COMP 1 Van der Waals theory in the spirit of Maxwell
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Van der Waals interactions between two arbitrary atomic systems - molecules clusters, crystals etc. of arbitrary sizes, geometries and compositions, except for the following limitations: No significant overlap and no significant retardation effects.

COMP 2 Van der Waals interactions from the exchange hole dipole moment
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Despite its importance in chemistry, the Van der Waals (or dispersion) interaction is difficult to model accurately. Standard Density Functional Theory (DFT) methods, very popular in computational chemistry today, do not include the necessary physics. This often leads to qualitatively incorrect predictions when DFT is applied to dispersion-bound systems. The dispersion interaction between molecules arises when an instantaneous dipole moment in one molecule induces a dipole moment in another. What, however, is the source of these instantaneous dipole moments? We have proposed a novel post-Hartree-Fock dispersion model in which the source is the position-dependent dipole moment of the exchange hole. This model is very economical and yields remarkably accurate C6 and higher-order C8 and C10 dispersion coefficients of intermolecular complexes. Intermonomer separations and binding energies are well predicted also.

COMP 3 Applications of van der Waals density functional (vdW-DF)
David C. Langreth, Department of Physics and Astronomy, Rutgers University, 136 Frelinghuysen Road, Piscataway, NJ 08854-8019, Fax: 732-445-4400, langreth@physics.rutgers.edu

A number of applications of the recently developed nonempirical density functional for general geometries are presented. These have been carried out by members of the Chalmers-Rutgers collaboration which developed the functional. The applications include a) bulk crystals, including layered structures and polymer crystals, b) physisorption on surfaces, including polycyclic aromatic hydrocarbons on graphite, c) various molecular van der Waals complexes, including dimers of polycyclic aromatic hydrocarbon dimers through pyrene, complexes involving benzene with substituents, and a number of nucleic acid base stacking complexes. In all cases our results give substantial improvements over standard density functional methods with respect to agreement with experiment where it is available, or with wave-function calculations where it is not. Nevertheless, the method scales as ordinary density functional calculations with system or unit cell size.

COMP 4 Improvements in density functionals theory and applications to nanoelectronics
William A. Goddard III, Chemistry, California Institute of Technology, 139-74 Caltech, Pasadena, CA 91125, Fax: 626 5850918, wag@wag.caltech.edu

We will summarize recent progress in reformulating Density Functional Theory (DFT) for better descriptions of London Dispersion and bond breaking processes. In addition we will apply DFT to nanoelectronics, particularly the potation of rotaxane based switches and the contact resistance and properties of metal-carbon nanotube contacts.

COMP 5 Hydrogen bonds and other weak interactions in DFT
Dennis R. Salahub, 110 Administration Building, University of Calgary, 2500 University Drive NW, Calgary, AB T2N 1N4, Canada, Fax: 403-289-6800, dennis.salahub@ucalgary.ca

Since its inception in 1964, Density Functional Theory has extended its frontiers in several important dimensions: potential energy surfaces, dynamics, various response functions and spectroscopies, excited states, to name only a few. Presently, the accurate calculation of weak interactions (hydrogen bonds, inter- and intra-molecular nonbonded interactions, van der Waals interactions, dispersion) presents a formidable challenge. Progress is being made on several fronts and I will review some of these, focusing on empirical dispersion corrections added to either DFT or Tight-Binding DFT, on the one hand, and attempts to reparameterize meta-GGA functionals, on the other. Applications to hydrogen-bonded and stacked biomolecules and to gas hydrates will be discussed, depending on progress in those projects.

COMP 6 Density functional theory for non-equilibrium systems
Matthias Ernzerhof, Department of Chemistry, University of Montreal, C.P. 6128, Succursale A, Montreal, QC H3C 3J7, Canada, Matthias.Ernzerhof@UMontreal.ca

Molecular electronic devices are described by non-equilibrium states. These states are characterized by the fact that initially there are two infinite metal contacts, with different chemical potentials, that are then connected to the molecule. After some time, a stationary state is reached, exhibiting a time-independent current. We consider such stationary non-equilibrium states and show how they can be obtained from a variational principle. This variational principle enables us to include exchange and correlation effects into the calculation of the molecular conductance. We present a density functional theory for stationary non-equilibrium states and discuss the construction of the corresponding exchange-correlation functionals.

COMP 7 Profiling protein kinase substrate specificity using peptide arrays
Benjamin E. Turk, Department of Pharmacology, Yale University School of Medicine, P.O. Box 208066, 333 Cedar Street, New Haven, CT 06520, Fax: 203-785-7670, ben.turk@yale.edu

Selection of target substrates by protein kinases is strongly influenced by the amino acid sequence surrounding the site of phosphorylation. We have developed a rapid and general combinatorial peptide library method that allows for determination of quantitative phosphorylation motifs for serine-threonine kinases. Information from peptide library screens is used to generate selective and efficient model substrates for kinases of interest. In addition, position-specific scoring matrices derived from peptide library data are used to search computer sequence databases to identify candidate substrates. We have initiated high-throughput analysis of protein kinases selectivity in an effort to identify kinase-substrate pairs and model signaling pathways on a proteome-wide scale.

COMP 8 Regulation of protein motions in MAP kinases
Natalie Ahn, Dept. of Chemistry and Biochemistry, University of Colorado, Campus Box 215, Boulder, CO 80309-0215, Fax: (303)492-2439, natalie.ahn@colorado.EDU

Structural and kinetic studies provide extensive information about mechanisms of kinase activation, however, it is still unclear how protein dynamics regulates catalytic function. Using hydrogen exchange mass spectrometry (HX-MS), which is sensitive to local perturbations of tertiary environments in proteins, we observed increased exchange within the hinge region accompanying activation of the MAP kinase, ERK2. Conformational differences in this region were not observed in X-ray structures, suggesting that the HX effect reflects altered conformational mobility. Increased exchange rates and backbone flexibility at the hinge following enzyme activation may favor closure between N- and C-terminal domains, and facilitate catalysis. HX-MS measurements showed protection from HX within conserved
N-terminal nucleotide binding motifs upon binding AMP-PNP, in both active and inactive ERK2. In contrast, greater protection was observed within the C-terminal domain in active ERK2. Thus, AMP-PNP simultaneously protects residues within the N- and C-terminus in active but not inactive ERK2, suggesting that active kinase adopts a closed conformation following nucleotide binding in solution, while inactive kinase adopts an open conformation. Our findings suggest that ERK2 activation facilitates hinge motions which may favor interdomain closure, allowing proper orientation between ATP and substrate for phosphoryl transfer.

**COMP 9 Surrogate approaches to AGC-kinase inhibition**

**Dirk Bossemeyer**, Structural Biochemistry, German Cancer Research Center DKFZ, INF 280, Heidelberg D-69120, Germany, Fax: +49 6221 423259, d.bossemeyer@dkfz.de, Michael Gassel, Intervet, Stefan Bonn, MPI for Medical Research, Christine B. Breitenlechner, Proteros, and Richard A. Engh, Roche Diagnostics GmbH, Penzberg

Because there are more than 500 protein kinases in the human genome, the specificity of low molecular weight inhibitors for the targeted kinase(s) is a crucial factor for therapeutic success. Selectivity of protein kinase inhibition remains the focus of extensive research. Many specificity mechanisms have been described, including subfamily specific refolding events, varying protein flexibilities, binding site sequence variability, and so on. Kinase chemogenomics is beginning to address these issues by empirically correlating inhibitor structures with kinase inhibition profiles and their mechanisms, but a priori prediction of kinase selectivities remains in its infancy. We use site directed mutagenesis to generate protein kinase templates for a structural understanding of target inhibitor interactions. PKA is one of the name-giving representatives of the AGC-kinase group, which comprises about 60 members of which many (PKB/Akt, PKC, Rho-kinase etc) are potential targets for the treatment of serious diseases such as cancer or coronary heart disease. PKA crystallizes reliably in active conformations under various conditions with a wide variety of ligands. Through the exchange of ATP-site residues the corresponding site of pharmacologically important AGC-kinases can not only be structurally mimicked, but also inhibitory profiles closely mirroring those of the target kinases can be constituted. This allows the structural analysis of inhibitor/protein kinase interactions and facilitates the understanding of drug binding parameters for the improvement and development of small molecule kinase inhibitors.

**COMP 10 Processing conformation of MAP kinases**

**Elizabeth J. Goldsmith**, SW Medical Center, University of Texas, 5323 Harry Hines Boulevard, Dallas, TX 75390-9038, Fax: 214-648-8954, betsy@chop.swmed.edu, and Tianjun Zhou, The University of Texas Southwestern Medical Center at Dallas

MAP kinases interact with substrates and processing enzymes at sites outside their active sites. We have now carried out high resolution crystallographic analysis of unphosphorylated ERK2 bound to docking site peptides derived from MEK2, an activator, and hematopoietic tyrosine phosphatase, a negative regulator of ERK2. Docking site interactions in the C-terminal domain of the kinase induce long range conformational changes that affect the activation loop of the kinase. Phosphorylation sites in the activation loop of ERK2, which are buried in low activity ERK2, become exposed to solution in the complex. We propose that the induced conformational changes in the activation loop serve to release the sequestered phosphorylation sites for processing. The conformational binding interactions and conformational changes that occur in ERK2 are distinct from those in p38 and JNK. The allosteric feature probably contributes to pathway specificity of MAP kinases. This work was supported by funding from the NIH (DK46993 to EJG).

**COMP 11 A structural view of the protein kinase family and family-based drug discovery**

**Sung-Hou Kim**, Department of Chemistry, University of California, Berkeley, CA 94720-1460,
The protein kinase family is one of the largest protein families in human, and their members play key roles in regulating most of the major signal transduction pathways by phosphorylation of target proteins. Abnormal phosphorylation is implicated in myriad of human diseases. The sequenced human genome revealed almost 500 distinct kinase genes, offering a rich collection of targets for developing novel therapeutics for human diseases. Small molecule inhibitors are being developed for kinases across all major subfamilies of the protein kinase family against various diseases.

There are a large number of 3-D structures with and without ligand or inhibitors available. We will present a structural demography of the protein kinase subfamilies in the protein kinase structure space, and a systems approach to drug discoveries using the kinase family.

COMP 12 A switched electrostatic network guides Src conformational activation
Elif Ozkirimli, Department of Medicinal Chemistry, Purdue University, West Lafayette, IN 47907-2091, and Carol Post, Dept. of Medicinal Chemistry and Molecular Pharmacology, Purdue University, 575 Stadium Mall Drive, West Lafayette, IN 47907, Fax: 765-496-1189, cbp@purdue.edu

Src tyrosine kinases are essential in numerous cell signaling pathways, and improper functioning of these enzymes has been implicated in many diseases. The activity of Src kinases is regulated by conformational activation, which involves several structural changes within the catalytic domain (CD): the orientation of two lobes of CD, rearrangement of the activation loop (A-loop), and movement of an important β-helix (.C) into or away from the catalytic cleft. Conformational activation was investigated using biased molecular dynamics to explore the transition pathway between the active and the down-regulated conformations of CD for the Src-kinase family member Lyn kinase, and to gain insight into the interdependence of these changes. Lobe opening is observed to be a facile motion, whereas movement of the A-loop motion is more complex requiring secondary structure changes as well as communication with .C. A key result is that the conformational transition involves a switch in an electrostatic network of six polar residues between the active and down-regulated conformations. The exchange between interactions links the three main motions of the CD. Possible implications for regulation conferred by interdomain interactions are also discussed.

COMP 13 Analytical electrostatics: Beyond the generalized Born model
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An analytical approximation to the Poisson-Boltzmann (PB) equation is proposed that goes beyond the generalized Born (GB) approximation. The new model (ALPB) does not have fitting parameters and permits definition of electrostatic potential everywhere in space. It is tested against numerical solutions of the PB equation on a large set of representative macromolecules: the computed electrostatic solvation energy is more accurate than that computed with the traditional GB model over the entire range of the solvent and solute dielectric constants. At the same time, the new approximation is as computationally efficient as the GB model.

COMP 14 Calculating free energies with fast implicit solvent models
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The free energy of binding determines the potency of an inhibitor and is as such, a very useful
property to predict. Free energy calculations on protein-inhibitors complexes are usually computationally expensive, which has prompted the development of many approximate free energy methods. In this work, we are aiming to develop a method that is more efficient than conventional free energy simulations while keeping a rigorous statistical mechanics framework. We achieve this by combining recently developed Monte Carlo based protocols that yield enhanced or more efficient sampling of phase space and by adopting a continuum electrostatics approach that simplifies the free energy landscape. The methodology is applied to the calculation of the relative binding free energy of inhibitors to a range of important pharmaceutical targets. Systematic comparison with explicit solvent simulations provides insights to guide further development of implicit solvation methodologies and help identify the fundamental limits introduced by this approximation.

COMP 15 Modeling polarization in MD
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Modeling Molecular Polarizabilities

Incorporating molecular polarizabilities into simulations is a way to model multibody energies arising from electrostatics. A commonly used method to model molecular polarizabilities is through atomic polarizabilities developed by Applequist\(^1\) and later modified by Thole\(^2\). We are interested in developing a set of atomic polarizabilities for the AMBER and GLYCAM force fields. Atomic polarizabilities can be fit by using point charge molecular probes and looking at the response of the electrostatic potential due to the probes\(^3\). The resulting parameters are specific to the molecule. A method will be presented for this procedure, and the resulting parameters will be compared to atom type specific parameters that were fit to a data set of molecular polarizability tensors. A method of re-fitting the charges will also be presented and the resulting parameters will be tested against electrostatic and polarization energy of dimers.

References:

\(^1\)Applequist, J. Am. Chem. Soc., 94, 9 (1972)


\(^3\)Kaminski, Stern, Berne, Friesner, Cao, Murphy, Zhou, Halgren J. Comp. Chem Vol. 23, No. 16, 1515 (2002)

COMP 16 Metadynamics study of the free energy surfaces of the alanine dipeptide in vacuum and in water: How do molecular mechanics force fields affect backbone conformational transition of proteins and peptides?
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The metadynamics (or hills) method is a relatively new and highly efficient MD technique in obtaining free energy surfaces (FES). We have used it to determine the two dimensional (Φ-Ψ) FES of the alanine dipeptide in gas phase and in water, with five different force fields, CHARMM27, AMBER94, AMBER03, OPLSAA and OPLSAA modified. We were able to compare the effects of these force fields on backbone conformational (Φ-Ψ) transition. The standard deviation of FES between force fields (1.0 to 2.4 kcal/mol) is much larger than that from the method (0.2-0.3 kcal/mol with tight parameter set and 0.4-0.7 kcal/mol with loose parameter
Further, we obtained the free energies of several selected points on the FES by ab initio calculation (B3LYP/6-31g(d,p)) with 6 explicit waters and continuum solvation model. We conclude that, in water, the OPLSAA force field fits better with the ab initio results.

**COMP 17 Implementation of SCC-DFTB in AMBER**

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Self-Consistent Charge Density Functional Tight Binding (SCC-DFTB) is a semi-empirical method based on a second order expansion of the Density Functional energy on the charge fluctuation. It has been shown to provide results comparable in accuracy to full DFT or ab-initio MP2 calculations using large basis sets. Furthermore, due to its semi-empirical nature, it is applicable to systems of much larger size. We have implemented the SCC-DFTB method within the Sander module of the AMBER program suite. The SCC-DFTB method has been implemented in such a way that it integrates into AMBER v9's new modular QMMM framework allowing QMMM simulations to be setup and run with the minimum in extra configuration. The AMBER QMMM approach has been designed to run as quickly and efficiently as possible while providing improved accuracy in the gradients and hence energy conservation. The implementation also supports QMMM explicit solvent simulations with periodic boundaries using either an Ewald or PME approach to long range electrostatics as well as support for implicit solvent QMMM simulations using a QMMM compatible implementation of Generalised Born. Examples of its applications to various systems will be shown, including comparison with DFT, ab-initio MP2 and traditional semi-empirical methods such as AM1 and PM3.

**COMP 18 Molecular dynamics integration and molecular vibrational theory**

Dusanka Janezic, Center for Molecular Modeling, National Institute of Chemistry, Hajdrihova 19, Ljubljana, Slovenia, Fax: 386 1 476 0300, dusa@mm.ik.si

New symplectic integrators have been developed by combining molecular dynamics integration with the standard theory of molecular vibrations to solve the Hamiltonian equations of motion. The presented integrators analytically resolve the internal high-frequency molecular vibrations by introducing a translating and rotating internal coordinate system of a molecule and calculating normal modes of an isolated molecule only. The translation and rotation of a molecule are treated as vibrational motions with the vibrational frequency zero. All types of motion are thus described in terms of the normal coordinates. The method’s time reversibility requirement was used to determine the equations of motion for internal coordinate system of a molecule. The calculation of long-range forces is performed numerically. The new methods for
integrating classical equations of motion using normal mode analysis allow us to use a long integration step and are applicable to any system of molecules with one equilibrium configuration.

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**COMP 19 Computational methods for the enhanced calculation of time-correlation functions**  
**Ioan Andricioaei**, Department of Chemistry, University of Michigan, 930 N. University, Ann Arbor, MI 48109

We present and analyze two general method to calculate time-correlation functions from molecular dynamics on scaled potentials or from molecular dynamics with artificial momenta distributions. They are useful for complex systems whose simulations are affected by broken ergodicity. Depending on the value of the scaling factor or of the details of the momentum distributions, correlation functions can be accurately calculated for times that can be orders of magnitude longer than those accessible to current molecular dynamics simulations.

We show that the exact value of the correlation functions of the original system can be obtained, in principle, using an action-reweighting scheme based on a stochastic path-integral formalism. Tests on model systems and peptides are exemplified. We also show that free energy profiles using Jarzynski’s identity can be more effectively calculated within this scheme.

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**COMP 20 Multi-mode molecular dynamics and QM/MM methods for binding affinity estimation of metalloprotein ligands**  
**Akash Khandelwal** and **Stefan Balaz**, Department of Pharmaceutical Sciences, North Dakota State University, Sudro Hall 8b2, Fargo, ND 58105, Fax: 7012318333

In drug design, a description of the ligand interactions with transition metals poses a challenge for approaches using molecular mechanics (MM) due to the possibility of multi-dentate coordination that is most appropriately treated at the quantum mechanical (QM) level. This study presents a QM/MM extension of classical Linear Response techniques for the receptor-based estimation of binding affinities of metalloprotein ligands. A treatment of MD simulations for slowly equilibrating ligands is also added. The approach is applied to inhibitors of matrix metalloproteinase 9. The inhibitors were docked into the active site of MMP-9 using FlexX. The complexes were minimized using QM/MM methods. The optimized complexes were then used for MD simulation. The MM and single point QM/MM energies were calculated from the relevant time-averaged structures and correlated using one-mode and multimode equations. The QM/MM multi-mode model provides significantly better correlations, explaining ~90% of the variation in experimental activity than other models.

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**COMP 21 Exact exchange as a component of density functional approximations**  
**JP. Perdew**¹, VN. Staroverov², GE. Scuseria², and J. Tao³. (1) Department of Physics, Tulane U, New Orleans, LA 70118, Fax: 504-862-8702, perdew@tulane.edu, (2) Rice U, (3) U. Missouri-Columbia

100% of the exact exchange energy is known to be incompatible with a semi-local density functional approximation for the correlation energy. Becke proposed using instead a fixed fraction (typically 25% or a=0.25) of exact exchange with the residual fraction 1-a of semi-local exchange. The resulting global hybrids are now widely used for the calculation of molecular and solid-state properties. We will first discuss the advantages and disadvantages of global hybrids. We will then discuss how the full exact exchange can be recovered in a self-interaction-free functional if we make instead a local hybrid or hyper-generalized-gradient-approximation, in which the admixed fraction of exact exchange energy density depends upon the electron density and upon position. We suggest that the required mixing fraction may be a highly nonlocal functional of the electron density.
COMP 22 New density functionals applied to old problems
Gustavo E. Scuseria, Department of Chemistry, Rice University, Houston, TX 77005, guscus@rice.edu

This presentation will address our current efforts to develop more accurate exchange-correlation functionals for density functional theory. The focus will be on screened exchange hybrids like HSE, which are particularly fast and accurate for periodic calculations. We will discuss the significant improvement in band gap estimates that this functional yields compared to LDA and GGAs, and also present applications to actinide and transition metal oxides, silicon and silicon defects, and other problems where electron localization seems to play a crucial role.

COMP 23 Use of the adiabatic connection for constructing exchange-correlation functionals in density functional theory
Paula Mori-Sánchez, Aron J. Cohen, and Weitao Yang, Department of Chemistry, Duke University, Durham, NC 27708, pmori@duke.edu

In this work we reexamine the adiabatic connection approach to density functional theory for functional construction. We show that the adiabatic connection constitutes a wonderful tool for the development of exchange-correlation energy functionals. Our strategy relies on simple modeling of the adiabatic connection curve in the coupling constant space using exact and approximate constraints. For example, the relation of the initial part of the adiabatic connection to perturbation theory on the Kohn-Sham determinant has allowed us to include exact exchange and many-body terms into the functional form in a straightforward manner. Our method of construction is simple and very flexible. Overall, we define different families of novel functionals which combine orbital exchange and correlation, GGA, and meta-GGA integrals in a highly non-linear way. These functionals perform very well on both thermochemistry and kinetics, while addressing the important problems of self-interaction error and hopefully van der Waals forces.

COMP 24 Spin-current density-functional methods
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A spin-current density-functional theory (SCDFT) is introduced that takes into account currents of the spin-density and thus currents of the magnetization in addition to the electron density, the non-collinear spin-density, and the density current, which are considered in standard current spin-density functional theory. An exact exchange Kohn-Sham formalism based on SCDFT is presented, which represents a general framework for the treatment of magnetic and spin properties including spin-orbit interactions. Results obtained with the new formalism for atoms and semi-conductors are discussed.

COMP 25 Advances in orbital-free density functional theory and its applications
Emily A. Carter, Department of Mechanical and Aerospace Engineering, Princeton University, Engineering Quadrangle, Princeton, NJ 08544-5263, Fax: 609-258-5877, eac@princeton.edu

The state of the art in orbital-free density functional theory (OFDFT) for condensed matter electronic structure calculations will be presented, including recent advances in local pseudopotential and kinetic energy density functional theories required for OFDFT. Applications to materials properties will be presented, including concurrent multiscale simulations of the mechanical response of materials.

COMP 26 Orbital-corrected orbital-free density functional theory
Baojing Zhou and Yan Alexander Wang, Department of Chemistry, University of British Columbia, Vancouver, BC V6T 1Z1, Canada, Fax: 604-822-2847, bzhou@chem.ubc.ca, yawang@chem.ubc.ca

Density functional theory (DFT) has been firmly established as one of the most widely used first-principles quantum mechanical methods in many fields. However, its general large-scale utilizations are still confronted with difficulties. Its two implementations, the orbital-based Kohn-Sham (KS) DFT and orbital-free (OF) DFT, have their own strengths and weaknesses. The former is accurate but lacks an effective linear-scaling algorithm, while the latter can achieve linear scaling but is accurate only for simple metallic systems. We have developed a new implementation of DFT, orbital-corrected OF-DFT (OO-DFT). With no more than two non-self-consistent iterations, OO-DFT accomplishes the accuracy comparable to the fully self-consistent KS-DFT, yet its efficiency remains essentially like OF-DFT. The accuracy of OO-DFT is demonstrated by its applications on the cubic diamond Si and the face-centered-cubic Ag systems. Our work paves the way for the general applications of linear-scaling high-quality DFT method on large systems of thousands of atoms within different chemical bonding environment.

COMP 27 Recent developments in conceptual density functional theory
Paul Geerlings, Department of General Chemistry /Faculty of Sciences, Vrije Universiteit Brussel (Free University of Brussels/VUB), Pleinlaan 2, Brussels 1050, Belgium, Fax: 32-2-6293317, pgeerlin@vub.ac.be, and Frank De Proft, Department of General Chemistry /Faculty of Sciences, Vrije Universiteit Brussel (Free University of Brussels/ VUB)

The term Conceptual Density Functional Theory has been given by R.G.Parr(1) to delineate that branch of DFT aiming to give precision to often well known but rather vaguely defined chemical concepts such as electronegativity, hardness, softness...and to use them either as such or in the context of principles such as the Electronegativity Equalization principle, the HSAB principle, the Maximum Hardness principle...(for a review see (2). In this contribution some recent developments in the field are discussed concentrating on the shape function as an alternative to the density and the study of reactivity descriptors in Spin Polarized Conceptual DFT. Applications involving the trends in properties of the Group 14 elements(C, Si, Ge, Sn, Pb, Uq) and the reconsideration of the Woodward Hoffmann rules in a Conceptual DFT framework are discussed.


COMP 28 Processive phosphorylation of splicing factors
Joseph A. Adams, Department of Pharmacology, University of California, San Diego, 9500 Gilman Drive, La Jolla, CA 92039-0506, Fax: 858-822-3361, joeadams@ucsd.edu

RNA splicing and transport rely on the participation of protein factors known as SR proteins. These splicing factors, named for their large arginine-serine dipeptide repeat regions, are phosphorylated by the SRPK and Clk protein kinase families. ASF/SF2, the prototypical SR protein, is composed of two RNA recognition domains (RRMs) and a C-terminal RS domain rich in Arg-Ser repeats. Both SRPK1 and Clk/Sty phosphorylate the RS domain although the regiospecificity and phosphoryl content is very distinct. SRPK1 phosphorylates 10 residues in the N-terminal portion of the RS domain whereas Clk/Sty phosphorylates all 20 available serines. Both kinases bind with unusually high affinity and catalyze multi-site phosphorylation without dissociating from the RS domain, an example of processive phosphorylation. The limited phosphorylation catalyzed by SRPK1 compared to Clk/Sty appears to be regulated by docking residues in the N-terminal portion of the RS domain. Mutations in this docking region allow increased phosphorylation of ASF/SF2 by SRPK1 suggesting that both kinases uniquely employ recognition sequences in the SR protein for regiospecific phosphorylation. The binding surfaces for both enzymes on ASF/SF2 are not entirely overlapping since excess SRPK1 can limit the
phosphorylation of the RS domain by Clk/Sty. This antagonistic relationship between the kinases is controlled in the cell by localization of Clk/Sty in the nucleus and SRPK1 in the cytoplasm. These findings are consistent with a model where the partial phosphorylation of ASF/SF2 in the cytoplasm is essential for nuclear transport and localization in speckles whereas full phosphorylation by Clk/Sty recruits the SR protein to sites of splicing.

COMP 29 Conformational energy landscape of Src kinase activation processes
Benoit Roux. Department of Physiology and Biophysics, Weill Medical College of Cornell University, 1300 York Avenue, New York, NY 10021, Fax: 212-746-4843, ber2004@med.cornell.edu, and Nilesh K. Banavali, Physiology and Biophysics, Weill Medical College of Cornell University

Regulation of Src kinase activity is implicated in coordination of downstream signal transduction pathways involved in cell proliferation. The activation of Src kinase Hck involves a large conformational change in two specific parts of its catalytic domain: the α-C helix region and the activation loop region. In the present study, molecular dynamics (MD) simulations are used to probe the energy landscape describing conformational variability of specific regions of the catalytic domain in the vicinity of the active site where phosphorly transfer takes place. Multiple transformation pathways between two endpoint conformations in conjunction with restrained umbrella sampling calculations and unrestrained MD simulations are used to understand the impact of conformational variability of key residues or substrates on kinase activity and regulation.

COMP 30 Conformational changes in protein loops and helices induced by post-translational phosphorylation
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We have undertaken a computational investigation of how post-translational phosphorylation perturbs the energy landscapes of proteins, driving changes in conformation and dynamics. In this talk, I will focus on activation loop phosphorylation in protein kinases, and demonstrate that it is possible to predict the structures of phosphorylated proteins starting from the structures of the unphosphorylated proteins, using loop and side chain sampling algorithms we have developed. CDK2 provides a case study where we analyze how and why the effects of phosphorylation differ depending on whether the kinase domain is unbound or bound to cyclin A or its phosphatase, KAP. In addition, we have investigated why substituting Glu or Asp for a phosphorylatable Ser or Thr sometimes, but not always, mimics the effects of phosphorylation.

COMP 31 Simple models for protein kinases and their interactions with small molecule inhibitors
Adrian H Elcock, Department of Biochemistry, University of Iowa, Bowen Science Building, 51 Newton Road, Iowa City, IA 52242, Fax: 319-335-9570, adrian-elcock@uiowa.edu

A simple computational method for rapidly modeling the interactions between small-molecule inhibitors and hundreds of protein kinases will be presented. The strengths and weaknesses of the methodology will be discussed and recent attempts to overcome existing limitations will be outlined. If time permits, recent work attempting to model the conformational dynamics of protein kinases will also be presented.

COMP 32 Classification of the human kinome based on active site features and small molecule interaction profile
Kiyean Nam, Molecular Systems, Merck & Co., Inc, RY50SW-100, P.O. Box 2000, Rahway, NJ 07065, Fax: 732-594-4224, kiyean_nam@merck.com, Robert P. Sheridan, Molecular Systems, Merck & Co, and Vladimir N. Maiorov, Molecular Systems, Merck Research Laboratories, Merck & Co., Inc

The human kinome consists of 518 kinases, which can be classified into 8 groups (AGC, CAMK, CK1, CMGC, STE, TK, TKL and Others) in the catalytic domain sequence space. However, the conventional sequence-based classification of the human kinome does not correspond well with selectivity profile of ATP competitive inhibitors. It is not uncommon to find inhibitors binding multiple kinases across these groups. From a drug design point of view, the lack of a metric reflecting kinase-inhibitor interactions can be problematic especially in choosing kinases to set up a counter screening panel. Here we present an alternative approach to classifying the human kinome based on 3D active site features and small molecule interaction profiles. This new metric provides a breakdown of the human kinome distinct from the conventional sequence-based classification, which may be more relevant in the kinase-inhibitor interaction space.

COMP 33 Electron and proton affinities of the 3d-block transition metals using quantum Monte Carlo methods
Ainsley Anthony Gibson, Floyd Fayton Jr., and John AW. Harkless, Department of Chemistry, Howard University, 525 College Street NW, Washington, DC 20059, Fax: 202-806-6882, ainsley.gibson@gmail.com

Quantum Monte Carlo (QMC) methods are used to determine both the electron affinities (EA) and proton affinities (PA) of the 3d-block transition metals (Sc-Zn). The use of QMC methods in these calculations is significant in that QMC methods are capable of producing highly accurate results when applied to difficult systems such as transition metals. The results obtained are compared with other commonly used theoretical methods as well as experimental data. We use an Ahlrichs TZV basis for the transition metals and a cc-pVTZ basis for hydrogen.

COMP 34 Ab initio determination of chiroptical properties
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Only in the last decade have quantum chemical models achieved sufficient maturity to allow the rigorous first-principles calculation of chiroptical properties. We have developed a series of Hartree-Fock, Möller-Plesset perturbation theory, and coupled cluster programs for computing optical rotation, electronic circular dichroism, and vibrational circular dichroism. In this work, we consider the importance of basis set, gauge, as well as electron correlation effects for chiral molecules such as (S)-methylloxirane and (S)-2-chloropropionitrile.

COMP 35 Analysis and development of basis sets for optimal ab initio and density functional performance
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The description of molecular properties to within chemical accuracy, and, at a reasonable computational cost, has been a long-standing, but yet quite challenging, goal of computational chemistry. We overview recent developments in our group towards this goal for energetic, structural, and spectroscopic properties of a number of species ranging from first-row through transition metal species. Developments include: improved basis set behavior for density functional theory with respect to increasing level of basis set, computational cost reduction via basis set truncation, and recontraction and modification of basis sets for improved description of
molecular properties.

**COMP 36 Efficient treatment of electronic structure in highly-correlated molecular systems**

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Radicals, diradicals, and transition states all prove much more challenging to standard quantum chemistry techniques than "ordinary" closed-shell molecules, in large part due to the inadequacies of the Hartree-Fock reference wave function. These failures of Hartree-Fock are particularly noticeable in the sometimes catastrophic errors of second-order Moller-Plesset perturbation theory (MP2) for such species. We propose an alternative method to MP2, based on a simplified coupled-cluster wave function that is equivalent to the perfect-pairing wave function, and a second-order perturbative correction, termed PP(2). The perfect pairing reference captures the strong, static correlation effects using the simplest correlated model wave function beyond Hartree-Fock, while the perturbative correction estimates the dynamical correlation contribution. Using the resolution of the identity approximation, PP(2) can be computed with only a factor of a few times more computational effort than canonical MP2, and it dramatically improves predictions as compared to MP2 in many systems with both standard and challenging electronic structure.

**COMP 37 A first-principles method for open systems**

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Based on its analyticity, the electron density function of a real physical system can be determined by its values on any finite subsystem. By introducing a new density functional for dissipative interactions between the system and its environment, we develop subsequently a time-dependent density-functional theory formulation for the open system, which depends in principle only on the electron density of the system. In the steady-state limit, the conventional first-principles nonequilibrium Green’s function formulation for the current is recovered. Two practical schemes are proposed for the new density functional: one with an explicit density dependence based on an adiabatic approximation and the other with an implicit dependence based on a wide-band limit approximation.

**COMP 38 Analytic energy derivatives for the locally projected methods: Theory and applications**

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Efficient implementation of the locally projected SCF method for molecular interactions (LP SCF MI) enables fast calculations of the energies for large systems of weakly bonded molecular clusters. This method accurately reproduces the full SCF molecular binding energies in the cluster, if the single-excitation infinite-order energy correction (LP SEInf) is computed. The formulation of the analytical first and second derivatives of the LP SCF MI energy as well as the analytical first derivative of the LP SEInf energy is presented. The performance of the locally projected methods is tested on a set of molecular complexes, including water clusters, solvated anions, and nucleic acid pairs.
COMP 39 Effective computational cost reduction via basis set truncation: Extended systems

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The reduction of computational cost via the truncation of the correlation consistent basis sets [cc-pVnZ where n=D(2), T(3), Q(4), and 5] has been investigated for a range of extended systems. The full and truncated basis sets have been used in combination with the coupled cluster with singles, doubles, and quasiperturbative triples excitation [CCSD(T)] method and second order Møller-Plesset perturbation [MP2] theory. The effect that basis set truncation has upon atomization energies, heats of formation, and computational CPU time is reported. The impact of truncation upon complete basis set (CBS) limits for energies is also examined.

COMP 40 Scaling of GAMESS quantum chemistry calculations on a small COTS cluster

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The scaling of quantum chemistry calculations using the General Atomic and Molecular Structure System (GAMESS) program on a small “commodity off the shelf” (COTS) computer cluster will be examined. With an investment in “sweat equity” this cluster was assembled in the presenter’s research group. Clusters can provide a very cost effective way to significantly increase the speed of calculations. As such, for large scale calculations in general, and computational chemistry in particular, they have become ubiquitous over the last several years. However, small research groups and departments can find themselves at a particular disadvantage because of the lack of support personnel for maintaining this kind of computer infrastructure. This necessitates a “do it yourself” approach that nevertheless can be quite successful.

COMP 41 The correlation-consistent Composite Approach (ccCA)

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The Gaussian-n (G1, G3) composite methods of computing molecular energies are revisited (and named the “correlation-consistent Composite Approach” [ccCA, ccCA-CBS-1, ccCA-CBS-2]) using the correlation-consistent polarized valence (cc-pVXZ) basis sets developed by Dunning and co-workers. The G2-1 test set of 125 atomic and molecular energies are computed, as well as $\Delta H_f$ values of 30 more systems. Equilibrium molecular geometries and vibrational frequencies are obtained using B3LYP density functional theory. When applying the ccCA-CBS method with the cc-pVXZ series of basis sets augmented with diffuse functions and adding corrections for scalar relativity and atomic spin-orbit splitting effects, the mean absolute deviation within the G2-1 test set compared to experiment is 0.79 kcal mol$^{-1}$ for $\Delta H_f$, 0.82 kcal mol$^{-1}$ for IPs, 1.09 kcal mol$^{-1}$ for EAs, and 1.55 kcal mol$^{-1}$ for PAs, without including a “high-level correction” (HLC) as contained in the original G3 methods. The ccCA methods require more computational time than the Gn methods due to increased basis set requirements. However, the ccCA-CBS method is a viable “black box” method that can handle systems with at least 10-15 heavy atoms.

COMP 42 Calculation of acid dissociation constants by the SM6 quantum mechanical implicit solvation model

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The calculation of acid dissociation constants is an important aspect of organic and biological chemistry. Several quantum mechanical methods have been developed for this purpose. Traditional forms of these methods have been limited due to computational and memory constraints. This paper describes a novel method for calculating the ionization of acids in solution. The method, known as the SM6 model, utilizes a quantum mechanical calculation to perform a series of ionization energy and charge density calculations, which are then used to estimate the ionization constant of the acid in solution. The model has been shown to be highly accurate and provides a new tool for chemists to use in their research.
Accurate prediction of molecular pKa values is a challenging task. To calculate these free energies, implicit solvent models that approximate the electrostatic response of a bulk solvent as a dielectric continuum are an attractive alternative to computationally more demanding explicit solvent simulations. Most previous attempts at using implicit solvent models to calculate pKa values have met limited success. We apply an explicit-implicit hybrid solvent approach to calculate pKa values. Solvent effects are accounted for in two ways: (1) explicitly, by using a single solvent molecule that is bound to the solute and (2) implicitly, by using the SM6 dielectric continuum and atomic surface tension model. This strategy yields solvation free energies for ionic solutes that are significantly more accurate than those obtained using an implicit solvent model alone. The present work thus presents a promising route to calculating accurate pKa values for a wide variety of compounds.

**COMP 43 Ab initio density functional theory: The seamless connection with wavefunction theory**

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The Optimized Effective Potential approach provides the seamless connection between density functional theory (DFT) and wavefunction theory. Its use requires that the functional be orbital dependent, although the associated exchange-correlation potential is a local, multiplicative operator. In prior work we have shown that using orbital dependent functionals from correlated wavefunction theory, we are able to obtain the correct behavior of the exchange and correlation potentials. We have applied the OEP2(sc) approach to many example systems with encouraging results. Dispersion in particular is well described. Unlike other DFT methods, ab initio dft has to converge to the right answer in the correlation and basis set limit. The initial time-dependent DFT results using OEP correlation will also be presented. Open shell generalizations show some interesting features. Infinite-order generalizations are also considered.

**COMP 44 New density functionals for electronic structure and dynamics**

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Recent developments are briefly reported:

1) For density functional theory (DFT) we discuss the problem of self-repulsion and a new functional which can overcome it[1]. The sensitivity to self-repulsion in molecular electronics is demonstrated by studying the charge distributions in biased systems.

