation of binding free energies between proteins and ligands could greatly help drug discovery and protein design, but this has proven difficult. We discuss our recent work in developing and applying methods for predicting absolute binding free energies between proteins and ligands, and some recent successful predictive tests of these methods. Protein flexibility plays a key role even in relatively rigid binding sites, and accurate binding free energies cannot be estimated from any static protein structure without a proper accounting of protein strain energies and thermodynamics.

COMP 329

Ab initio QM/MM free energy simulation: An opportunity and challenge

Hao Hu *and Weitao Yang, Department of Chemistry, Duke University, Box 90349, Durham, NC 27708*

With the steady improvement of computational resources, ab initio QM/MM free energy simulation becomes more and more a reality. In this talk, we will describe two methods we recently developed for carrying out efficient and accurate ab initio QM/MM free energy simulations. Application results of the solvation free energies of several organic compounds, which possess important biological resemblance to the side chains of amino acids, will be reported too. The comparison of the QM/MM and pure MM results strongly suggests that the ab initio QM/MM free energy simulations can play important role in the development of new generation of MM force fields. The results also suggest that ab initio QM/MM simulation poses an important challenge to the development of QM/MM Hamiltonian.

COMP 330

Transformation of nitrocompounds by nitroreductase

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Because of the recalcitrance of nitroaromatics compounds (NACs), they have been accumulated in the locations of manufacturing, storage, and decommissioning over the past several decades. NACs and their metabolites are known to be toxic, mutagenic and carcinogenic to various organisms including humans, and therefore should be removed from contaminated sites. Recently, biodegradation of NACs has been proposed as inexpensive and environmentally clean way for their disposal. Although the major processes affecting the biodegradation of NACs have been investigated qualitatively, many issues regarding a reaction mechanism and enzymatic selectivity remain unsolved.

Nitroreductase (NR) is a flavoprotein which catalyzes the pyridine nucleotide-dependent reduction of nitroaromatics. Previous studies established so called ping-pong kinetic mechanism. In order to clarify the poorly understood mechanisms of two-electron reduction of NACs by flavoenzymes, we examined the nitroreductase reactions by several distinctive QM/MM approaches. We also concentrate on the role of electronic and structural parameters of nitroaromatic compounds in their reduction by the bacterial NAD(P)H niroreductase.

COMP 331

The potential energy surface for the dehydrogenation of 4-hydroxy-tamoxifen and contribution of P450 conformational dynamics to enzyme-substrate interactions during tamoxifen metabolism

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The factors that contribute to the formation of reactive electrophilic intermediates during drug metabolism by hepatic cytochrome P450 (P450) enzymes are of great interest for improved drug safety. Dehydrogenated intermediates formed via P450-catalyzed reactions are believed to contribute to idiosyncratic and long-term toxicities that are difficult to predict during normal drug trials. To better understand the specific contributions of substrate-enzyme interactions during P450 catalysis for competing dehydrogenation and oxygenation mechanisms we have performed UHF/6-31G* and UB3LYP/6-31G* calculations for stretching of key covalent bonds involved in the P450 metabolism of 4-hydroxy-tamoxifen (4-OHT). We have performed these calculations for all reaction intermediates

predicted to exist at stable minima along the dehydrogenation reaction coordinate via both radical and cationic mechanisms. We have also performed molecular dynamics simulations to determine the contribution of predicted P450 conformational dynamics on docking studies of select tamoxifen metabolites to better understand the contributions of key substrate-enzyme interactions during P450-catalysis. These results provide encouraging biophysical insights into the electronic and conformational constraints that contribute to the selectivity for P450-catalyzed oxygenation versus dehydrogenation reaction mechanisms.

COMP 332

QM/MM calculation of driving force and reorganization free energy for intraprotein electron transfer in Ru(bpy)2(im) modified cytochrome b5 and cytochrome c

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We have previously devised a QM/MM//classical MD computational scheme that allows for the calculation of reaction and reorganization free energy for long-range electron transfer (ET) in redox proteins. In this contribution we present results for ET between the heme cofactor of cytochrome b5 (cyt b5) and a Ru(bpy)2(im) (bpy=bipyridine, im=imidazole) chromophore docked to His26 at the surface of cyt b5. We find that the reaction free energy is 0.27 eV lower than for the same ET reaction in cytochrome c in excellent agreement with the experimental estimate of 0.26 eV. However, the reorganization free energy is overestimated by a factor of two when compared to experimental data. Using a polarizable force field for protein and water the reorganization free energy in cyt b5 and cyt c decreases by about 30% to 1.2 eV. This value is in agreement with what is expected for ET between a heme cofactor and a solvent accessible acceptor. However, a considerable deviation with the experimental estimate for cyt c (0.74 eV) remains, and we argue that the experimental value is possibly underestimated. Finally we discuss the contributions of the cofactors, amino acid residues and solvent to ET free energies and highlight differences arising from the different folds in cyt c and cyt b5.

COMP 333

QM/MM studies of reactivity in metalloenzymes

***Jeremy N. Harvey**, School of Chemistry, University of Bristol, Cantock's Close, Bristol BS8 1TS, United Kingdom*

Understanding mechanisms of reaction and reactivity in enzymes is a challenging problem in computational chemistry. Excellent insight can be obtained in some cases from ab initio studies of cluster models of enzyme active sites. For quantitative results, and for study of fine details such as protein conformational effects, a model including the bulk of the protein will however be needed, and hybrid QM/MM approaches then appear best suited.

We have used QM/MM methods to study reactivity in a number of enzymes and metalloenzymes, and will discuss results, including relative successes, and challenges, in the paper.

COMP 334

Light-induced processes in biological systems: From first principles to biotechnology

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We are using multi-configurational (CASSCF) QM/MM molecular dynamics together with surface hopping to directly simulate photochemical processes in biological systems. Our simulations do not only allow us to correctly predict measurable quantities, such as fluorescence lifetimes and structures of intermediates, but also to provide structural and dynamical information at a resolution well beyond experiments. The talk will focus on recent applications on ultra-fast excited-state decay in DNA, and the photo-activation of photoreceptor proteins. Our most recent work concerns the effects of mutations on the photochemistry in these proteins and will also be discussed. Our ultimate aim is to re-design photoactive proteins for biotechnological applications, such as data storage and biomolecular imaging.

COMP 335

Toward routine long timescale QM/MM/MD simulations: Improvements in AMBER's QM/MM support

***Ross C Walker**, Strategic Applications Computing, San Diego Supercomputing Center, University of California, San Diego, 9500 Gilman Drive #0505, La Jolla, CA 92093*

Given recent advances in computing power, coupled with improvements in semi-empirical Hamiltonians, long timescale, on the order of a nanosecond or more, QM/MM molecular dynamics (MD) simulations are now becoming routinely possible allowing chemical reactions in proteins to be studied using MD methodology in explicit solvents. Only recently have QM/MM MD implementations been modified to permit such simulations. AMBER v9 addressed a number of issues including gradient accuracy, energy conservation, long range electrostatics (PME), execution speed, link atom stability, support for implicit solvents and ease of use. In this talk an overview of recent improvements in the AMBER QM/MM MD implementation will be given including discussion of new methodology supported by AMBER v10, improvements in parallel performance on multi-core architectures, improvements in supported features and performance of SCC-DFTB methods, newly supported Hamiltonians as well as recent experience in coupling replica-exchange approaches to QM/MM MD simulations.