2) A long-standing problem in time-dependent DFT is the description of multiply-excited states and electronic dephasing in metals. “Memory” functionals[2] can cope with such situations but are extremely difficult to apply in a general case. A simple approach is to use the center of mass frame[3]. Based on this, we developed a memory potential and applied it to electron dynamics in metallic gold clusters[4]. We discuss several conclusions for linear response and non linear dynamics, such as two-photon process and high order harmonic generation.


**COMP 45 Some progress in DFT: Efficiency, accuracy and open system**

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I will discuss three aspects of DFT: efficiency, accuracy and applicability to open systems, and present some recent progress. O(N) first-principles methods have been developed for complex systems. Focus will be on O(N) TDDFT. Despite its huge success, DFT is still not accurate enough for quantitative prediction (within the chemical accuracy). A novel approach has been developed to construct a Neural-Networks-based exchange-correlation functional, and will be presented. Finally, an exact DFT method for the dynamics of open systems will be given, and its steady state solution will be compared to the existing approaches.

**COMP 46 Subsystem functionals: A path to improved functionals**

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The accuracy of a density functional theory (DFT) calculation is determined by the performance of the exchange-correlation (EXC) functional. With the increase in computational precision arising from the continual development of computers and algorithms, the EXC functional has increasingly become the limiting factor for the success or failure of a DFT calculation. For the last several years we have been investigating a new approach for constructing functionals, the subsystem functional scheme. I will give an overview of the scheme itself and present recent results obtained with the first version of a subsystem functional. I will also discuss possible extensions and future directions. Sandia is a multiprogram laboratory operated by Sandia Corporation, a Lockheed Martin Company, for the United States Department of Energy’s National Nuclear Security Administration under contract DE-AC04-94AL85000.

**COMP 47 Exchange-correlation functional for organometallic, inorganometallic, and nonmetallic bonding, noncovalent interactions, and reaction barriers**

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Most density functionals that predict accurate barrier heights for chemical reactions do not predict reliable bond energies for many metal-metal and metal-ligand bonds and other systems with large multireference character. The contrapositive is also true: functionals that predicting accurate barriers are not usually reliable for metallic bonding. By incorporating kinetic energy density in a balanced way in the exchange and correlation functionals, enforcing the uniform-electron-gas limit, removing self-correlation effects, and shaping the functional by training with a small but diverse training set, we have designed a density functional that has broad accuracy for transition metal-transition metal bonds, metal-ligand bonds, main group thermochemistry, kinetics (barrier heights), and noncovalent interactions (including hydrogen bonding, dipolar interactions, weak interactions, charge transfer complexes, and pi-pi stacking). The new density functional, called M05 (short for Minnesota 2005), has been validated against a large set of data and is the most broadly accurate density functional currently available.

**COMP 48 Mixed relativistic and non-relativistic DFT calculations for large systems containing heavy elements**

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A scheme is proposed for density functional calculations of large systems with some parts containing heavy elements, by which relativistic(R) DFT calculations are carried out for the local regions containing heavy elements in a large system, while non-relativistic(NR) DFT calculations...
are performed for the other parts in order to reduce computational efforts. An identical energy density functional is used in R- and NR-DFT calculations both, considering the result from numerical examinations that the existent approximate energy density functionals show similar accuracy in R- and NR-DFT calculations. The method joining R- and NR-DFT calculations can be used in calculations of moderately large systems containing heavy elements. A very large system will be proper divided into many parts first, then the method joining R- and NR-DFT calculations is used to calculate the parts containing heavy elements, while NR-DFT calculations are performed for the other parts. The calculated results for a series of molecules will be presented to show the validity of the proposed mixed R- and NR-DFT calculation scheme.

**COMP 49 Density functional methods and vibronic interactions: Lessons from computational studies of DMX**

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In the dehydro-meta-xylylene (DMX) anion [J. Org. Chem. v. 69, 5735 2004, J. Chem. Phys. A, in press, 2005], 3 nearly degenerate orbitals host 4 electrons, which results in a large number of nearly-degenerate electronic states. Although many of these states, e.g., the ground triplet B2 state, can be described by single-reference methods, such as DFT, an unexpected artificial symmetry lowering was observed due to the incorrect description of vibronic interactions with other closely lying states.

**COMP 50 Structure based optimization of cyclin dependant kinase inhibitors**

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Structure based elaboration of the anilino-pyrimidine pharmacophore discovered using the high throughput docking program LIDAEUS has resulted in highly potent CDK inhibitors for development as anti-tumour therapeutics. Computational methods have been used to derive the structural basis for specific, high-affinity binding of inhibitors to the active site of CDK4 and this knowledge has been applied to the design of compounds that are potent and selective compounds. A comparison is presented of the crystal structures for a series of inhibitors in complex with the monomeric and activated forms of CDK2. The results of this study show that the inactive inhibitor structures are not an accurate reflection of structure-activity data obtained in the cyclin bound CDK2. The differences in interactions of the ligand between the two protein conformations and their implications for structure guided design are discussed.

**COMP 51 Docking studies to advance the discovery and optimization of kinase inhibitors**

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The availability of numerous crystal structures has enabled a greater understanding of the requirements for ligand recognition in the protein kinase family. Docking and scoring methods have therefore been optimized for this target class, and different approaches may be useful depending on the stage of the medicinal chemistry project. Examples of applications to kinases within the hit identification, lead identification, and lead optimization phases of drug discovery will be presented.

**COMP 52 Design of selective protein inhibitors using PASSA and PAS-Dock**

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Protein Alpha Shape Similarity Analysis (PASSA) is a new method for mapping protein binding sites and identification of interaction sites that can be utilized to achieve selectivity. Calculation of alpha spheres is used together with gaussian functions to generate gaussian property fields describing the properties of the protein binding site. Structural regions where the target protein differs from other, related proteins are identified with Discriminant Partial Least Squares Regression (DPLSR). Protein Alpha Shape (PAS) Dock is an empirical score function based on the same principle as PASSA. Due to the smoothing effect of the gaussian functions used, PAS-Dock is suitable for virtual screening using homology models. Use of a two-level scoring makes PAS-Dock computationally efficient. According to this study, PAS-Dock is more computationally efficient than both AutoDock and MOE-Dock, and gives a better prediction of the free energies of binding. PAS-Dock is also more robust against structural variations than AutoDock.

**COMP 53 Regulatory subunit RI-alpha and PKA: Allostery and dynamic binding**

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Recent crystal structures have revealed that regulatory subunit RI\alpha of PKA undergoes a dramatic conformational change upon complex formation with the catalytic subunit. Molecular dynamics studies were initiated to elucidate the contributions of intrinsic conformational flexibility and interactions with the catalytic subunit in formation and stabilization of the complex. Simulations of a single RI\alpha nucleotide-binding domain (NBD), missing cAMP, showed that its C helix spontaneously occupies two distinct conformations: either packed against the nucleotide binding domain as in its cAMP-bound structure, or extended into an intermediate form resembling that of the holoenzyme structure. C helix extension was not seen in a simulation of both RI\alpha NBDs. In a model complex containing both NBDs and the catalytic subunit, well-conserved residues at the interface between the NBDs in the cAMP-bound form were found to stabilize the complex through contacts with the catalytic subunit. The model structure is consistent with available experimental data.

**COMP 54 Biasing for favored substituents in kinase library design**

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Docking lead molecules is an effective way to identify potential leads in targeted libraries. Unfortunately, the speed of available docking programs makes this approach impractical for many large combinatorial libraries of interest. OptiDock is a program that addresses this problem by docking substructures using a series of alternative base placements and assuming that the scores produced will be additive. Here we will discuss a complementary method in which virtual intermediates are docked and the scores produced are used to bias reagent selection during design of a candidate sub-library. Docking scores from the products in the sub-library can then be used to identify final candidates for synthesis.

**COMP 55 Understanding hits and decoys in molecular docking**

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Molecular docking is widely used to screen compound collections for novel leads. Because of its approximations, many docking predictions prove false; even more perniciously, they are almost
impossible to understand because of the entangled approximations. We are taking two strategies to investigate this problem. First, we have turned to small buried cavities where the interactions are dominated by one term. Thus, the L99A cavity in T4 lysozyme is dominated by non-polar complementarity, the L99A/M102Q cavity has a single hydrogen bond acceptor, and the W191G cavity in cytochrome C peroxidase is dominated by an ionic interaction. The simplicity of these sites makes mis-predicted ligands and geometries as informative as correct predictions. We are testing predicted binding, geometry, and protein motion, using crystallography, in a cycle of theory and experiment. In a second strategy, we are developing a large database of good “decoy” molecules as a background for evaluating enrichments when docking to drugable targets. Perversely, we find that the quality of the decoy molecules in the database can be as important as the docking engine in evaluating docking based on criteria such as enrichment factors.

COMP 56 Finding inhibitors of protein association by ICM docking into induced surface pockets

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We developed a new method to identify ligand binding sites from protein structure using only receptor coordinates and applied this method to identify the “druggable pockets” that can be targeted to prevent protein-protein interactions. We also developed a procedure to predict possible induced fit in a ligand pocket. Here we report the procedure which was applied to identify the first small molecule inhibitors preventing polymerization of alpha-1 antitrypsin (AAT). AAT is the most abundant circulating protease inhibitor. One variant of AAT called the Z-allele (Glu342Lys) predisposes the homozygote to liver disease and early onset emphysema due to aggregation of AAT in the liver, followed by depletion of the extracellular pool of AAT needed to control the extracellular proteases. Our analysis validated and extended previous work around that site. A possible critical site was identified and modelled with a goal to prevent polymerization without distorting the native function of AAT. The Internal Coordinate Mechanics (ICM) program was used to screen 940,000 small molecules in silico for lead compounds that bind to the cavity. We identified 50 compounds for further testing and of these, 4 compounds significantly reduced polymerization as assessed by non-denaturating PAGE. We then built several alternative models of the pocket based on the flexibility analysis and searched the chemical database again. Two of the identified compounds completely inhibited polymer formation. Polymerization of the Z variant of AAT can thus be effectively blocked by a small molecule in vitro.

COMP 57 Use of negative data in the refinement of scoring functions for virtual screening

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Surflex-Dock employs an empirically derived scoring function to rank putative protein-ligand interactions by flexible docking of small molecules to proteins of known structure. The scoring function employed by Surflex was developed purely based on positive data, so scoring function terms for improper interactions received little weight in parameter estimation, and an ad hoc scheme for avoiding protein-ligand interpenetration was adopted. We present a generalized method for incorporating synthetically generated negative training data, which allows for rigorous estimation of all scoring function parameters. Geometric docking accuracy remained excellent under the new parameterization. In addition, a test of screening utility covering a diverse set of 29 proteins and corresponding ligand sets, showed improved performance. Maximal enrichment of true ligands over non-ligands exceeded 20-fold in over 80% of cases,
with enrichment of greater than 100-fold in over 50% of cases. Further refinement of the Surflex-Dock scoring function making use of this technique is underway as are applications of the technique in ligand-based modeling techniques.

**COMP 58 Accurate prediction of ligand-receptor binding energies**

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Computational techniques for predicting the correct binding mode of ligands in both rigid and flexible receptors have in recent years advanced to a sufficiently high level such that accurate results can be obtained in a very large fraction of cases. After a correct binding mode is obtained, a vital component of computational design is the accurate prediction of ligand-receptor binding free energies; however, such calculations have generally yielded acceptable results in only a few isolated cases. We have developed a methodology that couples traditional empirical docking scoring terms with additional terms derived from physics-based implicit-solvent models and QM/MM calculations, resulting in striking improvements in the accuracy of binding energy predictions.

**COMP 59 Validation of quantum-mechanical docking and scoring procedures**

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Macromolecular force fields are indispensable tools for studying bio-molecules at atomic resolution. However, their application to structure based drug design is limited due to the complexity of developing high quality parameters for ligands exhibiting high structural variation. Semiempirical quantum-mechanical (QM) methods are much more general in this respect and were therefore used in second phase docking to refine the list of hits. Multiple poses generated by using genetic algorithm software were geometrically optimized at QM level in the protein-ligand complexes. Protein active site side chains were relaxed in the complexes and the all-atom systems were treated at QM level with solvent effects included via the COSMO model. Native conformations were successfully identified from first principles for most of the complexes without preliminary training of the method.

**COMP 60 Better knowledge – better scoring: Tailoring DrugScore to a particular protein yields improved pose and affinity predictions and allows to incorporate conformational variability**

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The development of protein-specifically adapted scoring and objective functions with improved predictive power is described. Knowledge-based DrugScore pair-potentials are tailored by the recently developed AFMoC approach, which is a truly protein-based CoMFA-type approach that provides a link between the fields of tailor-made scoring functions and 3D-QSAR. When used as a scoring function, impressive improvements of binding affinity predictions could be achieved compared to the application of the original potentials by considering a sample of only 15 known training ligands. For application as an objective function in docking, a Shannon entropy based column filtering of the descriptor matrix and the capping of adapted repulsive potentials within the binding site turned out to be crucial, resulting in AFMoCob. Compared to nonadapted DrugScore or AutoDock fields, the binding mode prediction accuracy was significantly improved by 14% when applied to a dataset of 66 HIV-1 protease inhibitors. Noteworthy, very similar results were obtained for training and test set compounds, demonstrating the strength and robustness of the method. Finally, the AFMoC method was extended to consider ligand and
receptor conformational variability in a consensus way (AFMoCCon). This development was motivated by the need to account for receptor flexibility observed in experimental complex structures or structural inaccuracies of modeled receptors. AFMoCCon makes use of an ensemble of receptor structure-ligand alignments, and the extended descriptor matrix is analyzed by a multi-block PLS regression together with a VINFM-based region selection. Encouragingly, using homology modeled thrombin structures for validation, AFMoCCon models show a comparable or higher internal and external predictivity than the best single model (derived either from the experimental structure or an homology model).

**COMP 61 Assembling the small ribosomal subunit in silico: A novel approach to determine binding interdependencies**

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Antibiotics can target the assembly of the bacterial ribosome and thus kill infectious organisms or at least reduce their growth. To target the assembly process most efficiently one has to understand the interdependencies of the binding processes of the 21 proteins to the rRNA in great detail. To this end we introduce a new computational protocol that is suitable to detect energetic as well as entropic contributions to these relations. We show the similarities between the assembly of the experimentally determined binding map of E.coli and our results for T.thermophilus. We then discuss potential antibiotic targets.

**COMP 62 Exploring the assembly of the 30S ribosomal subunit**

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The 30S ribosomal subunit is a large assembly, comprising of 21 proteins and over 1500 nucleotide long 16S RNA. To study the energetics of the assembly, we compute relative binding free energies of the 30S proteins to the 16S RNA based on an implicit solvent model of electrostatic, nonpolar and entropic contributions. We find that late binding proteins of the E. coli assembly map do not bind to the naked 16S RNA. The 5' domain early kinetic class proteins on average, carry the highest positive charge, get buried the most upon association with 16S RNA, and show the most favorable binding. Some proteins have more stabilizing interactions while binding as dimers. Our computed assembly map of T. thermophilus resembles that of E. coli, however, the central domain path is more similar to that of A. aeolicus, a hyperthermophilic bacteria.

**COMP 63 Conformational change of the methionine 20 loop of Escherichia coli dihydrofolate reductase modulates protonation of the substrate dihydrofolate**

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The enzyme dihydrofolate reductase (DHFR) and its cofactor, NADPH, catalyze the enantioselective hydrogenation of 7,8-dihydrofolate (H2F) into 5,6,7,8-tetrahydrofolate (H4F), essential for cell division. The catalysis involves a controversial protonation of the N5 atom of the H2F. To evaluate the corresponding pKa shift of the H2F due to DHFR we perform free
energy perturbation simulation (FEP) with molecular dynamics (MD) of a stable closed ternary complex with NADP+ and closed and occluded transient Michaelis complexes with NADPH in explicit water. The simulations show that in the reactive Michaelis complex the relative position of the Met20 loop with respect to the rigid domain of the DHFR fluctuates substantially, strongly modulating the H2F pKa. The role of the cofactor and the Met20 sidechain in the pKa shift is discussed. Also the convergence of the FEP/MD simulations for determining pKa shifts in such complex systems as DHFR is analyzed.

**COMP 64 Deprotonation of solvated formic acid from Car Parrinello molecular dynamics plus the novel metadynamics method**

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The deprotonation of solvated formic acid was investigated theoretically with ab initio simulations. With the Car-Parrinello method, deprotonation and reprotonation by means of a proton wire were observed. The microscopics of these reactions were analyzed, and reveal the key role played by near-by water molecules in catalyzing the reactions. A constrained free energy calculation was carried out to estimate the dissociation free energy. Deprotonation of formic acid was further investigated with the recently developed metadynamics method using the formic acid oxygen coor-dination numbers as the collective variables. The determined free energy landscape gives barriers similar to that obtained with the constrained free energy calculation.

**COMP 65 Understanding the decarboxylation mechanism of N-carboxy-2-imidazolidinone, a Car-Parrinello molecular dynamics investigation**

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One crucial step in Fatty Acid synthesis is the transfer of carbon dioxide to the CoA substrate. Understanding this step has both fundamental and practical implications, e.g., in the anti-obesity and anti-microbial drug design. Although the gross mechanistic features of this enzymatic process have been extensively characterized, many chemical details of this carboxyl transfer process are still unresolved. In fact, an array of possible enzymatic mechanisms have been postulated in the literature, which appear to be consistent with the mechanistic studies on model systems such as aliphatic carbamates and N-carboxy-2-imidazolidinone. Car-Parrinello molecular dynamics simulations were carried out to examine the free energy surface along the various possible reaction pathways proposed for these model systems. These simulation studies have revealed important effects caused by the solvent and the protonation of the model carbamates on the detailed reaction mechanism. For example, the reaction barrier for the protonated N-carboxy-2-imidazolidinone was significantly lower than the anion form by more than 4 kcal/mol. This is equivalent to a three order magnitude increase on the first-order rate constant, comparable to the experimental report of a rate constant increase of 6000 times. In addition, decarboxylation was found to occur spontaneously when the nitrogen connected to the carboxyl group is protonated. The possibility of the N-protonated form involved as an activated species in the decarboxylation process will be discussed. The results for these model systems will be also compared to those obtained for a model reaction at the active site of carboxyltransferase.

**COMP 66 QM/MM model of the O\(_2\)-evolving complex of photosystem II**
Six oxomangenate complexes structurally related with the Oxygen-Evolving Complex (OEC) of PhotoSystem II (PSII), including two Mn$_3$O$_4$CaMn clusters (one hydrated and other with proteininatisng ligands analogous to the '3+1 Mn tetramer' of the OEC), were computed with DFT/B3LYP methods to characterize their geometrical, electronic and magnetic properties. The success of this approach let us extend this methodology to a Quantum Mechanics/Molecular Mechanics implementation at a two-layer ONIOM Electronic-Embedding link-hydrogen atom level of theory, to study the OEC of PSII and surrounding residues within a sphere of 15 Å. The model includes ligation of the OEC by amino-acid residues, water, hydroxide, chloride, and calcium ions. In the S1-state, the ligation includes monodentate coordination of D1-Asp342, CP43-Glu354 and D1-Asp170 to Mn(1), Mn(3) and Mn(4), respectively; D1-Glu333 to both Mn(3) and Mn(2); and D1-Glu189 and D1-His332 to Mn(2). The resulting structural model is consistent with X-ray diffraction models of PSII in cyanobacteria Thermosynechococcus elongates (PDB entry 1S5L), and agrees with EXAFS data. S0- and S2-states were also prepared, and also agree with EXAFS measurements.

COMP 67 Modeling the key recognition event at the heart of the immune response
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The recognition of antigenic epitopes by the T-cell receptors (TCRs) is the key molecular event at the heart of the immune response. Presented by the same major histocompatibility complex (MHC), peptides with single amino acid substitution have different binding affinities with the same TCR; on the other hand, the same MHC-bound peptide can be recognized by different TCRs. To explore the molecular principles underlying the selectivity of TCRs, we have performed molecular dynamics (MD) simulations of wild-type and variant HTLV-1 Tax peptides presented by the MHC to the TCR, and A6 and B7 TCRs bound to the same peptide-MHC. The binding free energy difference is calculated using the thermodynamic integration, the molecular mechanics Poisson-Boltzmann surface area and the linear interaction energy methods. The successful reproduction of the relative binding free energies shows that these methods can be useful for free energy calculations and the rational design of drugs and vaccines.

COMP 68 Multi-configuration molecular mechanics based on combined quantum mechanical and molecular mechanical calculations
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A new strategy is reported for constructing multi-configuration molecular mechanics (MCMM)[1] potential energy surfaces of very large reactive systems. The MCMM method was previously developed as an extension of standard MM to reactive systems by inclusion of multi-dimensional resonance between multiple MM configurations that are characterized by unique valence bonding patterns for a given geometry. The resonance matrix element is obtained by electronic structure calculations of local Taylor series at a small number of geometries. It is represented by multidimensional interpolation, which assures full accounting for the coupling between the reaction coordinate and the perpendicular coordinates. The extension of the MCMM scheme that is presented here is the use of combined quantum mechanics and molecular mechanics (QM/MM)[2] instead of straight electronic structure. The new, general QM/MM-MCMM scheme is...
tested for hydrogen-transfer reactions by comparison to calculations by the QM-MCMM method based on pure QM descriptions. For a selected small system, comparison is also made to direct dynamics calculations in which the potentials energies are computed quantum mechanically on the fly. Very encouraging results are obtained for rate constants including full-dimensional tunneling, suggesting that QM/MM-MCMM is robust, efficient, and accurate. This work was supported in part by the U.S. DOE, NSF, and ONR.


**COMP 69 Early days of DFT with RGP, and a general theory of hybrids**

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The first part of the lecture will involve recollections concerning Parr's entry into DFT in the 1970's and subsequent early work in the 1970's and 1980's. The second part of the lecture will analyze Density Functional hybrids through a general theory involving a synthesis of an integration by parts along the adiabatic connection and perturbation theory. New approaches will be presented.

**COMP 70 Importance of the exchange-correlation potential in Kohn-Sham theory**

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The importance of understanding and accurately representing the exchange-correlation potential and the exchange-only component will be highlighted, with reference to the calculation of second-order magnetic response properties; charge-transfer electronic excitations; negative electron affinities and the chemical hardness.

**COMP 71 Kohn-Sham calculations without density functionals**

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Instead of using an approximate density functional, we introduce a model system which generates the spherically and system-averaged pair density along an adiabatic connection. This directly allows to compute the correlation energy needed in Kohn-Sham calculations.

The method will be illustrated with simple preliminary applications.

**COMP 72 Assessment of exchange-correlation functionals from the adiabatic connection**

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The adiabatic connection has shown to be an extremely important theoretical tool for the construction of exchange-correlation functionals. We investigate non-linear forms of exchange correlation functionals that come from the use of various functions to model the adiabatic connection. We examine the performance of these adiabatic exchange-correlation functionals.
and compare with commonly used GGA and hybrid functionals such as BLYP and B3LYP. A wide range of properties are examined such as energies and geometries and also response properties such as polarisabilities and NMR shielding constants. The use of the optimised effective potential (OEP) method is also compared to the standard SCF method of minimisation of the energy with respect to the orbitals.

**COMP 73 A new hybrid DFT functional: Accurate description of response properties and van der Waals interactions**

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DFT has advanced to one of the most popular theoretical approaches to calculate molecular properties. The first-order molecular properties (energies, geometries, frequencies, dipole moments, etc) are well predicted by local GGA functionals. However, DFT fails to describe induced or response properties. This failure has been attributed to the wrong long-range behavior of the standard exchange-correlation functionals. Hybrid functionals can be improved through the introduction of an Ewald partitioning. Long-range corrected GGA has good energetics, good Rydberg behavior and good charge transfer predictions. LC-GGA with Andersson's functional predicts good van der Waals interactions.

**COMP 74 Density scaling and a generalized Kohn-Sham scheme**

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Using the density scaling proposed by Chan and Handy, a generalized Kohn-Sham scheme in which the correlation energy disappears, is presented. Therefore exchange energy has to be determined instead of the exchange-correlation energy and it can be calculated very accurately. Making use of the method a simple approximate relation for the correlation energy of the original Kohn-Sham scheme is derived. This expression supports an earlier extrapolation by Herschbach and co-workers, that correlation energy enters the large Z non-relativistic binding energy formula for the first time at the 4/3 power of Z.

**COMP 75 Time-dependent density functionals derived from variational functionals of the Green function**

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In this work we will consider a systematic approach to the construction of time-dependent density functionals. The approach is based on variational expressions for the action functional in terms of the many-body Green function. When the input Green functions are restricted to ones coming from a local potentials we obtain a time-dependent optimized effective potential scheme, from which exchange-correlation potentials and response functions can be calculated. The time-dependent density-functionals derived in this way automatically satisfy conservation laws and sum rules. When applied to ground state problems the functionals yield excellent agreement with fully self-consistent Green function calculations, at a fraction of the computational cost.

**COMP 76 Progress in Computer-Aided Drug Design**

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General issues for structure-based drug design will be covered based on our experiences with molecule docking, growing, fragment simulations, ADME-properties evaluation, similarity searching, and free-energy perturbation calculations. In-house drug development is being pursued through multiple computer-aided routes, followed by synthesis, and assaying. (a) In
one mode, the design begins with use of the ligand-growing program BOMB, which rapidly constructs combinatorial libraries given the structure of the target protein and a selected core and substituents. BOMB grows the analogs inside the protein's binding site, performs a thorough conformational search, and estimates the analog's binding affinity or activity using scoring functions. The QikProp program is applied to filter all designed molecules to insure that they have drug-like properties including solubility and cell permeability. MC/FEP simulations are then performed to refine the predictions for the best scoring leads using hundreds of explicit water molecules and extensive sampling for the protein and ligand. (b) Alternatively, screening of known compound libraries is performed by filtering for drug-likeness and similarity to known active compounds with QikProp and QikSim, followed by docking with Glide. (c) Lead compounds are also sought through multiple-copy simulations of small molecules (fragments) with BOSS. In this case a protein is saturated with hundreds of copies of a fragment, which are then annealed to seek consensus binding sites. Recent methodological advances and representative applications will be presented with emphasis on inhibitor development for HIV reverse transcriptase. Reference: The Many Roles of Computation in Drug Discovery. Jorgensen, W. L., Science 303, 1813-1818 (2004).

COMP 77 BACE: Accounting for flexibility in a scoring Function
Georgia McGaughey1, Bradley Feuston1, Samuel Graham2, M. Katherine Holloway1, Stacey Lindsley1, Philippe Nantermet2, Hemaka Rajapakse2, and Shaun Stauffer2. (1) Molecular Systems, Merck, WP53F-301, West Point, PA 19486, Fax: 215-652-4625, georgia_mcgaughey@merck.com, (2) Department of Chemistry, Merck

Beta-Secretase (BACE) is a transmembrane aspartyl protease intimately involved in the neurodegenerative disorder, Alzheimer's disease. Publicly available crystal structures of inhibitors binding to BACE have demonstrated that BACE is inherently flexible. Accounting for varied protein flexibility in a scoring function is a challenge due to the difficulty in reliably predicting entropic costs, water motion and protein/ligand movement, particularly when one is rank-ordering many ligands in a drug discovery program. However, we were able to estimate the free energy of binding by calculating the protein/ligand interaction energy. Given the known malleability of BACE, we scored several compounds in numerous poses of the protein. Through these analyses, we were able to develop chemotype-specific scoring functions for rank-ordering virtual compounds that have proven useful for explaining SAR. In addition, using an algorithm known as "Essential Dynamics", we have both predicted and depicted flexibility. This is achieved by calculating the low mode vibrations of the protein using either molecular dynamics or any of numerous available crystal structures. This presentation will discuss protein motion of BACE in complex with various compounds and will focus specifically on the critical S3 pocket. From these, I will discuss how we were able to come to an understanding of how certain R-groups affect interactions of the compound with key elements in this pocket with further implications for binding affinity and other characteristics.

COMP 78 Pharmacophore-based virtual screening
John Van Drie, Novartis Institutes for Biomedical Research, 250 Mass AVe, Cambridge, MA 02139, johnvandrie@mindspring.com

The nearly 20 years of success with virtual screening using pharmacophores will be reviewed, with an eye towards identifying those characteristics common to those successes. Attention will be paid to the construction of 3D databases, the treatment of chirality, the methods of conformational analysis, the types of 3D searching algorithms, the manner in which the pharmacophores are defined and created, and the many ways in which this type of search can be incorporated into the drug discovery process as a whole.

COMP 79 A comparison of structure-based and shape-based tools for virtual screening
Paul C. D. Hawkins, Applications, OpenEye Scientific Software, 3600 Cerrillos Road, Suite
Ligand docking is a widely used approach in structure-based virtual screening. In recent years a large number of publications have appeared in which docking tools are compared and evaluated for their effectiveness against a wide variety of protein targets. These studies have shown that the effectiveness of docking in virtual screening is very variable, due to a large number of possible confounding factors. Several direct comparisons of docking with a shape-based tool, ROCS, have been conducted using datasets from some of these recent publications and the results are presented herein. The results show that a ligand-centric approach as exemplified by ROCS, is often superior to the protein-centric approach taken by docking.

**COMP 80 PubChem: An information resource linking chemistry and biology**

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PubChem is an online public information resource from the National Center for Biotechnology Information (NCBI). The system provides information on the biological properties and activities of chemical substances, linking together results from different sources on the basis of chemical structure and/or chemical structure similarity. Following the deposition model introduced by GenBank, PubChem's content is derived from user depositions of chemical structure and bioassay data, including high-throughput biological screening data from National Institutes of Health's Molecular Libraries initiative. PubChem's retrieval system supports searches based on chemical names and chemical structure, as well as searches based on bioassay descriptions and activity criteria. PubChem provides further information on biological properties via links to other NCBI information resources, such as the PubMed biomedical literature database and NCBI's protein 3D structure database, as well as via links to depositor web sites.

**COMP 81 Beyond PEST descriptors: Binding site and ligand shape/property fingerprints**

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Both ligand and protein binding site surfaces may be characterized using a common set of shape/electronic property fingerprints based on PEST surface sampling technology. This approach allows important shape information and electronic spatial relationships to be identified within fingerprint space. This facilitates the rapid screening of ligand libraries for specific shape/property features that are favorable for interaction with a given binding site. Using appropriate machine learning techniques, the resulting fingerprints can be analyzed to reveal two-point interactions important to the binding of a given protein and ligand, and allow for the auto-discovery of two- and three-point pharmacophores for each class of protein/ligand complexes. The ligand and binding site fingerprints may then be used in database searches to identify potential hits.

**COMP 82 Wave-packets and density matrices: Using DFT for ab initio dynamics**

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A recently developed computational approach for simultaneous dynamics of electrons and nuclei is discussed. The approach is based on a synergy between quantum wavepacket dynamics and...
ab initio molecular dynamics. The quantum dynamics is performed using an efficient banded, sparse and Toeplitz representation for the discretized free propagator that is formally exact. Ab initio molecular dynamics is achieved using (a) an extended Lagrangian formalism that effects an adjustment of time-scales of the electronic motion, (b) Born-Oppenheimer treatment. In both cases the electronic structure is treated simultaneously using density functional theory. The quantum dynamics and ab initio dynamics schemes are coupled through a time-dependent self consistent field-like procedure. Higher order coupling is inherent when the Born-Oppenheimer procedure is used as opposed to the extended Lagrangian scheme. Example calculations dealing with water clusters and biological enzyme reactions exhibiting quantum nuclear effects are discussed.

COMP 83 Dopant effects on excited states of a novel photocatalyst: A QM/MM study of ETS-10

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ETS-10 is a microporous titanosilicate with promise as a photocatalyst. It is composed of chains of TiO\textsubscript{2}, which act as 1-D semi-conducting wires, insulated by a SiO\textsubscript{2} shell. Hybrid DFT/MM methods have been used to investigate the effect of dopants and defects on the electronic and local geometric structure of ETS-10. The origins of the experimentally observed decrease in the optical band gap with increasing [V] will be discussed, along with spectral assignments for experimental UV-vis spectra. Excited state wave functions will be used to analyze charge localization and carrier separation to predict the effects of V substitution on photocatalytic efficiency. The energetics of substituting V in different types of sites and the corresponding effects on reactivity will also be addressed. The theoretical results will be compared with recent experimental data.

COMP 84 Models and mechanisms of the DNA (6-4) photoproduct repair by (6-4) photolyase

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Ultraviolet irradiation of DNA induces formation of carcinogenic (6-4) photolesions, damaging genetic information and leading ultimately to cell death. This DNA damage is repaired in vivo by (6-4) photolyase which uses a unique light induced electron-transfer catalyzed mechanism to cyclorevert the (6-4) photolesions. The mechanistic details of cycloreversion and enzymatic repair remain unresolved. Hybrid DFT calculations that contrast four competing repair pathways will be presented. These results will be discussed within the context of a model of the enzyme-substrate complex that was developed by homology modeling to multiple templates, followed by docking of the (6-4) photoproduct. Classical molecular dynamics simulations in conjunction with quantum calculations of this model will be presented and evaluated in comparison to experimental data. A mechanism consistent with the available results will be proposed and the role of the different active site residues will be analyzed.
COMP 85 Unconventional Catalytic Mechanism for histone deacetylase suggested by a DFT-QM/MM study

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Histone deacetylases (HDACs) constitute an important family of zinc-dependent enzymes responsible for catalyzing the cleavage of acetyl groups from acetyl-lysine residues in histone N-terminal tails. HDACs can potentially play a key role treating various cancer, thus making knowledge of their catalytic mechanism highly important. Based on experimental structures, the initially proposed mechanism hypothesized enhancement of active water nucleophilicity by coordination to the zinc atom. Our theoretical study does not support the previous hypothesis but suggests a new catalytic mechanism for this important reaction.

COMP 86 Theoretical studies on farnesyl cation cyclization: pathways to pentalenene and diversions to other natural products

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Nature makes a wide range of complex, stereodense molecules starting with acyclic terpenes like farnesyl pyrophosphate (FPP). Natural terpenoids are abundant and thousands of diverse structures have been isolated.

This work deals with pentalenene, a sesquiterpenoid with three fused 5-membered rings. Pentalenene is formed by the cyclization of FPP in the presence of a single enzyme: pentalenene synthase. The study of possible cyclization pathways of the farnesyl cation is performed using quantum chemical calculations. Two distinct pathways with similar activation barriers are described; each differing from previous mechanistic proposals, and each involving unusual and unexpected intermediates. Inherent (i.e. gas phase) reactivity of the carbocationic intermediates along the pathways provide a standard against which the solvent effects (water for the biological reaction) and the active site of pentalenene synthase can be evaluated.

Diversions from these pathways lead readily to many natural products via various deprotonations, indicating that a key function of pentalenene synthase is to regulate the timing and location of proton removal. These diversions present a testable hypothesis for mutation studies.
COMP 87 Theoretical studies of intramolecular hydrogen bonding in malonamide derivatives
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Density functional (B3LYP/6-311++G(2d,p)) calculations have been performed on symmetric beta-substituted derivatives of malonamide in order to investigate the intramolecular resonant-assisted hydrogen bonds (RAHBs) present in these molecules. All were found to be low-barrier hydrogen bonds (LBHBs) possessing either Cs or C1 symmetry. In general, there is a good correlation between measures of hydrogen bond strength with the resonant electron withdrawing/donating ability of the substituent. However, significant exceptions to this general trend have also been investigated. These exceptions possess other intramolecular hydrogen bonds which serve either to enhance or diminish the resonance effect in the enolic O-H...O hydrogen bond.

COMP 88 The molecular properties of electronically excited states
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We have investigated the molecular properties of electronically excited states via coupled cluster theory through its equation-of-motion (EOM-CC) or linear-response (LRCC) variants. Truncation at the singles and doubles level (EOM-CCSD) has been shown to be very effective for states dominated by single-excitations. However, higher levels of electron-correlation are needed for cases where the excited state wave function exhibits an increase in double-excitation character or spin contamination. We have implemented an extension of the coupled cluster iterative-triples model, CC3, to the excited states of closed- and open-shell molecules. We report excited state dipole moments, oscillator strengths and electronic circular dichroism (ECD) absorption calculations and discuss the importance of including higher electron correlation levels.

COMP 89 Time-dependent density functional theory calculations of the electronic excited states of tryptophan in proteins
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Tryptophan is a widely exploited spectroscopic tool for studying proteins. Thus, there is much interest in modeling the influence of a protein environment on tryptophan, and its indole side chain. We have applied time-dependent density functional theory (TDDFT) to study the valence pi-pi* excited states of indole in the environment of the proteins barnase and human serum albumin. The approximate nature of TDDFT incorrectly reorders the calculated gas phase vertical transition energies to the singlet L states; the singlet La state responds more than the singlet Lb state to the local environment, described fully at the TDDFT level, and to bulk environment, described by point charges. Nevertheless, the transitions are readily identified. Calculations on human serum albumin predict distinct spectral characteristics for structures with different tryptophan side chain torsion angles. The computational tractability of TDDFT permits a sizeable part of the surrounding protein environment to be explicitly included.

COMP 90 Vibronic coupling in the ground and excited states of the oligoacene cations: A systematic density functional study
WITHDRAWN

The nature of hole-vibration coupling in the ground and lowest excited states of the radical-cations of oligoacenes containing from two to five rings (naphthalene, anthracene,
tetracene, and pentacene) is studied via a joint experimental and theoretical study of the ionization spectra. The results of density functional theory (DFT) calculations are compared to high-resolution gas-phase photoelectron spectroscopy data. The theoretical results show a significant redistribution of the vibronic coupling constants towards lower-frequency vibrations in the first two excited states of the cation. Our results also reveal that the DFT estimate of the strength of the vibrational coupling depends on the fraction of Hartree-Fock exchange included in the hybrid functional. Functionals that contain about 30% of the Hartree-Fock exchange were found to yield the best agreement with experiment.

COMP 91 Computing physical properties of simple aromatics

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We present a systematic comparison between entropies measured in the laboratory and entropies calculated via ab initio calculations for five simple aromatic compounds. The compounds are benzene, toluene, paraxylene, metaxylene and orthoxylene. We examined the effect of both method and basis set size for each compound. Hartree-Fock (HF) and B3LYP are used as the methods and the basis sets are: 6-31G(d), 6-31++G(d,p) and 6-311++G(3df,2pd).

The normal vibrational frequencies of the molecules were calculated using quantum mechanics. The calculated frequencies were assigned and compared to their corresponding experimental frequencies. For each set of normal frequencies, a scale factor was applied. After applying scale factors, the average percentage error is below 2.5%.

Using statistical mechanics, entropy was calculated for all molecules. We found all of the methods yield percentage errors less than 1% between calculated and experimental results. B3LYP/6-31++G(d,p) yields the smallest percentage error with the average error of 0.1%.

COMP 92 Kinetic approach to electron transport in nanoscale devices

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A general theoretical framework to study electron transport at the nanoscale is presented. The
approach is based on the Liouville-master equation for the electron reduced density operator and includes dissipative effects due to inelastic electron-phonon scattering. The Liouville-master equation is a fully quantum-mechanical approach that generalizes the well-known semi-classical Boltzmann kinetic equation to spatial dimensions of the order of the electron wavelength. In this approach not only the tunneling structure and the contacts are treated explicitly but also the source of the current. After discussing some general physical consequences of dissipative effects I will present numerical applications to carbon nanotube devices and to molecular structures suspended between metallic electrodes.

COMP 93 Advances in formal and practical time-dependent density-functional theory
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Density-functional theory (DFT), advocated and advanced by Robert G. Parr, has radically transformed computational chemistry scene. Time-dependent DFT (TDDFT) for excited states, linear and nonlinear properties, or general time-dependent phenomena, is proving to be another example of DFT's profound impact on chemistry. We will present our original contributions to this area, ranging from formal development to practical applications of TDDFT. They include: open-shell TDDFT and its applications to polycyclic aromatic hydrocarbon radicals; TDDFT for periodic extended systems (excitons in polymers); exact-exchange (or optimized effective potential) TDDFT for excitation energies, dynamic polarizabilities, and van der Waals coefficients; quantifying the effect of the so-called adiabatic approximation to the exchange-correlation kernel.

COMP 94 Excited-state spin-contamination in time-dependent density-functional theory for molecules with open-shell ground states
Mark E. Casida and Andrei Ipatov, Department of Chemistry, Laboratoire d’Études Dynamiques et Structurales de la Sélectivité (LEDSS), Université Joseph Fourier (Grenoble I), 301 Rue de la Chimie, F38041 Grenoble, France, Fax: 33.4.76.51.49.27, Mark.Casida@UJF-Grenoble.FR

A decade ago time-dependent density-functional theory (TDDFT) in its linear response formulation was introduced to the quantum chemistry community as the Casida equation for calculating excitation spectra. Since that time, this equation has been programmed in most world-class quantum chemistry programs with density-functional theory (DFT) capabilities and TDDFT has become a standard tool for examining the excited states of large molecules. Most calculations are for molecules with closed-shell ground states, however the original Casida equations were formulated to allow both different-orbitals-for-different-spin and fractional occupation numbers, thus opening the way to applying the method to molecules with open-shell ground states. A number of publications have now appeared applying TDDFT to molecules with open-shell ground states and give surprisingly good results for simple excitations. I will elaborate on the need to restrict adiabatic TDDFT to simple excitations in molecules with open-shell ground states and how polarization propagator corrections might be used to remove this restriction. I will then talk about how spin contamination is calculated for TDDFT excited states in the program deMon2k using the unrelaxed density matrix.

COMP 95 Nonperturbative treatment of atomic and molecular multiphoton processes in intense laser fields: Self-interaction-free TDDFT approaches
Shih-I Chu, Department of Chemistry, University of Kansas, 2010 Malott Hall, 1251 Wescoe Hall Drive, Lawrence, KS 66045, Fax: 785-864-5396, sichu@ku.edu

I will describe some recent developments of self-interaction-free time-dependent density functional theories (TDDFTs) and generalized pseudospectral methods for nonperturbative and accurate treatment of multiphoton processes of atomic and molecular systems in intense ultrashort laser pulses. In addition, an alternative generalized Floquet formulation of TDDFT will
be introduced for the treatment of multiphoton processes and the calculation of complex quasi-energies in intense periodic and quasi-periodic laser fields. Applications of these methods to the exploration of the underlying mechanisms responsible for several very-high-order (50th to 300th order) nonlinear optical phenomena in attosecond time scale will be presented.

**COMP 96 The application of TDDFT to systems with a spin or space degenerate ground state**  
*Tom Ziegler*, Mike Seth, and Fan Wang, Department of Chemistry, University of Calgary University Drive 2500, University of Calgary, 2500 University Drive, Calgary, AB T2N 1N4, Canada, ziegler@ucalgary.ca

Ordinary time-dependent density functional theory (TDDFT) is not able to treat single excitations involving spin-flips and can thus not treat systems with spin generate ground state. We introduce in the first part of our talk a formulation of TDDFT based on a non-collinear representation of the XC potential. Within the non-collinear representation, we are able to apply TDDFT to atoms and molecules with a spin-degenerate ground state and thus study spin-multiplet splittings. The second part of the talk deals with spatially degenerate ground states using time-dependent density functional theory (TDDFT). We propose here a new “Transformed reference via an intermediate configuration Kohn-Sham TDDFT (TRICKS-TDDFT) method. This method avoids the complications caused by the multi-reference nature of spatially degenerate ground state by taking a non-degenerate excited state with desirable properties as the reference for the TDDFT calculation. The scope and practical application of the method is discussed.

**COMP 97 Time-dependent relativistic density functional theory and applications**  
*Wenjian Liu*, Institute of Theoretical and Computational Chemistry, Peking University, College of Chemistry and Molecular Engineering, Beijing 100871, China, liuwj@pku.edu.cn

Since relativistic density functional theory is so far the only first principles method for describing large, complex systems containing heavy elements, it is of great value to extend it to the time-dependent domain in order to describe excited states of heavy elements. In this talk I shall present the underlying formalism[J. Chem. Phys. 121, 6658 (2004); J. Chem. Phys. 123, 054102 (2005)] with much focus on the appropriate form of the exchange-correlation kernel[. J. Chem. Phys. 123, 144101 (2005)]. Technical issues concerning the implementation and selected results will be discussed as well.

**COMP 98 Quantum defect and time-dependent density functional theory**  
*Kieron Burke*¹, Meta van Faassen¹, and Adam Wasserman². (1) Department of Chemistry and Chemical Biology, Rutgers, 610 Taylor Road, Piscataway, NJ 08854, Fax: 732-445-5312, kieron@rutchem.rutgers.edu, (2) Department of Chemistry, Harvard University

We apply quantum defect theory to time-dependent density functional theory for atoms. We show how one can extract the Rydberg series of excitations from even a short-ranged potential, such as those produced by the local density or generalized gradient approximations. We also show how careful extraction of quantum defects is the best way to test TDDFT calculations of electronic excitations in atoms.

**COMP 99 Exploration of GPCRs: Structure and function**  
*Kris Palczewski*, Department of Pharmacology, Case Western Reserve University, USA, 10900 Euclid Ave., Cleveland, OH 44106-4965, kxp65@case.edu

*Abstract text not available.*
COMP 100 Crystal structures of rhodopsin
Juan Ballesteros, Novasite Pharmaceuticals, 11025 Roselle St., San Diego, CA 92121, JBallesteros@novasite.com, and Kris Palczewski, Department of Pharmacology, Case Western Reserve University, USA

We will present a novel in vivo expression system based on transgenic mice that converts the rhodopsin expression system in retina into a bioreactor of the GPCR of interest. In parallel, we have recrystallized rhodopsin in a delipidated form, showing dimers with expected physiological significance and the activated “agonist” state.

COMP 101 High throughput membrane protein structure determination by electron crystallography
Henning Stahlberg, Zi Yan Zhang, Bryant Gipson, Rena Hill, Hui-Ting Chou, Po-Lin Chiu, Ludovic Renault, and Xiangyan Zeng, University of California at Davis, Davis, CA 95616, HStahlberg@ucdavis.edu

Electron crystallography studies the structure of membrane proteins in the membrane-embedded, yet two-dimensionally crystalline state. Reconstitution and two-dimensional crystallization of membrane proteins in phospholipid bilayers usually requires comparatively low amounts of purified proteins, and 2D crystals are generally easier to obtain than 3D membrane protein crystals. Here we present a high-throughput approach to accelerate and streamline the method of membrane protein electron crystallography. We have developed a user-friendly, optionally fully automated high-throughput data processing system for electron crystallography. Progress in the development of this software system and results of first applications on two-dimensional membrane protein crystals will be presented.

COMP 102 Protein interactions in GPCR signaling: A very moving story
Harel Weinstein, Department of Physiology and Biophysics, Weill College of Medicine of CORNELL University, 1300 York Ave., New York, NY 10021, Fax: 212-746-8690, haw2002@med.cornell.edu

The presentation will review some key advances in the characterization of dynamic mechanisms in signaling by G protein-coupled receptors (GPCRs). These emerged from a combined, multi-authored and multi-disciplinary computational and experimental approach carried out by a Consortium of investigators. The work revealed ligand-specific modes of receptor activation that produce distinct ligand-dependent receptor states. The signaling mechanism was further examined by this Consortium from the structural rules of GPCR interactions with other proteins involved in the cascade. Two examples will be discussed in mechanistic detail: dynamic oligomerization interfaces, and interactions with scaffolding proteins (e.g., PDZ domains). The first example involves mapping of the rearrangements at the homodimer interface upon transition from inactive-to-active form, identifying a conformational change as a critical part of the receptor activation mechanism. The second identifies a putative mechanism for the regulation of GPCR-PDZ interaction, and deals with selectivity of PDZ-domain recognition. Supported by NIH Grants DA012923 and DA00060

COMP 103 G Protein coupled receptors: Structure, ligand recognition, and receptor activation
Leonardo Pardo, Laboratory of Computational Medicine and Institute of Neuroscience, Universitat Autonoma de Barcelona, Campus Universitari Bellaterra, Barcelona 08193, Spain, Fax: 3493-581-2344, Leonardo.Pardo@uab.es

G protein coupled receptors (GPCRs) constitute a large and functionally diverse family of transmembrane proteins. They are fundamental in the transfer of extracellular stimuli to intracellular signaling pathways and are among the most targeted proteins in drug discovery.
Conceptually, the processes of transmembrane signal transduction can be divided into two groups. First, those processes initiated by the recognition of the extracellular ligand by the receptor. These processes will extensively depend on the specific subtype of receptor since wide ranges of extracellular ligands, from small neurotransmitters to large hormones, are recognized by GPCRs. And second, the processes that propagate the signal from the ligand binding site to highly conserved amino acids at the cytoplasmic side of the transmembrane bundle. Using a combination of site-directed mutagenesis and molecular modeling we have characterized important steps in the recognition of agonists, antagonists, or/and inverse agonists; and in the molecular mechanisms for agonist-induced activation of rhodopsin-like GPCRs.

**COMP 104 Modeling ligand interactions at adenosine and P2Y nucleotide receptors: Influence of ribose conformation**

**Kenneth A. Jacobson¹**, Soo-Kyung Kim¹, Andrei A. Ivanov¹, and Stefano Costanzi². (1) Molecular Recognition Section, NIDDK, NIH, Bldg. 8A, Rm. B1A-19, Bethesda, MD 20892-0810, Fax: 301-480-8422, kajacob@helix.nih.gov, (2) Computational Chemistry Core Laboratory, NIDDK, National Institutes of Health

Modeling methods recently applied to adenosine receptors (ARs) and P2Y nucleotide receptors include: homology modeling and protein-protein docking to study dimerization, small molecule modeling, ligand docking based on mutagenesis, and molecular dynamics in fully hydrated lipid bilayers. The effects of conformation of the ribose ring was probed by modeling and chemical synthesis using a variety of constrained ring systems. Comparison of nucleosides docked at A⁵₂ and A³ ARs indicates differences in the glycosidic angle. Flexibility and H-bonding ability of the ribose 5'-region are required for A³ AR activation. Methanocarba analogues fixed in a North (N) envelope conformation were optimized for affinity and selectivity at A³ and P2Y₁ receptors, leading to new approaches to tissue protective, antigliaucoma, and antithrombotic agents. This conformation is inactive at P2Y₆, P2Y₁₂ and P2Y₁₃ receptors. Docking and molecular dynamics of UDP analogues to P2Y₆ receptors indicated a strong preference for South (S) over (N) conformation, which was confirmed pharmacologically.

**COMP 105 Novel methods for modeling aluminum nanoclusters**

**Mark Iron**, Department of Chemistry, University of Minnesota, Minneapolis, MN 55455-0431, iron@comp.chem.umn.edu

Modeling reactions and other processes in large molecules, clusters, solids and other condensed-phase materials, especially those including metal atoms, poses many unique quandaries. Such systems are often too large to be amenable to accurate calculations using ab initio, or even Density Functional Theory (DFT), methods. Many different analytical potentials have been developed but they generally suffer the inability to describe bond breaking and formation processes even in a qualitatively correct manner. Herein, we present novel methods that are both efficient enough for modeling these systems yet still capture the essence of bond breaking and formation processes.

**COMP 106 Computational design of an enzyme mutant for anti-cocaine medication**

**Daquan Gao, Wenchao Yang, Yongmei Yang, Hsin-Hsiung Tai, and Chang-Guo Zhan**, Department of Pharmaceutical Sciences, College of Pharmacy, University of Kentucky, 725 Rose Street, Lexington, KY 40536, Fax: 859-323-3575, zhan@uky.edu

Cocaine is recognized as the most reinforcing of all drugs of abuse. There is no available anti-cocaine medication. The disastrous medical and social consequences of cocaine addiction have made the development of an anti-cocaine medication a high priority. An ideal anti-cocaine medication would be to accelerate cocaine metabolism producing biologically inactive
metabolites via a route similar to the primary cocaine-metabolizing pathway, i.e. cocaine hydrolysis catalyzed by plasma enzyme butryrylcholinesterase (BChE). However, native BChE has a low catalytic efficiency against naturally occurring (-)-cocaine. We have recently developed a novel computational design approach based on MD simulations of the transition state structures for the rate-determining step of (-)-cocaine hydrolysis catalyzed by human BChE and its hypothetical mutants (Proc. Natl. Acad. Sci. USA 2005, 102, 16656). By using the novel design approach, we have performed an automated virtual screening of numerous hypothetical BChE mutants, leading to discovery of a BChE mutant with a ~1000-fold improved catalytic efficiency, which is sufficient for use as an exogenous enzyme in human to prevent (-)-cocaine reaching central nervous system. The encouraging outcome not only provides a hopeful anti-cocaine medication, but also demonstrates that the novel, automated virtual screening approach based on transition-state simulation is promising for rational enzyme redesign and drug discovery. The same approach can be used to rationally design high-activity mutants of other enzymes for possible therapeutic treatments of a variety of metabolic diseases.

**COMP 107 Effects of tautomerism and hydration on the speciation of molecules: A study using SPARC**

Saravanaraj N Ayyampalayam and LA. Carreira, Chemistry, University of Georgia, University of Georgia, Athens, GA 30602, raj@sunlc3.chem.uga.edu

Tautomerism and hydration have a profound effect on the speciation of molecules. We have developed a calculator to compute the different tautomeric forms and their respective equilibrium constants. A similar calculator for computing the hydration equilibrium constants and speciation is already available in SPARC. The macro constants were determined by coupling three chemical property models (tautomer, hydration and speciation) in series to form a network of chemical property models. A molecule of interest is given to the hydration model and the resulting species are introduced to the tautomer model. Finally, the resultant species are processed by the speciation model to determine the macro constants. Macro constants for various molecules were analyzed using this methodology.

**COMP 108 Interaction of Protegrin-1 (PG-1) with lipid bilayers: Membrane thinning effect**

Hyunbum Jang¹, Buyong Ma², Thomas B. Woolf³, and Ruth Nussinov². (1) Center for Cancer Research Nanobiology Program, Basic Research Program, SAIC - Frederick, Inc. NCI-Frederick, Frederick, MD 21702, Fax: 301-846-5598, jangh@ncifcrf.gov, (2) Center for Cancer Research Nanobiology Program, Basic Research Program, SAIC, NCI-FCRDC, (3) Departments of Physiology and of Biophysics, Johns Hopkins University

Protegrins are important in defending host tissues preventing infection via an attack on the membrane surface of invading microorganisms. Protegrins have powerful antibiotic abilities but the molecular-level mechanisms underlying the interactions of their beta-sheet motifs with the membrane are not known. Protegrin-1 (PG-1) is composed of 18 amino-acid residues with a high content of basic residues and two disulfide bonds. Here we focused on the stability of PG-1 at the amphipathic interface in lipid bilayers and on the details of peptide-membrane interactions. We simulated all-atom models of the PG-1 monomer with explicit water and lipid bilayers composed of both homogeneous POPC lipids and a mixture of POPC:POPG (4:1) lipids. We observed that local thinning of lipid bilayers mediated by the peptide is enhanced in the lipid bilayer containing POPG, consistent with experimental results of selective membrane targeting. The beta-hairpin motif of PG-1 is conserved in the both lipid setting, while it is highly bent in aqueous solution. The conformational dynamics of PG-1, especially the highly charged beta-hairpin turn region are found to be mostly responsible for disturbing membrane. Even though the eventual membrane disruption requires PG-1 oligomer, our simulations clearly show the first step of the monomeric effects. The thinning effects in the bilayer should relate to pore/channel formation in lipid bilayer and thus responsible for further defects in the membrane...
caused by oligomer.

**COMP 109 A minimal model for stabilization of biomolecules by hydrocarbon cross-linking**

Kay Hamacher, Center for theoretical biological physics, University of California at San Diego, 9500 Gilman Drive MC 0374, La Jolla, CA 92093, Arnd Hübsch, Max-Planck-Institute for the Physics of Complex Systems, and J Andrew McCammon, Howard Hughes Medical Institute and Department of Chemistry and Biochemistry and Department of Pharmacology, University of California, San Diego

The development of an organism, its immune response and other disease-related cellular mechanisms are to a large extent determined be correct apoptosis inducing signaling capabilities. One important motif to this end is the BH3-domain of the BCL-2 family. We parametrized a coarse-grained, dynamic model for the stability effects of covalent cross-linking hydrocarbons that were recently found to enable the otherwise unstructured isolated BH3-peptide to regain function as a molecule on its own. We show how this modification affects the dynamics of the peptide. The resulting model is suitable for rational design of generic cross-linking systems in silico.

**COMP 110 Metadynamics molecular simulations with accurate quantum chemistry calculation for the study of the anions forms of Malonic Acid**

Eliana K Asciutto, Center for High Performance Simulations and Department of Physics, North Carolina State University, 127 Stinson Drive, 308 Cox Hall, Raleigh, NC 27606, ekasciu@ncsu.edu, and Celeste Sagui, Center for High Performance Simulation and Department of Physics, North Carolina State University

We have determined the optimized structures, relative energies and intramolecular reactions for two anionic forms of malonic acid, anion malonate(-1) (H02CCH2CO2-) and malonate(-2) (-O2CCH2CO2-). For this purpose we employed accurate quantum chemistry calculations using MP2 theory and Density Functional Theory to determine the structures and energies, and a novel metadynamics method based on Car-Parrinello molecular dynamics for the thermal reactions. For both malonates, we found new isomers (keto and enol structures) characterized by CO2 rotations and intramolecular proton transfers. These proton transfers characterize the keto-enol tautomerism that takes place both in the monoanion and dianion. In all cases, the keto tautomer is the more stable configuration. The metadynamics method allows the system to explore the potential energy surface in a few picoseconds, crossing activation barriers of 20-50 kcal/mol.

**COMP 111 Replica exchange molecular dynamics study on aralyamide and heparin in water: Sampling effects and analysis of the detailed binding mode**

Zhiwei Liu and Vojislava Pophristic, West Center for Computational Chemistry and Drug Design and Department of Chemistry & Biochemistry, University of the Sciences in Philadelphia, 600 S. 43rd Street, Philadelphia, PA 19104, z.liu@usip.edu

We will present the continuation of a series of computational studies aiding the design of aralyamide oligomer as heparin antidote. Heparin is an anticoagulant drug to prevent thrombosis. Due to serious side effects, an effective antidote is needed to prevent life-threatening complications. Using the modified GAFF force field developed previously, we performed Replica Exchange Molecular Dynamics (REM, i.e. Parallel Tempering) simulation on a system containing an aralyamide, the pentasaccharide sequence of heparin responsible for its binding to antithrombin III, as well as ~5400 water molecules. 96 replicas, with temperature from 290K to 553K, are simulated for 4ns per replica. The results confirm the conclusions from previous conventional MD studies of the effects of backbone rigidity. Furthermore, significantly enhanced sampling is seen with REM. We will present our analysis on the detailed binding mode between
aralyamide and heparin, the convergence of conformational sampling and temperature dependence of the structural characteristics.

**COMP 112 Replica-exchange molecular dynamics simulations of protein adsorption on a hydrophobic surface**

Yu Sun and Robert A. Latour, Department of Bioengineering, Clemson University, 501 Rhodes Research Center, Clemson, SC 29634, LatourR@clemson.edu

The two primary obstacles in the development of molecular simulation capabilities to accurately predict the orientation, conformation, and bioactivity of adsorbed proteins on a materials surface are force field accuracy and the ability to adequately sample the conformational space of a large molecular system. In this study, we addressed both of these issues for the case of a model protein (lysozyme) adsorbing on a model hydrophobic surface (CH3-functionalized self-assembled monolayer, SAM) by employing replica-exchange molecular dynamics (REMD) simulations with CHARMM combined with a generalized Born-based implicit solvent model (ACE). Prior to the REMD simulations, the ability of the ACE model to represent adsorption energies was first improved by adjusting its parameters to match the results of potential of mean force calculations for peptide/CH3-SAM surface interactions in explicit (TIP3P) water. The REMD simulations predict moderate conformational changes and three different predominant orientations of lysozyme when adsorbed on the CH3-SAM surface.

**COMP 113 Discontinuity of the chemical potential in reduced-density-matrix-functional theory**

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We present a novel method for calculating the chemical hardness of molecules and the fundamental gap of solids. To this end, reduced-density-matrix-functional theory (RDMFT) is generalized to fractional particle number. For each fixed particle number, N, the total energy functional is minimized with respect to the natural orbitals and their occupation numbers, employing various approximate reduced-density-matrix functionals for the exchange-correlation energy. This yields the ground-state energy as a function of particle number, E(N), whose derivative with respect to the particle number has a discontinuity identical to the fundamental gap. In contrast to density functional theory, the energy minimum is generally not a stationary point of the total-energy functional. Numerical results are presented for alkali atoms, small molecules and periodic solids. We demonstrate [1] that the resulting discontinuity of the chemical potential represents an excellent measure of the chemical hardness/gap. Furthermore, we generalize RDMFT to treat open-shell systems by introducing spin-dependent occupation numbers [2]. We demonstrate that the additional constraint of total-spin conservation is indispensible for the proper treatment of open-shell systems: It reduces the difference between calculated and experimental total energies by a factor of 2.


**COMP 114 A canonical transformation theory for multireference problems**

Garnet K. Chan and Takeshi Yanai, Department of Chemistry and Chemical Biology, Cornell University, Baker Lab, Ithaca, NY 14853-1301, gc238@cornell.edu

The accurate treatment of dynamical correlation in the presence of multi-reference non-dynamical correlation is crucial to quantitatively model problems involving e.g.
bond-breaking or multiple transition metal centres.

Here I will describe an approach that goes beyond the perturbative treatment of dynamical correlation commonly employed in multi-reference methods. The theory uses a canonical (unitary exponential) transformation to remove dynamical correlations resulting in an effective Hamiltonian that can be solved by other means. The effective Hamiltonian thus constructed depends only on the one and two-particle reduced density matrices of the system. I will describe the technique and present results for bond-breaking reactions.

COMP 115 Quantum phase space and the local virial theorem
Leon Cohen, Physics, City University of New York, Hunter College, 695 Park Ave., New York, NY NY, leon.cohen@hunter.cuny.edu

We show that an immense simplification occurs if wave functions are transformed into a quantum mechanical phase space. The simplification is both conceptual and computational. We show that generally speaking when a wave function is transformed into phase space it takes the form of a ridge where the ridge trajectory turns out the be the quantum mechanical current and the width of the ridge is proportional to the rate of change of the amplitude of the wave function. Moreover, we derive an exact relationship for momentum spread and show that it always consists of two terms. We give a simple probabilistic interpretation of the two terms and also show which of the two is responsible for the uncertainty principle. Using these methods we are able to define a local virial theorem. We generalize these concepts to arbitrary operators. Simple wave functions are used to illustrate the results presented.

COMP 116 Stress tensor in the standard model of elementary particles and the origin of the electronic spindle structure of chemical bond
Akitomo Tachibana, Department of Micro Engineering, Kyoto University, Yoshida Honmachi, Sakyo-ku, Kyoto 606-8501, Japan, Fax: +81-75-753-5184, akitomo@scl.kyoto-u.ac.jp

A new energy density visualization scheme is obtained using the Rigged QED (Rigged Quantum Electrodynamics). The spindle structure of the electronic stress tensor has been disclosed and visualized in the course of the covalent chemical bond formation. The chemical energy density visualization scheme is originated from the standard model where non-Abelian gauge fields mediates the binding force of elementary particles.

COMP 117 Designing molecules by optimizing potentials
David N. Beratan, Department of Chemistry, Duke University, P.M. Gross Chemical Laboratory, Durham, NC 27708, Fax: 919-660-1605, david.beratan@duke.edu

The astronomical number of accessible chemical structures makes rational molecular design quite challenging. We formulate the design of molecules with specific tailored properties as performing a continuous optimization in the space of electron-nuclear attraction potentials. The optimization is facilitated in a general framework that creates a smooth property landscape from an otherwise unlinked set of discrete molecular-property values. We show that the optimal structures can be determined without enumerating and separately evaluating the characteristics of the combinatorial number of possible structures. The seminar describes a collaborative project with Weitao Yang, Mingliang Wang, Xiangqian Hu, Dequan Xiao, Shahar Keinan, Nan Jiang, and Parag Mukhopadhyay.

COMP 118 New computational strategies for density functional calculations
Robert J. Harrison, U. Tennesee and ORNL, Knoxville, TN 37831, harrisonrj@ornl.gov, and Ariana Beste, Computer Science and Mathematics Division, Oak Ridge National Laboratory

Recently developed multiresolution and separated representations enable fast and accurate fully
numerical simulation of all-electron molecular and periodic systems. In addition, the framework provides a much simpler implementation of new models since applications are composed in terms of functions and operators rather than explicitly indexed sparse arrays of matrix elements. We shall also present results from a new approach for the direct computation of chemical energy differences that promises increased precision and reduced scaling of the computational cost with respect to system size.

This research was supported by the U.S. Department of Energy, the division of Basic Energy Science, Office of Science, under contract DE-AC05-00OR22725 with Oak Ridge National Laboratory, and in part by ORNL Laboratory Directed Research and Development Funds. This research was performed in part using the resources of the Center for Computational Sciences at Oak Ridge National Laboratory under contract DE-AC05-00OR22725.

**COMP 119 Using Density functional theory, new algorithms and computer simulation to probe biophysical, materials and chemical systems**

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The goal of simulation studies is to provide insight into important systems of scientific and technical interest. Today, these systems involve treating accurately complex heterogeneous interfaces. The modeling of nanostructures using Density Functional Theory based methods is described followed by application to problems in engineering, physics, and biochemistry. In particular, doping of single wall carbon nanotube field effect transistors, organic semiconductors and the properties of biometric systems are discussed. Emphasis is placed on multicomponent nature of the systems, the role of new algorithms in allowing effective simulations to be performed and how complex heterogeneity leads to exciting chemistry and physics.

**COMP 120 How bilayers cope with transmembrane helices: Insights from translocon-assisted helix insertion**

*Stephen H. White*, Dept. of Physiology and Biophysics, University of California at Irvine, Med. Sci I D346, University of California at Irvine, Irvine, CA 92697, blanco@helium.biomol.uci.edu

Membrane protein structure prediction requires knowledge of (1) the thermodynamic stability of proteins in the complex environment of the lipid bilayer and (2) the rules the translocon follows during the constitutive, cotranslational assembly of MPs. My main focus will be recognition of TM helices by the endoplasmic reticulum translocon, which is work carried out in collaboration with Gunnar von Heijne's laboratory. A complete description of the translocon 'code' for TM helices will make it possible to predict TM helices with high precision. Using test helices expressed in vitro in dog pancreas microsomes, we have established a 'biological' hydrophobicity scale. A surprising finding is the very strong positional dependence of polar amino acids in the TM segments. This and other features of translocon-assisted folding, explored by MD simulations, are providing remarkable new insights into the properties of lipid bilayers in the vicinity of transmembrane helices.

**COMP 121 Ab initio modeling of the loops in G-protein coupled receptors**

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In contrast to the trans-membrane helices (TMHs) in G-protein coupled receptors (GPCRs) the determination of loop structures is much less advanced because of the variability in sequence and length of the loops in different sub-families of GPCRs. This makes it necessary to use *ab initio* approaches for predicting loop structure. Using rhodopsin, an algorithm for calculating loop structures has been developed that uses simulated annealing-Monte Carlo (MC) and biased scaled collective variables in MC techniques to find the native ensemble of structures at the
absolute free energy minimum. This approach is required because the GPCR models provide incomplete structural information, i.e., only the coordinates of the TMHs. The protocol has been applied to the loops of rhodopsin ranging from 6 to 26 residues in length. The results indicate that the Cα-RMSD between the predicted and crystal structures range from 0.4Å to 1.5Å. Application to the dopamine receptor will be reported.

**COMP 122 Studying the photochemistry of retinal proteins with quantum chemical methods**

*Marcus Elstner*, Theoretical Physics, University of Paderborn, Pohleweg 100, Paderborn 33098, Germany, Fax: ++49-5251-602333, elstner@phys.upb.de

In the last years, we have studied the photochemistry of rhodopsins using QM/MM MD techniques. The retinal chromophore is a considerable challenge for theoretical chemistry methods, since already the ground state structure is sensitive with respect to a balanced description of electron correlation effects and the excitation involves considerable charge transfer. CIS and CASSCF methods have been shown to be quantitatively inaccurate and TD-DFT approaches fail completely. We have applied the approximate DFT method SCC-DFTB [1] for QM/MM ground state geometry optimisations and MD simulations, which are the basis for the calculation of excitation energies and absorption spectra [2] along the MD trajectories using SORCI [3] and OM2/MRCI [4]. The computational efficiency allows for the computation of vibrational and optical absorption spectra and the consideration of various mutated structures. Our results allow to explain the spectral shift between bR and SRII, in particular to discriminate between the effects of the Schiff base region and global electrostatic interactions. In order to investigate the effect of protein polarization on the excited states energies, we have combined the MRCI methods within QM/QM/MM algorithms and with a polarizable force field model. The initial dynamics of the retinal isomerization is studied using the OM2/MRCI Hamiltonian within a QM/MM implementation and a surface hopping algorithm. First results for small model systems will be presented.


**COMP 123 Models for the GPCR proton sensors OGR1, GPR4, and TDAG8**

*Romain M. Wolf¹, Marie-Gabrielle Ludwig², and Klaus Seuwen²*. (1) Novartis Institutes for Biomedical Research GDC/CADD, Novartis Pharma AG, Basel 4002, Switzerland, romain.wolf@novartis.com, (2) Novartis Institutes for Biomedical Research GPCR-EP, Novartis Pharma AG

The three family A GPCRs OGR1, GPR4, and TDAG8 have been identified as proton sensors [1-4], signaling the extra-cellular pH to the cell interior. All three receptors have a sequence close enough to that of rhodopsin to allow the use of the x-ray structure of the latter as a template to build 3D homology models. The models reveal several histidines close to the extracellular region the interactions of which seem to play a crucial role in proton sensing, as confirmed by subsequent mutation studies. The histidines are supposed to be protonated when the pH drops below the physiological pH around 7.2, leading to modified electrostatic interactions which induce strong enough changes in the overall receptor geometry to be sensed at the intracellular interface. Despite their common proton-response, the three proton sensors are different enough to pose a number of challenging problems regarding the detailed understanding of their functioning. They are used here as an example to discuss various computational chemistry aspects using explicit 3D homology modeling in the GPCR field. The importance of the interplay be-tween computational chemistry and molecular biology (relevant assays, point mutations, etc.) is emphasized.
COMP 124 Binding site expansion and induced fit docking for GPCR ligand binding mode prediction: Application to the b-adrenergic and chemokine receptors
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Crystal structures of rhodopsin has become invaluable templates for the modeling of class-A G protein-coupled receptors as they likely represent the overall topology of this family of proteins. However, because of low sequence homology within the class and the inherent mobility of integral membrane proteins, it is unlikely that this single model reflects the ensemble of conformations accessible for any given receptor. We have devised a procedure using induced fit modeling coupled with binding site expansion that enables an ensemble approach to binding mode prediction. The utility of models for b-adrenergic receptors will be discussed. A more complex example includes the chemokine receptors because the putative binding site is completely occluded in the rhodopsin derived model. Chemokine GPCR modeling requires expansion of the binding site coupled to active site re-modeling. The computation models will be evaluated in terms of development of binding modes consistent with mutagenesis and ligand SAR.

COMP 125 The molecular basis of antagonist binding to CCR1: Molecular modeling and experiment
Sabine K. Schlyer¹, Richard Horuk², Sunil Koovakkat¹, Monica J. Kochanny¹, Rene Trabanino³, William A Goddard III³, Ravi Abro³, Wely B. Floriano³, James Pease⁴, James Fox⁴, Filipa Lopez de Mendoca⁴, Shantanu Sharma³, and Vaidehi Nagarajan³. (1) Department of Medicinal Chemistry, Berlex Biosciences, 2600 Hilltop Drive, Richmond, CA 94804, Fax: 510-262-7844, sabine_schlyer@berlex.com, (2) Department of Immunology, Berlex Biosciences, (3) Materials and Process Simulation Center, California Institute of Technology, (4) Leukocyte Biology Section, Imperial College London

A major challenge in the development of subtype specific drugs for the superfamily of G-protein coupled receptors (GPCRs) is the lack of structural data. The eighteen chemokine receptors, belonging to the GPCR family, are important drug targets not only for autoimmune diseases like multiple sclerosis, but also for HIV. Using the MembStruk computational method, we predicted the three-dimensional structure of the human, mouse, and rat CCR1 receptor. In addition, we predicted the binding sites and the relative affinities of several small molecule CCR1 antagonists including one that is in phase II clinical trials. Based on the predicted antagonist binding sites we designed 16 point mutants of CCR1 to validate our predictions. Competitive ligand binding and chemotaxis experiments with these mutants gave an excellent correlation to predictions. Finally, we used the binding site for virtual ligand screening of the Maybridge database that was seeded with a range of selective hCCR1 antagonists. The screening method resulted in identification of all the seeded hCCR1 antagonists in the top 5% of the hits. This opens a way to carry out rational drug design for the superfamily of GPCR drug targets.
**COMP 126 Toward a force field based on density fitting**

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Advances on a force field based on density fitting methodology termed the Gaussian Electrostatic Model (GEM) will be discussed. Initial calculations of total intermolecular interaction energies performed with molecular electronic densities fitted using s-type gaussian functions (GEM-0) will be presented. In this method the interaction energies are computed by separately fitting each of the individual components (Coulomb, exchange-repulsion, polarization and charge transfer) to its reference counterpart calculated with the Constrained Space Orbital Variations (CSOV) or Symmetry Adapted Perturbation Theory (SAPT) energy decomposition methods. The use of auxiliary basis sets for the fitting of the density allows for a straightforward calculation of the intermolecular electrostatic interaction terms. Exchange-repulsion contributions are calculated by a density fitting implementation of the Wheatley-Price overlap model. The polarization and charge transfer interactions are calculated with the SIBFA energy scheme using the electrostatic potential and electric fields generated by the fitted densities. GEM-0 has been tested on ten stationary points of the water potential energy surface and three water clusters (n = 16, 20 and 64). All results show very good agreement with reference calculations, with errors below k_BT at room temperature for each component. Additional extensions to auxiliary basis sets with higher angular momentum (GEM), as well as algorithms to increase computational efficiency will be discussed. Electrostatic interaction energies calculated with GEM for the ten water dimers, as well as for n-methyl-formamide and benzene dimers will be presented.

**COMP 127 Assigning the protonation states of the key aspartates in β-secretase using QM/MM X-ray structure refinement**

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β-Secretase, a.k.a. β-APP cleaving enzyme (BACE), is an aspartyl protease that has been implicated as a key target in the pathogenesis of Alzheimer's disease (AD). The identification of the protonation states of the key aspartates in β-secretase is of great interest. However, the resolutions of currently available crystal structures for BACE are not sufficient to determine the hydrogen atom locations. We have assigned the protonation states of the key aspartates using a novel method, QM/MM X-ray refinement, where a total number of 8 protonation configurations of the aspartyl dyad were considered. While all 8 refined structures fit the observed electron density about equally well, we find the mono-protonated configurations are strongly favored energetically, especially the configuration with the inner oxygen of Asp 32 protonated and the hydroxyl of the inhibitor pointing towards Asp228. We suggest that one of the strengths of this approach is that the result is a consensus of theoretical and experimental data and remark on the significance of our findings in structure based drug design and mechanistic studies.

**COMP 128 Virtual screening: The king (quite often) has no clothes**

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Virtual screening in the absence of knowledge of the biological receptor usually utilises molecular similarity methods. Typically, a few molecules that show activity are used to create a query that ranks other molecules in a database (of likely drug-like structures) according to the probability that they will display similar effects. This can be useful in e.g. escaping previous
patents or enhancing ADME properties. Numerous methods of achieving this goal have been described and compared in the literature (by us and others), usually by comparison to random selection from such datasets using e.g. cross validation or enrichment to deduce measures of utility. In a recent virtual screening competition run by McMaster University, we were led to question the methodologies of experimental design and methods of ranking used in virtual screening. Here, we will outline our results and conclusions as well as outline guidelines for more efficient virtual screening.

**COMP 129 Iterative focussed screening using Random Forest: A comparison with HTS/random screening for two extreme cases**

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Focussed screening is reasserting its role as a lead-searching method complementary to traditional HTS. Advances in informatics and lab automation increase throughput and decrease cycle time for screening, making an iterative approach practical. The relatively small size of the compound sets has made it possible to improve the data quality by assaying at three concentrations. The Random Forest QSAR method was used to predict activity for a large compound collection based on a training set of active and inactive compounds; the predicted actives were then cherry-picked and screened. Results from two examples of iterative focussed screening will be shown and compared with HTS or random screening data, examining not only hit rates but the ability to identify novel scaffolds.

**COMP 130 Solvation studies by DFT of Carbohydrates: a/b-anomeric ratios of epimers of glucose using a continuum-solvation model (COSMO)**

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It is commonly known that solvation effects play an important role in carbohydrate chemistry. Until recently, most theoretical work was reported on vacuum structures which can not be easily compared to the experimental data of carbohydrates in solution. To remedy this shortcoming it has been recently shown that using an explicit stepwise hydration and solvation model achieves a more accurate description of the properties and behavior associated with carbohydrates. Geometry optimization, at the B3LYP/6-311++G** level of theory with COSMO, was carried out on the low energy structures of glucose and its epimers allose, mannose, and galactose. Zero point energy, enthalpy, entropy, and relative Gibbs Free energies are reported at the harmonic level of theory. The a/b-anomeric ratios of glucose and its epimers have been calculated from the relative free energies. A comparison of the difference in a/b-anomeric ratios between the vacuum structures and solvated (COSMO) structures will be given.