COMP 336

The affinity and position of protons in biomolecules: Insights from QM/MM simulations

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Determining the affinity and location of protons is important in the mechanistic analysis of many biomolecules, especially for those involved in proton pumping. In this talk, I'll discuss the development and application of QM/MM methods to probe related issues in several protein systems, including pKa prediction for buried residues in SNase, the issue of an extra proton in the D-channel of cytochrome c oxiase and the nature of the proton release group in bacteriorhodopsin. To gain a thorough understanding of these issues, the importance of sampling and a careful analysis of systematic errors in the QM/MM potential are discussed.

COMP 337

Insights into enzymatic halogenation from QM/MM studies

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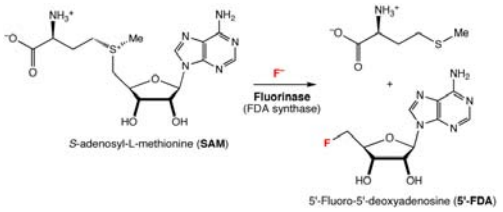
Thousands of natural organohalogens are known, most of which are bioactives, produced by organisms from across the phylogenetic tree. However, the biosynthetic details are only just being established. X-ray structures of three novel enzyme families – the first fluorinating enzyme, the flavin-dependent halogenases, and the non-haem iron halogenases – have only recently become available. Our work so far has concentrated on the fluorinase, which catalyses the formation of 5′-fluoro-5′-deoxyadenosine from *S*-adenosyl-L-methionine (SAM) and F^- (Scheme). We have performed QM/MM studies at the DFT/CHARMM level to gain insight into the C–F bond formation step in the enzyme and compared it to the intrinsic reactivity of the substrates in solution. We will discuss the role of the enzyme in promoting and controlling the reaction, resulting in a 10^8-fold rate acceleration relative to solution. We will also report on the influence of substrate modifications. We will give preliminary results and an outlook on future work on the flavin-dependent and non-haem iron halogenases.

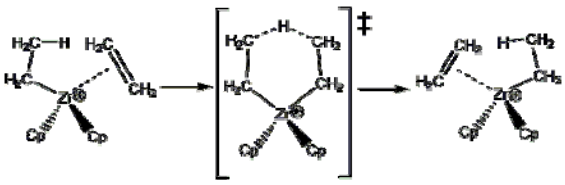


COMP 338

Simulating the dynamics of catalytic reactions: Using transition path sampling to overcome the rare event problem in QM/MM molecular dynamics

Christopher N. Rowley *and Tom K. Woo, Department of Chemistry, University of Ottawa, 10 Marie-Curie, Ottawa, ON K1N 6N5, Canada*

DFT calculations have become an indispensable tool for studying organometallic reaction mechanisms. Finite-temperature dynamical effects, which are known to be significant in many of these reactions, can be challenging to discern from routine quantum chemical calculations. In principle, a direct molecular dynamics simulation can provide an avenue to explore these effects. In practice, the bond breaking and forming processes that are of interest often involve large barriers that are impractical to simulate, as >μs waiting times are typical. Transition path sampling is an innovative technique to overcome these timescale limitations (Dellago, Bolhuis, Geissler. Adv. Chem. Phys. 2002, 123, 1-78). Given an initial reactive trajectory(Rowley, Woo. J. Chem. Phys. 2007, 126, 024110/1-024110/8), an ensemble of short, dynamical trajectories is harvested using a Monte Carlo algorithm. In conjunction with QM/MM methods, path sampling has allowed us to investigate the frictional and electrostatic effects of the solvent on the dynamics of two prominent organometallic reactions mechanisms (Rowley, Foucault, Woo, Fogg, Organometallics 2008, in press).



COMP 339

Catalytic mechanism and performance of artificial Kemp elimination enzymes

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A series of active enzymes and catalytic antibodies for Kemp elimination have been recently designed and tested experimentally. A detailed analysis and evaluation of the catalytic performance of seven artificial enzymes and two catalytic antibodies is presented herein. Enzyme-catalyzed reactions are simulated using QM/MM Monte Carlo, in the context of the Free Energy Perturbation method, and in explicit solvent represented by the TIP4P water model. Simulations yield information about the catalytic mechanisms, activation barriers, and structural changes at the binding sites in the course of the reactions. The results interpret the experimental observations and reveal the origins of differences in catalytic performance. The work contributes toward the progress of artificial enzyme design.

COMP 340

Coarse grain simulations of proteins and peptides: Parameterization from all-atom simulations of 400 tetrapeptides (GXYG) in aqueous solutions

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All-atom MD simulations of four hundred tetrapeptide GXYG, in which G is glycine and XY stands for any two amino acid residues (20 times 20 combinations), are carried out in aqueous solutions by utilizing the AMBER99 force fields. The conformational data (2 ns for each tetrapeptide) collected from these 400 simulations are mapped to our coarse grain (CG) models of proteins and peptides. Then distribution of CG bonds, bends and torsions are fitted to

generate a complete set of CG parameters for all amino acids. The generated parameters are compared with those extracted from PDB structures of proteins when available.

COMP 341

Cold and heat adaptation of citrate synthase: Effects on the general base catalyzed keto-enol isomerization step

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Life has adapted to most extreme environments on earth, with growth temperature spanning between water freezing and boiling points. The adaptations have also affected chemical reactions taking place in organisms and enzymes are optimized to work efficiently at different temperatures as a result. This temperature adaptation of catalysis is investigated by molecular simulations of citrate synthase, which is part of the citric acid cycle and catalyzes the formation of citrate form oxaloacetate and acetyl-coenzyme A. Reaction free energy profiles are calculated for the proton abstraction from acetyl-coenzyme A by psychrophile, mesophile and hyperthermophile homologues of citrate synthase with the very good agreement with experimental rates. The calculated energetics clearly point towards the degree of electrostatic transition state stabilization as the major difference between the catalytic characteristics of these enzymes. Activation enthalpy for psychrophilic citrate synthase, as determined by van't Hoff plots, is lower then for the mesophilic enzyme, which is in agreement with the establish trend in temperature adaptation. Similarly, active site flexibility, as determined by atomic positional fluctuations of key residues, and overall flexibility, does not appear correlated with temperature adaptation of the catalytic rate.

COMP 342

Mathematical modeling and sensitivity analysis for the nociceptive signaling by P2 receptors and protein kinases

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Intracellular Ca2+ dynamics in a sensory neuron underlies a wide range of neuronal functions involved in pain signaling. In this study, we used mathematical modeling and sensitivity analysis to explore the ATP-induced Ca2+ signaling mechanisms. Two distinct signaling pathways, P2X and P2Y activations, were modeled based on mass action kinetics and most parameter values were compiled from literature. The model could quantitatively reproduce experimental data generated from dorsal root ganglion neurons. We then used Monte Carlo sensitivity analysis to gauge the fragile and robust mechanisms in the signaling network in no agonist activation and P2X/P2Y activations. The sensitivity results revealed that Ca2+ pumps (ATPases:SERCA, PMCA) and Na+-Ca2+ exchangers are the most important mechanisms in the intracellular Ca2+ signaling network, regardless of agonist activations, corroborating in vivo and in vitro experimental evidence. Analysis of the sensitivity results for ATP-induced P2X and P2Y activations revealed that they have distinct mechanisms of fragility, indicating that they have different pathway to control Ca2+ signaling in the cytosol and distinct regions of molecular influence. We also modeled possible interactions of P2X and P2Y/other metabotropic receptors that may contribute to the P2X3 desensitization or hypersensitivity underlying pathological pain states. Our simulation results showed that cross-talks between P2X and P2Y via protein kinases (PKC, PKA, CaMKII) can control the pain signaling by modulating the P2X receptor activity under certain pathological conditions. Overall, the mathematical model provided quantitative insights into P2 receptor signaling network and the sensitivity analysis of the model provided qualitative insight into fragile and robust mechanisms that can be targeted in drug design, despite parameter uncertainty.