**COMP 131 Molecular modeling insights into the catalytic mechanism of a family 38 glycosyl hydrolase, Golgi α-mannosidase II**

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Elucidation of the mechanism of an enzyme active site at an atomic level of detail has been a long standing objective of biochemistry. While X-ray crystallography has provided a great deal of information about the ground state structures of enzymes, it has proved extremely difficult to discriminate between the alternate reaction mechanisms and associated intermediate structures or to determine the precise relative energies of these intermediates by experimental means.
alone. In principle, accurate computational methods can complement experiments to address these questions. In the present work we apply QM and QM-MM calculations to explore the catalytic mechanism of Golgi α-mannosidase II (GMII), a mannose trimming enzyme which acts late in the N-glycan processing pathway. We have performed a quantum mechanical potential energy surface scan along two reaction coordinates that define the bond-making and bond-breaking process during the actual mechanism to identify important intermediates in the catalytic mechanism such as the transition states and the covalent intermediate. The effect of the basis sets, solvation and protein environment on the energy profile has also been studied. Theoretical investigations of the catalytic mechanism mediated by this enzyme, and in general, by other mannosidases, will enhance our understanding of different intermediates in the reaction pathway, their geometries and relative energies and their interactions with protein residues. It has been shown that inhibition of this enzyme blocks oncogene-induced changes in cell surface oligosaccharides, and reduces tumor progression and metastasis. Thus, a possible application of this study is designing transitions state analogues, which may act as potential inhibitors selective against GMII.

COMP 132 Modeling of complex hydrides: Lattice anomaly in NaAlH₄

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Following experimental observation that the c-axis expands anomalously faster than the a-axis in NaAlH₄, we undertook an ab initio incursion into the nature of this anomaly. We have found that contrary to the experimental deductions the anomaly is even more pronounced in a than in c. There is also an interdependence of in-plane and inter-planar chemical bonding leading to compensating effects in terms of changes in the lattice parameters. An energy loss caused by expansion of the axial lattice parameters is exactly compensated by the contraction of the basal lattice parameter. Other possibilities we are investigating in this interesting arena includes phase transition. We have ascertained that our results is not an artifact of the potential by using both the Ultra Soft (US) pseudo-potentials and the much hyped PAW potentials as implemented in VASP, with the same conclusions. Moreover, during our simulations we allowed the structure to break symmetry. The immediate implication of our results apart from adding rich information on the structural properties of NaAlH₄ is that it gives ideas on how to load(unload) hydrogen from the material. In addition these results also spectacularly shows that our structure is stable along the (001) plane without the need to do surface energy calculations!

COMP 133 Solvation of bihalide anions with water

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Second-order perturbation theory is used to perform geometry optimizations on BrHBr- and IHI-solvated by water. Of particular interest is how the solvent molecules orient themselves around the solute. BrHBr(H₂O)ₙ⁻, n=1-4, prefers to have the water molecules orient themselves symmetrically around the anion with both hydrogen atoms from the water molecules bridging the halides. This pattern changes for n=5 when the bridging arrangement for all water molecules is no longer a minima. Preliminary calculations on IHI(H₂O)ₙ⁻, n=1-4, show that while the symmetric arrangement of bridging water molecules may be a stable geometry, it is not necessarily the lowest energy structure.

COMP 134 Theoretical study of solvation of NaOH

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Program Report

Fundamental understanding of the behavior of a strong electrolyte involves a systematic study of its dissociation in both gas and aqueous phase. The present study investigates the effects of solvation on dissociation of a single NaOH molecule in its ground and excited states. One goal is to determine the number of water molecules required to "fully" solvate a single NaOH by a step-wise addition of water molecules. Another aim is to investigate the convergence of properties, such as dissociation energy, of NaOH(H2O)n as n increases. The calculations are performed by treating the NaOH molecule with MCSCF wave functions and the 6-31G(d,p) basis set, and the water molecules by the effective fragment potential model. Global minima of the clusters are determined using a Monte Carlo simulated annealing method.

**COMP 135 Cyanogen and diacetylene dimer potential energy surfaces: New π-π prototypes**

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Cyanogen dimer [(NCCN)2] and diacetylene dimer [(HCCCCH)2] are among the smallest closed-shell, neutral prototype systems exhibiting significant π-π interactions with binding properties similar to those observed in the benzene dimer (i.e., large contributions from connected triple excitations). With only eight heavy atoms and generally high symmetry, these small complexes can be studied in much more detail than the dimer of benzene. This talk will present a thorough examination of the cyanogen and diacetylene dimer potential surfaces. Six stationary points have been identified on each dimer potential surface. These include linear, crossed, parallel displaced, rectangular, T-shaped, and Y-shaped geometries. In addition, the effects of electron correlation, basis set, and counterpoise correction on the interaction energy, optimized geometry, and nature of the stationary points are examined in detail.

**COMP 136 Structural and vibrational properties of boron nitride (BN) analogs of diamondoids**

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Diamondoids are stable cage-like hydrocarbon molecules that possess a structure which is superimposable upon the diamond crystal. These highly symmetric structures have a generic structural formula C_{4n+6}H_{4n+12}, and they have been isolated from petroleum oil. Because of their various shapes and sizes, there has been speculation in the literature that diamondoids might be suitable building blocks for possible applications in nanotechnology. One could ask whether boron nitride (BN) analogues of diamondoids might exist. It is known experimentally that cyclotriborazane, B_3N_3H_12, the BN-analogue of the smallest diamondoid molecule adamantane exists, but there is no experimental evidence for the existence of higher-order BN-diamondoids at the present time. In this work we use accurate all-electron density-functional theory (DFT) calculations to study the structural and vibrational properties of a small set of lower order BN-diamondoids (e.g. BN-adamantane (B_6N_4H_16), BN-diamantane (B_7N_7H_20), BN-triamantane (B_10N_8H_24), and BN-anti-tetramantane (B_11N_11H_28). We discuss the relative stability of each of these representative BN-diamondoids molecules and provide theoretical infrared and Raman spectra for future identification of this novel class of molecules.
**COMP 137 Silica-supported silver salt for paraffin/olefin separation: A DFT study**

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Separation of olefins from paraffins, e.g., ethylene from ethane, is of great importance in the chemical industry. Current technology generally employs cryogenic distillation, a process that is unfortunately very energy-intensive. An alternative approach is to use adsorbents. Recent experiments show that mesopore-silica-supported silver salts display excellent adsorption selectivity of ethylene/ethane and propylene/propane. Using first principles density functional theory techniques, we investigated silver salts on a silica surface. Our model includes Ag⁺'s counter ion, silica support and surface silanols. Both adsorption geometry and energetics of ethylene/ethane and propylene/propane were explored. Our results indicate that the Ag-olefin interaction is much stronger than that of Ag-paraffin due to the formation of a d-π bond in the former. Our work supports recent experiments, which indicates that Ag⁺/silica may be a very promising adsorbent for paraffin/olefin separation. This work is supported by Office of Basic Energy Sciences, U.S. Department of Energy.

**COMP 138 Importance of basis set construction in density functional theory**

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The effect of basis set construction has been examined for use with pure and hybrid density functionals (BLYP and B3LYP). Our focus is upon molecular systems composed of first row atoms. The correlation consistent basis sets of Dunning (cc-pVnZ, where n = D, T, Q, and 5) have been employed in all calculations. In particular, we examine the effects of systematic removal of high angular momentum functions, as well as recontraction of basis sets, upon atomic and molecular ionization potentials, optimized geometries, and atomization energies. We show that reduced basis sets in the d functions in atomic calculations and in the f functions for molecular calculations affect calculated properties (>0.01 angstrom in bond lengths and >0.04 eV in atomization energies and ionization potentials).

**COMP 139 Conformational study of small molecules in the protein environment**

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Crystallographic determined coordinates of small molecules, such as lead compounds, ligands, substrate analogs, etc., are often considered as starting point for most modeling studies like conformational search, docking etc. and the criteria of exploring the conformational changes of ligands in the protein environment. Earlier we have reported (Bioorg. Med. Chem. 3, 1995, 411-428) the conformational changes of small molecules when binding to proteins using molecular mechanics analysis. We have analyzed strain energies and conformational changes of 111 ligand structures, whose crystal structures were present both in the Cambridge Structural Database (CSD) and the protein data bank (PDB) at resolution of 2 A, or better in the protein environment. All optimization were done starting at 3-21 level, followed by RHF/6-31(d), followed by B3LYP/6-31(d) and finally at B3LYP/6-31+G(d). The results obtained so far will be presented here.

**COMP 140 Flexible docking of the inhibitors into Tyrosyl-DNA Phosphodiesterase (Tdp1) active sites**

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Tdp1 inhibitors have become a major area of drug research and structure-based design, with Tdp1, works synergistic and selectively in the cancer cells. Tdp1 can repair DNA topoisomerase I (Top1) covalent complexes by hydrolyzing the tyrosyl-DNA phosphodiester bond. In the present study, we report docking the various inhibitors into a structural model of tdp1 enzyme, based on a multiple crystal structures of tdp1 substrate complex with resolution 2.0 A, or better. All off the above work is done by using the Glide software (Schrodinger Inc.) on Silicon Graphics workstation. These models have been used for predicting a priori the binding affinity of newly designed ligands. Virtual screening method using NCI databases such as ChemNavigator were submitted. The results obtained so far will be presented here.

COMP 141 Computational modeling of kinases
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The Protein Kinase-C (PKC) family consists of at least 11 members, which play a crucial role in transducing extracellular signals generated by growth factors, hormones and neurotransmitters. They possess a variable domain (called V5) at the C-terminal end of the catalytic domain that has much lower sequence conservation across the isozymes when compared with the catalytic domain. Recent truncation studies of PKCα performed by us demonstrate the importance of the V5 domain for both PKCα-specific functions and for conferring full catalytic competence to the enzyme. To complement these studies, we used computational techniques to probe the effects of the truncation mutants on the structure and function of PKCα. A comparative model of native PKCα, spanning the catalytic and V5 domains, was prepared, as were two truncation models known to be deleterious to the enzyme activity (PKCα-Δ672 and PKCα-Δ663). The models were probed using molecular dynamics simulations. It was observed that while the native PKCα remained stable, the truncation mutants underwent severe deformation of the V5 domain; in the case of the Δ663 mutant this additionally caused disruption of the ATP-binding site pocket. The origins of these deformations were found to lie in the loss of critical hydrogen bonds/salt bridges as result of the deletions.

COMP 142 Novel empirical free energy function for use in the protein-protein docking problem
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The protein-protein docking problem involves the use of computational methods to predict the structure of the native state complex, given the structures of the unbound monomers. This leads to two distinct sub-problems: the search problem and the scoring problem. The search problem has to do with the development of efficient and effective strategies to search the six-dimensional binding space. The scoring problem deals with the development of a criterion or mathematical function to score and rank the complexes generated during the search phase. Given that the native state complex represents a free energy minimum, the use of free energy functions to solve the scoring problem has obvious appeal. Importantly, any viable free energy function for use in docking studies must combine the virtues of accuracy and computational efficiency. Here we propose a novel, empirical free energy function for use in the protein-protein docking problem that seems to satisfy both demands. The function is fast, yet rigorously derived from fundamental thermodynamic principles. Moreover, to the best of our knowledge the function includes explicit terms that are without precedent. It is our hope that our energy function will ultimately contribute to the solution of the protein-protein docking problem.

COMP 143 SemDrug: Application of Semantic Relationship Discovery to expedite lead identification
WITHDRAWN

The sheer volume of existing information and the anticipated explosion of data generated in the life sciences domain pose a major hurdle in drug discovery research. Although a significant proportion of this data is organized in a structured form, the relationship between these data and their interpretation has not been fully exploited. The application of semantic techniques to drug discovery will facilitate in extracting and understanding relationships, for instance between genes and diseases or compounds and side effects which are fundamental for drug discovery. The focus of this semantic approach is to build multiple ontologies that can help in representing the relationships between different domain information. By understanding the complex relationship between these data and eliminating unwanted information, the process of lead identification in drug discovery can be expedited. This can have a significant impact on drug discovery productivity in pharmaceutical companies. We have developed a prototype system, wherein we have exploited the relationships between drug targets, bioactive compounds and their chemical information to answer questions critical to speeding the process of lead identification.

COMP 144 Solvent polarization and kinetic isotope effects in nitroethane deprotonation and implications to the nitroalkane oxidase reaction
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Mixed molecular dynamics and centroid path integral simulations using a combined quantum mechanical and molecular mechanical (QM/MM) potential were employed to study the anomalous Bronsted relationship between rates and equilibria for deprotonation of nitroalkanes in water, which is known as the nitroalkane anomaly. This study focuses on the deprotonation of nitroethane by an acetate ion, which is a model reaction for the process catalyzed by the enzyme nitroalkane oxidase. The results show that the difference in solvent polarization effects for the TS and products is a major factor for the differential solvent effects on rate and equilibrium of nitroalkane deprotonation. This is due to poor charge delocalization as a result of slow rehybridization compared to bond breaking. Although solvent effects do not affect significantly the computed kinetic isotope effects in comparison with the gas phase value, there is slight solvent-induced increase in tunneling. The present results suggest that an effective means by which the transition state can be stabilized in the enzyme nitroalkane oxidase is to facilitate the C# rehybridization.

COMP 145 A line integral reaction path approximation for large systems via nonlinear constrained optimization: Application to alanine dipeptide and β-hairpin of protein G
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A variation of the line integral method with self-avoiding walk has been implemented using a state of the art nonlinear constrained optimization procedure. The new implementation is robust in finding approximate reaction paths for small and large systems. Exact transition states for the resulting paths can be pinpointed with subsequent application of the conjugate peak refinement method. Unlike previous implementations utilizing penalty function approach, the present implementation generates an exact solution of the underlying problem. Most importantly, this formulation does not require an initial guess for the path, which makes it particularly useful for studying complex molecular rearrangements. The method has been applied to conformational rearrangements of the alanine dipeptide in the gas phase and in water, and folding of the
&beta–hairpin of protein G in water. In the latter case a procedure was developed to systematically sample the potential energy surface underlying folding and reconstruct folding pathways.

**COMP 146 Absence of aromaticity at residue 6.44 contributes to cannabinoid CB2 receptor constitutive activity**

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It has been proposed that GPCR activation is characterized by a W6.48 chi 1 g+ to trans rotamer shift and that aromatic residues flanking W6.48, such as F6.44, contribute to reduced GPCR constitutive activity. In work to be presented, we test the hypothesis that the high constitutive activity of the cannabinoid CB2 receptor is in part due to the lack of an aromatic residue at position 6.44. Monte Carlo/simulated annealing (Conformational Memories) calculations of WT CB2 TMH6 and L6.44F TMH6 revealed that a Phe at 6.44 tends to promote the W6.48 g+ (inactive state) rotamer. To test this result experimentally, a CB2 L6.44F mutant was stably transfected into HEK293 cells and the effects of this mutation were examined with Western blot, ligand binding, and CAMP accumulation assays. Consistent with our working hypothesis, the CB2 L6.44F mutant was found to lose constitutive activity. (Support: DA03934 and DA00489 (PHR), DA11551 (ZHS))

**COMP 147 Absolute binding free energy calculation for theophylline and its analogs to RNA aptamer using BAR method with GAFF**

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The RNA aptamer displays high affinity and high selectivity for a target molecule. The binding affinity of the TCT8-4 RNA for theophylline is 10000 times larger than that for caffeine, which differs from theophylline by a single methyl group. Therefore, we adopted this system typically to examine the validity of theoretical approach. BAR method gives us the absolute binding free energy of realistic complex systems. Our previous reports indicated that the GAFF parameters and the RESP charges for ligands lead to the sufficient results. To obtain further consistency, we introduced the GAFF parameters and the AM1-BCC charges to represent the behavior of the RNA. The RNA charges are calculated by the AM1-BCC model using MOPAC2002. The comparison of this work with the previous one is investigated. The Fujitsu BioServer is used to efficiently perform the independent MD simulation suitable for BAR method.

**COMP 148 Analyzing force field and charge conditions to enhance biological activity predictions of Cathepsin D inhibitors**

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Cathepsin D has become an important target for drug design due to its association with the development of many biological processes, including cancer. Sybyl software was used to minimize inhibitors in ten different force field and charge combinations to determine the most favorable conditions. Ki values for known inhibitors were predicted using a fuzzy neural network and, in order to validate the efficiency of our model, they were compared to their corresponding experimental values. Novel compounds were designed and their biological activities were predicted using the optimized fuzzy neural network.
COMP 149 Atomistic simulations of carbon dioxide diffusion within zeolites
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To efficiently separate CO₂ from multi-species gas streams, sorbents must have high CO₂ selectivity and CO₂ mobility within the materials must not be a limiting factor. Zeolites are one attractive option as sorbents. In the past we have investigated the influence of pore geometry alone on the adsorption of CO₂ and relevant mixtures within silica-only zeolites. We found that silicalite, ITQ-3, and ITQ-7 (zeolites with identical chemical composition but different structure) vary in their CO₂ adsorbance capacity and selectivity. We present here the complementary studies of non-isotropic CO₂ diffusion within these materials. Molecular Dynamics simulations have been used to compute CO₂ self-diffusion, corrected diffusion, and transport diffusion within ITQ-3, ITQ-7, and silicalite. Significant diffusion occurs, and carbon dioxide molecules explore large regions in all three zeolites. Rates of diffusion vary between zeolites, decreasing with increased pore loading in ITQ-7 and silicalite but showing a non-monotonic dependence in ITQ-3.

COMP 150 Better than RMSD: Faster methods for conformer comparison
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Correctly modelling the molecular flexibility essential to protein-ligand interactions is a challenge with current technology. Progress requires processing more geometry data, more conformers, and larger molecules. Hence, despite continual improvements in computing machinery, methodological and algorithmic advances are needed. RMSD is the standard measurement for conformer comparison. RMSD is effective in many applications but has limitations, both theoretical and practical. An alternative approach compares the distance matrices of each coordinate set, which offers the significant practical advantage that no alignment of the conformations is needed, since all distances are intra-molecular. This study explores whether intra-molecular distance matrix based methods can provide significant computational advantages to standard RMSD-based methods for conformational comparison, as some data already suggests. Special attention is given to the computationally demanding task of de-duplicating large conformation ensembles.

COMP 151 Biomolecular electrostatic potential: An analytical approach
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Electrostatic interactions are a key factor for determining many properties of bio-molecules. The ability to compute the electrostatic potential generated by a molecule is often essential in understanding the mechanism behind its biological function such as catalytic activity, ligand binding, and macromolecular association. We propose an approximate analytical solution to the (linearized) Poisson-Boltzmann equation that is suitable for computing electrostatic potential around realistic biomolecules. The approximation is tested against the numerical solutions of the PB equation on a test set of 600 representative structures including proteins, DNA, and macromolecular complexes. The approach allows one to generate, with the power of a desktop PC, electrostatic potential maps of virtually any molecule of interest, from single proteins to large protein complexes such as viral capsids. The new approach is orders of magnitude less computationally intense than its numerical counterpart, yet is almost equal in accuracy. When studying very large systems, our method is a very practical and inexpensive way of computing bio-molecular potential at atomic resolution.
**COMP 152 Computational analysis of conformational diversity of FLPs neuropeptides**

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The animal nervous system employs a number of chemical neurotransmitters (neuropeptides) to relay messages from one neuron to the next. The largest family of these peptides, FLPs or FMRFamide-like peptides have been implicated in a variety of neural activities such as cardioregulation, muscle control and learning. Parallel tempering (replica-exchange) molecular dynamics technique as well as quantum mechanical methods are applied to DFDGAM-NH\(_3\) peptide and its most dominant conformational states are predicted after an NMR chemical shifts analysis. Calculations were carried out for both implicit and explicit solvent models and chemical shifts were monitored for two different pH states where the peptide is either in the unprotonated phase (DFDGAM-NH\(_3\)) or in the full protonated phase (D-HFD-HGAM-NH\(_2\)). Our results procure important additional information to the NMR experimental data.

**COMP 153 Computational methods for the analysis of small angle scattering spectra**

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We are developing a suite of computational methods to aide in the design and analysis of small angle scattering data with applications to macromolecular systems. Specifically, we are merging methodologies developed to search conformational space of small molecular pharmaceuticals with the conformational search problem posed by intrinsically disordered proteins and nucleic acids. This is achieved by generating an ensemble of macromolecular structures by varying sets of backbone dihedral angles and using importance sampling methods to rapidly determine structures that have small angle scattering spectra that are consistent with experiment. In addition, we have developed algorithms to determine the relative orientation of macromolecules binding in solution. We have used these tools to predict a set of structures for the HIV-1 Gag protein under high salt conditions. These tools, once mature, may be useful in the study of intrinsically disordered proteins and the elucidation of macromolecular interactions in solution.

**COMP 154 Computational studies into the mechanism of human tyrosyl-DNA phosphodiesterase**

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Human tyrosyl-DNA phosphodiesterase I (Tdp1) is a repair enzyme for lesions in DNA caused by topoisomerase I and is a potential target for anti-cancer drugs. Recently, it was shown that hTdp1 uses an acid/base catalytic mechanism (J.Mol.Biol. 2004, 338, 895-906). It is also proposed to catalyze a two step sequence. To validate this proposed sequence, we used computational methods to calculate thermodynamic parameters and electronic structures of the substrates, intermediates, and products. Two sets of calculations were performed: one using methyl groups in the positions of biological side chains and a second using simulated biological fragments. Calculations were performed in vacuo and in aqueous solution. All calculations were performed using density functional theory with exchange-correlation functional (B3LYP) and 6-31G(d) basis sets. Solution calculations utilized the Conductor Like Polarizable Continuum Model (CPCM).

**COMP 155 Computational studies of asymmetric organocatalysis**

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The reverse-docking of a series of organocatalysts to rigid transition state (TS) representations of their reaction substrates is described for several reactions. The organocatalyzed azidation, Diels-Alder, hetero-Diels-Alder and Strecker reactions are studied in detail. The exact catalytic mechanisms of these reactions has yet to be elucidated. The resulting docking poses provide a simplified view of the TS for these reactions. Each pose is scored and ranked based on its molecular mechanics (MM) docking energy. All poses are subjected to a structural clustering procedure to highlight those showing attributes thought to be critical for molecular recognition. The reverse-docking procedure reveals a clear energetic trend favoring the formation of the experimentally favored enantiomeric product for all reactions. Analysis of the best pose for each reaction suggests mechanisms that are consistent with principles of molecular recognition, catalysis, and reported experimental data.

**COMP 156 Computational tools for LIPID metabolite and pathways strategy**  
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Lipids and their metabolites play a key role in the regulation and control of cellular function and disease. In order to develop compounds of therapeutic interest, it is vital to not only identify and characterize existing and novel lipids but also quantify changes in their metabolites, and develop biochemical pathways and interaction network maps. LIPID MAPS consortium is involved in this endeavor. To integrate, analyze, track, and disseminate large volumes of heterogeneous chemical, biological, and analytical data being generated by multidisciplinary research groups, we have developed a computational infrastructure which includes a variety of tools with both web-based and batch access. We will present our current and on-going work on development of these tools to support LIPID MAPS research activities.

**COMP 157 Computer simulations of glycolytic enzyme/enzyme association and implications for substrate binding**  
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The association of sequential enzymes within a given metabolic pathway may bring enzyme active sites close together and enable the transfer of metabolite from one enzyme to the next without allowing for equilibration with bulk solution. This phenomenon known as substrate channeling, which is now well established for some pathways such as the citric acid cycle, is still highly debated in glycolysis. Herein, Brownian dynamics simulations were used to investigate the interactions between glycolytic enzymes, fructose-1,6-bisphosphate aldolase (aldolase) and glyceraldehyde-3-phosphate dehydrogenase (GAPDH) in a different species, including human, fish, rabbit and yeast. The simulations revealed favorable enzyme-enzyme interactions, yielding two types of complexes. In Type 1 complexes, a single subunit of aldolase interacts with a single subunit of GAPDH and in Type 2 complexes, two subunits of aldolase form salt bridges with two subunits of GAPDH. Most favorable complexes were then used to simulate the binding of substrate, glyceraldehyde-3-phosphate (GAP), to bound and free GAPDH. The percentages of successful trajectories in which GAP came within 6 Å of the active site cysteine (Cys151 for human & fish; Cys149 for rabbit & yeast) of free GAPDH were 9.9, 4.0, 3.6, and 0.48 for rabbit, fish, human and yeast, respectively. These efficiencies were markedly decreased by the presence of phosphates in the active sites and by mutation of active site arginine (Arg233 for human & fish; Arg231 for rabbit & yeast) to alanine. Hence, GAP binding is initially electrostatic and the local charge around the active site, rather than the overall net charge, may be important. Results also showed GAP preference for two active sites in human and rabbit
enzymes which, although requires further investigation, is consistent with the “half-of-the-sites reactivity” phenomenon noted for GAPDH.

### COMP 158 Computer-aided molecular design of Histone Deacetylase Class I inhibitors

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The inhibition of Human Histone Deacetylase Class I (HDAC-I) enzymes is a fresh approach to cancer and Lupus treatments that focuses on controlling the cell’s cycles, progression, differentiation, and apoptosis. Due to the multiple growth pathways of a cell, the inhibition of one or several pathway(s) does not always result in the death of the cell, as other pathways continue the life cycle. The HDAC-I class of enzymes are different in this respect. They are a main controller of the cell cycle and their inhibition will subsequently obstruct cell differentiation and apoptosis. A firm understanding of the HDAC-I isozymes’ binding site region provides information for the design of novel isozyme specific inhibitors. The construction and implementation of “true” HDAC-I enzyme models provided the basis for a sound in silica inhibitor study. The use of known HDAC-I inhibitors as building blocks enabled the design of novel inhibitors to exploit specific features of each isozyme’s active site. Molecular docking and targeted molecular dynamics were used as a screening method to determine promising inhibitors and their probable orientation in the active site. Relative binding affinities, energetic and physical interactions between the novel inhibitors and the HDAC-I isozyme models were further explored with molecular dynamics. These results will be discussed as will their impact on the selection of novel inhibitor to be synthesized and tested.

### COMP 159 Conformational analysis of a GBR 12909 analog

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GBR 12909 analogs are an important class of dopamine reuptake inhibitor that appears to be useful in the treatment of cocaine abuse. This study focuses on a GBR 12909 analog (1) that has less flexibility and higher binding affinity for the dopamine transporter (DAT) than the parent compound. Several random search conformational analyses using the vacuum phase MMFF94 force field were carried out with different random seeds. As the first step in the modeling of a pharmacophore for DAT binding, significantly-populated local energy minima on the conformational potential energy surface of 1 were identified for use as templates for 3D-QSAR calculations.

![GBR 12909 analog](image-url)
COMP 160 Conformational sampling and folding in polyalanine peptides
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Replica-exchange molecular dynamics simulations in peptides were performed to understand the thermodynamics and kinetics of protein folding. In this work, an alanine model peptide (alanine-20) was explored using an AMBER based force field with the generalized Born/solvent-accessible surface area implicit solvent model. Two highly populated structural clusters were found at low temperature, one is fully α-helical and the other is a coiled-coil. These ensembles were used as a starting point for computation of folding and unfolding rates using distributed computing techniques. By analyzing two-dimensional distributions in Cα root-mean-square deviation (RMSD) space, we estimated a melting temperature. Simulations of Temperature-jump (T-jump) were performed and our results were analyzed using calculated CD spectra to obtain the folding and unfolding rate.

COMP 161 Contributions of conformational flexibility to Brugia malayi asparaginyl-tRNA synthetase specificity for inhibitors identified by structure-based screening

We are targeting the Brugia malayi asparaginyl tRNA synthetase (AsnRS) for drug development against this parasite. SLIDE, the protein structure-based screening and docking software developed in our laboratory, is being used to screen databases of small organic molecules to find new classes of molecules that bind to the catalytic site in the 1.9 Å resolution Brugia AsnRS structure. Three classes of compounds identified by SLIDE have been confirmed as having micromolar inhibition constants against the enzyme in vitro. The long side-chain derivatives of one of these classes of compounds, the variolins, cannot bind to the closed crystal structure conformation of Brugia AsnRS due to steric clashes, even though the short side-chain variolins apparently bind isosterically with the adenine moiety of the co-crystallized product analog. To understand the structural determinants of specificity and the role of protein backbone flexibility in ligand binding, conformational sampling of known flexible regions of Brugia AsnRS was carried out using ROCK. The low-energy conformers generated by ROCK showed significant backbone motions of up to 4.5 Å in the adenine binding loop, which is so flexible that its conformation could not be determined in the apo crystal structure of the protein. The docking of the long side-chain variolins to the binding site of the open conformation of the protein generated by ROCK supports our hypothesis that conformational changes, combined with the sequence differences at the base of this loop, can explain the selectivity of the variolins for Brugia AsnRS relative to human AsnRS.

COMP 162 Crystal-GA: A program for crystal structure determination via X-ray powder diffraction data
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A new genetic algorithm-based program, Crystal-GA, for crystal structure determination from non-indexed X-ray powder diffraction data is described. Common space-groups {e.g. P-1, P21, P21/c, C2/c, P212121, Pbca, etc.} are searched over a user-defined range of unit cell dimensions, and experimental density is employed to eliminate unreasonable unit cell values. Target molecules are minimized using DFT, and are then input to Crystal-GA for analysis in the various space groups. The fit of the calculated X-ray powder pattern, based on the position and orientation of the molecule, to the experimental data is used as the primary figure of merit, and the calculated packing energy of the model is also considered. The best trial structure is then used as a starting model for Rietveld refinement1. Crystal-GA has produced correct structures for several test compounds: benzene, naphthalene, dimethylnaphthalene, benzoquinone, and 1,3-diethyl-2-thiobarbituric acid. Also, Crystal-GA has produced the correct crystal structure for an unknown crystal, 5-quinodiacylene. The results of these analyses and continued development of the technique will be discussed.

**COMP 163 Cyclopentane: Forcefield and molecular dynamics analysis**

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Cyclopentane is a good molecule to benchmark forcefields and molecular dynamics algorithms, due to its pseudorotation. A number of forcefields were examined to see which most closely mimics cyclopentane, and the MMFF94 forcefield gave the best agreement with the energy barrier to the planar conformation (within 0.2 kcal/mol). Using MMFF94, it was found that the pseudorotational velocity and amplitude are interdependent, so if the pseudorotational velocity matches experiment, the amplitude will not, and vice versa. It was found that the controlling factor is actually inherent in the molecular dynamics - the thermal inertia parameter of the NVT ensemble. In addition, different molecular dynamics algorithms were used to simulate cyclopentane for an extended period of time (800 ns) to see if error introduced by the different algorithms affected the dynamics of the system. It was found that the choice of algorithm will not affect the final results, so algorithms that run faster are best in the regime of very small timesteps.

**COMP 164 De novo structure-based design of tris-urea tripodal and macrocyclic anion receptors**

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This paper describes how the structure-based design software, HostDesigner, was modified to generate symmetrical tripods and macrocycles. This feature was used to identify architectures for tris-urea hosts that are organized for targeted anion shapes. When interfaced with the GMMX molecular mechanics program subsequent evaluation of these candidates using force field-based scoring methods identified structures with large interaction energy and low conformational energy. The approach has suggested new architectures for achieving anion shape selectivity via the manipulation of steric constraints.

**COMP 165 Design of novel enzyme catalysts: Combining the benefits of quantum mechanics, rational design and directed evolution**

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Enzyme design is a daunting task, but recent advances in computational algorithms, computer power, and success in the field of computational protein design provides incentive and a powerful context in which to undertake such an endeavor. Accordingly, the focus of my research is to develop computational methods for the design of novel enzyme catalysts. In this proposal, the design strategy is described step-by-step. It involves first building a catalytic site for the rate-determining transition state of the reaction based on quantum mechanical calculations, grafting the catalytic site and transition state into a foreign scaffold, and repacking the active site with the EGAD library developed for protein design. Designs which satisfy specific criteria will be synthesized and tested for foldedness and catalytic activity, and if necessary and feasible, optimized by directed evolution. Designs currently under consideration are versatile, ranging from hydrolase to Diels–Alderase. They are chosen because the reactions are simple yet some of them may have applications in therapeutics and synthesis. Although the long term goals are to design enzyme catalysts for any desired chemical reactions, from shorter term successes and failures we will continue to learn about the chemical mechanisms that make enzymes such extraordinary catalysts.

**COMP 166 Detection of hidden sequence propensity for amyloid fibril formation using support vector machine**

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It is of essential importance to avoid the inherent tendency of protein misfolding and aggregate to form potentially harmful deposits in normal biological system. In many human diseases associated with protein deposition, such as Alzheimer’s and Parkinson’s diseases, normal soluble peptides or proteins are transformed into β-rich deposits referred as amyloid fibril. Here, we present a new computational method to detect amyloid fibril formation propensity under influence of tertiary contacts (TCs) using support vector machine. Analysis of 2401 nonhomologous protein domains showed that the tertiary environment is a major determining factor of native secondary structure of either α-helix or β-strand. The present method correctly pinpointed the peptide fragments that are likely local mediator of amyloid fibril formation determined by experimental results in amyloidogenic proteins, such as β-amyloid peptide, islet amyloid polypeptide, α-synuclein and human acetylcholinesterase. Furthermore, the calculated propensities are well correlated (r = 0.78) with the experimental effects of mutations on the aggregation rates. All these results support that the present method is a sensitive and accurate approach for detection of core sequences that may trigger amyloid fibril formation. Its attractive features, including fastness, simplicity and accuracy, will make it wide use in proteome study and analysis of amyloidogenic nature.

**COMP 167 Development of quantitative structure-activity relationship models of Sodium/Potassium ATPase inhibition by cardiac glycosides**

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Cardiac glycosides are compounds that inhibit the ion-translocation activity of the transmembrane enzyme sodium/potassium ATPase (Na/K-ATPase). In the form of digoxin and digitoxin, cardiac glycosides have been used for the treatment of congestive heart failure symptoms for many years. Although effective, the usage of cardiac glycosides is limited by their narrow therapeutic index, which can cause severe toxicity in the case of an overdose. For the
development of new and potentially safer drugs, the interactions between cardiac glycosides and their target, the Na/K-ATPase, need to be known at the molecular level. A method that can provide this information is three-dimensional quantitative structure-activity relationship (3D QSAR) modeling. Previous studies have shown that the inhibitory potency of cardiac glycosides is particularly sensitive to modulation of the compounds' lactone moiety. Thus, we used literature data for the development of 3D QSAR models by comparative molecular field analysis (CoMFA) and comparative molecular similarity index analysis (CoMSIA) that focus on structural modifications exclusively about the lactone ring. The contour maps generated by these models allow the identification of nature and location of crucial interactions between the inhibitors and the Na/K-ATPase. These models can also be the basis for virtual screening of compound databases for novel inhibitors that can be evaluated experimentally in inhibition assays.

COMP 168 Differential DNA-binding by some Rel/NF-κB proteins: Molecular dynamics of a κB DNA element
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The cell biologies of many multicellular and higher organisms are regulated by a broad family of Rel/NF-κB proteins, with members of this family having been implicated in both normal and aberrant physiological pathways (e.g., immune and inflammatory responses, cell differentiation, apoptosis). Rel/NF-κB proteins are active as homo- or hetero-dimeric transcription factors that bind to κB-like DNA sequences with variable specificities and affinities; moreover, differences in binding of NF-κB proteins to regulatory κB elements affords a means of differential gene regulation of target proteins (which include classes such as cytokines, chemokines, adhesion molecules, antimicrobial peptides, etc.). An NF-κB variant known as c-Rel is one of the five abundant mammalian Rel proteins, and, intriguingly, minimal mutagenesis converts this protein to an oncogenic variant (v-Rel) with vastly different biochemical properties and cellular activities. The research described here aims to elucidate the physico-chemical basis of these differences, particularly with regards to DNA-binding and indirect readout. Several well-established computational methods - including electrostatics calculations and molecular dynamics (MD) simulations - are being applied to c-Rel and v-Rel in order to explore any salient differences in the properties of these two proteins. Other differences between these proteins will be investigated as well (e.g., differences in DNA-binding affinities via free energy calculations), with the overall goal of understanding how differences in the physical properties of two similar proteins translate into their vastly different biochemical properties.

COMP 169 Distance dependence of flurbiprofen and dapsone in the CYP 2C9 active site as studied by molecular dynamics
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It has been shown that flurbiprofen (substrate), when in the presence of dapsone (effector) exhibits atypical kinetics with respect to metabolism by cytochrome P450 2C9 (CYP2C9). It has been suggested that these kinetics can be explained by a multiple substrate model (ie both substrate and effector simultaneously bind in the active site). In our studies we examined the effect that active site residues have on the substrate-effector pair, both in relationship to each other and to the heme, by molecular dynamics. The results indicate that certain key residues, when mutated in silico, alter the distances of the substrate or effector with respect to heme. In
particular, residues 208 and 209 are directly responsible for positioning sulfone effectors and consequently the substrate and demonstrate the importance of these residues for substrate positioning. From this data we can begin looking at what type of interactions may be occurring in the system by site directed mutagenesis. (Supported by WV-INBRE and NIH Grant P20 RR016477).

**COMP 170 Docking and molecular dynamics studies of copper containing enzyme diamine oxidase**

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Copper amine oxidases (CAO) are ubiquitous enzymes that catalyze the oxidative deamination of primary amines. While the general structure of the catalytic site is well known, the function of copper and some of the conserved residues is still to be determined. Several physiological roles for human amine oxidases are being developed that suggest a pharmacological importance for the inhibition of CAO's in human nervous system functioning. MacroModel and Glide molecular modeling packages (Schrödinger Inc.) were used to perform molecular dynamics calculations in order to evaluate the effect of conserved residues and potential inhibitors on the enzyme activity. Single amino acid mutation experiments toward the residues involved in catalytic mechanism were performed and their role will be presented. Combining our modeled structures for each CAO subunit with known structural, genetic and biochemical data, we also propose detailed model of how two subunits of this enzyme interact.

**COMP 171 Dramatically different structural strategies to achieve the same metabolic goal: Molecular modeling comparison of CYP6B8v1 and CYP321A1**

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In order to survive, insects must deal with both naturally-occurring plant toxins and synthetic insecticides in their diets. Detoxification by coupled P450: P450 reductase systems represents one of the most prominent routes responsible for the inactivation of synthetic as well as natural toxins. H. zeae CYP6B8v1 and CYP321A1 proteins have been reported to metabolize many of the same allelochemicals and insecticides despite only 32% identity between these two H. zeae proteins (Li et al., 2004; Sasabe et al., 2004). To further define the molecular relationships between these two P450s, we have built homology models for both and docked several allelochemicals and insecticides into these apo-protein models. A comparison of these apo-protein and substrate-docked models indicates that H. zeae CYP6B8v1 and CYP321A1 proteins have employed very different structural strategies to achieve the same goal with predicted side chain in nearly all of the substrate recognition sites showing variation due to the high degree of sequence divergence in these P450s. Despite these variations in the catalytic sites, nearly all of the docked substrates exhibit similar binding modes within the CYP6B8 vs. CYP321A1 catalytic sites suggesting similar attack positions on each substrate. Analysis of the products generated from each of these heterologously expressed P450s has provided evidence supporting the similarities of their products.