COMP 343

Molecular dynamics simulations of R67 dihydrofolate reductase: Investigation into the cooperative binding

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R67 dihydrofolate reductase (DHFR) catalyzes the reduction of dihydrofolate (DHF) to tetrahydrofolate (THF). The active site binds either two reactants (DHF), two cofactors (NADPH) or one of each. Binding of a second ligand shows either negative or positive cooperativity. Molecular dynamics simulations were initially performed on the truncated ligands. Unlike other allosteric enzymes which achieve binding cooperativity through conformational changes, this enzyme does not appear to undergo any backbone alterations upon ligand binding. Therefore, a different mechanism must be involved in the cooperativity. Binding energy analysis reproduced the negative cooperativity of two NADPHs and the positive

cooperativity of the ternary complex. Further analysis indicated that the residue Q67, the electrostatic potential, and ligand contacts may play an important role in the binding cooperativity. Preliminary results from simulations of the full ligands will be presented to further address the source of the cooperativity.

COMP 344

Molecular modeling, synthesis and activity studies of inhibitors targeting Alzheimer's disease beta-secretase (BACE1)

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There exists a broad consensus among the Alzheimer's disease research community that the key to successful treatment lies in the specific inhibition of beta-amyloid converting enzyme 1 (BACE1). A series of transition-state analogues of BACE1 inhibitors containing fused aryl or biaryl moieties were designed computationally to probe the S2 pocket of BACE1, synthesized, and tested for inhibitory activity. The structure-activity relationship of these inhibitors is discussed. It has been shown that unlike the bi-aryl, the fused-ring moiety is successfully accommodated in the binding site resulting in ligands with excellent inhibitory activity. The best ligands were also tested for their ability to reduce production of Abeta40 in mouse neuroblastoma cells. To harness our future BACE1 ligand design, we have developed a quantitative structure activity relationship (QSAR) for ‘non-peptidomimetic' BACE1 inhibitors using comparative molecular field analysis (CoMFA) and comparative molecular similarity indices (CoMSIA). In silico blood-brain barrier penetration is also discussed.

COMP 345

Efficient propagator methods for calculations on large molecules

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Efficient, predictive calculations of electron binding energies, double electron binding energies and excitation energies for large molecules are enabled by a new series of approximate electron, two-electron and polarization propagators. Generalizations of second order and renormalized electron propagators that accommodate the fractional occupation numbers of the transition operator method yield excellent results for core as well as valence ionization energies. Improved virtual orbitals that are adapted for specific transitions produce impressive efficiencies in higher-order calculations. New, finite-order methods for the two-electron propagator are capable of aiding assignments of Auger spectra. A combination of finite-order and renormalized self-energies in the polarization propagator yields promising predictions of excitation energies.

COMP 346

Efficient resolution-of-the-identity implementation of local scaled opposite spin second-order Møller-Plesset perturbation theory: A correlated look at mutual orientation in the fullerene dimer

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In this work, scaled opposite spin second-order Møller-Plesset perturbation theory (SOS-MP2) is recast within the framework of the local triatomics-in-molecules (TRIM) model. The resultant model, SOS-TRIM MP2, emerges as a robust, fourth-order methodology with the ability to treat electron correlation at the MP2 level for hundreds of atoms on a single processor. An efficient algorithm for performing SOS-TRIM MP2 single-point energy evaluations is presented along with computational timings for extended β-pleated glycine strands and compact α-helical DNA sequences within the TATA box using polarized double- and triple-ζ atomic orbital basis sets. A chemical application of SOS-TRIM MP2 theory follows in which the potential energy surface describing intermonomer separation among two competing mutual orientations of the fullerene dimer is explored at the extrapolated SOS-TRIM MP2/cc-pV(DT)Z level.

COMP 347

Generating benchmark energetics for water clusters and other noncovalent systems with the 2-body:many-body multicentered QM:QM method

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Convergent electronic structure techniques are invaluable tools for probing the subtle energetics of weakly-bound, non-covalent clusters. These demanding computational procedures, however, are generally limited to fairly small systems. For example, one can easily find databases of benchmark interaction energies for a wide range of dimers [See for example, J. Chem. Theo. Comput. 2005, 1, 415 and Phys. Chem. Chem. Phys. 2006, 8, 1985] while the same data for larger non-covalent molecular clusters (trimers, tetramers, etc.) are fairly scarce. Here we show how these high-accuracy benchmark procedures can be extended to larger clusters by taking advantage of the recently developed multicentered QM:QM methods [J. Comput. Chem., 2003, 24, 1563 and Mol. Phys., 2005, 103, 309]. In particular, a 2-body:many-body ONIOM scheme is used to generate CCSD(T) complete basis set (CBS) limit energetics for the trimers, tetramers, pentamers and hexamers of important weakly bound prototypes like water. Extensions to larger clusters (1-2 dozen fragments), to explicit solvation, to energy gradients and to Hessians will also be discussed.

COMP 348

Perturbation theory on vibrational-rotational spectroscopy

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The general scheme of doing Rayleigh-Schrödinger perturbation theory in vibrational-rotational spectroscopy is presented. Second and fourth orders anharmonic corrections to vibrational energy levels as well as second and fourth orders vibrational corrections to rotational constants illustrate the perturbation procedure. Analytical derivations and numerical determination of different spectroscopic parameters resulting from the theory are discussed and their interplay with the experimental evidence analyzed.

COMP 349

Post-DFT dispersion correction based on the atomic intrinsic polarizability tensor

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The recent approach presented by A. Becke and E. Johnson (*J. Chem. Phys.* **2007**, *127*, 154108) for the evaluation of dispersion interactions based on the properties of the exchange-hole dipole moment was combined with a Hirschfeld-type partitioning for the molecular polarizabilities into atomic contributions (A. Krishtal *et al*, *J. Chem. Phys.* **2006**, *125*, 034312). Preliminary results suggested that the resulting dispersion energy is sufficiently accurate for practical use without any empirical correction (A. Olasz *et al*, *J. Chem. Phys.* **2007**, *127*, 224105). Consequently, we extended the methodology into a full post-DFT model that includes gradients. Additionally, an equivalent of Becke and Johnson's formula that takes into account the polarizability's anisotropy was derived and implemented.

COMP 350

The golden age of computational thermochemistry in the sub-kJ/mol regime

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The recently developed high-accuracy W4 computational thermochemistry protocol, and several variants thereof, will be presented. We consider such contributions to the total atomization energies as connected quadruple excitations, T_4, connected quintuple excitations, T_5, diagonal Born-Oppenheimer corrections (DBOC), as well as basis set convergence of valence and core-valence post-CCSD correlation effects near the one-particle basis set limit. We found that quasiperturbative connected triple excitations, (T), converge more rapidly than L^{-3}, while higher-order connected triples, T_3-(T), converge more slowly — empirically, proportional to $L^{-5/2}$. The CCSDTQ-CCSDT(Q) difference converges quite rapidly with the basis set, and the formula 1.10[CCSDT(Q)/cc-pVTZ+CCSDTQ/cc-pVDZ-CCSDT(Q)/cc-pVDZ] offers a very reliable as well as fairly cost-effective estimate of the basis set limit T_4 contribution. Connected quintuple excitations, T_5, and higher excitations converge very rapidly with the basis set, and even an unpolarized double-zeta basis set yields useful numbers. In cases where fully iterative CCSDTQ5 calculations are not an option, CCSDTQ(5)$_\Lambda$ represents a viable alternative. DBOCs are significant at the 0.1 kcal/mol level in hydride systems. Post-CCSD(T) contributions to the core-valence correlation energy are only significant at that level in systems with severe nondynamical correlation effects. Our W4 atomization energies for a number of key species that cover varying degrees of nondynamical correlation

are in excellent agreement (better than 0.1 kcal/mol on average, 95% confidence interval narrower than 1 kJ/mol) with the latest experimental data obtained from the Active Thermochemical Tables (ATcT) thermochemical network. We then proceed to explore the performance of W4 theory for atomization energies and barrier heights of a few systems that exhibit severe multireference character such as the halogen oxides.

COMP 351

Mechanical and chemomechanical coupling in F1-ATPase

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F1-ATPase is the smallest rotary motor in biology. With ATP binding, hydrolysis, and product release, the motor induces a torque on the central shaft gamma-subunit, which rotates about 1000/sec in one direction. When an applied torque rotates the gamma-subunit in the reverse direction, the motor synthesizes ATP, its normal function in living cells. In this presentation, we will discuss the progress of using a multiscale approach that combines coarse-grained model, targeted molecular dynamics and free energy simulations to elucidate how the rotary motion is achieved via intimate coupling between the ligand binding/catalytic subunit conformations and the gamma-subunit.

COMP 352

Examining reaction free energies using QM/MM methods with chain of states methods or with vibrational subsystem analysis

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This presentations focus on a comparison of recent methods to examine the free

energy reaction profiles of enzymatic systems using QM/MM methods coupled with chain of states methods or with vibrational subsystem analysis. Recent chain of states efforts have been based on using distributed replicas based on the REPD code in CHARMM. The vibrational subsystem analysis allows the

estimate of vibrational free energies without the noise of the environment, nor the requirement that the environment be considered as a rigid block.

1. H. L. Woodcock, M. Hodoscek, A. T. B. Gilbert, P. M. W. Gill, H. F. Schaefer and B. R. Brooks. "Interfacing Q-chem and CHARMM to perform QM/MM reaction path calculations," Journal of Computational Chemistry, 28 (9): 1485-1502 (2007)

2. H. L. Woodcock, M. Hodoscek and B. R. Brooks. "Exploring SCC-DFTB paths for mapping QM/MM reaction mechanisms," Journal of Physical Chemistry a, 111 (26): 5720-5728 (2007)

3. Zheng W, Brooks BR. Probing the local dynamics of nucleotide-binding pocket coupled to the global dynamics: Myosin versus kinesin. Biophysical Journal. 89(1):167-78 (2005)

COMP 353

Classical free energy calculation of an enzymatic reaction mechanism for isopenicillin N synthase based on the ONIOM(QM:MM) method

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Isopenicillin N synthase (IPNS) is an important enzyme in the process of synthesizing penicillin. The reaction pathway can be split with several chemical steps. We investigate the IPNS enzymatic reaction energetics, applying the free energy perturbation (FEP) method combined with the ONIOM(QM:MM) method. We describe the reaction mechanism at the non-heme iron center by active site QM (DFT) as well as by ONIOM(QM:MM) optimization including protein environment, and then include the thermal fluctuation of the protein using classical MD simulation. Contributions of the protein environment and its dynamics can dominate the energy change of certain chemical step.

COMP 354

A triplet code in writing epigenetic marks

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Histone proteins play an important role in packaging DNA into nucleosome. The tails of histone proteins are subject to a variety of post-translational covalent modifications. These modifications form so-called epigenetic histone code and lead to distinct downstream events in the regulation of chromatin structure and gene expression. One such modification is histone lysine methylation which can govern many important biological processes. The biological consequences of the lysine methylation may differ depending on whether the lysine residue is mono-, di- or tri-methylated. Therefore, the ability of different protein lysine methyltransferases (PKMTs) to generate different methylation states for lysine (product specificity) adds more complexity to the histone code and provides an additional layer of regulatory control. Here we demonstrate that it may be possible to apply QM/MM free energy simulations to generate a triplet code for the prediction of how epigenetic marks of histone lysine methylation are written by PKMTs.

COMP 355

Probing the free energy barriers in rare chemical and biological events with advanced simulation techniques

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For a variety of rare events (including phase transitions, chemical reactions, and protein folding), the thermodynamics and kinetics can be characterized by a free energy profile expressed as a function of order parameters. Therefore, finding the appropriate order parameters and computing the corresponding free energy profile are among the most important themes in current simulation research of long time-scale processes. This presentation will focus on the recent development of the aggregation-volume-bias Monte Carlo based simulation method and the application of this atomistic approach to the molecular-level characterization of various long time-scale events. Topics will be selected from: (i) multi-component vapor-liquid nucleation involving water, organic substances, and salts; (ii) nucleation of crystallites in supercooled molecular clusters or crystallization of proteins from solution; and (iii) solvation induced conformational transitions of biological molecules.

COMP 356

Computational inference method for protein structure evolutions

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With the development of extensive databases of genetic sequence and phylogenetic inference methods, the reconstruction of ancestral protein sequences is an increasingly common practice. Inferred ancestral sequences may be synthesized and experimentally characterized, allowing the deduction of historical conditions. Even though the phylogenetic inference method is a powerful technique for the study of molecular evolution, any conclusions drawn from such studies are only as good as the accuracy of the method. Here, molecular modeling and computational simulation techniques have been employed to further refine predicted ancestral protein sequences and to study their possible structures. We present results from applying our approach to hypothetical proteins. Additionally, we demonstrate a possibility of extending our study to predict a future evolutionary direction for a protein from antibiotic resistance bacteria. Our results exhibit that the combination of phylogenetic analysis with advanced computational chemistry methods may lead better inference methods for protein structure evolutions.