**COMP 172 Effects of the L100I and L100I+K103N mutations on the binding of etravirine analogs to HIV-1 reverse transcriptase based on Monte Carlo simulations**

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The activity of etravirine and three closely related analogs for the L100I single mutation and L100I+K103N double mutation of HIV-1 reverse transcriptase (HIVRT) were examined via Monte Carlo/free energy perturbation (MC/FEp) calculations. The calculations agree excellently with the experimentally observed effects of the mutations. The accompanying structural analyses show that the importance of the primary amino group in etravirine is to allow for redistribution of hydrogen bonds with the mutant protein environment. The bromine in etravirine is essential in keeping water out of the hydrophobic region between the E138 and Y181 side chains.

**COMP 173 Errors in gel acrylamide electrophoresis due to effect of charge**

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Four mammalian genomes have been sequenced in its entirety recently. These are the human, rat, mouse and chimp genomes. The emergence of dtabases to store the sequence information in DNA and protein has increased the interest in gel acrylamide electrophoresis. A calibration method is used and the migration distance is translated into a species molecular weight information. By deduction the sequence is estimated. By shotgun sequencing the entire sequence can be calculated from the sequence information available. The charge effect is not accounted for in a explicit fashion. This can induce some errors in the estimation of sequence distribution. The manifestation of errors to the extent of gene finding is explored. A mathematical model that includes a charge balance in addition to mass balance in transience is developed. The finite speed non-Fick diffusion effects are accounted for by using the damped wave diffusion and relaxation equation.

**COMP 174 Evaluation of loop prediction protocols**

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One of the critical issues in predicting protein structure is proper modeling of loop regions. A variety of approaches to this problem, including knowledge-based and ab initio methods, have been described in the literature and are available in academic as well as commercial software modeling packages. We have organized an unbiased evaluation of four of the most commonly used, commercially available loop modeling programs. Loops with lengths ranging from 4-12 amino acid residues were taken from a literature set of high resolution (< 2Å) crystal structures. Loops were modeled in all four software programs and the accuracy of loop prediction was assessed by comparison to native structure. Variations in software performance and computational cost as a function of loop length will be presented.

**COMP 175 Exploring the mechanism of Trypanosoma cruzi trans-sialidase**

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The enzyme trans-sialidase catalyzes the transfer of sialic acids from sialoglycoconjugates to other glycoconjugates and has a critical role in virulence of Trypanosoma cruzi, the etiological agent of Chagas’ disease. Inhibition of Trypanosoma cruzi trans-sialidase (TcTS) is seen as a potential therapeutic target for this lethal chronic disease. TcTS is also of interest due to its strong similarity in sequence and structure to a strict hydrolase, Trypanosoma rangeli sialidase.
(TrSA). An extensive comparison of the two will reveal structural requirements for sialyl-transferase activity and also be a guide for future efforts to transform sialidases into trans-sialidases that are of synthetic value. This theoretical study focuses on molecular dynamics simulations starting from different X-ray crystal structures that correspond to different points on the reaction paths of the two enzymes. Potential energy profiles for hydrolysis reactions of TcTS and TrSA and sialyl-transfer reaction of TcTS will also be explored using QM/MM methods.

**COMP 176 Feed-forward neural network models of potential sulfonamide-substituted cycloalkylpyranone HIV protease inhibitors**

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Application of neural network (NN) approaches takes advantage of the computing power available today, even in ordinary desktop PCs. This approach yields QSAR models with more predictive ability, at the expense of interpretability. Feed-forward neural network (FFNN) models were developed for predicting the biological activities of a dataset of sulfonamide-substituted cycloalkylpyranone HIV protease inhibitors. These models are based on Multiple Layer Perceptrons (MLP) and closely resemble a Multiple Linear Regression (MLR) QSAR model. The physicochemical parameters and molecular descriptors were used directly to compute the biological activities of compounds. The best models will be reported.

**COMP 177 First principles molecular dynamics simulations of benzene in water**

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The hydrophobic effect is instrumental in the stability of protein structures. A simplified model of phenylalanine, tyrosine and tryptophan is benzene. Benzene has been predicted and shown to act as a hydrogen bond acceptor. We have used first principles molecular dynamics to study one benzene molecule in a cubic box of 73 water molecules with periodic boundary conditions. For the water molecules both fully-flexible and rigid water approximations were used. We have determined the structural properties of the water environment surrounding the benzene, the exchange process of water molecules in the axial and the equatorial orientation, and the electronic properties of the water molecules. This work was performed under the auspices of the United States Department of Energy by the University of California, Lawrence Livermore National Laboratory under contract number W-7405-ENG-48.

**COMP 178 Free energy calculation from non-equilibrium simulations**

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The probability of finding a molecular system in a particular state is determined by its free energy. As a consequence, free energy difference directly determines a wide range of important chemical quantities. However, free energy difference is among the most difficult quantities to calculate by computer simulations. Traditional methods require the system to be in proper equilibrium at all times during simulations to obtain reliable estimates. The Jarzynski’s equality[1], \( \Delta F = f'_j - f'_i = -k_B T \cdot \ln \left( \frac{1}{f'_i} \right) \), relates equilibrium free energy difference to non-equilibrium work done to switch the system from initial state to final state. This equality extends calculation of free energy difference to non-equilibrium simulations, thus provides great flexibility for computational studies to find the most efficient way to calculate free energy difference. The main difficulty of this non-equilibrium method is the systematic error induced by
the exponential average in Jarzynski's equality, when averaging over a finite number of switchings. This error is not fully understood in applications yet. We simulate pullings of a simple octa-alanine peptide molecule by molecular dynamics. The molecule is pulled to stretch from [\(\alpha\)]-helical state to fully extended state under various pulling rates. Free energy profile curves along pulling length are calculated by Jarzynski's equality and compared with the "true" free energy profile from ultra slow pullings. Our results show that reliable free energy profile can be obtained by relatively fast pullings, which also yield better statistical properties. Computational efficiency is achieved over equilibrium methods. Improvement of this nonequilibrium method is also discussed.

Work is supported in part by DOE Contract DE-F602-02ER45995.


**COMP 179 Free energy profiles of DNA unzipping under tension and torque**

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The understanding of DNA strand separation from its duplex structure and the nature of its deformed conformations under external forces reveal intricate details of a broad range of biologically relevant processes such as replication, transcription, and supercoil removal. The development of single-molecule manipulation techniques has spurred a significant number of exciting studies on the mechanical response of DNA to external forces applied to each strand in a perpendicular direction to the helical axis. Moreover, other studies suggest that the combination of a minute stretching force and a torsional force applied to generate a negatively supercoiled duplex effectively lowers energy barriers for base pair separation. By simulating the molecular dynamics of a DNA dodecamer under tension and torque, different models of base pair separation can be studied. To study the energetics of DNA unzipping, a potential of mean force profile has been calculated as the distance between the strands increases by 20 Å in .25 Å steps with various tensions and torques. By comparing these types of unzipping experiments, the dynamics and the energy profiles for each specific manipulation technique can be effectively correlated to the nature of nucleic base pair separation and the native replication and transcription processes.

**COMP 180 Guiding chemical reaction path searches with graph theory**

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A technique for the theoretical prediction of novel chemical reactions and reaction mechanisms based on graph theory will be presented. The method uses graph theory to systematically guide reaction path searches. In principle, graph theory provides the means for the a priori determination of all possible atomic patterns on a potential energy surface as well as convenient matrix representations of molecules, electronic structure, and chemical reactions. As such, graph theory has been used extensively in chemistry. These uses have included reaction path searches for very specific classes of compounds. Our current work focuses on generalizing these graph theoretical techniques to all types of molecules, and also on predicting previously unknown chemical reactions. The mathematics behind this approach and the associated programming challenges are the subject of this poster. The current state and several applications of the method will be detailed.

**COMP 181 Hydrophobic-aided replica exchange: An efficient algorithm for sampling biological systems in explicit solvent**

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A new replica exchange method, Hydrophobic-Aided Replica Exchange (HAREM), for protein folding in explicit solvent is presented. In the present scheme, different replica-walkers have different scaling factors multiplying the protein-water interaction to different strengths of the hydrophobic interaction. When the factor is smaller than 1, the hydrophobic interaction will be exaggerated, mimicking the "Chaperone effect" for protein folding. Thus, the folding event can be accelerated greatly because the hydrophobic effect is one of the main driving forces for protein folding. By applying this method to one representative system, an alpha helix (3K(1)) in SPC water molecules, the advantage of this new scheme is demonstrated. In the meanwhile, the number of replica exchange required will be much smaller than that of the regular replica exchange. This new algorithm makes it possible to fold proteins into their native structures in a reasonable computational time without using implicit water model.

**COMP 182 Improved efficiency of replica exchange simulations through use of a hybrid explicit/implicit solvation model**

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The use of parallel tempering or replica exchange molecular dynamics (REMD) simulations has facilitated the exploration of free energy landscapes for small biomolecular systems, but application to larger systems is hampered by the scaling of number of required replicas with increasing system size. Use of continuum solvent models reduces system size and replica requirements, but these have been shown to provide poor results in many cases, including overstabilization of ion pairs and secondary structure bias. Hybrid explicit/continuum solvent models can overcome some of these problems through an explicit representation of water molecules in the first solvation shells, but these methods typically require restraints on the solvent molecules and show artifacts in water properties due to the solvation interface. We propose an REMD variant in which the simulations are performed with fully explicit solvent, but the calculation of exchange probability is carried out using a hybrid model, with the solvation shells calculated on the fly during the fully solvated simulation. The resulting reduction in the perceived system size in the REMD exchange calculation provides a dramatic decrease in computational cost of REMD, while maintaining very good agreement with results obtained from standard explicit solvent REMD. We applied several standard and hybrid REMD methods to a 10 residue polyalanine, obtaining ensembles that were essentially independent of initial conformation, even with explicit solvation. We demonstrate that the ensembles in explicit solvent from standard and hybrid REMD are in close agreement, with predominantly polyproline II conformations, while REMD employing only the continuum models differ significantly, with an alpha-helix as the major conformation. Similar improvement is demonstrated for a salt bridge in the Trp-cage mini-protein.

**COMP 183 Improvements in predictive ADMET modeling stemming from atomic partial charges obtained by a new empirical method**

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The concept of partial electric charges localized on atoms serves as an approximation of the electron density distribution in molecules. The latter, in turn, is a primal determinant of ADMET properties of molecules. A data set composed of 473 organic molecules was composed with maximum diversity of individual atomic environments in mind. Molecular geometries were optimized at the B3LYP/6-31G** level, followed by extraction of partial atomic charges with the aid of the NPA (natural population analysis) scheme. One part of the data set was used to train a new empirical model for very fast estimation of the atomic charges, the remainder was sequestered as an external validation set. Next, several predictive ADMET property models have been retrained using the new charge related descriptors. Quality of these new models was subsequently compared to their earlier versions that utilized PEOE charges of Gasteiger and Marsili.

**COMP 184 Influence of structural characteristics over the cytotoxic and hepatoprotective activities of cucurbitacin analogs**

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Plant extracts with high cucurbitacin (highly oxygenated triterpenes) content have been used in folk medicine for their liver protective and curative activities. However, these compounds exert a relatively high cytotoxicity as well. Therefore, we are studying the influence of structural properties, determined by ab initio (GAMESS) and other (ALOGPS) calculations, on both bioactivities. These correlations may point to specific structural characteristics influencing both or only one of the bioactivities, and therefore may suggest specific structural alterations that would improve the margin between the two biological effects. Totally, 17 analogs were isolated from two Cucurbitaceae plants and structurally modified. Hepatocytes (HepG2) and liver stellate cells (HCS-T6) were considered for bioassays as the former one plays important role in xenobiotics metabolism and the later one is the major source of fibrosis in response to hepatic injury. The cytotoxic and hepatoprotective activities were monitored on both cell lines. Lipophilicity was found to be the major descriptor for models involving either activity on HepG2; therefore it is less likely to improve compounds hepatoprotection without enhancing toxicity. On the other hand, various descriptors defined the two activities on HSC-T6, therefore majority of the cucurbitacins are very good candidates for further studies of liver fibrosis. The statistically significant multiple linear equations and the proposal of novel derivatives will be discussed in detail.

**COMP 185 Investigation of HIV protease cyclic urea inhibitors using computational approach**

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Acquired Immunodeficiency Syndrome (AIDS) and its causative agent, Human Immunodeficiency Virus (HIV) have been extensively studied. HIV protease was identified as a suitable target for AIDS therapeutics. The inhibition of the enzyme results in the production of noninfectious viral particles. The availability of structure activity data has made HIV protease an attractive target for computer-assisted drug design. In the present study, a comparative analysis of QSAR (Quantitative Structure-Activity Relationship) study performed for cyclic urea based HIV protease inhibitors will be presented. Preliminary results indicate the importance of hydrophobicity and McGowan volume.
**COMP 186** Ligand-based approach for the identification of novel inhibitors: Application to Salvinorin A, a selective kappa opioid receptor (KOP) agonist

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A molecular modeling strategy using Salvinorin A derivatives recently reported in the literature as kappa opioid receptor (KOP) agonist was designed. A 3D pharmacophore model was developed using Catalyst software, which produced 10 pharmacophore hypotheses. The top-ranked hypothesis, characterized by a high correlation coefficient (r² = 0.93), consisted of one hydrogen bond acceptor, three hydrophobic, and one ring aromatic. This hypothesis was in agreement with the site directed mutagenesis studies on KOP and correlated well with the actual and estimated activity both in, training and test sets. Additionally, the hypothesis complements a three-dimensional KOP model developed in our laboratory. This pharmacophore will be used in conjunction with the homology model to screen large chemical databases for the identification of potential KOP agonists. It is anticipated that this hybrid computational screening approach may be more effective for lead discovery as against making use of pharmacophore or comparative model alone.

**COMP 187** Ligand-docking-based homology model of the melanin-concentrating hormone 1 receptor

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Melanin-Concentrating Hormone Receptor 1 (MCH-1R) is a G-Protein Coupled Receptor (GPCR) which is a target for the development of therapeutics for obesity. MCH-1R antagonists reduce food intake, weight and fat gain in rats. The structure-based development of new antagonists to MCH-1R is hampered by the lack of an atomic structure. A modeling method for the MCH-1R structure has been developed based on docking of selected known ligands. Antagonists with different chemotypes were used to validate the models through docking and virtual screening. The resulting structures can accurately reproduce the critical interactions with Asp172 which indicates that the model can be used in screening of virtual chemical libraries to identify new antagonist molecules. This ligand-docking—based method for the modeling of the MCH-1R antagonist binding site followed by virtual screening can also be applied to other GPCRs of interest.

**COMP 188** Limitations in the modeling of physical properties using the Hosoya Index

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Molecular descriptors, such as topological indices (TI’s), have been used extensively in modeling the physical properties of many types of molecules. These quantitative structure-property relationship (QSPR) studies have only occasionally been extended to macromolecules, in part due to the computational difficulty of evaluating the TI for molecules composed of thousands of atoms. The Hosoya index is unique among TI’s in that it is frequently possible to obtain an analytical formula which makes its evaluation easy for molecules composed of even millions of atoms. We have undertaken a systematic study of the Hosoya index for saturated hydrocarbons, especially as it applies to macromolecules. A significant limitation in the use of the Hosoya index involving degeneracy has been identified and is illustrated for molecules exhibiting values of this index equal to Fibonacci numbers.

**COMP 189** Lipid properties on nano-disc particles of Apo A-I

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High-density lipoproteins particles play important roles in reducing cholesterol levels in the blood stream. A series of molecular dynamics simulations were carried out on nano-disc particles formed by two molecules of (Δ1-40) apolipoprotein A-I. The smallest particles correspond to a lipid patch of 160 POPC and/or 178 DMPC molecules. The biggest particles correspond to a patch of 176 POPC and/or 194 lipids molecules. A decrease in the number of lipids of about 8% has a big influence in the particle size, shape and flexibility on the protein, independently of the lipid bilayer systems used. Decreased lipid content also produces changes in the lipid dynamics that resemble partial phase transitions from the fluid lamellar state to a more gel-like phase. In addition, the head group dipole presents a radial ordering, with an annular region (liquid phase structure) around the protein and an inner core (gel-like phase).

**COMP 190** Modeling of human blood:air and tissue:air partition coefficients using structural descriptors

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Human blood and tissue (fat, brain, liver, muscle, and kidney) air partition coefficients of a diverse set of organic compounds were correlated and predicted using structural descriptors by employing CODESSA-PRO. Four and five thousand structures were used in the training set and up to 100 structures were used in the test set. The results were evaluated using the correlation coefficient (r²) and the root mean squared error (RMSE). The results were encouraging with r² values ranging from 0.78 to 0.91 and RMSE values ranging from 0.01 to 0.05.
descriptor regression models developed using CODESSA-PRO and were validated on three different test sets. Overall, these models have reasonable values of the correlation coefficients (R2) 0.881 - 0.959, and cross validated correlation coefficients (R2cv) 0.887 - 0.943. The models can be used reliably to predict biological partition coefficients for a wide range of chemical structures, including those not yet synthesized.

COMP 191 Modeling of peptidic inhibitors of Immunoglobulin-G degrading enzyme of Streptococcus pyogenes
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The tripeptidic cysteine protease inhibitor Z-LVG-CHN2 has been shown to be display antibacterial activity against Streptococcus pyogenes, however no enzymatic target has been identified. Recently, a novel cysteine protease has been discovered, the Immunoglobulin-G degrading enzyme of S. pyogenes (IeDS). This work describes docking studies conducted against this enzyme using peptidic ligands, beginning with mimics of the hinge region of the natural substrate, Immunoglobulin-G. In addition to the putative active site, potential sites for allosteric binding have been studied to investigate possible mechanisms of enzyme activity. The docking studies have been performed in parallel with enzymatic assays for multiple peptide libraries. Initial results indicated inhibition by a particular peptide motif. Our further studies will attempt to elucidate a mode of binding for this motif, and aid in directing synthesis of more potent inhibitors.

COMP 192 Molecular dynamics analysis of the interaction of Lys237 with the H-cluster of Fe-only hydrogenase
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This paper presents a theoretical study about the role of protein dynamics on the structure of the active site (H-cluster) of Fe-only Hydrogenase found in Desulfovibrio desulfuricans (DdH); specifically, it presents molecular dynamics simulation results about the conformational interplay between Lys237 and the distal iron, Fed, of the H-cluster. X-ray crystallographic studies show that Lys237 is ca. 4.4 Å away from Fe\textsubscript{d}. The activity of Lys\textsuperscript{237} was also found to be catalytically more efficient than d(thiomethyl)amine bridge, (DTN::CH2NHCH2S-) found in the H-cluster. A 1 ns simulation was performed for Hydrogenase in water (NPT ensemble). The trajectory was used to study the role of Lys\textsuperscript{237} and DTN bridge dynamics in creating favorable spatial arrangements for transferring protons from Lys\textsuperscript{237} to distal iron. In order to perform molecular dynamics (MD) simulations on the solvated enzyme, OPLS force field parameters were determined for two types of prosthetic groups found in DdH (4Fe-4S cluster, and H-cluster).

COMP 193 Molecular dynamics and stochastic simulations of surface diffusion
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The diffusive motion of adsorbates on metal surfaces is a result of numerous dynamical processes each occurring on different time scales. This fact poses a significant challenge for current theoretical efforts. A general methodology consisting of various computational techniques has been developed to model this phenomenon spanning the disparate length and time scales inherent to these systems. A detailed atomistic description is employed to accurately model the small scale events and serves as the basis for a coarse-grained method. The latter consists of Langevin model driven by a stochastic potential of mean force fluctuating on a slower time scale than the thermal noise. Its parameters are determined using the equilibrium fluctuations in molecular dynamics of the atomistic surface. Once determined, however, the coarse-grained model can be used for rapid determination of correlation functions ---such as the diffusion rate--- of an adatom on the surface. In this manner, a hierarchy of interconnected tools have been developed which allow for both the elucidation and verification of new transport phenomena.

COMP 194 Molecular dynamics simulation of conformational changes in nicotinic acetylcholine receptor triggered by agonist binding
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The nicotinic acetylcholine receptor (nAChRs) is a ligand-gated ion channel responsible for rapid signal transduction across different synapses. The channel is opened transiently in response to the binding of neurotransmitter molecules such as acetylcholine. Recently, comprehensive structural analyses of acetylcholine binding protein (AChBP), a water-soluble homolog of nAChR ligand binding domain, complexed with different ligands have revealed significant structural change in loops C and F. However, how these structural changes, observed in AChBPs, relate to channel gating in nAChRs is still not known. Here, the primary structural changes associated with the binding of different ligands are studied with
targeted molecular dynamics (TMD) simulations. By applying forces on the C-loop so as to steer its conformational change from an 'open' or 'extended' state to a 'closed' state, we are able to observe how the C-loop closure may induce further conformational change of the transmembrane domain of the nicotinic receptor. The result also explains why the three membrane-facing loops are so important in triggering opening of ion channel.

**COMP 195 Molecular dynamics study of hydrogen bonding interactions of dapsone and flurbiprofen within the CYP 2C9 active site**

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Cytochrome P450 (CYP) 2C9 is an enzyme that plays an important role in the metabolism of xenobiotics. The active site of this enzyme has been shown to accommodate more than one substrate. Molecular modeling is being used to determine what may be responsible for the increased rate of metabolism of flurbiprofen when it is inside the active site with dapsone and related sulfones. Hydrogen bonding of active site residues with both substrates has been investigated, and several residues appear to contribute to this rate increase. The effects of these residues were examined using in silico mutation and molecular dynamics. The molecular dynamics suggests that several single amino acid mutations may lead to greater substrate-substrate interactions. Mutations of various active site residues indicate the importance of amino acid hydrogen bonding to dapsone and flurbiprofen within the active site of CYP 2C9. (Supported by WV-INBRE and NIH Grant P20 RR016477)

**COMP 196 Molecular modeling of phase behavior and microstructure of acetone-chloroform-methanol binary mixtures**

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Force fields based on a Lennard-Jones (LJ) 12-6 plus point charge functional form are developed for acetone and chloroform specifically to reproduce the minimum pressure azeotrope found experimentally in this system. Point charges are determined from a CHELPG population analysis performed on an acetone-chloroform dimer. The required electrostatic surface for this dimer is determined from ab initio calculations performed with MP2 theory and the 6-31g++(3df, 3p) basis set. LJ parameters are then optimized such that the liquid-vapor coexistence curve, critical parameters and vapor pressures are well reproduced by simulation. Histogram-reweighting Monte Carlo simulations in the grand canonical ensemble are used to determine the phase diagrams for the binary mixtures acetone-chloroform, acetone-methanol and chloroform-methanol. The force fields developed in this work reproduce the minimum pressure azeotrope in acetone-chloroform mixture found in experiment. The predicted azeotropic composition of x(CHCl₃)=0.77 is in fair agreement with the experimental value of x(CHCl₃)=0.64 The new force fields were also found to provide improved predictions of the pressure-composition behavior of acetone-methanol and chloroform-methanol when compared to other force fields commonly used for vapor-liquid equilibria calculations. NPT simulations were conducted at 300 K and 1 bar for equimolar mixtures of acetone-chloroform, acetone-methanol and chloroform-methanol. Analysis of the microstructure reveals significant hydrogen bonding occurring between acetone and chloroform. Limited interspecies hydrogen bonding was found in the acetone-methanol or chloroform methanol-mixtures.

**COMP 197 Molecular modeling, circular dichroism and FTIR studies of conformation adopted by tetrapeptides with inhibitory activity for thrombin**

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A structure-based design of a library of tetrapeptides containing the sequence space D-Phe/X(P3)-L-Pro(P2)-D-Arg(P1)-P1 was employed to discover potential inhibitors for thrombin (X= analogs of Phe, such as constrained analogs (L)/(D)-Tic [1,2,3,4-tetrahydro-isoquinoline-3-carboxylic acid] and trans/cis-cinnamic-acids). The peptides were docked into active site of thrombin template 1ABJ.pdb using the software "SCULPT" provided by MDL. Circular dichroism investigations showed a sequence-dependent beta turn structures (I and III) in solution at low and neutral pH. FTIR microscopy studies using peptides solid films confirmed at least 3 wavenumber shifts for the double bond stretch frequencies of the two geometric isomers trans and cis-cinnamoyl peptides. SAR (structure-activity relationship) suggests that tetrapeptides which adopt beta turn conformation in solution are more active toward inhibiting thrombin and the trans isomers are better inhibitors than the cis-cinnamoyl peptides.
COMP 198 Molecular modeling studies of novel cyclic urea HIV protease inhibitors
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There is an ongoing need for novel, effective AIDS/HIV therapeutics. HIV protease has become a prime target for drug design. Inhibition of this enzyme results in the production of non-infectious viral particles. This utilizes common computational technique in an attempt to understand the factors affecting antiviral activity of HIV protease inhibitors, specifically cyclic urea derivatives. Comprehensive QSAR (Quantitative Structure Activity Relationships) models were constructed for previously reported structure activity data. Series of novel inhibitors were designed based on these results. The inhibition efficiency of these compounds was studied via modelling studies using MOE (Molecular Operating Environment). The results of this analysis will be presented here.

COMP 199 On the derivation of a damped wave transport equation from Spring-Dashpot viscoelastic model
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In transient transport phenomena the finite speed of transfer is not accounted for by the Fourier, Fick and Newton's laws. An addition of a accumulation term in the kinetic theory of gases [Sharma, 2005, Damped Wave Transport and Relaxation, Elsevier, Amsterdam, Netherlands] can lead to a extended transport equation such as the Cattaneo & Vernotte non-Fourier heat conduction and relaxation equation. In this paper another approach is provided to derive the damped wave transport and relaxation equation. Viscoelastic behaviour is found in materials which respond to an applied stress by both recoverable and permanent deformations which are time dependent. This behaviour is commonly found in noncrystalline organic polymers and creep phenomenon in crystalline materials. The Spring-Dashpot model combines the linear laws of Hooke and Newton. The dashpot represents the viscous behaviour and the spring represents the perfectly elastic behaviour. The Maxwell element is a series combination of a spring and a dashpot. The shear stress can be shown to be:

\[ \tau = - (\eta)\gamma^* - t^* \frac{d\tau}{dt} \]

where \( t^* \) is the relaxation time and is found to be the ratio of viscosity to the Young's modulus of elasticity. The strain from the spring and dashpot are added to give a total strain. Differentiating the equation with respect to the strain rate is obtained. The strain rate for the spring element and dashpot element are replaced with the stress and property terms to yield the above relationship. By analogy between viscous flow and heat conduction the Cattaneo nd Vernotte non-Fourier heat conduction and relaxation equation can be written as;

\[ q = -k \frac{dT}{dx} - t^* \frac{dq}{dt} \]

where \( t^* \) is the relaxation time. In a similar fashion the generalized Fick and generalized Newton's laws can be written.

COMP 200 On the second law violation in Fourier heat conduction
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Consider a thin rod undergoing a exothermic chemical reaction maintained at a constant surface temperature on one end and at another end of the rod of length l. The heat source strength is U'' (w/cu.m/K). O K is the theoretical lowest achievable temperature. The governing equaion at steady state using Fourier's law of heat conduction can be written for

\[ q = T/T_{s} \]
U^*u + uxx = 0

The solution to the equation after substituting for the two boundary conditions at X = 0 and X = 1^* is found to be;

\[ u = \cos(U^*^0.5X) - \cot(U^*^0.5X) \sin(U^*^0.5X) \]

It can be seen that from this expression that for values of X < Xl the value of temperature can be negative. This is a violation of the laws of thermodynamics. So a critical length \( lcrit \) can be defined beyond which the temperature will be unchanged from that at X = Xl. During transient heat conduction using the damped wave conduction and relaxation equation the critical length beyond which null transfer can be expected is found as;

\[ X_{crit} = \text{SQRT} \left( \frac{5.7831}{U^*} + \text{tou}^2 \right) \]

**COMP 201 On the use of cutrices in restriction mapping of three enzymes**  
Ranganathan Sharma, SASTRA Deemed University, Shanmugha Arts, Science, Technology & Research Academy, School of Chemical and Biotechnology, Jiva Chaitanya, Bioinformatics Laboratory, III Floor, Thanjavur, Tamil Nadu 613402, India, Fax: 91 04362 264120, jyoti_kalpika@yahoo.com

A three dimensional matrix representation in restriction mapping is discussed. A simple case of A,B,C maps are taken as a example and a cutrice of 3 rows by 3 columns by 3 floors is constructed. The transpose and multiplicaion operations are defined for the 3 dimensional matrix. The incidence relation can be written as a extension of the binary case;

\[ I(A,B) = I(A,A^B)* \text{Trans.I} (B, A^B) \]

Ternary Case; \[ I(A,B,C) = \text{Trans.I} \{ I(A,A^B^C) \}^* \{ I(B,A^B^C) \}^* \text{Trans.} \{ C,A^B^C \} \}

The relation for the general case of k enzymes is discussed. The proof of the ternary case is an extension of the binary case; \[ \text{Sum} \ \{ X_{1l} Y j \ Z_{k1} \} \]

**COMP 202 Principal mode analysis for calculating vibrational frequencies and modes of models for the peptide bond**  
Ralph A. Wheeler, Kurt Brorsen, and Scott E. Boesch, Department of Chemistry and Biochemistry, University of Oklahoma, 620 Parrington Oval, Rm. 208, Norman, OK 73019, Fax: 405-325-6111, rawheeler@chemdept.chem.ou.edu

Principal component analysis is widely used in multivariate statistics, pattern recognition, signal processing, and informatics fields, but our adaptation to calculate molecular vibrational modes and frequencies, called “principal mode analysis” (PMA), shows that the method also gives optimal spectra in statistical mechanics. Numerical tests verify that PMA of classical molecular dynamics trajectories (using a quantum mechanical potential) gives vibrational frequencies of N-methylacetamide (NMA), a simple model for the peptide bond, that are closer to experiment than those from conventional quantum chemical methods. In addition, PMA gives vibrational frequency shifts of N-methylacetamide in water and shows coupling of NMA modes with those of water molecules hydrogen bonded to it.

**COMP 203 Probabilistic neural networks: Predicting good HIV protease inhibitors**  
Chad R Bernier1, Barun Bhattarat1, Sunil Kumar2, and Rajni Garg1. (1) Department of Chemistry, Clarkson University, 8 Clarkson Avenue, Potsdam, NY 13699-5810, berniecr@clarkson.edu, (2) Department of Electrical and Computer Engineering, Clarkson University

Neural Networks (NN) allow for the modeling of data without prior assumptions. They often return good results, although without revealing much of the mechanism. Nevertheless, their use has many potential uses. The list of potential drug candidate molecules for any given target is substantial. NNs can be used to shorten that list tremendously. Probabilistic neural networks (PNN) were developed to model a dataset of cycloalkylpyranones, intended to be HIV protease inhibitors. PNNs are based on statistical distributions. Atomic and molecular descriptors were used as inputs. The model predicted the underlying distribution of the data, and classified each molecule into one of several pre-defined classes. Classes were chosen based on activity. Classification accuracy, model usefulness, and descriptor importance will be discussed.

**COMP 204 Proteomics and dimensional separation**  
Ranganathan Sharma, SASTRA Deemed University, Shanmugha Arts, Science, Technology & Research Academy, School of Chemical and Biotechnology, Jiva Chaitanya, Bioinformatics Laboratory, III Floor, Thanjavur, Tamil Nadu 613402, India, Fax: 91 04362 264120, jyoti_kalpika@yahoo.com

The next great challenge after completion of genome may be the proteome. Two dimensional gel electrophoresis followed by mass spectrometry can be utilized. Technical hurdles in the project include distinguishing proteins which
differ only in post translational modifications. Proteins are the functional end products of gene expression and sequencing of the human and other genomes will result in the next generation of biological materials. The critical steps involved are the identification of a useful protein and subsequent production and purification. When working with proteins from sample where genomic information is available (eg. Escherichia Coli) proteins are separated by charge and molecular weight in two dimensions. The protein spot is then subjected to MALDI-TOF mass spectrometry and peaks matched against expected peptides. The extraction and purification of proteins currently relies on traditional protein biochemistry techniques. Glycosylation, phosphorylation and amidation steps in the post translational modified protein is reviewed. A third dimension is proposed in addition to charge and molecular weight in the separations scheme. This has to do with exploiting the relaxation times and finite speed diffusion.

**COMP 205 Quantum Monte Carlo simulations in high-dimensional configuration spaces: A comparison of second- and fourth-order propagators**  
**Brent Magnusson** and Robert J. Hinde, Department of Chemistry, University of Tennessee, Knoxville, TN 37996, Fax: 865-974-3454

The finite-duration imaginary-time propagator $\exp(-2\pi\hbar \Delta t/\hbar)$ is at the heart of many quantum Monte Carlo simulation algorithms. Because the propagator cannot be evaluated in closed form for most systems of interest, approximations to the propagator must be employed in these simulation algorithms. We perform diffusion quantum Monte Carlo simulations of a model high-dimensional system using two approximate propagators, accurate to either second or fourth order in the time step $\Delta t$. We assess the accuracy of the two propagators by comparing the stationary states of the quantum Monte Carlo simulations with those obtained by numerically solving the integral equations based on the finite-time-step Green function associated with each propagator, and show how the performance of each propagator varies with the dimensionality of the underlying configuration space.

**COMP 206 Rotational disorder in conjugated oligomers: A nonlinear one-dimensional configuration-coordinate model**  
**Lu Liu**, Dept. of Chemistry, Carnegie Mellon University, Pittsburgh, PA 15213, lulu@andrew.cmu.edu, Mark A. Berg, Department of Chemistry and Biochemistry, University of South Carolina, and David Yaron, Department of Chemistry, Carnegie Mellon University

The torsional motions in many conjugated polymers have low rotational barriers and this leads to a large degree of torsional disorder. Also, the electron-phonon coupling for torsions is nonlinear, since rather than the oscillators being linearly displaced on electronic excitation, the minimum remains at the planar structure and it is the force constant that changes on excitation. A one-dimensional configuration-coordinate model is developed that includes both nonlinear electron-phonon coupling and configurational entropy, the latter of which begins to dominate on long oligomers. This model can account for the unusual effects seen in (p)-phenylethene-(1ene) oligomers/polymer, including a large asymmetry between absorption and emission spectra and an unusual chain length dependence of the absorption spectra. Extension to other conjugated oligomers, such as PPV, allows a more general understanding of spectral evolution with chain length, including the deviation of the absorption maximum from a linear dependence on 1/N for long chains.

**COMP 207 Side-chain mobility and binding selectivity of naphthylquinoline derivatives**  
**Angela Sood**, M. Jeannann Lovell, G. Reid Bishop, and David H. Magers, Department of Chemistry & Biochemistry, Mississippi College, 200 South Capitol Street, Clinton, MS 39058, Fax: 601-925-3933, sood@mc.edu

A library of naphthylquinoline derivatives satisfying hypothesized structural criteria for triplex DNA selectivity have been designed and synthesized by Dr. Lucjan Strekowski of Georgia State University. High-throughput competition dialysis experiments among fourteen of these test compounds demonstrated that the replacement of the secondary amine function found in LS8 with an ether oxygen producing MHQ12 greatly increased selectivity towards triplex DNA over the more common duplex DNA. The binding study has been extended to include two additional compounds, OZ121 with a thio linkage and G106 with an amide linkage. Here we present results from computational studies designed to examine the dynamic flexibility of the naphthylquinoline side-chain for the four compounds. The systems are studied as both neutral systems and as cations with both DFT and SCF theory, and the results are coupled with results from thermodynamic binding studies. We gratefully acknowledge the support of NSF EPSCoR (EPS-0132618).

**COMP 208 Site-of-metabolism prediction: A computational model based on reactivity and P450-substrate complementarity**  
**Min Wu**¹, Michael R. Wester², You-Ai He², Deepak Dalvie², Barry Holwerda², Robert Love², Hans Parge², Caroline Lee¹, and Ben Burke². (1) Pharmacokinetics, Dynamics and Metabolism, La Jolla Laboratories, Pfizer Inc, 10777 Science Center Drive, San Diego, CA 92121, min.wu@pfizer.com, (2) Structural & Computational Biology & Design, La Jolla Laboratories, Pfizer Inc

Identification of the potential site of metabolism could be a significant advance in designing new potential drugs with a
better metabolic profile. Fast in silico approaches towards the prediction of the site of metabolism can be used in the early stages of drug discovery. We have started to construct a computational model to identify likely site(s) of compound metabolism based on intrinsic reactivity and P450-substrate complementarity. The goal of the model was to provide the binding mode of compounds in the active site of various P450 models, that would suggest likely modifications to alter metabolism and help in understanding P450 preferences. The computational model was based on a prediction of a compound's intrinsic chemical reactivity and the P450 heme's accessibility for each proton of interest to identify likely sites accessible to reaction. The combination of the intrinsic reactivity and protein-ligand complementarity profile were evaluated in order to identify the most likely site of metabolism. Chemical reactive moieties were identified by using various levels of Quantum Mechanical (QM) methods. To determine steric accessibility, docking and scoring strategies were employed to predict energetically favorable conformations, orientations of ligands in the protein binding site, and to estimate the tightness of protein-ligand interactions. MetaSite, a pharmacophore-like method, was also used as an alternative to docking to address the protein-ligand complementarity issue. The performance of these methods will be reported for various P450 substrates. Results on the modeling efforts will be discussed and compared to the known site of experimental metabolism data.

**COMP 209 Strategies for building fullerenes and nanotubes on Spartan**

*Justin Mann*, Ken Jones, Thomas Manning, and Ike Barton, Department of Chemistry, Valdosta State University, 1500 Patterson, Valdosta, GA 31698, just2063@hotmail.com

Fullerenes and nanotubes can be challenging to assemble on a program such as Spartan. Most of the structures have various isomers and rings that contain five, six or seven carbon atoms. We have built dozens of these structures on Spartan and developed a systematic approach to their design. This presentation will focus on how a two dimensional "chicken wire" layout can be used to put together larger structures such as different isomers of C84, C96 and C260.