COMP 357

A network of conserved interactions mediate allosteric signal transmission

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We use a combination of bioinformatic analysis and equilibrium molecular dynamics simulations in order to probe the mechanism of allosteric regulation in two biomolecular complexes - the histidine biosynthesis enzyme imidazole glycerol phosphate (IGP) synthase and the glutamyl-tRNA synthetase:tRNA (GluRS:tRNA) complex. Principal component analysis and correlation analysis of the biomolecular complex indicate that the dynamics involved in the allosteric transition are mediated by coupled motion between distant active sites in both proteins. An evolutionary analysis of IGP synthase revealed a conserved network of interactions leading from the effector binding site to the glutaminase active site, forming conserved communication pathways between the remote active sites. We used a network analysis of contact maps and correlation data from molecular dynamics simulations of GluRS:tRNA complex to identify amino acid/nucleic acid communities, regions of local structure that are highly intraconnected but loosely interconnected. While monomers within a single community can communicate through many alternate pathways, the communication between monomers in different communities takes place through a smaller number of critical paths. The shortest communication pathways

between all of the monomers in the network were calculated, and the evolutionarily conserved monomers that occurred in the majority of pathways for intercommunity signal transmission were predicted as residues important for allostery.

COMP 358

Group entropy analysis and hybrid quantum mechanical/molecular mechanical simulations for elucidation of enzyme function

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We will describe our research that has lead to a successful integration of sequence-based bioinformatics and atomic scale simulation on the Aldehyde Dehydrogenase (ALDH) family. This integration has resulted in compelling hypotheses concerning the molecular basis for two metabolic diseases as well as a novel enzyme mechanism. We developed and applied analyses that identify residues in biological macromolecules that confer specificity of interaction on the members of a paralogous family of molecules. The analysis uses the Kullback-Leibler (KL) distance; an information theory measure of entropy. Residues that have a high KL distance represent positions in the alignment where there are large systematic differences in the kinds of residues present in the two subfamilies (i.e., the defined subfamily under investigation and the rest of the alignment). We also sought to better understand how these residues impact on the ALDH chemical mechanism. Therefore, we employed molecular dynamics (MD) simulation methods using both Molecular Mechanical (MM) potentials for studies of substrate binding and hybrid Quantum Mechanical (QM)/MM potentials for the subsequent reactions. The results suggest that the intermediate formed upon nucleophilic attack of the enzyme on the substrate is stabilized by a proton transfer from a mainchain amide. This proton transfer is supported by interactions with a residue with high group entropy. Mutating residues that disrupt this “second sphere” interaction could be the molecular basis behind two metabolic diseases.

COMP 359

Concurrent bioinformatics and computational chemistry visualization of biomolecules

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Computational chemistry benefits from the integration of bioinformatics with structural computations. Concurrent visualization of sequence, alignment and crystal structure are used to identify an active site in human purine nucleoside phosphorylase (PNP) from the active site in tuberculosis PNP. The human PNP crystal is an open active site that must be closed to compare to the TB PNP active site. Concurrent bioinformatics and structural visualization suggests a successful computational modeling protocol that closes the active site so that it can be used for docking.

COMP 360

The class a – class b gpcr alignment

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We present a new approach to the class A - class B GPCR alignment based on the observation that GCR1, a well characterized plant GPCR, has sequence similarity to both class A and class B GPCRs. Thus, although standard alignment techniques fail to present a plausible alignment between class A and class B GPCRs, the class A – GCR1 and the class B – GCR1 alignments effectively define a class A – class B alignment. However, for some transmembrane helices, most notably transmembrane helix 5, the alignment is not completely clear and so additional techniques have also been employed, such as those used previously in the class A/B alignment by Frimurer and Bywater and those used by Baldwin et al. in the development of the rhodopsin C(alpha)-template structure.

COMP 361

DARS (Decoys As the Reference State) potentials extracted from structures of protein complexes

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DARS is a new class of interaction potentials, based on the inverse Boltzmann approach, and extracted from structures of protein complexes. The novelty of the approach is that we generate a large decoy set of docked conformations using

only shape complementarity as the scoring function (i.e., without any account for the atom types), and use the frequency of interacting atom pairs in these decoy structures as the reference state. Thus, developing the potential we compare the frequency of contacts between two specific atom types in X-ray structures of protein complexes to the frequency of contacts in the decoys that are devoid of specific interactions. The resulting potential is excellent for docking enzyme-inhibitor and most signal transduction complexes. Results are weaker for docking antigens to antibodies. We show that the problem is due to the biased amino acid composition in the CDR regions of antibodies, and it can be resolved by constructing potentials that account for the asymmetry of interfaces in antigen-antibody complexes.

COMP 362

Evolving force fields for implicit solvent and polarizable intermolecular interactions

***Charles L Brooks III**, Department of Chemistry, Biophysics Program, University of Michigan, 930 N. University Avenue, Ann Arbor, MI 48109*

In this talk I will review our progress over the past several years in the development of new force fields for use with implicit solvent models as well as ongoing efforts to develop the CHARMM polarizable force field. Focus will be given to novel additions to the force fields required to achieve improvements in performance for structure and thermodynamics. In discussing the development of new force fields for use with implicit solvent, we will illustrate the importance of developing a balance between the range of intermolecular interactions between explicit and implicit species. We will present recent findings regarding protein simulations using our present generation of polarizable force field.

COMP 363

New issues in the description of molecular energetics

***William L Jorgensen** and Julian Tirado-Rives, Department of Chemistry, Yale University, New Haven, CT 06520-8107*

Description of molecular energetics has been pursued through the development of the OPLS force fields and semiempirical quantum mechanical methods. The OPLS-AA force field was introduced in 1996 for classical modeling of the structures, conformational energetics, and condensed-phase properties of organic and biomolecular systems. The work has included extensive Monte Carlo simulations of pure liquids and dilute solutions. Recent pursuits have addressed cases where polarization is significant including aqueous solutions of alkali and

halide ions, cation-pi interactions, and substituent effects on hydrogen bonding. This has led to the investigation of the OPLS/CM1A and OPLS/CM1AP force fields, which represent efficient means for the inclusion of intramolecular and full polarization. For quantum methods, PDDG/PM3 has been developed as an improved semiempirical procedure. In recent testing, it was found to out-perform B3LYP/6-31G(d) for heats of formation and isomerization energies of large sets of organic molecules and to yield results of similar quality as B3LYP/6-31+G(d,p). In QM/MM studies of numerous organic reactions in solution, PDDG/PM3 has also performed well in reproducing observed medium effects on reaction rates.

COMP 364

Development and test of a set of dipole interaction models

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In this work, three dipole interaction models, the Applequist, the Thole linear and Thole exponential models, have been optimized to reproduce the high-quality experimental static molecular polarizabilities of a set of 420 molecules obtained from the molecular refraction measurements by Bosque and Sales. Among the three models, the Thole's exponential scheme with 14 atomic polarizability parameters exhibited the best performance in the ability to reproduce the experimental data and achieved an average unsigned error (AUE) of 1.18 au, a root mean square error (RMSE) of 1.79, and an average percent error (APE) of 1.35%. The reliability of the developed models has been extensively validated through an independent data set used by van Duijnen and Swart. Then the three models have been tested in the solvation free energy calculations with thermodynamic integration for a set of small molecules, which include the amino acid side chain analogs.