**COMP 210 Structural determinants of binding of small molecules to extracellular matrix: Multi-species, multi-mode 3-D-QSAR analysis**

*Yufen Zhang*, Viera Lukacova, Vladimir Bartus, and Stefan Balaz, Department of Pharmaceutical Sciences and Center for Protease Research, North Dakota State University, Sudro Hall B, Fargo, ND 58105, Fax: 701-231-8333, yufen.zhang@ndsu.edu

For small molecules acting in tissues, including signaling peptides, effectors, inhibitors, and other drug candidates, non-specific binding to ECM is a critical phenomenon affecting their disposition. Using a commercial ECM mimic, Matrigel, binding constants of small molecules to averaged putative ECM binding site have been measured assuming fast linear binding with 1:1 stoichiometry. The 3D-QSAR procedure CoMFA was used to correlate the binding affinities with structures of 23 simple aromatic compounds (19 in the training set and 4 in the test set) based on a FlexS alignment. The statistical indices for 5 components and 431 columns showed a comparatively large gap between calculated values (r²=0.994) and predicted values (q²=0.606). The 3D-QSAR was re-examined taking consideration that multiple modes and multiple species may be involved. The tested compounds were aligned using FlexS and the top six poses were retained for each compound as possible binding modes. All species that contributed more than 0.1% to the population for the pH=7.4 were used. Since the overall observed ligand/receptor binding association constants was the sum of the association constants of individual modes weighted by fractions in the species, the observed binding energy was non-linearly correlated to the probe energy. The best predictive model (n=19, r²=0.966, q²=0.829, SSE=0.053) was obtained for steric or electrostatic fields in 14 grid points. Considering the satisfactory predictivity, along with the drastic decrease in the number of descriptive variables, the multi-species, multi-mode CoMFA model was used to extract structural determinants for ECM binding.

**COMP 211 Structure-based design of reversible peptides inhibitors for Factor VIIa**

*Cristina Clement¹, Lisa Gingold²*, and Manfred Philipp². (1) Department of Chemistry, Lehman College, CUNY, 250 Bedford Park BLVD, West Bronx, New York City, NY 10468, clement_us@yahoo.com, ms_lisag@msn.com, (2) Chemistry Department, Lehman College and Biochemistry Ph.D. Program, City University of New York

A structure-based design of peptides reversible inhibitors for Factor VIIa was conducted using the docking software SCULPT from MDL. The peptides were docked within the active site of the protein target 1qfk.pdb and the lead compounds were discovered using scoring functions based on predicted free energy of interaction between Factor VIIa and each ligand (van der Waals and electrostatic forces included). The original tripeptide D-Phe-Phe-Arg-methylketone cocry stallized with 1qfk.pdb was used as a template for designing a new library of peptides. This research presents the first library of peptides for which a structure-activity relationship was established as a function of peptide sequence space.
### COMP 212 Understanding agonism in the NMDA receptor: Comparing NR2A and NR2D using MD

Matthew T. Geballe¹, Kevin Erreger², Stephen F. Traynelis², and James P. Snyder¹. (1) Department of Chemistry, Emory University, Atlanta, GA 30322, mgeball@emory.edu, (2) Department of Pharmacology, Emory University

The NMDA receptor, a neuronal ionotropic receptor for glutamate, is pervasive in the central nervous system. It has been tied to many neurologic function and afflictions. Recent structural breakthroughs have enabled the use of computational techniques such as Molecular Dynamics to examine the relationship between structure and function in critical regions of this receptor. In this work, models of the ligand binding domain (S1S2 domain) of the NR2A and NR2D subtypes were derived from crystal structure and homology modeling. Several agonists have been docked into the modeled binding site and subjected to extended MD simulation using the GROMACS package. Comparison of the MD trajectories with biological properties are capable of correlating structural characteristics and the functional and pharmacological differences between these receptor subtypes. Ligand disposition at the subtype binding sites will be described.

<table>
<thead>
<tr>
<th>Amino acid sequence</th>
<th>Free energy of interaction kcal/mol</th>
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<tr>
<td>Ala-Ala-Ala-D-Phe-Phe-Arg-CONH₂</td>
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<td>Ala-Ser-Ala-D-Phe-Phe-Arg-CONH₂</td>
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<td>-345</td>
</tr>
<tr>
<td>Gly-Ser-Ala-D-Phe-Phe-Arg-CONH₂</td>
<td>-350</td>
</tr>
</tbody>
</table>

### COMP 213 Using QSAR techniques: Analysis of estradiolic ligand binding to the estrogen receptor

Lauren C. Streeter, Department of Chemistry, Clarkson University, 8 Clarkson Ave, and Rajni Garg, Department of Chemistry, Clarkson University, 8 Clarkson Avenue, Fax: 315-268-6610, rgarg@clarkson.edu

Hormone-responsive breast cancer, which involves the estrogen receptor and requires estrogens for growth, makes up 60% of all new diagnoses. Several computational approaches are used to develop ligands that would effectively bind the estrogen receptor (ER). One such approach is QSAR (Quantitative Structure-Activity Relationships). QSAR endeavor to correlate the structural properties of compounds with their bio-chemical activities. This approach has been applied to drug design, environmental toxicity, and chembioinformatics. QSAR plays an important role in predicting the important physico-chemical parameters for improving the biological activity of the lead compounds. A QSAR study on estradiolic ligands interacting with the estrogen receptor will be presented. We hope that our results will help in further understanding the interactions of these ligands with the ER and provide insight for development of effective anti-breast cancer drugs.

### COMP 214 Vibrational mode mixing analysis of a HIV-1 protease-inhibitor complex

Hitoshi Goto and Toshiyuki Kmakura, Department of Knowledge-based Information and Engineering, Toyohashi
In order to elucidate the predominant structures and biological function of protein-ligand complex, it is important to understand both the kinetical and thermodynamical behaviors in biological environment. Especially, temperature dependency on their biological activity reveals that the thermal fluctuation plays an important role on the dynamic interaction between protein and ligand. In this study, we propose a practical conformational analysis approach to understanding thermal behaviors of HIV-1 protease-inhibitor complex. Mixing of low vibrational modes based on the thermodynamic normal mode analysis for the complex gives an important knowledge for finding many plausible bio-activated conformations. This vibrational dynamics simulation represents some characteristic motions of the residues surrounding the binding site. We measured displacements of Ca atoms on 26-60 residues, generally called "flip-region", from equilibrium structure. Large fluctuations at Gly49 and the neighbors are observed only in the single protease system(PR), but not in both the protease-ligand system (PL) and protease-ligand with crystalline waters (PLW). On the other hand, as a characteristic of the active site common to all model systems, silent motions of Ca at Ser37, and also both Asp25 and Asp25' are observed.

**COMP 215 Web-based entropic scoring functions: Advances in protein structure validation**  
Jonathan Foley IV, Shi Zhong, Gungor Ozer, and Rigoberto Hernandez, School of Chemistry and Biochemistry, Georgia Institute of Technology, 770 State Street, Atlanta, GA 30332-0400, gtg724t@mail.gatech.edu

Two related scoring functions assessing the correlations in dihedral angles of a protein structure in comparison with the experimental protein structures in the protein data bank have recently been developed. The scoring functions use psi and phi dihedral angles to characterize correlation between pair residues and provide insight into correlations between distant residues. A suite of computer programs have been developed which measure the psi and phi angles for all pair residues in a structure and score the structures as a whole and/or by each residue pair in reference to a library of most probable psi and phi values. A fully automated web server is now under development in order to make our scoring software available to the scientific community and interested general public. The server performs server-side calculations on submitted structures and provides the user with an intuitively-accessible assessment of their structure within seconds of submission. The server is presently in early development mode and is expected to be ready for release during the first quarter of 2006.

**COMP 216 Computational study of the desensitization process in GPCRs: A comparison between rod and cone cells**

**WITHDRAWN**

We present our computational studies on the desensitization process of the visual GPCR receptors rhodopsin (rod cells) and green opsin (cone cells). These simulations utilizes our Monte Carlo Simulated Annealing algorithm to locate low energy binding configurations of acidic peptides, which mimics the GPCR proteins, interacting with the corresponding rod and cone arrestin proteins. Because little is know about cone desensitization, we also present a theoretical model of the human cone arrestin protein, required for this process. We find that the phosphate sensitive residues on the cone arrestin conserve the initial desensitization charge-charge interactions, however; other key residues required for rod desensitization are missing in the corresponding cone desensitization. When possible, we compare our computational studies with in vitro binding assays. This work highlights the strength of computational studies in predicting binding structures and amino acids involved in initiating the visual desensitization process.

**COMP 217 Molecular dynamics simulation of the human P2Y_{14} receptor and study of ligand-receptor interactions**  
Andrei A. Ivanov and Kenneth A. Jacobson, Molecular Recognition Section, NIDDK, NIH, Bldg. 8A, Rm. B1A-23, Bethesda, MD 20892-0810, Fax: 301-480-8422, ivanovan@niddk.nih.gov

The P2Y_{14} receptor is one of eight P2Y nucleotide receptors, which are G-protein coupled receptors belonging to the rhodopsin class. The P2Y_{14} receptor is expressed in many human tissues, namely in placenta, brain, heart, lung, stomach and spleen. The P2Y_{14} receptor plays a role in neuroimmune system, with expression in T cells, dendritic cells, and hematopoietic stem cells. The human P2Y_{14} receptor was modeled before using a rhodopsin template. In the present study, the model was inserted into a phospholipid bilayer and subjected to 10 ns molecular dynamics simulation. The molecular docking of known agonists of the P2Y_{14} receptor, namely UDP-glucose and UDP-galactose, was performed. Based on the results obtained, the configuration of the putative binding site was characterized. A general binding site common to the ligands studied was proposed, and the role of specific functional groups of the ligand and receptor was investigated.

**COMP 218 Systematic active site refinement of GPCR models through molecular dynamics simulation**  
S. Roy Kimura, Department of Computer-Assisted Drug Design, Bristol-Myers Squibb Pharmaceutical Research Institute,
Homology modeling of class A GPCRs based on rhodopsin is becoming a widely used tool in drug discovery. However, the rhodopsin template is often inadequate to accurately describe the entire range of GPCRs that can bind ligands of differing sizes. We have previously described a molecular dynamics (MD) based methodology to expand and refine model GPCR active sites to specifically address the problem of not being able to fit large ligands into models of certain GPCR subfamilies. Here we present a systematic analysis of the geometric properties of expanded GPCR active site models and corresponding ligands. A separate presentation will include the application of this analysis to the beta-2 adrenergic and CCR2 receptor models in the context of a more comprehensive GPCR refinement protocol.

**COMP 219 Quantum chemical treatment of the Ene reaction activation parameters**
**Michael Rectenwald,** Department of Chemistry, Mercyhurst College, 501 East 38th Street, Erie, PA 16546, Fax: (814) 824-2188, mrecte00@mercyhurst.edu, and Jeffrey D. Evanseck, Department of Chemistry and Biochemistry, Duquesne University

The experimental activation energies and entropies have been reported for the ene reactions of simple alkenes. High level quantum chemical methods with moderately sized-basis sets have been used to compute the activation parameters for the ene reaction. The reactions include ethene and propene to pentene (1), propene and propene to hexene (2), propene and propene to 4-methyl pentene (3), and ethane and 2-methyl propene to 2-methyl pentene (4). The common employed 6-31G(d) basis set gives poor results using all quantum chemical methods utilized; however density functional theory gives acceptable results for two reactions. Larger basis sets show a divergence across all quantum chemical methods used in this investigation. Continued studies are required to determine appropriate levels of theory in computing the activation parameters of the ene reaction.

**COMP 220 Quantum dynamics of [1,5] hydrogen shift in 1,3-pentadiene: implications for kinetic isotope effects and Swain-Schaad exponents**
**John D. Thoburn and Dana N. Peles,** Department of Chemistry, Randolph Macon College, Ashland, VA 23005, Fax: 804-752-4724, jthoburn@rmc.edu, dpeles@rmc.edu

Variational transition state theory with multidimensional tunneling is used to calculate rates, kinetic isotope effects, and Swain-Schaad exponents for the [1,5] suprafacial hydrogen shift in 3Z-1,3-pentadiene and a variety of isopropyls. Rates were calculated at the B3LYP/6-31G* level using GAUSSRATE/POLYRATE. Tunneling corrections were incorporated into the transmission coefficients using a one-dimensional tunneling model (ZCT) as well as a multi-dimensional tunneling model (SCT) that allowed for “corner-cutting”. The effect of tunneling on the KIE was found to be moderate, in line with experimental results. Interestingly, “inverse” secondary KIEs become positive when tunneling is included. Inclusion of tunneling actually deflates the Swain-Schaad exponent in some cases, in contrast to the commonly held belief that tunneling should always inflate the exponent. An analysis that rationalizes both deflation and inflation is presented. The origin of the misconceptions regarding the relation between tunneling and the Swain Schaad exponents is discussed.

**COMP 221 Quantum mechanical analysis of cadmium sulfide/selenium quantum dots**
**Jacqueline M. Bair** and Jeffry D. Madura, Department of Chemistry and Biochemistry, Center for Computational Sciences, Duquesne University, 308 Mellon Hall, 600 Forbes Ave., Pittsburgh, PA 15282, bairj@duq.edu

Quantum dots are popular due to their potential application as biosensors. Quantum dots made with semiconducting materials have been shown to have different optical and electrical properties compared to bulk phase semiconductor. Our research focuses on small capped and uncapped CdS and CdSe quantum dots with a Cd4 base. We are studying these quantum dots in order to find a suitable basis set and level of theory. Hartree-Fock, MP2, and Density Functional Theory quantum mechanical calculations are being tested with different basis sets to determine which model chemistry is best to study the size dependency and effects of the capping agents on the quantum dot characteristics. Preliminary results indicate that pseudopotentials are inadequate for the wurtzite structure of Cd4 quantum dots and that a TZVP basis set is needed.

**COMP 222 Prediction of excited states for carbon, nitrogen and oxygen systems using quantum Monte Carlo**
**Floyd Fayton Jr.,** Ainsley Anthony Gibson, and John AW. Harkless, Department of Chemistry, Howard University, 525 College St., NW, Washington, DC 20059, Fax: 202-806-5442

Quantum Monte Carlo (QMC) refers to a class of ab initio methods that use a stochastic simulation to solve the many-body Schrödinger equation. Electronic excited states of C, N, and O, and of the respective binary compounds were investigated. These structures include, CN, NO, CO, N2, O2, C2, and selected excited states of the constituent elements.
In order to show the accuracy of the techniques (DMC, VMC, B3LYP/6-31G*, MP2/6-31G*, and CISD/6-31G*) values were compared against experiment.

**COMP 223 Semiempirical and QM calculations of absorbance wavelengths of environmentally sensitive near-IR dyes for biosensor applications**

**Douglas B. Sherman**, K. Joseph Thomas, Arounaguiry Ambroise, and J. Bruce Pitner, BD Technologies, 21 Davis Dr, Research Triangle Park, NC 27709, Fax: 919-597-6400, Douglas_Sherman@bd.com

Environmentally-sensitive dyes offer considerable advantages as reporter molecules in biosensor design, particularly when conjugated to binding proteins that undergo a conformational change during ligand binding. Near-Infra Red (Near-IR) dyes are particularly attractive for implantable biosensors, since these dyes fluoresce beyond 600 nm, a region relatively free of interference from tissue and other biological components. Few reactive, environmentally-sensitive near-IR dyes are commercially available; however, multi-step syntheses are required to prepare new dyes. To aid in the design of near-IR dyes, absorbance wavelengths were calculated for five novel dyes prepared in our laboratory based on squaraine, phenoxazine, and coumarin. Geometries were optimized using AM1, HF/3-21G, and HF/6-31G(d) methods, and absorbance calculations were performed using Zindo/S and CIS calculations in Gaussian. The calculated wavelengths will be compared with the absorption spectra of these dyes obtained in solvents of varying polarities and the role of solvation modeling will also be discussed.

**COMP 224 Theoretical study of the isomerization mechanism of azobenzene and symmetrically disubstituted azobenzene Derivatives**

**Christina R. Crecca** and Adrian Roitberg, Department of Chemistry, University of Florida, NPB 2331, PO Box 118435, Gainesville, FL 32611-8435, Fax: 352-392-8722, c_crecca@qtp.ufl.edu

A series of azobenzenes was studied using ab initio methods to determine the substituent effects on the isomerization pathways. Energy barriers were determined from three-dimensional potential energy surfaces of the ground and excited states. In the ground state (S₀), the inversion pathway was found to be preferred. Our results show that electron donating substituents increase the isomerization barrier along the inversion pathway, while electron withdrawing substituents decrease it. A conical intersection was found between the ground and first excited state (S₁) along the rotation pathway indicating a preference for the rotation mechanism after S₁ → S₀ excitation. Upon S₂ → S₀ excitation, there may be sufficient energy to open an additional pathway (concerted-inversion). We find this pathway is only accessible for unsymmetrized azobenzene and 4,4-dinitroazobenzene. The concerted-inversion channel explains the experimentally observed difference in trans-to-cis quantum yields between S₁ and S₂ excitations. The concerted inversion channel is not available to the remaining azobenzenes studied.

**COMP 225 Ab initio study of meta-substituted diphenyl ureas**

**Shoaleh Dehghan**, Victoria M Wurster, Christina A. Capacci, Rupa Hiremath, and Jennifer A. Swift, Department of Chemistry, Georgetown University, 37th and O Streets NW, Washington, DC 20057, Fax: 202-687-6209, sd268@georgetown.edu

*Ab initio* studies can be useful in understanding the relative energies and geometries of conformationally flexible organic compounds. *Ab initio* calculations at the HF/6-31G* level of theory for geometry optimization and MP2/6-31G* and MP2/6-311G** levels for single point total energy calculations are reported for a series of symmetrical and unsymmetrical *meta*-substituted diphenyl ureas (MXPU) with X=CH₂, Cl, Br, I, CN. Potential energy scans for the rotation of either one or both phenyl rings of MXPU shows three regions of low conformational energy related to *anti-anti*, *anti-syn* and *syn-syn* conformers. The relative energies follow the order *anti-anti* < *anti-syn* < *syn-syn* in all of the compounds. Single crystal structures for many of these *meta*-substituted compounds have been determined. Comparisons will be made between the calculated torsion angles and those observed in the crystalline solid state.

**COMP 226 Ab initio studies of diboracarbonyl molecules**

**James L. Meeks**, Department of Physics, University of Kentucky-Paducah (Retired), 320 Wexford Court, Paducah, KY
42003, padmeeks@prodigy.net

These diboracarbonyl molecules are being proposed to act as buffer for neutrons for nanotube chemotherapy. When nanotube capsules are used as smart bombs for the treatment of cancer tumors, these diboracarbonyl molecules would be used to absorb the excess neutrons from the nanotube enclosed radioactive isotopes, such as Cobalt-60. The neutrons are the ones, which escape from the treatment of the cancerous tumor. Since boron is being substituted for nitrogen in the urea, biuret and diurea molecules, the diboracarbonyl molecules would be biologically active. The optimized molecular energies and geometries of urea, biuret, diurea, and the novel diboracarbonyl molecules, H$_4$B$_2$CO, H$_8$B$_4$C$_2$O$_2$, and H$_8$B$_4$C$_2$O$_2$, were computed. These computations used ab initio Hartee-Fock (HF/6-31G**) and Density Function Theory, DFT, (with the B3LYP hybrid functional) of Gaussian 2003. The changes of the molecular energies, bond distances and angles of the diboracarbonyl molecules are compared. Analyses, by ab initio calculations, of similar urea carbonyl systems are reported. Geometry optimizations and minimum energies for the different diboracarbonyl molecular systems using the different basis sets of Gaussian 2003 will be discussed. The optimized (B3LYP/6-31G, 6-31G**, and 6-311++G**) geometrical structures of the diboracarbonyl molecules are presented.

**COMP 227 A computational study of 1,2-HBr elimination and 1,2-CIBr interchange in hydrobromocarbons and bromochlorocarbons**

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The transition geometry for 1,2-HBr elimination has been characterized using all-electron calculations and an ECP treatment for a range of small organobromine compounds. Effects of the level of theory and effect of the pseudopotential are compared to the experimentally-determined rate constant for HBr elimination from CH$_3$CH$_2$Br and CH$_2$BrCH$_2$Br. Calculations on CH$_2$BrCH$_2$Cl provide a comparison of 2,1-HBr and 1,2-HCl eliminations, and consideration of the vibrational frequencies allow for comparison with the experimentally-determined kinetic isotope effect between CH$_2$CICH$_2$Br and CD$_2$CICH$_2$Br. In these molecules a comparison of using ECPs on both Cl and Br is presented, as well as the possibility of a 1,2-CIBr interchange analogous to the 1,2-FCI interchange we have observed in hydrofluorocarbons.

**COMP 228 Stability of H$_2$ clathrates vs. cavity occupancy**

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Hydrogen clathrates form a type II structure, with hydrogen molecules inside both cages. We are using ab initio and molecular dynamics methods to study stability vs. the number of H$_2$ molecules in the various cavities and also to study the diffusion of H$_2$ molecules between cavities. Finally, we will present the results of exploratory calculations examining whether fractional occupation of the cavities by other molecules can promote H$_2$ uptake.

**COMP 229 A computational study of the barrier height of the 1,2-FCI exchange reaction of substituted ethanes**

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A 1,2-FCI interchange mechanism has been shown by our research group to be an important step in many reactions of chlorofluorocarbons (CFCs) and hydrochlorofluorocarbons (HCFCs). In this paper we examine the 1,2-FCI interchange reaction for all possible two-carbon CFCs and HCFCs and determine the effects of fluorine and chlorine substitution on the barrier height and transition geometry. For the molecules CH$_2$FCH$_2$Cl, CHF$_2$CH$_2$Cl and CH$_2$FCHCl$_2$, we examine the reaction at a number of levels of theory and basis sets in order to determine a consistent and effective level of theory. For all other exchanges, comparisons are made at the B3PW91/6-311+G(2d,p) level of theory. The relative energies of the transition geometries of isomeric species correlate well with the relative energies of isomeric substituted alkenes that would result from the elimination of FCI, and this can be used to rationalize the trends in barrier heights.
COMP 230 The effect of chromophore conformation in green fluorescent protein on its absorption spectrum: A QM/MM and TDDFT study
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Recently, Green Fluorescent Protein (GFP) mutants have been developed with improved photostability and red-shifted absorptions. In this work, we performed time-dependent density functional theory (TDDFT) calculations of the absorption spectra, based on B3LYP/UFF geometries, and compared them to molecular dynamics simulations of wild type and mutant GFP with neutral and anionic chromophores. In addition, we calculated the absorption maxima as a function of geometry variations because our molecular dynamics simulations show that the angle formed by the two bonds bridging the chromophore's rings falls within a range of about 20°. The excitation energies as a function of the bridging angle illustrate shifts in the absorption.

COMP 231 Accuracy of FMO-MO for Large Scale Molecule
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The molecular orbital based on the fragment molecular orbital method (FMO-MO) was proposed to calculate the highest occupied and lowest unoccupied molecular orbitals (HOMO and LUMO) in short time. In this study, we checked the accuracy of the FMO-MO for large-scale molecule by comparing with HOMOs and LUMOs obtained in the FMO-MO and conventional MO methods for the Lysozyme molecule. Our calculation showed that the FMO-MO reproduced well the locations and shapes of orbitals around HOMO and LUMO in the conventional MO method even for large-scale molecules. Thus, the FMO-MO method is the promising technique for the theoretically determination of the active site of enzymes with high throughput.

COMP 232 Theoretical studies of dissociation of perfluorohydroxylamine
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A computational study is report of the potential energy surface containing trifluoroamine oxide (NF3O) and its less well-known isomer perfluorohydroxylamine (F2NOF). Stationary points were located with several types of DFT methods (B3LYP, BB1K, MPWB1K) using a 6-311+G(d) basis set and were found to be in good agreement with stationary points located at the CCSD/6-31+G(d) level. At the CCSD(T)/cc-pVQZ//B3LYP/6-311+G(d) level the enthalpy (298K) of cis-F2NOF was 4.31 kcal/mol lower than trans-F2NOF. Interestingly, the lowest-energy concerted activation barrier separating F2NOF and NF3O was 13.27 kcal/mol higher than the enthalpy of F2NO + F radicals. The most favorable process is the concerted loss of F2 which has an activation enthalpy of 13.8 kcal/mol (cis-F2NOF -> F2NO+). Rate constants were calculated for the dissociation of F2NOF by using transition state theory and variational transition state theory. The intrinsic reaction coordinate (IRC) or minimum energy path is constructed starting from the saddle point and going downhill to both asymptotic reactant and product channels. The transition states for the concerted reaction, cis-F2NOF -> FNO+F2, was characterized by significant spin-symmetry breaking. For this reaction, single-point calculations were carried out at the MCDQPT2(16e,11o)/6-311+G(d)//B3LYP/6-311+G(d) level (a sixteen-electron in eleven- orbital active space) for points along the IRC in both reaction paths in order to determine the rate constant. For the fragmentation reaction, trans-F2NOF -> F2NO+F is a barrierless reaction, the reactive flux was evaluated by the phase-space-integral based VTST (PSI-VTST) method, as implemented in Variflex.

COMP 233 Accurate proton affinity and gas-phase basicity values of molecules important in biocatalysis
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Benchmark calculations of proton affinities and gas-phase basicities of molecules most relevant to biocatalysis are presented and compared with available experimental results. The accuracy of proton affinity and gas-phase basicity results obtained from several multi-level model chemistries (CBS-QB3, G3B3, G3MP2B3, MCG3/3, and MC-QCISD/3) and density-functional quantum models (PBE0, B1B95, B3LYP, MPW1K CIS, PBE1K CIS, and MPW1B95) are assessed and compared. From these data, a set of empirical bond enthalpy, entropy, and free energy corrections are introduced that considerably improve the accuracy and predictive capability of the methods. These corrections are applied to the prediction of proton affinity and gas-phase basicity values of important biological molecules for which experimental data does not currently exist. In addition, W1 calculations were performed on a subset of molecules. Comparison is made with results from semiempirical quantum models that are commonly employed in hybrid quantum mechanical/molecular mechanical simulations. Data suggest that the design of improved semiempirical quantum models with increased accuracy for relative proton affinity values is necessary to obtain quantitative accuracy for simulating biocatalysis
COMP 234 Theoretical studies on adduct formations of Pt (IV) and Pd (IV) complexes with an engineered oligonucleotide
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Metal-based anticancer drugs containing Pt (II) (e.g., cisplatin) are among the most effective drugs used in chemotherapy. These agents interfere with DNA's functions and inhibit its ability to divide, thus destroying cancer cells. However, studies have shown that these types of drugs show limitations because of their lack of specificity in destroying cells. Thus, it is of interest to investigate other candidates as possible anticancer drugs. In this investigation, the binding effects of cisplatin analogues complexes, Pt (IV) and Pd (IV) metal complexes with engineered oligonucleotide were analyzed using theoretical approaches. The adduct formations were studied using hybrid computational procedure called ONIOM. Within the ONIOM approach, the oligonucleotide was modeled using molecular mechanics and the metal complexes were modeled quantum mechanics and density functional theory. Entropy, enthalpy and free energy for the binding process of these adduct formations were calculated using statistical thermodynamics.

COMP 235 Activation of the C-X bond by palladium: Ab initio benchmarks and evaluation of DFT
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The catalytic activation of the C–X bond is of major importance for synthetic chemistry. In the present study, an overview is given of the oxidative addition reactions of palladium with CH2X, with X = H, CH3, and the halogens F and Cl. We have obtained reliable ab initio benchmarks for the energetics of the reactions. With these we have evaluated the performance of density functional theory (DFT) for a large collection of popular density functionals, covering LDA, GGA, meta-GGA and hybrid density functionals. Stationary points on the reaction surface have been optimized using various GGA functionals, giving geometries that differ only marginally. Interestingly, all important features of the CCSD(T) benchmark potential energy surfaces are reproduced by important functionals such as BLYP, OLYP and B3LYP while at the same time none of these functionals is the "very best one" in each individual case.

COMP 236 Theoretical studies on iron-substituted barium titanate perovskite clusters
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The stability of iron-substituted barium titanate perovskite nanoclusters was studied by theoretical methods. Perovskites are a family of crystalline ceramics, with face-centered cubic lattices, containing large cations at the corners of the unit cells (e.g., barium), anions at the facial centers (e.g., oxygen) and a small cation at the cell's centers (e.g., titanium or iron). Density functional theory was used to model the clusters, within the Gaussian 2003 quantum mechanical program, using various exchange functionals. Clusters with different number of unit cells were considered. These perovskite
materials have properties that might lead to new high-performance capacitors, superconductors and semiconductors, dielectrics, piezoelectrics or magnetoresistant materials, for nanoscale applications.

COMP 237 Alternate mechanisms for the formation of volatile selenium species
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Alternate mechanisms which do not include free radicals have been found for the formation of volatile selenium species by photodissociation in the presence of low molecular weight organic acids. The B3LYP functional has been used along with the LANL2DZ(d,p) basis set and the Onsager model in order to take solvent effects into account. Selenite is reduced by CO (from UV irrigation of formic acid) to produce the volatile species SeH2 (ΔE = -518.81 kcal/mole) and SeCO (ΔE = -590.32 kcal/mole). In acetic acid solution, selenite is reduced by CH2CO to produce the volatile species Se(CH3)2 (ΔE = -566.88 kcal/mole). The experimentally observed inhibition of SeH2 and Se(CH3)2 production in the presence of NO3- or H2O2 has been accounted for by the reaction of OH radicals (from NO3- or H2O2 irradiation) with CO to form SeCO (ΔE = -374.98 kcal/mole) and CH2CO to form SeCH2CO (ΔE = -429.05 kcal/mole).

COMP 238 Theoretical study of the magnetic properties of quinoidal oligothiophenes
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Traditionally inorganic materials have been used in the fabrication of semiconductors. Inorganic materials are not easily modified and somewhat expensive to fabricate. Organic compounds, on the other hand, can easily be tailored to display the desired properties, and are cost effective. It has been recently reported that the quinoidal form of oligothiophenes presents magnetic properties, which does not agree with the expected electronic structure of the molecule. The display of magnetic properties reflects the presence of unpaired electrons and potential for semiconductor use. Unpaired electrons are charge carriers, useful in electronic devices. The purpose of this research is to determine the influence of the number of thiophene units in a quinoid oligothiophene on the stabilization of its magnetic aromatic form. The study was performed considering two different oligothiophene structures: aromatic oligothiophenes and quinoidal oligothiophenes. The procedure consisted in obtaining the optimized geometry of the quinoidal form, both closed shell singlet and open shell triplet, and the aromatic form of the oligothiophene. The same systems, with added cyano end groups were also studied. Maestro 3.0 and Jaguar 4.0 were the computational chemistry software packages used to study the systems. All structures were entered into Maestro 3.0, via its graphical interface. Afterwards, a geometry optimization calculation at the DFT-B3LYP level was performed for each structure and spin state, using the basis set of 6-31G*.
This study will discuss the energy differences trend, as well as the bond lengths patterns, as we add thiope units to each of the systems, with and without added cyano end groups.

COMP 239 Anomeric control of high energy bonds
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High energy bonds such as the O-P bond in triphosphates and the N-P bond in phosphagens have central roles in biological phosphoryl transfer reactions. Breaking and forming of these bonds serve in multiple roles from energy provision to phosphorylation. Determinants of strengths and weaknesses of the high energy bonds thus disproportionately impact many biochemical processes. Electronic structure calculations at levels of theory ranging up to B3LYP/6-311++G(d,p) have been performed on model phosphagens and triphosphate tails to understand the stereoelectronic factors contributing to the lability of the high energy bonds. Natural bond orbital analysis shows that the length of both the O-P and N-P bonds correlate strongly with bond weakening anomeric interactions; the nO→σ*(O-P) anomeric interaction in triphosphates and the nO→σ*(N-P) anomeric interaction in phosphagens. The computed nO→σ*(X=Y) anomeric effect provides a novel explanation of high energy bond lability.

COMP 240 Application of FMO-MO for Large-Scale Molecule: Effect of solvent molecules
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The fragment molecular orbital (FMO) method is an excellent approximation of full ab initio calculation with reasonable computational cost. In the FMO method, large molecule is divided into many small fragments and the molecular orbital calculations of each calculations and fragment-pairs give the total energy and electronic density of whole large molecule with chemical accuracy. However the molecular orbitals (MOs) of whole molecule can not be calculated by the FMO method, and the FMO-MO method makes possible to calculate the MOs of whole molecule using the results calculated by the FMO method. The MOs of biomolecule are largely affected by the solvation media. The FMO-MO method is applied
to lysozyme, which is relatively small biomolecule, in gas phase and in water molecules, and the solvent effect for the MOs is discussed.

![HOMO LUMO](image)

**COMP 241 Benchmark quantum mechanical computations on the acid-catalyzed Diels-Alder reaction between butadiene and methyl acrylate**

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Experimental activation energies, enthalpies and entropies are well known for the AlCl3 catalyzed and uncatalyzed Diels-Alder reaction between butadiene and methyl acrylate in benzene. Activation barriers and geometries have been computed for the AlCl3 catalyzed and uncatalyzed Diels-Alder reaction between butadiene and methyl acrylate in benzene at different levels of theory. The MP2 and B3LYP quantum chemical methods have been employed with a variety of basis sets ranging from small inflexible basis sets to large basis sets with additional polarization and diffuseness. Pople basis sets and Dunning basis sets were used for the comparison of activation barriers. Computed and experimental results have been compared to determine the best level of theory to describe accurately the AlCl3 catalyzed Diels-Alder reaction between butadiene and methyl acrylate as well as the uncatalyzed parent system. The focus of this work is to identify appropriate levels of theory in describing acid catalyzed Lewis acid Diels-Alder reactions. The different levels of theory and their performance will be discussed.

**COMP 242 Calculation of nuclear spin-spin coupling constants of molecules with first and second row atoms in study of basis-set dependence**

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A systematic way is presented to modify standard basis sets for use in NMR spin-spin coupling calculations, which allows the high sensitivity of this property to basis set to be handled in a manner which remains computationally feasible. The new basis set series is derived by uncontracting a standard basis set, such as correlation-consistent aug-cc-pVTZ, and extending it by systematically adding tight s and d functions. For elements in different rows of the periodic table, different progression of functions are added. The new basis sets are shown to provide accurate coupling calculation results on a range of molecules containing hydrogen, first and second row atoms.

**COMP 243 Computational studies of gas and condensed phase properties of donor-acceptor complexes of sulfur trioxide**

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Donor-acceptor complexes of sulfur trioxide, such as those formed with water and ammonia, are important species in atmospheric chemistry. These donor-acceptor complexes also exhibit large structural and property differences in the gas and condensed phases. Gas and condensed phase density functional calculations of donor-acceptor complexes formed between sulfur trioxide and nitrogen-containing donor molecules, H3N, (CH3)2N, (CH3)2HN, and (CH3)3N, have been carried out. The condensed phase was modeled using the Polarizable Continuum Model. Systematic studies of the unusual differences between the gas and condensed phase geometries and other properties of these complexes are
reported. Similar investigations of donor-acceptor complexes formed between oxygen-containing donor molecules and sulfur trioxide also have been completed. Gas and condensed phase results for two intriguing complexes never before studied, CH$_3$OH-SO$_3$ and (CH$_3$)$_2$O-SO$_3$, will be given. Results from the application of Natural Resonance Theory analysis to the study of the bonding in the donor-acceptor complexes also will be presented.

**COMP 244 Computational study of Cadmium Sulfide with amino acids as organic capping agents**

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Cadmium sulfide nanoclusters are of great interest due to their size-dependant properties. One means of preparing CdS nanoclusters with fixed structure for study requires stabilizing the nanoclusters by saturating dangling bonds using organic ligands. Amino acids have been found to bind to metals in bio-systems, which suggest applications as organic ligands. In approaching the problem computationally, we first study smaller clusters in order to make the research computationally feasible. In this work we begin with a (CdSH)$_4$ cluster capped with –SH "ligands" which are then successively replaced by amino acids. We employ Hartree-Fock, density functional and 2nd order Moller-Plesset perturbation theory using Gaussian 03. We calculate the total energies of the clusters to gauge their stability, the HOMO and LUMO energies and the difference between them, as these are related to the properties we are interested in. We identify trends in the electron density distribution in the HOMO and LUMO.

**COMP 245 Conventional ring strain in unsaturated four-membered rings**

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In order to study the effect of unsaturation on the ring strain in small cyclic molecules, the conventional strain energies for cyclobutene, azetidin-1-ene, phosphetane-1-ene, azetidine-2-ene, and phosphetane-2-ene are determined within the isodesmic, homodesmic, and hyperhomodesmic models. Optimum equilibrium geometries, harmonic vibrational frequencies, and corresponding electronic energies are computed for all pertinent molecular systems using SCF theory, second-order perturbation theory, and density functional theory (DFT). The DFT functional employed is Becke's three parameter hybrid functional using the LYP correlation functional. Two basis sets, both of triple-zeta quality on valence electrons, are employed: 6-311G(d,p) and 6-311+G(2df,2pd). Results are compared to the conventional strain energies of cyclobutane, azetidine, and phosphetane to determine what effect double bonds have on the conventional strain energies of these saturated homocycles. We gratefully acknowledge support from NSF EPSCoR (EPS-0132618).

**COMP 246 Conventional strain energy and sigma delocalization in small heterocycles of carbon and germanium**

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The conventional strain energies for three- and four-membered heterocycles of carbon and germanium are determined within the isodesmic, homodesmic, and hyperhomodesmic models. These include germacyclop propane, digermacyclobutane, germacyclobutane, 1,2-digermacyclobutane, 1,3-digermacyclobutane, and trigermacyclobutane. Optimum equilibrium geometries, harmonic vibrational frequencies, and corresponding electronic energies are computed for all pertinent molecular systems using SCF theory, second-order perturbation theory (MP2), and density functional theory with the B3LYP functional. Basis sets of triple zeta quality on valence electrons are employed. Computed strain energies are compared to those obtained for heterocycles of carbon and silicon to determine if germanium has the same effect on the conventional strain energy of cyclopropane and cyclobutane as silicon which reduces the conventional strain energy of cyclobutane, but increases the conventional strain energy in cyclopropane. We gratefully acknowledge support from NSF EPSCoR (EPS-0132618).