COMP 365

Toward accurate potentials for condensed-phase chemical reactions: Electrostatically embedded multiconfiguration molecular mechanics

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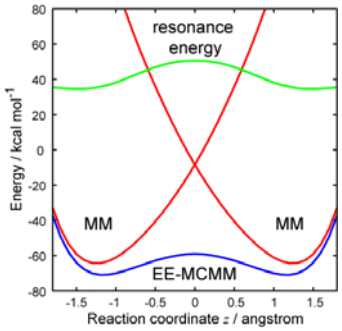
Combined quantum mechanical and molecular mechanical (QM/MM) methods have provided powerful means for studying chemical reactions in condensed phases such as liquids, enzymes, and solids. However, the high computational cost of quantum mechanical (QM) calculations prevents carrying out QM/MM molecular dynamics simulations with reliable accuracy and adequate sampling. In order to reduce the computational cost of the QM calculation, we have developed a new method called electrostatically embedded multi-configuration molecular mechanics (EE-MCMM) for generating global potential energy surfaces (PESs) in the presence of an electrostatic potential. EE-MCMM describes the global PES of a condensed-phase reaction with electronic structure information, in particular energies and partial charge distributions, obtained in the gas phase at selected geometries. Because this new method is efficient, high-level QM calculations can be used in QM/MM methods. We illustrate the method by applying it to the reaction of methyl chloride with chloride anion in aqueous solution.



COMP 366

Optimization of a polarizable force field based on the classical Drude oscillator

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Empirical force field development requires a systematic approach allowing for the development of a practical potential energy function and optimization of physically realistic parameters that reproduce a range of target data. Ongoing efforts in our laboratory include the development of a polarizable force field based on the classical Drude oscillator for a range of molecules representative of biological systems. A central theme in these efforts is the accurate treatment of both atomic interactions as well as condensed phase properties. To achieve this goal extensions of the energy function have been implemented and parameter optimization has been performed targeting a variety of quantum mechanical

results and experimental condensed phase properties. An overview of these studies will be presented.

COMP 367

Accurate calculation of binding energy contributions: Can computational methods explain the exceptional role played by chlorine in the FXa S1 pocket?

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A consistent feature of many of the most potent neutral FXa inhibitors is the presence of a chlorine or other halogen atom that binds at the base of the S1 pocket, however few studies have critically and quantitatively examined the reasons for this apparent preference over the methyl-containing analogs. This work examines the effects of replacing the chlorine with a methyl group in several related FXa ligand series both experimentally and computationally, in an attempt to explain the source of the preference. The results suggest that hydrophobicity is only partly responsible for the preference; electrostatic effects also play a significant role. Additionally, Tyr228, which is often described as having strong interactions with chlorine in S1, does not interact more strongly with chlorine versus methyl-containing ligands. The computational methods provide some new insights, but difficulties in computing binding energies remain, even in this comparatively rigid protein.

COMP 368

Treating chemical reactions with classical force fields

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Chemical reactions are among the most important processes relevant to living organisms. Their understanding is a challenge to computational methods and their successful exploration depends critically on an accurate description of the intermolecular interactions between the participating molecules and the nuclear dynamics of the atoms involved. Here we describe two methods which allow to follow bond breaking and bond formation in gas- and condensed-phase systems whereby the intermolecular interactions are described by a force field. The first method - adiabatic reactive molecular dynamics - is applied to ligand rebinding in solvated myoglobin. It is shown that with this approach it is possible to understand the two time scales observed experimentally. The second method - molecular mechanics with proton transfer - is used to better understand proton transfer dynamics and infrared spectroscopy of small molecules.

COMP 369

Including polarization effects in the RESP charge derivation method

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We will describe recent developments in the RESP charge fitting methodology. This will include implementation of iterative charge fitting for derivation of atomic charges that can be used with the force fields that take into account polarization effects. The appropriate i_RESP program takes atomic polarizabilities and high level quantum mechanically derived electrostatic potentials for single molecule or a set of molecules as an input and generates atomic charges that take into account self-polarization of the molecule(s). The polarization effects will be available through incorporating the following types of atomic polarizabilities models: Applequist-like, Thole-linear and Thole-exponential. The i_RESP program is capable of generating atomic charge sets for complex collection of molecules with various charge constraints, which are necessary for creating databases of standard and non-standard residues. The results of our charge fitting for standard residues will be available from AMBER program website (http://amber.scripps.edu) while for the nonstandard systems will be available through the R.E.DD.B. database at the http://q4md-forcefieldtools.org/ web site.

We will demonstrate potential applications of new schemes of charge derivation in molecular mechanical and dynamical calculations.

COMP 370

Development and application of a hybrid method involving interpolation and ab initio calculations for the determination of transition states

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Efficient determination of transition states is important in understanding chemical reaction rates. Previous methods, like the nudged-elastic band, often fail if there is not a good initial guess of the TS. The growing-string method (GSM) only requires reactant and product geometries, but is still computationally intensive. Several modifications have been implemented to alleviate the bottlenecks in the GSM: internal coordinates have replaced Cartesians, the conjugate gradient method has replaced steepest descent during minimization of orthogonal forces, and most importantly an interpolation scheme has been used to estimate the energy and gradient rather than performing quantum mechanical calculations. These modifications have been tested to measure the reduction in computational time on four cases: the Müller-Brown PES, alanine dipeptide rearrangement, H-abstraction in methanol oxidation, and C-H bond activation in oxidative carbonylation of toluene. The modified GSM represents a 2-3 time speed-up over the previous method without compromising accuracy of the final TS.

COMP 371

Predicting enzyme function by docking high-energy intermediates of potential substrates

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Due to many genome sequencing and structural genomics initiatives, there is an abundance of enzymes of known 3D structure but unknown function. To use in

vitro experiments to annotate them is clearly not tractable. Moreover, bioinformatics methods are not applicable in all cases, especially when sequence similarity is low.

As an alternative computational approach and a complementary method in general, docking of high-energy intermediates of substrates is an emerging technology. Its basic idea is to dock structures mimicking reaction intermediates instead of the groundstates of molecules, because enzymes are preorganized to recognize and stabilize the intermediate states.

We have applied this approach to the functional annotation of amidohydrolases, a large enzyme superfamily which catalyzes hydrolysis reactions. In multiple cases, we have successfully predicted the correct catalyzed reaction without any prior knowledge of the substrate class.

COMP 372

Docking populations for predicting multiple binding modes by the iterative stochastic elimination algorithm

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Multiple near-optimal conformations of protein-ligand complexes provide a better chance for accurate representation of biomolecular interactions, compared to single docked structures. Multiple conformations are the result of applying our Iterative Stochastic Elimination (ISE) algorithm to flexible docking. Applications of ISE find global and local minima in highly complex combinatorial problems. ISE-dock, based on that algorithm, produces high quality large docking populations. Flexible ligand - rigid protein docking by ISE-dock has been validated using a large concensus set of protein-ligand complexes from the PDB. With that set, ISE-dock was shown to be superior to Glide, GOLD and AutoDock (Proteins, Epub on Dec. 3, 2007). ISE-dock's capability of dealing with limited flexibility of protein side-chains was validated using multiple Acetylcholinesterase and trypsin complexes. We also demonstrate the connection between results of ISE-dock and experiments that support multiple binding modes in p38 MAP kinase and in Human Transthyretin.