**COMP 247 Conventional strain energy and sigma delocalization in small heterocycles of carbon and silicon**

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The conventional strain energies for three- and four-membered heterocycles of carbon and silicon are determined within the isodesmic, homodesmic, and hyperhomodesmic models. These include silacyclop propane, disilacyclop propane, silacyclobutane, 1,2-disilacyclobutane, 1,3-disilacyclobutane, and trisilacyclobutane. Optimum equilibrium geometries, harmonic vibrational frequencies, and corresponding electronic energies are computed for all pertinent molecular systems using SCF theory, second-order perturbation theory (MP2), and density functional theory with the B3LYP functional. Basis sets of triple zeta quality on valence electrons are employed. Additionally, single-point coupled-clustered calculations at the optimized MP2 geometries were used to investigate the effects of higher-order electron correlation. All results indicate that silicon substitution reduces the conventional strain energy of cyclobutane, but increases that of cyclopropane by destroying the stabilizing factor of sigma delocalization. Electron-density plots show that only in cyclopropane is the electron density thoroughly delocalized in the sigma bonds of the ring. We gratefully acknowledge support from NSF EPSCoR (EPS-0132618).
**COMP 248 Conventional strain energy in boracyplopropane, diboracyplopropane, boracyplobutane, and diboracyplobutane**

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The conventional strain energies for boracyplopropane, diboracyplopropane, boracyplobutane, and 1,2-diboracyplobutane are determined within the isodesmic, homodesmic, and hyperhomodesmic models. Optimum equilibrium geometries, harmonic vibrational frequencies, and corresponding electronic energies are computed for all pertinent molecular systems using SCF theory, second-order perturbation theory (MP2), and density functional theory. The DFT functional employed is Becke's three-parameter hybrid functional using the LYP correlation functional. Two basis sets, both of triple zeta quality on valence electrons, are employed: 6-311G (d,p) and 6-311+G(2df,2pd). Results are compared to the conventional strain energies of cycloplopane and cyclobutane to determine what effect boron substitution has on the conventional strain energies of these prototypical homocycles. We gratefully acknowledge support from NSF EPSCoR (EPS-0132618).

**COMP 249 Core-valence correlation consistent basis sets revisited for the second-row atoms (Al-Ar)**

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Prior studies have suggested deficiencies in the correlation consistent basis sets for the second-row atoms (Al-Ar) which can lead to surprisingly large errors in the description of molecular properties (i.e., dissociation energies, enthalpies of formation). This problem can be remedied by the inclusion of a tight-d function in the correlation consistent sets, and is particularly important in the sets for sulfur. Dunning, Peterson, and Wilson have introduced the cc-pV(n+d)Z basis set series, resulting from modification of the d functions. For all-electron calculations, Peterson and Dunning developed the core-valence (cc-pCVnZ) and weighted core-valence (cc-pwCVnZ) correlation consistent basis sets. These sets are based upon the original cc-pVnZ sets, rather than upon the now recommended cc-pV(n+d)Z sets. Therefore, we introduce a revised family of core-valence basis sets, cc-pCV(n+d)Z, to provide sets that provide a systematic improvement upon the recommended valence basis set. Benchmark calculations are provided using these new basis sets in combination with the coupled cluster method including single, double and perturbative triple excitations [CCSD(T)].

**COMP 250 Counter-ion effects of bis(oxazoline) copper(II) catalyzed Diels-Alder reactions**

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Large-scale density functional calculations of C2-substituent and counter-ion effects of bis(oxazoline) copper(II) complexes on the rate and selectivity of Diels-Alder reactions have been performed. Using Becke's three-parameter density functional theory with the nonlocal correlation of Lee, Yang, and Parr and the 6-31G(d) basis set, the steric and electronic effects of tert-butyl, isopropyl, and phenyl substitution are reported with regard to the Diels-Alder reaction of cyclopentadiene and acrylate imide. The computed transition structures provide an understanding of how C2- substituent variation modulates the copper(II) catalyst. Additionally, counter-ion effects of two models, hexafluoroantimonate and triflate, are discussed with respect to metal center coordination geometry, stereoelectronic effects, computed activation energies, and selectivity enhancements.

**COMP 251 Coupled cluster calculations of the H\(^+\)/H\(_2\) potential energy and dipole moment function**

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Wang and Andrews [J. Phys. Chem. A 108, 1103 (2004)] recently observed a feature in the infrared absorption spectra of metal doped solid hydrogen matrices, substantially red-shifted from the H\(_2\) gas phase vibrational frequency, that they attributed to H\(^+\) molecules near H\(^+\) atomic anions. To provide further insight into this observation, and lay the groundwork for first-principles calculations of the lineshape of this feature, we have performed high-level quantum chemical calculations of the H\(^+\)/H\(_2\) potential energy and dipole moment functions. We investigate how the accuracy of our calculations depends on both the size of the one-electron basis set and the level at which electron correlation is treated, and compare the properties of the H\(^+\)/H\(_2\) van der Waals complex to those of its H/H\(_2\) neutral counterpart.

**COMP 252 Density functional theory study on the mechanism of the ribosome**

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Ribozymes are catalytic RNA molecules that have been found to catalyze a broad range of reactions in biological
systems, such as phosphodiester cleavage and amide bond formation. One particular ribozyme that has attracted considerable interest is the ribosome, which catalyzes protein synthesis, i.e., amide bond formation, within cells. Based on initial crystal structures of the ribosome, it was proposed that the active site contains an adenine nucleobase that acts as a general base catalyst. However, there is now increasing evidence that a sugar residue, the one to which the growing peptide is attached, is the catalytically active moiety, again acting as a general base catalyst for amide bond formation. The adenine is thought to possibly play a role by forming a hydrogen bond with the substrate amino acids, though the exact effect of such an interaction is unclear. We have employed density functional theory methods to investigate the effect and role of various proposed active site residues. Some recent results of these studies will be presented.

**P-site**

**A-site**

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**COMP 253 Development of protonic and deuteronic basis functions using Gaussian-type functions**

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We analyzed the exponent ($\alpha$) values in Gaussian-type functions (GTFs) of proton and deuteron for the development of nuclear basis functions which are used for the molecular orbital (MO) calculation including nuclear quantum effects directly. The optimized $\alpha$ value in single s-type [(1s)] GTF for proton is changed due to the difference of flexibility of electronic basis sets. We clearly demonstrated that the protonic and deuteronic basis functions enable us to extend the sample molecules. Our developed protonic and deuteronic basis functions are effective to treat quantum effects of proton and deuteron and to extend the application range of the MO calculation including nuclear quantum effects.

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**COMP 254 Direct Born-Oppenheimer dynamics of the Bauld-plateau rearrangements**

**Chris Harrison**, Charles Doubleday, and Olaf Wiest. (1) Department of Chemistry and Biochemistry, University of Notre Dame, Notre Dame, IN 46556-5670, charris5@nd.edu, (2) Department of Chemistry, Columbia University

The ring opening of the cyclobutene radical cation (1) yields cis-butadiene radical cation (3). Alternatively, 3 may be formed from 1 via another path involving a series of cyclopropylcarbinyl-like structures (5) constituting a flat, high-energy potential energy plateau. This plateau is proposed to contain four channels corresponding to the conversion of 5 to four products that are linked by $C_2$-symmetric conversions outside the Bauld-plateau. Three of these $C_2$-symmetric channels connect 1 to both cis-butadiene radical cation (3) and trans-butadiene radical cation (2). Direct Born-Oppenheimer ab initio dynamics permitting a statistical sampling of trajectories beginning from 5 will be presented. The possibility of a dynamic control of this reaction is discussed.

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COMP 255 Disconnection of maximum stereoelectronic effects from the transition structure
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The Diels-Alder reaction between butadiene and acrolein, catalyzed by BF$_3$OCH$_3$ has been investigated computationally utilizing the B3LYP/6-31G(d) level of theory. The anomeric effect between the uncomplexed carbonyl oxygen lone pair and the coplanar boron-fluorine antibonding orbital has been computed and studied along the reaction coordinate. Natural bond orbital analysis (NBO) has been carried out on selected structures along the computed intrinsic reaction coordinate (IRC). The anomeric effect has been followed along the reaction coordinate and analyzed in terms of geometric parameters, bond orders, hybridization changes, formal charges, and energy levels of the interacting orbitals to explain this phenomenon. It has been rationalized that the anomeric effect has a strong influence on the asynchronicity of the Diels-Alder reaction. It is of interest that maximum stereoelectronic effects do not coincide with the transition structure.

COMP 256 Enthalpies of formation for thio ethers by homodesmotic reactions
Ryan Fortenberry and David H. Magers, Department of Chemistry & Biochemistry, Mississippi College, 200 South Capitol Street, Clinton, MS 39058, Fax: 601-925-3933, rfortenb@mc.edu

Recently, the study of thio ethers (sulifides) in polymer chemistry has been rekindled in the field of ultraviolet-curable resins. Different thiols and alkenes are allowed to react to form sulfides that serve as precursors to polymerization. In an effort to judge the relative stability of these systems, the current study focuses on the computation of their standard enthalpies of formation by homodesmotic reactions. In homodesmotic reactions the number and types of bonds and the bonding environments of all atoms are conserved. Results support the initial hypothesis that the enthalpy of reaction for homodesmotic reactions for simple organics such as alkanes and sulfides should be close to zero. Therefore, such reactions can be used to quantify types of energy that systems may possess other than bond energy. As a result, we have expanded the current study to compute the resonance energy in 1,3-butadiene. We gratefully acknowledge support from NSF EPSCoR (EPS-0132618).

COMP 257 Generalization of planar hexacoordinate carbon
Keigo Ito, Zhongfang Chen, Chaitanya S. Wannere, and Paul V. R. Schleyer, Department of Chemistry, Center for Computational Chemistry, University of Georgia, 1004 Cedar St, Athens, GA 30602-2556, keigito@ccqc.uga.edu

The previously reported planar hexacoordinate carbon (phC) molecules, CB$_6^{2-}$ ($D_{gh}$) and the C$_3$B$_4$ ($D_{2h}$ and C$_{2v}$) isomers, seemingly preclude the possible generalization due to the lack of hydrogens for replacement. However, the perimeter B-B bond of CB$_6^{2-}$ can be opened and appropriate groups, such as olefins and arenes, can be inserted. One or two atom bridging groups can be added on one edge of the CB$_6$ unit. Based on this strategy, we find that variety of new phC molecules are viable. Hence the CB$_6$ unit can be used as a phC building block. For example, a figure below demonstrates the use of above approach, e.g. C$_7$B$_9$H$_4$ ($C_{2v}$), a stable aromatic minimum with 10 p electrons. Such suitable selections of the substituents can offer the basis for the limitless experimental realization of the phC molecules.

![Diagram of planar hexacoordinate carbon molecules](image-url)
COMP 258 Hydrogen abstraction reactions using hybrid density functional theory with specific reaction parameters

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Our studies are focusing on the hydroxyl radical attack on the C–H bonds in hydrofluorocarbons that are important atmospheric processes. We are investigating theoretically both the barrier heights and the rate constants for these reactions, and we compare our calculated values to both experimentally and previously estimated values. We have carried out rate constant calculations using variational transitional state theory with multidimensional tunneling contributions. We have also performed calculations for hydrogen abstraction from fluoromethanes with the goal of determining hybrid density functional theory methods that give highly accurate calculated rate constants. We looked on three functional: BB95, mPW95, and mPW91 in conjunction with 6-31+G(d,p) basis set, and non-standard Hartree-Fock contributions were optimized for these methods to obtain the accurate rate constants. The use of these new methods is now being extended to further investigate more complex hydrofluorocarbons, and we are presenting results obtained for hydrogen abstraction reactions from hydrofluoromethanes.

COMP 259 Investigation of metal dependent behavior of HIV-1 integrase inhibitors: DFT calculations

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The metal dependent behavior of two HIV-1 integrase (IN) inhibitors, SCITEP and its analog (DKA), were investigated by means of density functional theory calculations. According to the crystal packing effect in the X-ray complexed structure of SCITEP and HIV-1 IN, six different possible binding structures of each inhibitor to IN, in particular to either Mg2+ or Mn2+ ion, were modeled. For every model, including inhibitor, metal ion, and surrounding amino acids within 8 Å from inhibitor was subjected to interaction energy calculations at the B3LYP/6-31++G(d,p) level of theory. The results indicate that the lowest total interaction energy model of each inhibitor has a similar binding mode, e.g. the keto-enolate moiety interacts directly with either Mg2+ or Mn2+. The interaction energy of these four systems agrees with experimental data that DKA is more potent than SCITEP. The obtained data are useful for further set up of MD simulations geared to probe metal ion dependencies of the inhibitor complexes.

Table 1 Biological activities and the lowest interaction energy of all four systems

<table>
<thead>
<tr>
<th>IC50 (µM)</th>
<th>System</th>
<th>Interaction Energy (kcal/mol)</th>
</tr>
</thead>
<tbody>
<tr>
<td>3'processing</td>
<td>Strand transfer</td>
<td>Mg-SCITEP</td>
</tr>
<tr>
<td>400, &gt;333</td>
<td>97 ± 32</td>
<td>Mn-SCITEP</td>
</tr>
<tr>
<td>59, 40</td>
<td>0.93 ± 0.23</td>
<td>Mg-SCITEP</td>
</tr>
<tr>
<td>25, 30</td>
<td>7, 15</td>
<td>Mn-SCITEP</td>
</tr>
<tr>
<td>1.93 ± 0.93</td>
<td>0.12 ± 0.04</td>
<td>Mn-DKA</td>
</tr>
</tbody>
</table>

COMP 260 Investigation of the inhibition of Fe-only and Ru-modified H-cluster by molecular oxygen: A density functional theory study

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This poster presents a study of the H-cluster (the active site of Hydrogenase) inhibition by molecular oxygen. The calculated enthalpies of dissociation for molecular oxygen and hydrogen bound to H-cluster show that the dissociation
enthality of oxygen bound to Ru is about four times lower than for the native Fe-only H-cluster. Previous DFT calculations reported for the H-cluster with water bound to distal iron, Fe$_d$, revealed that the removal of the coordinating water from the distal iron in Fe$^{II}_p$-Fe$^{II}_d$ is endothermic (+23 kcal/mol), but the dissociation upon reduction of Fe$^{II}_d$ to Fe$_d$ was not investigated. The central CO$_c$ (bound to both irons) plays a significant role in the reaction mechanism; water removal shifts CO$_c$ to Fe$_d$, and is favored thermodynamically (-3.2 kcal/mol). The reactivation of the H-cluster is completed upon the reduction of Fe$^{II}_d$ to Fe$_d$. This reduction is highly exothermic (-62.4 kcal/mol at B3LYP/6-31+G(d,p)).

COMP 261 Modeling of d10 coinage-metal complex excited states
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Coinage metal complexes show interesting photophysical properties, for example, thermochromism, luminescence solvatocromism, and dual-emission spectroscopy. The two classes of compounds examined in this research include d$^{10}$ coinage metal pyrazolates and gold(I) tris-phosphines. Both classes of compounds have bright, tunable luminescence and a substantial Stokes shift (ca. 16,000 cm$^{-1}$). The Stokes shift is consistent with the calculated geometric distortion due to Jahn-Teller instability in the excited triplet state. This research is directed toward understanding the origin of these photophysical properties in greater detail, and their response to modification of the chemical environment, with the ultimate goal of guiding the synthesis of rationally-tuned phosphors, e.g., for novel light-emitting devices.

COMP 262 Parallel Fock matrix construction on the Grid
Hiroaki Umeda, Yuichi Inadomi, Tosio Watanabe, Takayoshi Ishimoto, and Umpei Nagashima, Research Institute for Computational Sciences, National Institute of Advanced Industrial Science and Technology, and CREST-JST, 1-1-1 Umezono, Tsukuba, Ibaraki, Japan, Fax: +81-29-862-6611, h-umeda@aist.go.jp

Fock matrix construction routine of a RHF calculation has been parallelized on the Grid environment. Until now, we had developed multi-level dynamic load-balancing routine of Parallel Fock matrix construction on a layered multi-processor system such as EHPC system, and it shows good parallelization performance. In this paper, we extended this parallel Fock matrix construction method to a Grid Remote Procedure Call (GridRPC) model, which is RPC programming model on the Grid. For developing a Grid application, we adopt Ninf-G (http://ninf.apgrid.org/), which is a reference implementation of the GridRPC API proposed GGF standard. By MPI/GridRPC hybrid parallelization, distributed clusters act like a layered-multi-processor system.

COMP 263 DFTB Energy decomposition analysis of interactions in Fullerene@SWNT nanopeapods
Zhi Wang$^1$, Stephan Irle$^1$, Guishan Zheng$^1$, Keiji Morokuma$^1$, Ryo Kitaura$^2$, and Hissanri Shinohara$^2$. (1) Cherry L. Emerson Center for Scientific Computation and Department of Chemistry, Emory University, 1515 Dickey Drive, Atlanta, GA 30322, Fax: 404-727-7412, zwang6@emory.edu, (2) Department of Chemistry, Nagoya University

Nanopeapods are a new type of self-assembled hybrid material, consisting of fullerene arrays inside single-walled carbon nanotubes. These materials exhibit unique physical, chemical, optical, mechanical, magnetic, and electronic properties, thus have various potential applications ranging from nanometer-sized containers for chemical reactions to data storage, and possibly high temperature superconductors. We have employed the Density-Functional based Tight-Binding (DFTB) method to study the energetics of nanopeapods composed of C60, C70 and C82 in different types of nanotubes, which shows that the dispersion energy plays an important role in determining the reaction energy. Also, because of the anisotropy of fullerenes, the energetics are different with different fullerene orientation inside the nanotubes, and in particular we confirm the experimentally observed “squeezed” packing of fullerenes.

COMP 264 Enthalpies of formation of TNT derivatives by homodesmotic reactions
Amika Sood, Patricia L. Honea, and David H. Magers, Department of Chemistry & Biochemistry, Mississippi College, 200 South Capitol Street, Clinton, MS 39058, Fax: 601-925-3933, csood@mc.edu

TNT (2,4,6-trinitrotoluene) is a well known and widely used explosive. In the current study, we focus on the computation of the standard enthalpy of formation of TNT and similar aromatic compounds by homodesmotic reactions. In homodesmotic reactions the number and types of bonds and the bonding environment of each atom are conserved. We first computed standard enthalpies of formation for certain smaller aromatics whose enthalpies are known to validate our method. We obtained excellent results for these systems with the exception of 3-nitroaniline for which our computed enthalpy was almost 3 kcal/mol too high. We then used different homodesmotic reactions to compute the standard enthalpies of formation of the TNT derivatives. Results are consistent with the exception of those obtained from reactions that utilize the experimental enthalpy value for 3-nitroaniline. Better convergence is obtained with our theoretical value for this system. We gratefully acknowledge support from NSF EPSCoR (EPS-0132618).
COMP 265 Theoretical study of the electronic and geometrical structures of organic semiconductors
Mamoun M. Bader, Gregory P. Gutshall, Aniello Scotto Di Marco, and Hui Lin, Department of Chemistry, Pennsylvania State University, Hazleton, PA 18202, mmb11@psu.edu

Density Functional Theory calculations of the electronic and geometrical structures of some well-known organic semiconductors will be presented. Representatives molecules with some carefully chosen molecular modifications are considered with emphasis on thiophene-based and oligocene-based materials. Trends obtained are analyzed in the context of the impact of molecular structures on the HOMO-LUMO levels. Comparisons with experimental data will be made whenever possible.

COMP 266 Thermodynamic studies on the effect of metal complexes, similar to those used as anticancer drugs, on an oligonucleotide
Jaketa Stoudmire, Antonee Renee Siler, and Beatriz Cardelino, Department of Chemistry, Spelman College, 350 Spelman Lane, Atlanta, GA 30314, jastoud@yahoo.com, asiler@spelman.edu

The primary goal of this investigation is to study the effect of adduct formation between metal complexes and nucleotides. The complexes examined were those similar to existing anticancer drugs. Presently, platinum-based antitumor drugs, such as Cisplatin, are the most effective and commonly used drugs. However, the mechanisms of action of the metal complexes on the nucleotides are still unknown, which motivated this study. The adducts investigated contained Group VIII transition metals with halide or other ligands and the double-stranded dodecamer engineered by Gelasco and Lippard (Biochemistry Vol. 37, pp. 9230-9, 1998). Quantum and molecular mechanic calculations were performed using the ONIOM approach which allowed for treating these systems with different levels of approximations. Thus, the metal complexes were modeled using density functional theory and the oligonucleotides were modeled using molecular mechanics. Thus, the calculations provided the energetics, as well as information relative to the structural changes resulting from the adduct formation.

COMP 267 N1s and C1s core electron binding energies for 2-, 3-, and 4-substituted pyridines calculated by density functional theory (DFT): Correlations with Hammett substituent constants
Yuji Takahata, Department of Chemistry, State University of Campinas, Cidade Universitária Zeferino Vaz, Distrito de Barão Geraldo, Campinas 13084-862, Brazil, Fax: 55-19-37883023, taka@iqm.unicamp.br

Core-electron binding energy (CEBE) of an atom in a molecule is intimately related to its physical and chemical environment. Experimental technique, X-ray Photoelectron Spectroscopy (XPS), to measure CEBE, has been developed since mid sixties. However, a theoretical method to calculate accurate CEBEs employing DFT has been developed only recently. We use the DFT method to calculate accurate CEBEs of the title compounds and investigate the relation between calculated CEBE shifts and Hammett substituent constants. We use Amsterdam Density Functional (ADF) package for the calculations. The average absolute deviation (AAD) of 34 calculated N1s CEBEs from experiment is 0.22 eV. CEBE shift of a certain atom in a mono substituted pyridine ring is calculated as the difference between the CEBE of the mono substituted pyridine and that of pyridine. Good agreement between the numerical values of CEBE shifts expressed in unit of eV and Hammett substituent constants were observed.

COMP 268 Philicity concept revisited
Pratim Kumar Chattaraj1, Utpal Sarkar2, Debesh Ranjan Roy1, Ramakrishnan Parthasarathi2, Jaganathan Padmanabhan3, and Venkatesan Subramanian2. (1) Department of Chemistry, Indian Institute of Technology, Kharagpur, Kharagpur 721 302, India, Fax: +91-3222-255303, pkc@chem.iitkgp.ernet.in, (2) Chemical Laboratory, Central Leather Research Institute, Adyar

A local reactivity descriptor, viz., philicity, has been defined through the resolution of identity associated with the normalization condition of the Fukui function. Its usefulness is assessed by analyzing its potential in explaining various intramolecular and intermolecular processes. Locating the transition state, kinetics of Friedel-Crafts reactions, Toxicity of electron donor and acceptor type toxins, Reactivity of carbonyls and amines, Effects of solvent and external field etc. have been studied for this purpose.

COMP 269 Spin-Potential functional formalism for current-carrying noncollinear magnetic systems
Tim Heaton-Burgess1, Paul W. Ayers2, and Weitao Yang1. (1) Department of Chemistry, Duke University, Durham, NC 27708, thb2@duke.edu, (2) Department of Chemistry, McMaster University

We develop a spin-potential functional formalism for ground states of systems in the presence of spin-coupling external potentials. In particular, this provides a well defined potential theory dual to current-density functional theory that is free of the issues arising from the nonunique mapping between spin-potentials and wavefunctions. Further, this allows us to circumvent the v-representability issue and provides a basis for the optimised effective potential method.
COMP 270 Confined atoms and molecules: Some new results
K. D. Sen, School of Chemistry, School of Chemistry, University of Hyderabad, Hyderabad, India, University of Pune, Gachhi Bowli, Hyderabad-500 046, India, Fax: +91-40-23012460, sensc@uohyd.ernet.in

We report some new results on the degeneracy of confined hydrogen atom and on the variation of the Shannon information entropy of confined = light atoms, respectively. Further, we present our most recent work reporting the benchmark calculations of energy spectrum of spherically confined He atom in the ground and lowest excited states using elaborate Hylleraas type wave functions. Using these results we have evaluated the exact density functional theory (DFT) exchange-correlation potentials and found them to be inadequate under the confined conditions. The effect of spherical confinement on the atomic and molecular DFT reactivity parameters of electronegativities and hardness and softness are presented. We show that as the confinement radius is reduced, the electronegativity decreases and becomes negative while the global hardness increases. Due to the orbital cross-over, however, the hardness does not increase to infinity as the confinement is increased. Effects of spherical confinement on several other standard potentials will be presented.

COMP 271 Control and monitoring of physical objects in biomolecular systems: Some novel experimental tools and theoretical models
Kresimir Rupnik, Department of Chemistry, Louisiana State University, Baton Rouge, LA 70803, chrupn@lsu.edu

Even after decades of investigations many very important basic molecular mechanisms in biomolecular systems are not well understood. We report here some novel experimental and modeling efforts, including Polarization Phase Selective and Nuclear Resonant Vibrational methods, aimed at monitoring and controlling physical objects in biomolecular systems in very brief processes.

COMP 272 Correlation energy density functionals for two-electron systems
Jacob Katriel, Sudip Roy, and Michael Springborg. (1) Department of Chemistry, Technion - Israel Institute of Technology, Haifa 32000, Israel, Fax: (972) 4 829 5703, jkatriel@tx.technion.ac.il, (2) Physical Chemistry, Saarlandes University

The correlation energies of the helium isoelectronic sequence IS and of Hooke's atom IS have been evaluated using an assortment of local, gradient and meta-gradient density functionals. The results are compared with the exact correlation energies, showing that while several of the most recent density functionals reproduce the exact correlation energies of the helium IS rather closely, none are satisfactory for Hooke's atom IS.

COMP 273 EEM and Spectrophores
Wilfried Langenaeker, Hans De Winter, Gert Thijs, and Jonatan Taminau, Silicos, Wetenschapspark 7, Diepenbeek 3720, Belgium, Fax: +32 11 22 05 25, wilfried.langenaeker@silicos.com

We will describe the application of atomic properties calculated using the Electronegativity Equalization Method in a proprietary chemoinformatics technology, called Spectrophores™. This new technology allows to rapidly convert three-dimensional molecular properties into one-dimensional molecular fingerprints. Typical molecular properties that can be converted into Spectrophores™ include electrostatic potentials, atomic lipophilicities, and hardness and softness. Molecules with similar 3D-properties, and as such similar biological activities, will always yield similar Spectrophores™. Therefore this technology is well-suited as a rapid and accurate virtual screening tool. To illustrate the power of Spectrophores in combination with the EEM-calculated atomic properties several examples of applications in the fields of virtual screening and database characterization will be provided.

COMP 274 From coordinate space density to momentum-space density sans wave functions
Rajeev K. Pathak, Department of Physics, Department of Physics, University of Pune, Pune 411 007, Maharashtra, India, University of Pune, Ganeshkhind, Pune 411 007, India, Fax: 011-91-20 2 569 1684, pathak@physics.unipune.ernet.in
Invoking a variant of the constrained-search formulation of the density functional theory, a general scheme is developed yielding momentum-space properties starting exclusively from the coordinate-space electron density. We illustrate the scheme for some inert monatomic systems in terms of their Compton profiles. This procedure lays a bridge between the position-space and its canonically conjugate momentum-space.

**COMP 275 Fundamental importance of the Coulomb hole sum rule to understanding of the Colle-Salvetti wave function**

Xiao-yin Pan, Virah Sahni, and Lou Massa, The Graduate School of the City University of New York, New York, NY 10016, xiaoyinp@hotmail.com, lmassa@hunter.cuny.edu

The Colle–Salvetti (CS) formula for the correlation energy follows from an approximate satisfaction of the Coulomb hole sum rule. Although it enjoys wide success, it has been shown [1] that the CS wave function is not normalized. In this work we review a proof [2] which shows that exact satisfaction of the Coulomb hole sum rule is both a necessary and sufficient condition for exact normalization, that is to say, charge conservation. It follows that the idea one can satisfy the Coulomb hole sum rule only approximately is fundamentally wrong, since that will cause non-conservation of charge. In recent work [3–5] we have developed the concept of wave functions that are functionals depending on a set of functions. These functions are determined by a constrained search such that the wave function satisfies a sum rule or reproduces a physical observable. By application of these ideas to the ground state of the helium atom, we have determined a wave function functional that satisfies the Coulomb hole sum rule for each electron position. This wave function is normalized, consistent with the above mentioned theorem.


2. One-to-one Correspondence of the Normalization and Fermi–Coulomb and Coulomb Hole Sum Rules for Approximate Wave functions, X.-Y. Pan, V. Sahni, and L. Massa (In Preparation.)


**COMP 276 Molecular dynamics simulations with the ABEEM force field based on density functional theory**

Zhong-Zhi Yang, Department of Chemistry, Liaoning Normal University, 850 Huanghe Road, Dalian 116029, China, Fax: 086-411-82158977, zzyang@lnnu.edu.cn

For Professor Robert G. Parr, on the occasion of his 85th birthday


**COMP 277 An "atoms" in "molecules" based chemical reactivity theory**

Morrel H. Cohen, Department of Physics and Astronomy, Rutgers University, 136 Frelinghuysen Rd., Piscataway, NJ 08854-8019, Fax: 732-445-4400, mcohenn@physics.rutgers.edu, and Adam Wasserman, Department of Chemistry, Harvard University

The Extremely fruitful density-functional-based formulation of chemical reactivity theory of Parr and collaborators retains certain inconsistencies with DFT. Reactivity indices which are first derivatives with respect to electron number are staircase functions of number, making electronegativity equalization problematic. Second-derivative indices such as hardness vanish. We have reexamined CRT within the framework provided by our "atoms" in "molecules" theory. The exact electron density of the "molecule" is partitioned into contributions from its parts. These are determined by constrained minimization of the sum of the density functionals of the individual parts. The constraint is embodied in a unique reactivity potential and an internal chemical potential. Electronegativity equalization is restored; a
positive-definite self and mutual hardness matrix is defined; a Fukui matrix is defined whose diagonal elements reduce to Fukui functions when the parts are separated; and the softness kernal is defined with respect to the reactivity potential.

**COMP 278 Fractional charge in diatomsics-in-molecules hamiltonians**

Steven M. Valone, MST-8, MS G75S, Los Alamos National Laboratory, PO Box 1663, Los Alamos, NM 87545, Fax: 505-667-8021, smv@lanl.gov, and Susan R. Atlas, Department of Physics and Astronomy and Center for Advanced Studies, University of New Mexico

The diatomsics-in-molecules (DIM) representation of a polyatomic hamiltonian takes advantage of the natural decomposition of a system into overlapping atomic and diatomic fragments. Historically, DIM calculations fixed the distribution of electrons among the fragments according to the number of electrons for the constituent, neutral atoms. Here we lift this restriction to permit electron exchange among fragments. Permitting electron exchange actuates the open system behavior originally envisioned in the pioneering work of Perdew, Parr, Levy, and Balduz. Because the number of electrons in the fragment hamiltonians is variable, the energies of those fragments depend on fractional charges. Consequently, both diatomic as well as atomic fragments must be treated as open systems. As we shall discuss, two distinct charge-dependent energy contributions then emerge for each fragment within the DIM hamiltonian, arising from intra- and inter-fragment charge transfer.

**COMP 279 Elements of information theory of electronic structure**

WITHDRAWN

Importance of variational principles in the information-entropy representation for determining such sub-molecular concepts of chemistry as bonded atoms and chemical bonds is emphasized and illustrative applications of the IT-probes of molecular electronic structure are presented. The elements of the Communication Theory of the chemical bond will be summarized. In this approach molecules are interpreted as information channels and the covalent and ionic components the system chemical bonds are respectively measured by the average communication "noise" and the amount of information flowing through the molecular communication network. Alternative strategies for bond indices of molecular subsystems are summarized and comparison of the information-theoretic and molecular-orbital bond-orders and their covalent/ionic composition will be examined in the simplest two-atomic bond model. Atomic components of bond-multiplicities/valence-numbers will be established using the probability-partition from the model partial communication channels.

**COMP 280 Chemical reactivity indexes and the auxiliary density**

Alberto Vela, Chemistry, CINVESTAV, Av. I.P.N. 2508; A.P. 14-740, Mexico City 07000, Mexico, Fax: 52 55 50 61 71 13, avela@cinvestav.mx

Through the use of the variational fitting of the electron density it is possible to reduce the formal scaling of the solution of Kohn-Sham's equations. After a brief description of the implementation of this approach in the LCGTO code deMon2k, and some selected applications, the calculation of several global and local reactivity indexes is presented. Emphasis will be given to the partitioning of space with Hirshfeld weights, electronegativity and global hardness and the Fukui function. The complementary vision provided by several molecular scalar fields as an aide to understand chemical phenomena is also presented.

**COMP 281 Link between reaction force and DFT reactivity descriptors**

Soledad Gutiérrez-Oliva, Bábara Herrera, and Alejandro Toro-Labbé, Laboratorio de Química Teórica Computacional (QTc), Facultad de Química, Pontificia Universidad Católica de Chile, Avda. Vicuña Mackenna 4860, Macul, Santiago, Chile, Fax: 56-2-686 4744, msg@puc.cl, atola@puc.cl

The classical model in which a chemical reaction proceeds from one energy minimum to another via an intermediate maximum gives valuable information about the energetic and kinetic aspects of chemical reactions. A third crucial aspect to understand chemical processes is the reaction mechanism and it is incorporated through the introduction of the reaction force along the reaction coordinate &omicron;: \( F(\&omicron;) = -\Delta E(\&omicron;)/\Delta \&omicron; \). The reaction force allows the characterization of specific types of interactions that are activated or inhibited at different regions that are defined along \&omicron;. The features observed in the \( F(\&omicron;) \) profile are rationalized in terms of the variations of few DFT reactivity descriptors along \&omicron;. Illustrative examples of representative systems and processes suggest the chemical potential as being a key property to elucidate reaction mechanisms.

**COMP 282 Role of the density response function in the interaction of a hard and a soft species**

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When a proton interacts with a chemical species, the presence of the proton (a hard species) can be treated as a perturbative point charge potential. In this case, up to first order, the protonation energy can be approximated by the electrostatic potential. There are many cases where the electrostatic potential correctly predicts the protonation site.

The prediction of the protonation of anions with several basic sites is a more complex task. Usually anions are soft species and the polarization of the electron distribution coming from the proton’s electric potential is not a small response. In fact, for most of the enolate anions (keto and enol conjugated bases), the electrostatic potential and the Fukui function do not correctly predict the protonation place.

In this work, the contribution of the density linear response kernel to the protonation energy (second order term) of some enolate anions is analyzed.

**COMP 283 Why does the Hard-Soft Acid-Base Principle work? Insights obtained by considering acid (or base) exchange reactions**

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Reactions where a hard (or soft) acid (or base) replaces a soft (or hard) acid (or base) to form the product predicted by the hard/soft acid/base (HSAB) principle are examined. When electron transfer effects dominate the reactivity and other effects are negligible, the HSAB principle is driven by the surpassing stability of the soft acid/soft base product. Electrostatic effects are also treated, focusing on the tendency for hard reagents to be small and possess charged reactive sites. When electrostatic effects dominate the reactivity and other effects are negligible, the HSAB principle is driven by the surpassing stability of the hard acid/hard base product. Because electron-transfer and electrostatic considerations separately favor the HSAB principle, the overall picture of reactivity (which includes both effects) provides strong support for the HSAB principle. Because electron transfer effects favor soft/soft interactions, while electrostatic effects favor hard/hard interactions, hard/soft acid/base exchange reactions can be used to classify whether a reagent’s reactivity is dominated by electron-transfer or electrostatic effects.

**COMP 284 Beyond keeping it together: Extracellular loops in the cannabinoid receptor and rhodopsin play a key role in receptor stability and ligand binding**

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The rhodopsin crystal structure provides a unique framework for understanding GPCR activation and attenuation. However, this helpful structure also gives rise to some perplexing questions. For example, the extracellular (intradiscal) loops in rhodopsin appear to form a tight “lid” over the ligand (retinal). How does the ligand get into or out of the binding pocket? Do these loops move to allow binding and/or release, or does the ligand enter from the side, slipping past the helices? Do other GPCRs share similar structures in this region? We are investigating these questions through comparative structure-function studies of rhodopsin and the cannabinoid receptor. I will present some recent results, and discuss thoughts on why this region may be important for ligand binding and receptor stability.

**COMP 285 Molecular dynamics simulations of cannabinoid CB1 receptor/endogenous ligand recognition via the membrane bilayer**

**Patricia H. Reggio** and Diane L. Lynch, Department of Chemistry and Biochemistry, University of North Carolina, Greensboro, 1000 Spring Garden St., Greensboro, NC 27403, Fax: 336-334-5402, phreggio@uncg.edu

The endogenous cannabinoid, N- arachidonylethanolamine (anandamide; AEA) is a highly lipophilic compound. In work to be presented, we explore via multi-nanosecond molecular dynamics (NAMD2) lipid bilayer simulations, the hypothesis that AEA’s entry into the G protein-coupled cannabinoid CB1 receptor is via the lipid bilayer. The results of two NAMD2 simulations will be presented. The first is an exploration of the properties of AEA in a 1,2-dioleoyl-sn-glycero-3-phosphocholine (DOPC) phospholipid bilayer. The second is an exploration of possible initial interaction sites for AEA on the lipid face of CB1 TMH6 in DOPC. These studies have indicated that two lipid facing residues (valine 6.43/ isoleucine 6.46) form the initial recognition site for the AEA acyl chain at CB1, a result that we have recently confirmed experimentally via receptor mutation studies. (Support: NIH DA03934 and DA00489; PSC MCB030006P)

**COMP 286 Molecular dynamics simulations of the structural stability of the cannabinoid-CB1 receptor inactive state model in a POPC bilayer**

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The cannabinoid CB1 receptor is an integral membrane protein belonging to the class A family of G-protein coupled receptors (GPCRs). Rhodopsin, a member of this class of receptors, is the only GPCR for which there is an available
x-ray structure. Although there is a great deal of structural similarity between GPCRs and rhodopsin, there are also distinct differences. For example, the salt bridge between the D(E)RY motif in helix 3 and D6.30 in helix 6 has been discussed as an ionic lock restraining the receptor in the off state. However, it has become clear that this function may not be shared across all GPCRs. We have therefore studied, via multinationanosecond molecular dynamics the integrity of this structural motif in our model of the inactive (R) state of CB1 embedded in a POPC bilayer. Results of these simulations and comparison to mutagenesis experiments will be presented and discussed.

**COMP 287 Computational studies of G-protein coupled receptor oligomers**  
**Marta Filizola**, Physiology & Biophysics, Weill Medical College of Cornell University, 1300 York Ave, Box 75, New York, NY 10021, maf2037@med.cornell.edu

Currently proposed signaling models of G-Protein Coupled Receptors (GPCRs) involve macromolecular assemblies rather than monomers, with the dimer as the minimal oligomeric arrangement required for functional coupling to hetero-trimeric G-proteins. Structural information about GPCR oligomeric complexes is therefore crucial to obtain a detailed characterization of the dynamic properties underlying receptor function. This presentation will discuss current efforts in the lab to develop, interpret, and disseminate to the scientific community detailed information about the structural context of GPCR oligomerization. To enable understanding of the dynamic mechanisms of signaling assemblies of GPCRs compared to their monomeric forms, we are studying nanosecond time-scale molecular dynamics simulations of receptor dimers and monomers in explicit membrane bilayers. In addition, we are building a specialized information management system that will contain both computational and experimental information on GPCR oligomers to serve in experimental verification and drug design.