COMP 373

Structural and mechanistic studies of lung cancer mutations in the EGFR kinase reveal a novel mechanism of drug resistance

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Mutations in the EGFR kinase are a cause of non-small cell lung cancer, and the presence of these mutations correlates with response to small-molecule tyrosine kinase inhibitors (TKIs). Interestingly, some of the mutant kinases are as much as ~100-fold more potently inhibited by gefitinib and erlotinib than the wild-type kinase, despite the fact that these TKIs were developed to target the WT enzyme. We have explored the mechanism for this enhanced sensitivity through structural and enzymological studies. Binding studies reveal markedly tighter binding of gefitinib to the L858R mutant, and structural studies reveal an altered binding mode that may in part explain its enhanced sensitivity. Additionally, kinetic studies show that the L858R and other mutants have diminished affinity for ATP, rendering them more sensitive to these ATP-competitive TKIs. Although patients with tumors harboring a mutant EGFR initially respond to these drugs, longer-term efficacy has been limited by the emergence of drug resistance, often conferred by an additional mutation of Threonine 790 in the EGFR to Methionine (T790M). This “gatekeeper” mutation lies in the kinase ATP binding pocket, and has been thought to confer resistance by sterically interfering with drug binding. However, we show through binding studies, enzyme kinetics, and x-ray crystallography that the T790M mutant and L858R/T7890M double mutant retain low nanomolar affinity for gefitinib, and that the T790M mutation does not alter the binding mode of the inhibitors. Instead, clinically observed drug resistance is due to an increase in the ATP affinity conferred by the T790M substitution. Since TKIs must compete with ATP to achieve their intended effect, their effective potency is diminished by the enhanced ATP-affinity. Thus the T790M mutation is a “generic” resistance mutation that can be expected to diminish the potency of any ATP-competitive inhibitor. Irreversible inhibitors, as a class, overcome this effect through covalent binding.

COMP 374

Potent inhibitors of mutant-B-Raf and Fms kinases designed using a scaffold-based drug discovery approach

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Plexxikon's approach has yielded two clinical programs to date, and several compounds nearing initiation of clinical development. The most advanced clinical compound in oncology targets a mutated form of BRaf kinase; inhibitors selective for this mutant are expected to possess a high efficacy-to-safety window, given presence of the target only in select tumors. Compounds targeting the Fms kinase have shown effects specifically targeting macrophages and osteoclasts, leading to efficacies in both oncology and inflammation models. Starting with a combination of high-throughput biochemical and crystallographic screening, we have discovered a novel series of compounds selective for the mutant form of B-Raf over the wildtype form and other kinases, and a series of compounds selective for Fms over other kinases, even those closely related by sequence and structure. The technological foundations of the platform, the structural discovery of selectivity determinants and their application to these targets will be discussed.

COMP 375

Novel mechanisms of drug resistance in KIT mutants from patients with gastrointestinal stromal tumors: Structural biology of wild-type and mutated proteins

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Majority of gastrointestinal stromal tumors (GISTs) exhibit aberrant activation of the KIT receptor tyrosine kinase. The efficacy of imatinib and sunitinib in GIST patients is based on the ability of each drug to inhibit the kinase activity of these mutant KIT proteins. However, secondary KIT mutations that render the kinase resistant to the inhibitor can evolve during treatment. Sunitinib has been shown

to be effective against imatinib-resistant mutants such as T670I and V654A, although a subset of imatinib-resistant mutants, including D816H/V, are also resistant to sunitinib. Biochemical and structural biology studies were undertaken to determine the molecular basis of resistance to sunitinib. The structure of KIT was determined for both WT and D816H-mutant proteins complexed with sunitinib. Results suggest that sunitinib targets the auto-inhibited conformation of WT KIT. A unique resistance mechanism was demonstrated in the D816H mutant KIT, which shifts the conformational equilibrium away from the KIT auto-inhibitory state.

COMP 376

Chemical approaches for making "inactive-conformation" kinase inhibitors

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There is an ever increasing demand for new protein kinase inhibitors both as potential therapeutics and as tools for dissecting complex signaling pathways. Despite the tremendous efforts to develop new kinase inhibitors, the vast majority of kinases are not targeted by an inhibitor with a reasonable level of selectivity. Currently the majority of known small molecule kinase inhibitors target the ATP-binding site of the fully activated kinase (Type I inhibitors). A second class of inhibitor was subsequently identified that exploits a hydrophobic pocket adjacent to ATP binding site created by a unique DFG-out loop conformation characteristic of an inactive kinase (Type II inhibitors). Because Type II inhibitors recognize regions of the kinase active cleft outside of the highly conserved ATP-binding site, they might be expected to exhibit a higher degree of kinase selectivity. To date, all the known type II inhibitors have been identified serendipitously and only later determined to be Type II binders through examination of x-ray co-structures. Here we discuss a pharmacophore model which enables the rational design of new type II inhibitors. In conjunction with screening against a panel of 350 kinases, this rational design strategy is leading to a synthesis of a new generation of kinase inhibitors, which although not mono-selective, will provide the chemical diversity needed create compounds targeting the majority of kinases. We will discuss examples of compounds that can overcome ATP-site resistance mechanisms and discuss examples where a high degree of kinase selectivity is obtained.

COMP 377

Insights on cell potency, kinase selectivity and drug-like properties of protein kinase inhibitors: Case studies from c-met inhibitors

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Human protein kinases play important roles in regulating most cellular functions. It is challenging for obtaining potent and highly selective kinase inhibitors due to the high endogenous ATP concentration and sequence homology in kinase catalytic domain. Significant knowledge has gained on how to obtain the potency and selectivity of kinase inhibitor in the past decade. However, the development of mono-specific kinase inhibitor with drug-like properties is still challenging. A number of c-Met inhibitors have been discovered and developed at Pfizer which covers a spectrum of kinase selectivity from pan-c-Met inhibitor to exquisitely selective c-Met inhibitor with a variation of cell potency and drug-like properties. The protein structure features which contribute to the cell potency and selectivity of c-Met inhibitors will be discussed. The learning from the discovery of small, potent and exquisitely selective c-Met inhibitors will provide general insights on the strategies for developing potent and highly selective kinase inhibitors.

COMP 378

Structure based design of benzimidazle inhibitors of CDK5

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The protein kinase CDK5 co-localizes with intraneuronal neuro-fibrillary tangles (NFTs) found in multiple neurodegenerative diseases including Alzheimer's disease. The major component of NFTs is the protein tau. CDK5/p25 or CDK/p35 phosphorylates tau at Ser202 or Thr205; this is the phorphorylated form that is found in the NFTs. Beginning with the x-ray crystal structure for CDK5/p25 we surveyed the putative ATP binding site, designed a series of potential inhibitors for CDK5/p25, docked the inhibitors with MOEdock, and evaluated the interactions with a comprehensive force field algorithm. The design, predicted in-silico potency, calculation of BBB partitioning parameters, and preliminary findings will be presented.

COMP 379

Modeling the fracture of defective carbon nanotubes and graphene sheets using coupled quantum mechanical/molecular mechanical methods

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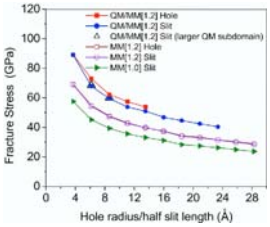
The effects of large defects and cracks on the mechanical properties of graphene sheets and carbon nanotubes were investigated using coupled quantum mechanical/molecular mechanical (QM/MM) calculations. The semi-empirical method PM3 was used for the QM subdomains and a Tersoff-Brenner potential was used for the molecular mechanics, with some of the QM calculations also performed using density functional theory (DFT). In order to obtain meaningful coupled calculations of the mechanical properties, it was essential that the Tersoff-Brenner potential be scaled so that the modulus and overall stress-strain behavior of the QM and MM models matched quite closely. The numerical results indicate that at the nanoscale, the weakening effects of holes, slits and cracks vary only modestly with the shape of the defect. Instead, they depend primarily on the cross-section of the defect perpendicular to the loading direction and the structure near the fracture initiation point. The fracture stresses for defective graphene sheets are in good agreement with the Griffith formula for defects as small at 10 angstroms. This result is surprising, and calls into question the notion of nanoscale flaw tolerance. The energy release rate at the point of crack extension in graphene was calculated by the J-integral method. It exceeds twice the surface energy density by 10% for the QM(DFT)/MM results, indicating a modest amount of lattice trapping.



COMP 380

WITHDRAWN

COMP 381

Enzyme polarization in qm/mm, application to docking and the origin of transition state stabilization in chorismate mutase

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We describe implementation of MM polarization in QM/MM methods and application to docking and to assessing the effect of polarization on transition state stabilizarion in chorismate mutase.

For docking, the induced dipole at a given target MM atom, due to polarization by the QM ligand, was reformulated as induced charges, and these were allowed to re-polarize the ligand. The final set of polarized charges was evaluated in docking using AutoDock 4.0

The method was also applied to the chorismate to prephenate rearrangement within the enzyme chorismate mutase. MM polarization is shown to be a short-range effect. MM polarization was shown to have a greater magnitude within the enzyme catalysed reaction than in the aqueous reaction. For the specific structures studied here, MM polarization lowered the energy barrier for the aqueous reaction, but the calculated contributions of MM polarization to both the reactant and transition structure stability were similar.

COMP 382

Semiempirical methods for the description of biochemical systems

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The ability of the OMx semiempirical methods to describe biochemical systems, particularly their non-covalent interactions, and the usefulness of augmenting these methods with an empirical dispersion term (OMx-D) is discussed. The OMx methods provide a superior description of biochemical interactions relative to traditional semiempirical methods, and this is further improved by the addition of a dispersion function. The use of such methods in the system preparation stage of QM/MM studies, as the QM method in the equilibration of systems is also considered, where the enzyme 34E4 with its bound hapten provides a useful case study.

COMP 383

QM/MM investigation of the enzyme catalyzed reactions

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Decarboxylation of orotidine 5'-monophosphate (OMP) produces uridine 5'-monophosphate (UMP) and occurs with a half-life of 78 million years in pure water. [1] Biosynthesis of UMP takes place with a half-life of 18 msec and catalyzed by orotidine 5'-monophosphate decarboxylase (ODCase). [2] This corresponds to a 23 kcal/mol lowering of the activation free energy of the decarboxylation reaction by this enzyme. The mechanism by which this decarboxylation reaction takes place has been an ongoing debate in the last decade. [3] In spite of the previous calculations that support the direct decarboxylation mechanism, our QM/MM simulations showed that direct decarboxylation mechanism lowers the activation free energy by only 7 kcal/mol, significantly lower than the experimentally observed value. [4] Recently, Kotra and co-workers resolved an X-ray crystal structure of ODCase with a covalently bound inhibitor. [5] Therefore we investigated the decarboxylation of OMP via nucleophilic attack to C5 position (Michael addition mechanism) by using QM/MM MD simulations. We will present the activation free energy lowering that can be obtained via the Michael addition mechanism for the ODCase.

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COMP 384

Replica exchange QM/MM simulations of peptides in solution

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We will present the results of a combination of advanced sampling techniques (Replica Exchange Molecular Dynamics) with a QM/MM treatment of a peptide in solution. In this way we can explore the true potential energy surface underlying the Hamiltonian chosen and compare directly with experimental data.

Questions about accuracy of present-day QM methods are raised and we show that advanced and costly methods do not necessarily outperform classical force fields.

COMP 385

New linear-scaling QM and QM/MM methods for biocatalysis

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New linear-scaling QM and QM/MM methods are introduced to study chemical reactions catalyzed by biological molecules. The new 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. 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 386

QMMM study of the thymine dimer radical anion splitting reaction: A comparison between the self-repair and the photolyase catalyzed process.

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Formation of the thymine dimer is one of the most important types of photochemical damage in DNA, responsible for several biological pathologies. Though specifically designed proteins (photolyases) can efficiently repair this type of damage in living cells, an autocatalytic activity of the DNA itself was recently discovered, allowing for a self-repair mechanism.

A thorough analysis of both the auto-catalytic and enzymatic thymine dimer radical anion splitting reaction will be presented. Analogies and differences between the two processes will be inspected on the basis of a QMMM molecular dynamics study of the splitting process, exploiting density functional theory (DFT) to describe the quantum region.

A set of 7 statistically representative molecular dynamics trajectories is analyzed for both the auto-catalytic and the enzymatic reaction.

Our calculations predict an asynchronously concerted reaction for both processes, in which the C5-C5' bond breaking is barrierless while the C6-C6' bond breaking is characterized by a small free energy barrier in the case of the auto-catalytic reaction and essentially barrierless for the enzymatic one. An upper bound of 2.5 kcal/mol for the barrier of the auto-catalytic process is estimated. Moreover, the present molecular dynamics study and the low free energy barrier involved in the C6-C6' bond-breaking, characterize the splitting of the thymine dimer radical anion as being an ultrafast reaction for both processes.

COMP 387

Born-Oppenheimer ab initio QM/MM molecular dynamics simulations of enzyme reactions

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To simulate enzyme reactions, extensive sampling on a reasonably accurate potential energy surface is needed to obtain reliable results. We are pushing the envelope of on-the-fly Born-Oppenheimer MD simulations with ab initio QM/MM methods and umbrella sampling to determine free energy profiles of chemical reactions in complex systems. At each time step, the atomic forces as well as the total energy of the QM/MM system are calculated with the pseudobond ab initio QM/MM approach on-the-fly, and Newton equations of motion are integrated. This on-the-fly ab initio QM/MM MD approach, which takes account of dynamics of reaction active site and its environment on an equal footing, has been recently demonstrated to be feasible and successful in elucidating the catalytic power of SET7/9, understanding methylation state specificity of histone lysine methylation, and characterizing the Sir2 catalyzed nicotinamide cleavage reaction.

COMP 388

Development and applications of ab initio QM/MM minimum free-energy path method

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Simulating the structural and energetic changes of a condensed-phase reaction is very challenging because of the computational cost associated with the QM calculations and phase-space sampling. Routinely, extensive sampling can only be achieved with semiempirical QM or (very) small QM subsystems. Ab initio QM/MM methods, due to the expensive computational costs, are often restricted to narrow regions of the potential energy surface so that the results can be statistically less significant.

To overcome those difficulties, we develop a new method to determine the QM/MM minimum-free-energy-path for reactions in solutions and enzymes. By simplifying the complex phase space of the whole system into the potential-of-mean-force surface of the QM conformations, we are able to compute the free energies and free energy gradients for a chain of QM conformations which allow a smooth search for a unique minimum free energy path. The recent development of an iterative, sequential optimization algorithm further improved the efficiency by iteratively carrying out minimization with a fixed-size, finite ensemble of MM conformations. The applications of this method on the reactions of CH3Cl+Cl, ODCase, and Cdc25 will be discussed.