**COMP 288 Defining the ligand binding site on the human C5a receptor**  
**Peter N Monk**, 1, Adrian Higginbottom, Praveen K Madala, Joel D. A. Tyndall, Martin Stoermer, and David P. Fairlie. (1) Division of Genomic Medicine, University of Sheffield, Medical School, Beech Hill Road, Sheffield S10 2RX, United Kingdom, Fax: +44 114 2261312, p.monk@shef.ac.uk, (2) Centre for Drug Design and Development, University of Queensland

Complement fragment (C)5a is a 74-residue chemotactic polypeptide produced following the activation of a proteolytic cascade that is an important component of innate immunity. Receptor activation is a 2-stage process with an initial interaction between the receptor N-terminus and the core of C5a that results in the association of the C-terminal ligand decapetide with juxta- and transmembrane residues. The best-characterized antagonist, developed from the C-terminal sequence, is a cyclic peptide that binds pseudo irreversibly. Using an iterative mutagenesis/modelling process, we have further defined a ligand binding site for the cyclic antagonist and detected distinct differences from the binding of other peptide ligands and non-peptidic antagonists. The NMR-derived structures of these ligands have allowed us to model the binding site in the absence of a receptor structure and predictions tested by a further round of receptor mutagenesis. A refined model of antagonist binding to C5aR using these data will be presented.

**COMP 289 Inactive and active states and supramolecular organization of GPCRs: Insights from computational modeling**  
**Francesca Fanelli**, Dulbecco Telethon Institute and Department of Chemistry, University of Modena and Reggio Emilia, Via Campi 183, Modena 41100, Italy, Fax: 0039-059-373543, fanelli@unimo.it, and Pier G. De Benedetti, Department of Chemistry, University of Modena and Reggio Emilia

Our study is aimed at understanding, through computational modeling, the molecular mechanisms of GPCR functioning either in their normal conditions or when hit by gain-of-function or loss-of-function mutations. Molecular simulations of the wild type luteinizing hormone receptor (LHR) and of its spontaneous and engineered mutants were instrumental in inferring the structural features, which differentiate the mutation-induced active from the inactive states of the receptor [1]. These features were translated into computational indices instrumental in in silico functional screening of novel LHR mutants [1]. Similarly to mutation-induced activation, the interface between the cytosolic extensions of helices 3 and 6 resulted to be the target of the structural modifications induced by activating ligands. Computational modeling of the supramolecular organization of GPCRs and their intracellular partners is the current challenge towards a deep understanding of their functioning mechanisms.


**COMP 290 Computer simulation of nano tin melting behavior: Effect of particle size and temperature ramping up rate**  
**Hai Dong**, Kyoung-sik Moon, Hongjin Jiang, CP. Wong, M. I. Baskes, and Fay Hua. (1) School of Materials Science and Engineering, Georgia Institute of Technology, 771 Ferst Drive, Atlanta, GA 30332, hai.dong@mse.gatech.edu, (2) School of Chemistry & Biochemistry, Georgia Institute of Technology, (3) Materials Science and Technology Division, Los Alamos National Laboratory, (4) Materials Technology Operation, Intel Corp
The Modified Embedded Atom Method (MEAM) was employed in conjunction with Molecular Dynamics (MD) simulations to investigate the effect of particle size and temperature ramping up rate on nano tin melting behavior. Tin spheres with different diameters in the range of 4nm-10nm will be prepared, and the temperature will be raised up at different ramping up rates from 0.1K(ps)/1K(ps). [010] projection and pair correlation function (PCF) will be applied to study the structural evolution of tin particles as temperature is ramping up. The melting point will be derived by observing the transition of the patterns of potential energy. The effect of particle size and temperature ramping up rate on melting point will be investigated. Surface melting behavior will be studied by comparing the micro-structure of tin atoms located in core/shell regions.

COMP 291 Diffusion of atomic oxygen on Si(100) surface
WITHDRAWN

Adsorption of Oxygen atoms on the silicon surface has many applications in semiconductor devices. Understanding the physical processes such as aggregation, etching and diffusion, on the Si surface is important. These processes can be well comprehended if we understand the mechanisms at the microscopic level and then bridge it with a macroscopic scale by integrated multi scale modeling codes. In our present study, we investigate the process of diffusion of atomic oxygen on a reconstructed Si (100) surface at the microscale level using a combination of Quantum Mechanical methods with a hybrid QM/MM (Quantum Mechanics/Molecular Mechanics) method. Hopping of a single oxygen atom to the adjacent empty site via on-top and on-dimer structures is observed on a Si9H12 cluster model using SIMOMM: MCSCF method with effective core potential, Hay-wadt (d) basis set. A long-range diffusion process, which involves hopping of the atomic oxygen along the silicon dimer rows on a Si15H16 cluster, is also investigated. The above studies will describe the energetics of all the intermediate structures involved in the diffusion process and hence produce the potential energy surface. Finally the energy barriers will provide the key parameters for macroscale non-equilibrium statistical mechanics studies.

COMP 292 Hydration and dewetting near fluorinated superhydrophobic plates
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The pioneering experimental work of Genzer and Efimenko has shown that semi-fluorinated molecules such as CF3(CF2)7(CH2)2SiH3 can form a superhydrophobic surface by a careful mechanical assembly process [Science 290, 2130, 2000]. In this work, we use molecular dynamics simulations to study the water dynamics near the nanoscale superhydrophobic surface as well as the possible dewetting transition within two such superhydrophobic surfaces (plates). A partial water dewetting with an expansion of approximately 7-8Å and a water density ~20% lower than the bulk is found near the single superhydrophobic surface. The fluorinated molecules are also found to be water impermeable, consistent with experiment. More remarkably, a strong dewetting transition is found in the inter-plate region for the double plates with a critical distance Dc up to 10Å (3-4 water diameters). This transition, although occurring on a microscopic length scale, is reminiscent of a first order phase transition from liquid to vapor. Furthermore, simulation results show that the fluorinated carbons are more hydrophobic than their hydrogenated counterparts (with Dc = 8.0Å) in terms of the dewetting transition critical distance, despite their much larger partial charges and dipoles. The unusual superhydrophobicity of fluorocarbons is found to be related to their larger surface areas, while the intrinsic hydrophobicity is roughly the same for both fluorocarbons and hydrocarbons based on a detailed water-plate interaction energy profiling. Somewhat surprisingly, we find that even though the electrostatic energies do contribute slightly more in the fluorocarbon plates than the hydrocarbon plates, the van der Waals energies dominate the water-plate interactions (with more than 90% contributions for close shells) and they contribute almost the same in both plates. Once the inter-molecular separations of hydrocarbons are `inflated' to those of fluorocarbons to have the same surface area, the critical distance of hydrogenated plates approaches to that of the fluorinated plates.

COMP 293 Mass transport of O2 and N2 in nanoporous carbon (C168 Schwarzite) using quantum mechanical force field and molecular dynamics simulations
Gaurav Arora and Stanley J. Sandler, Department of Chemical Engineering, University of Delaware, 150 Academy Street, Colburn Lab, Newark, DE 19716, arora@che.udel.edu

A hierarchical approach is used to calculate the fluxes of N2 and O2 in nanoporous carbon molecular sieves represented by C168 Schwarzite over a wide range of pressures and pressure drops. Self- and corrected diffusivities are calculated using equilibrate molecular dynamics simulations with force fields for the gas-carbon interactions obtained from quantum mechanical calculations. These results are combined with previously reported adsorption isotherms of N2 and O2 in C168 to obtain transport diffusivities and by use of the Fick's equation of mass transport to obtain fluxes across the membrane. The diffusion coefficients and fluxes are also calculated with empirical Steele potential, which was obtained by fitting low coverage adsorption data of N2 and O2 on planar graphite sheet. It is found that the ab initio potential better explains the large O2/N2 selectivities of similar sized molecules that has been observed experimentally. An
interesting reversal in selectivity is observed by suitably adjusting the pressure at the two ends of membranes. As a consequence, we predict that a highly selective kinetic separation in favor of either nitrogen or oxygen can be obtained with the same membrane depending on the operating conditions.

COMP 294 Nucleation, growth and domain formation in solid-solid phase transitions
Stefano Leoni and Dirk Zahn, Max Planck Institute for Chemical Physics of Solids, Noethnitzer Strasse 40, D-01187 Dresden, Germany, leoni@cpfs.mpg.de

The fundamental importance of reconstructive phase transition and the simplicity of the structural types involved contrasts with the theoretical and experimental difficulty in assessing their mechanisms. Combining advanced molecular dynamics simulations and topology [1-6], we can elucidate the mechanistic details of reconstructive phase transitions at the experimental temperature and pressure. We are able to discriminate between many mechanisms suggested for ionic compounds [1-4] and semi-conducting materials [7]. We observe nucleation events, coexisting nucleation centers, and the formation of domain with different orientations, separated by grain boundaries. The latter are preferred nucleation places for the transition, and cause an asymmetry between forward and backward transition [8]. The approach opens new simulation scenarios at a level of detail that was not accessible up to now, for solid-solid transformations in periodic and finite systems.


COMP 295 Nucleation and growth in the fluoride to PbCl2-type pressure-induced phase transition in CaF2
Salah Eddine Boufelfel1, Dirk Zahn1, Oliver Hochrein2, Yuri Grin2, and Stefano Leoni2. (1) Max Planck Institute for Chemical Physics of Solids, Noethnitzer Strasse 40, D-01187 Dresden, Germany, boufelfel@cpfs.mpg.de, (2) CPS, MPI

The high-temperature regime of CaF2 is characterized by a superionic state. Before becoming a liquid, the fluorine anions show a liquid-like mobility inside a sublattice of calcium cations that stays solid. Under pressure, the cubic fluorite structure transforms into an orthorhombic modification of the PbCl2 structure type (cotunnite). The transition is reconstructive and occurs around 9.5 GPa [1]. Using an approach which combines advanced molecular dynamics simulations and topological modeling [2-4], we have investigated the pressure-induced transition at the atomic level of detail. The space groups of the two limiting phases can be related by several paths going over intermediate symmetries [5]. Our simulations show that this does not imply a collective mechanism. On the contrary, we find that the transition is initiated by fluoride ions. The latter jump from a tetrahedral to an octahedral void. This event promotes a shuffling of layers in the calcium sublattice, that is followed by a displacement of the fluorine anions into the transformed sublattice. This sets up a nucleation front that propagates through the bulk, until complete transformation [6]. The unique simulation approach, allowing calculation at the experimental temperature and pressure, is the key to discovering this beautiful blend of liquid-like and solid state as the central feature of the phase transition in CaF2.


COMP 296 Quantitative chiral recognition in silico, from chromatography to proteins
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The basic molecular interaction should be the same both in chromatography and for proteins. Hydrogen bonding, van der Waals force, and Coulombic force are main interaction, and the steric effect is the specific for chiral-phases and proteins. Such basic knowledge can apply to quantitative analysis of chiral recognition of proteins. The difference is the location of molecular interaction. It occurs on the surface of chiral phase in chromatography, and does inside of protein molecules. This means proteins can select small molecules but not large molecules in general. Furthermore, ion-ion interaction should be the main driving force of molecular recognition of proteins. Ionized amino acid residues should exist at the molecular interaction site of proteins. Molecular mechanics calculation is applied for the quantitative analysis of chiral recognition of proteins, D-amino acid oxidase, based on the results obtained in chromatography.

COMP 297 The Brownian dynamics in suspension of swelling/shrinking colloids
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The motion of particles in a stationary medium is described by the generalized Langevin equation (GLE). This equation can be found as a projection of a Hamiltonian system with the bilinear coupling between the tagged particle and the oscillatory bath modes. In recent experiments on colloidal suspensions the dynamics of colloidal particles are affected by
their fast swelling or shrinking due to the change in the temperature or pH of the solution. Under such nonequilibrium conditions of the changing environment, the irreversible form of the GLE (IGLE) can be applied to study the particle's motion. Using numerical simulations, we show that the dynamics of colloidal particles in the nonstationary medium can be surmised by the memory-less form of the IGLE, viz., the so-called ILE. The ILE greatly reduces the dimensionality of the all-particle MD simulations and provides additional insights into nonequilibrium processes in colloid suspensions.

**COMP 298 Density functional studies of organometallic systems**

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Abstract text not available.

**COMP 299 Using hybrid DFT methods to understand the structure and reactivity of transition metal-dependent enzymes**

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The role of metalloenzyme structure in modulating transition metal reactivity is difficult to assess using experimental approaches. Density functional theory (DFT) calculations represent a method for determining the electronic structure of metal centers, investigating the properties of hypothetical reaction intermediates, and probing the importance of specific protein residues in controlling metal chemistry. I will discuss recent DFT investigations of the electronic structure and reactivity of the metal centers in (i) Fe(III)-dependent nitrile hydratase, and (ii) Mn(II)-dependent oxalate decarboxylase. For nitrile hydratase, these DFT calculations have given insight into the structural features of the protein underpinning the low-spin preference of the non-heme Fe(III), the photochemical regulation of the metal center, and the mechanism of the enzyme-catalyzed reaction. Studies on the Mn(II) center in oxalate decarboxylase have yielded new information on the role of dioxygen in the radical-based mechanism employed by this enzyme to cleave the C-C bond in oxalate.

**COMP 300 DFT and approximate SCC-DFTB methods applied to biological systems: Successes and problems**

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**COMP 301 A DFT and QM/MM study of the active site of human DNA Polymerase Beta**

**Lee G. Pedersen**, Department of Chemistry, Univ N. Carolina, CB#3290, Chapel Hill, NC 27759, and Ping Lin, Department of Chemistry, University of North Carolina

We have applied B3LYP/6-311G** and ONIOM(B3LYP/6-31G*:Amber) calculations to probe the activity of human DNA polymerase beta. Several complexes were chosen in DFT calculations to investigate the roles of several water molecules in the catalytic reaction of a dNTP with the terminal O3', the reactive focus of a growing DNA strand. A recent, high resolution x-ray crystal structure of the ternary (ds-DNA-dNTP-Pol-beta) complex is employed to construct the initial structure for the QM/MM calculation, and to establish a core of essential atoms for the DFT calculation that describes the catalytic reaction. Estimates of the reaction barriers and the key structures along the reaction path are established. The dynamical roles of the Asp256 side chain that coordinates the catalytic magnesium ion, the alpha-phosphate and two aspartates that bridge the two magnesium ions, the beta- and gamma-phosphate unit and four water molecules are reported. Contributions from residues outside the core region are also reported from ONIOM calculations. We find that the polarization of the bridging (Palpha-O-Pbeta) oxygen by a nearby proton and/or water molecule lowers the activation barrier significantly.
**COMP 302 Clusters: Structures and properties**

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The results of investigations of metal-containing clusters using different levels of theory will be reported. The clusters of interest include gold and silver clusters up to 8 metal atoms, both neutral and ionic species, as well as clusters that represent the Si(100) surface. Comparisons of density functional theory, second order perturbation theory, coupled cluster theory, and multi-reference approaches will be compared.

**COMP 303 Development and application of density functional theory QM/MM approach to studying metalloenzymes**

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The field of development and application of density functional theory QM/MM methods is expanding rapidly. The methods have become increasingly powerful in complementing experimental methods to elucidate the chemistry of the complex biological process and to investigate chemical reactions in the condensed phase. For applications, one niche for density functional theory QM/MM methods is the study on enzymes containing transition metal at its active site, which are often medically significant while posing special challenges for computational methods. In this talk, I will describe our recent efforts to further improve DFT QM/MM methods, and applications to study several metalloenzymes, including peptide deformylase, histone deacetylase and α-ketoglutarate dioxygenases.

**COMP 304 Modeling biological reactions with density-functional theory: Multi-scale**

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The development of density-functional theory (DFT) has had perhaps the single most profound impact on the understanding and modeling of reactions catalyzed by biological molecules. DFT methods have made accurate electronic structure theory accessible to a host of complex problems that involve truly large systems with near-biochemical accuracy. This work focuses on the application of density-functional methods to the study of a very important class of reactions catalyzed by molecules of RNA called ribozymes. Ribozymes are highly-charged molecules that interact strongly with solvent and metal ions in order to effect tremendous catalytic efficiency for specific target molecules, and as such, are of tremendous interest in the development of medical therapies and new nano/biotechnology. In order to explore the reaction mechanisms and free energy barriers of these systems, new quantum and classical models for the reactive species and complex solvate macromolecular environment are interwoven to form so-called multi-scale methods able to reliably examine processes that involve inherently large spatial domains and long time scales. The focus of the present work is to outline recent progress in the design of new multi-scale quantum models to study ribozyme mechanisms. Methodological advances will include: 1) linear-scaling electrostatic and generalized solvent boundary methods for hybrid QM/MM simulations, and 2) new-generation DFT-based quantum models for phosphoryl transfer reactions. Applications to large-scale simulations of ribozyme catalysis in the hammerhead and hairpin ribozymes will be outlined.

**COMP 305 Structure-based design of opioid ligands**

David M. Ferguson, Department of Medicinal Chemistry and Center for Drug Design, University of Minnesota, 7-125 Weaver-Dendford Hall, University of Minnesota, Minneapolis, MN 55455, ferguson@umn.edu

The structural basis to opioid ligand recognition is explored using a combination of molecular modeling, organic synthesis, and experimental ligand binding studies. Models of the μ-, δ-, and κ-opioid receptors are described and applied to understand the structural basis to ligand recognition and selectivity. The resulting binding site models are used to guide the synthesis of opioid ligands with differing selectivities and in the design of site directed mutagenesis studies that target specific sites or residues within the receptor. The results indicate opioid receptors contain multiple sites of recognition which may explain the failure of previous structure-activity relationship (SAR) studies in the development of potent analgesics. In addition, evidence is presented that suggests opioid receptors are activated or triggered by several mechanisms, providing clues to the design of novel ligands with mixed agonist/antagonist properties.

**COMP 306 Predicting and understanding GPCR-ligand binding using feature-map vectors**

Julie E. Penzotti and Gregory A. Landrum, Rational Discovery LLC, 555 Bryant St. #467, Palo Alto, CA 94301, penzotti@RationalDiscovery.com

GPCRs are attractive molecular drug-discovery targets in a variety of therapeutic areas including allergy, obesity, cardiovascular problems, cancer, pain, diabetes, and depression. Insight into the three-dimensional structure of GPCRs is crucial for understanding their function and designing new drugs. However, the challenges of X-ray or NMR structure determination for transmembrane receptors like GPCRs limit the use of structure-based drug design methods for this
important family of targets. We have developed a new class of descriptors, feature-map vectors (FMVs), that are highly interpretable and informative for use in building predictive models. One significant advantage of FMVs is that they can be derived in the absence of structural data using our previously published conformation-mining algorithm. Here we report the results of applying conformation mining and FMVs to identify ligands for specific GPCRs. We will compare the conclusions that can be drawn from the FMV results to previous SAR and QSAR studies.

**COMP 307 Homology modeling of angiotensin II type 1 (AT1) receptor and in silico screening in search of unique AT1 antagonists with selective PPAR-ã modulating activity**

Akshay Patny, Prashant V. Desai, and Mitchell Avery, Department of Medicinal Chemistry, University of Mississippi, 417, Faser Hall, School of Pharmacy, University, MS 38677, akshay17@olemiss.edu

Angiotensin II type 1 (AT1) receptor belongs to the super family of G-protein-coupled receptors and AT1 receptor antagonists like losartan and telmisartan are effectively used in the treatment of hypertension. Recently, it has been reported that telmisartan, a structurally distinctive AT1 receptor antagonist also acts as a partial agonist of the peroxisome proliferator activated receptor-γ (PPARγ) and reduces glucose, insulin and triglyceride levels in rats. Availability of antihypertensive agents possessing the ability to improve insulin resistance and dyslipidemia can prove beneficial for the prevention and treatment of cardiovascular disease and diabetes in high-risk populations. To understand the molecular interactions of antagonists like telmisartan with the AT1 receptor, a homology model of the human AT1 receptor with all connecting loops was constructed from the 2.6 Å resolution crystal structure (PDB id: 1L9H) of bovine rhodopsin. The model was validated based on its ability to explain several site-directed mutagenesis and known ligand-binding data. The developed homology model of the AT1 receptor along with other ligand-based strategies and the available PPARγ crystal structure are being utilized to perform in-silico screening of commercial databases. The results of this hybrid virtual screening approach for both AT1 as well as the PPARγ receptor will be presented. The knowledge gained from these studies will be utilized for the identification and design of lead candidates which can act as antagonists at the AT1 receptor while simultaneously acting either as agonists or partial agonists at the PPARγ receptor, with a potential use in the management of metabolic syndrome.

**COMP 308 Optimizing diverse combinatorial libraries around known targets**

Tamsin E. Mansley, Farhad Soltanshahi, and Robert D. Clark, Tripos, Inc, 1699 S. Hanley Rd., St. Louis, MO 63144, tmansley@tripos.com

General screening libraries are designed to cover the known chemistry space while having good physicochemical properties. Targeted libraries, in contrast, are designed to be similar to more or less specific leads or drugs. But this implied dichotomy is a false one, in that it is possible to design both properties into the same library. We will discuss an incremental construction method for designing a structurally diverse library that is targeted to GPCRs, is optimized on shape similarity to known leads, and satisfies practical constraints on synthetic accessibility.

**COMP 309 Large-scale ligand-based modeling for predictive drug design**

Ajay N. Jain, Cancer Research Institute, University of California, San Francisco, Box 0128, San Francisco, CA 94143-0128, Fax: 650-240-1781, ajain@jainlab.org, and Ann E. Cleves, BioPharmics LLC

The space of small-molecule therapeutics comprises slightly over 1,000 compounds. Systematic annotation of the primary targets of these drugs reveals that over 700 of these modulate the activity of approximately 85 biological targets, with a very large proportion represented by targets such as GPCRs and ligand-gated ion channels. We constructed ligand-based models of 22 diverse targets and tested the models’ ability to identify cognate drugs from a background of random screening molecules. In 20/22 cases, we observed excellent enrichment of cognate drugs versus random screening ligands (≥ 100-fold). Using a background of drug molecules, enrichment of greater than 80-fold was observed in 17/22 cases, illustrating strong selectivity of the computational models for known cognate drug ligands, and performance with GPCR targets was particularly strong. In addition to providing a predictive tool for target-directed ligand design, analysis of the predicted patterns of biological activity derived from crossing all modeled targets against numerous drug chemical classes identified a number of known side-effects, drug specificities, and drug-drug interactions that have a rational basis in molecular structure.

**COMP 310 A computational study on the stability of new krypton-bonded molecules**

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Density functional theory (B3LYP) and ab initio [MP2 and CCSD(T)] methods have been used in combination with the correlation consistent basis sets (cc-pVnZ, where n = D, T, Q, 5) to predict the stability of new noble gas compounds of the form XNgCCNgX (where Ng = Ar, Kr and X = F, Cl, Br). To help understand the stability of these molecules minimum energy structures, transition states, dissociation pathways, relative energies, charge distribution, and vibrational frequencies have been determined.
**COMP 311 Activation of the C-X bond by palladium: Direct oxidative insertion vs. S_N2 and the importance of relativistic and solvent effects**

G. Theodoor de Jong and F. Matthias Bickelhaupt, Department of Theoretical Chemistry, Vrije Universiteit Amsterdam, De Boelelaan 1083, NL-1081 HV Amsterdam, Netherlands, dejong@few.vu.nl

The catalytic activation of the C–X bond by palladium complexes is of major importance for synthetic chemistry. There are two competing pathways: direct oxidative insertion and an alternative S_N2 pathway, see illustration. The preference for one of both pathways can be steered through the choice of ligands (for example, Cl') in the model catalyst. In the present study, using density functional theory (DFT), we explore the oxidative addition reactions of Pd and PdCl with CH_3X, with X = F, Cl, Br, I and At. Trends in reactivity are analyzed using our Activation Strain model, in which the activation energy is decomposed into the strain of the reactants and their mutual interaction energy. We also investigate how relativistic and solvent effects influence the characteristics of the reactions.

**COMP 312 Adsorption of H2S on carbon nantube**

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To validate an appropriate density functional theory which can well describe noncovalent interactions between H2S and single walled carbon nanotube (SWNT), adsorptions of H2S on benzene and coronene (C24H12) are firstly investigated with MP2 as well as a variety of novel exchange-correlation DFT functionals such as PW91PW91, PBEPBE, MPW1PW, and PBE1PBE. PBEPBE provides the most agreement result with MP2 in terms of geometries and binding energies. Adsorptions of H2S on (10,0) were then investigated with the three layer Onion method (MP2:PBEPBE:MM). A number of binging geometries, electron transfer and diffusion of H2S on SWNT were discussed in detail.

**COMP 313 Combined ab initio and ab initio molecular dynamics studies on the oxygen reduction reaction on Pt surface**

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An understanding about the oxygen reduction reaction (ORR) has very important implications into the design of more efficient cathode catalysts for the proton exchange membrane fuel cell. Ab initio molecular dynamics (CPMD) simulation was first employed to explore the ORR on a surface of Pt(111) in the presence of H+(H2O)4 to mainly address the question: whether the ORR proceed in the 4-electron direct or the series pathway? On the basis of new insights into the mechanism of the ORR, DFT was then used to calculate Gibbs free energy changes for the rate-determining-step (rds) as well as for the rest of the complete reduction for most of the transition metals. Gibbs free energies were found to have a strong correlation on the valence electronic structures of the metals. Finally, an ab-initio-derived thermodynamic guideline was suggested for the design of oxygen reduction bimetallic catalyst.

**COMP 314 Investigation of H2 adsorption sites in MOFs using ab initio methods**
The Metal Organic Frameworks – MOFs, are porous materials with very promising H2 uptake capabilities. Several ab initio electronic structure methods including DFT, MP2 and RI-MP2 are employed to elucidate the potential adsorption sites. Emphasis has been given to the recently identified sites located at organic linker within MOFs. Different models of the existing adsorption have been defined subject to the computational capabilities of the underlying method. The calculated adsorption sites are in good agreement with latest experimental data. In addition, it is predicted that by chemically manipulating the organic linker, a further improvement of the hydrogen uptake capabilities of these materials would be achieved.

**COMP 315 Quantum chemical molecular dynamics study of single-walled carbon nanotube (SWCNT) nucleation on metal catalyst nanoparticles Fe38/Co38/Ni38**

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The unique properties of Single-Walled Carbon Nanotubes (SWCNT) make them a promising new material for a wide range of applications. However, it is desirable for realistic applications to produce specific types of SWCNT with narrow diameter distributions and designed electrical properties, which is still a big challenge for experimentalists and has not yet been achieved. The parameters influencing diameter and chirality distributions of SWCNT during nucleation are inaccessible to experiment, and classical mechanics based molecular dynamics simulations fail to correctly describe both time scales as well as π-conjugation mediated self-assembly processes of high-temperature sp2 carbon structures. In particular, the role of different catalyst elements responsible for different yields and tube parameters in experiments is not clear. Understanding the SWCNT formation mechanism is thus imperative to clarify the effects from different experimental conditions. In order to study the metal-catalyzed SWCNT formation mechanism on relatively long time scales, we employ the Density-Functional based Tight-Binding (DFTB) method for which we have developed Fe, Co, and Ni parameters with H, C, N, and O elements. Detailed benchmark test results show that the new DFTB transition metal parameters will qualitatively reproduce the potential energy surface features from first principles Density Functional Theory (DFT) calculations, therefore are expected to produce similar dynamics. The QM/MD trajectories (several tens of picoseconds) are run under different temperatures using metal nanoparticles Fe38/Co38/Ni38. There are some interesting phenomena observed from our preliminary studies: (1) the reactions are more sensitive to temperature than pure carbon systems, which agree with experimental observation, and (2) we also observe diffusion of carbon fragments into cobalt nanoparticles contrary to the iron and nickel case.

**COMP 316 Electronic structure of oxo-Mn(salen)**

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Using single- and multi-reference approaches we have explored many of the low-lying electronic states of oxo-Mn(salen), some of which have yet to be explored theoretically. We have observed the existence of multiple Hartree-Fock solutions for this system and have investigated the stability of these wavefunctions. We have also carried out calculations using several popular density functionals, such as BP86 and B3LYP. Although the DFT approaches do not seem to suffer from the wavefunction instability problems of Hartree-Fock theory, each of the functionals gives a qualitatively different ordering for the spin-states of this system. We attempt to obtain an accurate ordering for the relevant electronic states of this system using large CASSCF and SA-CASSCF approaches, comparing the results to those from DFT.

**COMP 317 Ab initio insight on the interaction of Urate with Li+, Na+, K+, Be2+, Mg 2+ and Ca2+ Metal Cations**

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The geometries and energetics of complexes of urate with Li+, Na+, K+, Be2+, Mg2+, and Ca2+ metal cations were studied. The complexes were fully optimized utilizing the density functional level theory employing the B3LYP exchange correlation functional and the 6-311++G(d,p) basis set. The interactions of the metal cations at the different binding sites of urate were considered. In this investigation it was revealed that the metal cations would interact with urate in a bicoordinate manner. In the gas phase, the most preferred position for the interaction of urate with Li+, Na+, and K+ cations is between the N3 and O2 sites, while all divalent cations Be2+, Mg2+, and Ca2+ prefer binding between the N7 and O6 sites of urate. However all of the metal cations possessed the strongest binding energy toward the N7 and O6 sites. The influence of aqueous solvent on the relative stability of different complexes has been examined using the Tomasi's polarized continuum model. The basis set superposition error (BSSE) corrected interaction energy was also
computed for complexes. The AIM theory has been applied to analyze the properties of the bond critical points (electron densities and their Laplacians) involved in the binding between urate and the metal cations.

**COMP 318 MFCC-DM with pairwise interaction correction for quantum chemical study of protein**

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Pairwise interaction correction (PIC) that is compatible with the Molecular Fractionation with Conjugate Caps (MFCC) is introduced to account for the short-range interactions such as hydrogen bonding and close contact in the MFCC treatment of proteins in a divide-and-conquer (DAC) fashion. With this correction, the MFCC-Density Matrix (DM) approach to calculate protein energy and other electronic properties is improved and can be used to study a real protein with short-range structural complexity. In this MFCC-DM-PIC method, a protein molecule is partitioned into properly capped fragments and concaps. The short-range inter-residual interactions are represented by a pair of small molecules (interacting units) which are made from the two residues that fall in a certain distance criterion. The density matrices of fragments, concaps, interacting units and pairs are then calculated by conventional Hartree-Fock (HF) or Density Functional Theory (DFT) methods and assembled to construct the full density matrix which is finally employed to calculate the total energy, electron density, electrostatic potential, dipole moment, etc., of the protein. Numeric tests on seven conformationally varied peptides are presented to demonstrate the accuracy of this MFCC-DM-PIC method.

**COMP 319 Questionable spin parameters from DFT**

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Density functional theory is now often used to obtain the exchange parameters for the Heisenberg Hamiltonian. Some examples will be given to show how this often fails but occasionally succeeds.

**COMP 320 Further development and applications of the DFTB (Density Functional Tight Binding) method**

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The DFTB method, developed by two groups in Paderborn and Dresden, is a semiempirical two-center approximation to the density functional method, and has been shown to provide reasonable reliability at modest cost. We have been involved with the Paderborn group in further development of the method on three fronts: 1. analytical geometrical second derivative and numerical derivative of gradient with respect to external electric field, 2. determination of parameters for first row transition metals with HCNQ atoms, 3. implementation of DFTB in the Gaussian package. We applied this method as stand alone or ONIOM(DFT:DFTB) scheme, sometimes combined with molecular dynamics (MD), to many nanostructure and catalysis applications. Some examples including those on formation mechanism of single-walled carbon nanotubes (SWCNTs) and functionalization of SWCNTs will be discussed.

**COMP 321 Hydrogen-bonded clusters**

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Our laboratory has been involved in determination of structures and energetics of small hydrogen-bonded clusters by various quantum chemical methods including semiempirical, density functional, and ab initio Möller-Plesset perturbation theory and coupled cluster methods. Hydrogen-bonded clusters involving formic acid, nitric acid, glycolic acid, oxalic acid and water molecules have been studied. The computational challenges encountered, the strategies used to face them, and some of the results obtained are surveyed.

**COMP 322 Density functional theory of materials modeling at different length scales**

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Materials modelling has been one of the important areas of research in various disciplines of science and engineering. Depending on the interest and application one is concerned with, an appropriate length scale is chosen for a theoretical description of the structure and properties of materials. One of the concepts that has played a major role in the conceptual as well as computational developments covering all the length scales of interest in a number of areas of chemistry, physics and materials science is the concept of single-particle density.

In the microscopic length scale, it is the electron density that has played a major role in providing a deeper understanding of chemical binding in atoms, molecules and solids. In the intermediate mesoscopic length scale, an appropriate picture of the equilibrium and dynamical processes has been obtained through the single particle number
density of the constituent atoms or molecules. A wide class of problems involving nanomaterials, interfacial science and soft condensed matter has been addressed using the density based theoretical formalism as well as atomistic simulation in this regime. In the macroscopic length scale, however, one usually considers matter as a continuous medium and a description using local mass density, energy density and other related density functions has been found to be quite appropriate.

In spite of the differences in the nature of the density variables used in all these descriptions, the corresponding theoretical frameworks have been found to possess an underlying unified structure. Besides attempting to project the many-particle picture to a single particle one, this density functional theory based description provides a unified theoretical framework for quantum as well as classical systems encompassing the diverse length scales involved in materials modelling, the basic features and some recent developments of which form the subject matter of the lecture.

**COMP 323 Chemical accuracy along reaction paths: Full ab-initio calculation of the full vibrational spectrum of the fluorine molecule to wavenumber accuracy**

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For energies along reaction paths, including transition state barriers, chemical accuracy has remained a challenge because the relevant zeroth-order wavefunctions are typically multiconfigurational, a fact that creates serious difficulties for density-functional as well as coupled-cluster approaches. We have developed a new method that recovers the full dynamic correlation energy with equal efficiency for multi-determinant as well as single-determinant reference functions. It was made possible by the discovery of certain intrinsic scaling relations between the convergence rates of the correlation contributions at different CI excitation levels. These relations have led us to efficient accurate CI extrapolations. Using double-, triple- and quadruple-zeta basis sets, complemented by complete-basis-set extrapolation and relativistic corrections, the method has yielded the binding energy of N2 within less than 0.06 kcal/mol of experiment, and those of O2 and C2 within less than one kcal/mol of experiment, accuracies not previously achieved. For F2, we calculated the entire dissociation curve, fitted an even-tempered Gaussian expansion to it and complemented it by a long-range dispersion tail. The dissociation energy agrees with the experimental value within 0.1 kcal/mol, which is less than the experimental uncertainty of 0.15 kcal/mol. The calculation of the energy levels of this fully ab-initio potential energy curve has yielded all 23 levels of the experimentally observed vibrational spectrum with a deviation of a wavenumber or less. The approach also yielded a decoupling of the value of the coefficient in the dispersion term A/r^6 from the experimental spectrum in the absence of a van-der-Waals minimum.

**COMP 324 Solving the Schrödinger and Dirac-Coulomb Equations and developing the Giant SAC/SAC-CI Method**

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Very accurate prediction and giant-system applicability are two targets of modern quantum chemistry. For the first target, a straightforward way is to develop a general method of solving the Schrödinger equation and the Dirac-Coulomb equation. We are currently developing such method. For the second target, we have to develop size-extensive, correlated, and widely applicable theory for giant molecular systems. As such method, we are extending the SAC/SAC-CI method to giant molecular systems. A review of these two approaches will be given.

**COMP 325 A DFT study of the action of Vitamin K Carboxylase**

**Lee G. Pedersen**, Department of Chemistry, Univ N. Carolina, CB#3290, Chapel Hill, NC 27759, and Charles H. Davis, Department of Biochemistry and Biophysics, University of North Carolina at Chapel Hill

Vitamin K is an essential element of the blood coagulation system. The human vitamin K carboxylase and vitamin K epoxide reductase have now both been cloned and sequenced. In the Vitamin K cycle, glutamic acid is converted to gamma-carboxy glutamic acid and the catalytic cofactor vitamin K is conserved. The carboxylase creates a quinone-epoxide functionality from the hydroquinone unit of vitamin K; the reductase takes the epoxide back to the starting form. It is this latter step that is presumably blocked by the drug Warfarin. Previously we have focused on modeling the reductase part of the cycle that involves vitamin K; in this work we consider the formation of the reactive epoxide from the hydroquinone. The fundamental mechanism studied is the reaction of the hydroquinone form of vitamin K with a singlet oxygen molecule to form the quinone form of vitamin K with the epoxide unit in place. We report on stable intermediates and several transition states found applying DFT (method/basis=B3LYP/6-311G**).

**COMP 326 Did amyloid seed the origins of life?**

**David Lynn**, Anil Mehta, Kun Lu, Jijun Dong, Yan Liang, Peng Liu, Rong Ni, W. Seth Childers, James Simmons, and
As the structures and functions of natural genomes are unveiled, it becomes possible to extend the chemical principles most central to living systems beyond the realm of present-day organisms. Armed with this thought, we have attempted to look back in "functional" evolutionary history to identify a common structural ancestor of proteins and nucleic acids. I will argue that amyloid, best known for its association with degenerative maladies including diabetes, prion disorders including mad cow cross-species infectious particles, and Alzheimer's diseases (AD), represents a possible ancestor. Control of the self-assembly of this supramolecular ordered protein assembly, seemingly accessible to all polypeptide sequences, is certainly critical for disease intervention but is now becoming relevant for nanotechnological applications. Here we report various solid-state NMR and scattering experiments that have defined diverse morphologies evolving from peptide solutions of the Alzheimer's disease related Aβ peptides. These morphologies range from fibrils, sheets, helical ribbons, twisted ribbons, and nanotubes, each emerging from nucleating clusters that propagate in the presence of free peptide. Physical stabilization of a nucleus or arresting its propagation dictates successful selection of any given morphology. Nucleation can also drive covalent bond formation, stabilizing and further increasing the half-life of a selected structure. These findings we view as initial steps towards a synthetic biology where a rich diversity of approaches is emerging for the construction of supra-molecular self-assemblies -- ones that can be selected for desired functional properties.

COMP 327 Development of diffusion ordered NMR spectroscopy: Promise and pitfalls
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The development of novel magnetic field gradient methods in NMR for the study of transport properties in mixtures is reviewed. Modern experiments make use of pulsed magnetic field gradients (PFG-NMR) and fast Fourier transforms (FFT) to obtain high-resolution NMR spectra encoded with information about the diffusion and flow of components. Special algorithms permit the generation of multidimensional displays in which a distribution of diffusion coefficients is displayed in one of the dimensions. Difficulties often arise in (a) the determination of unique diffusion coefficients from NMR data sets and (b) the interpretation of diffusion data in the presence of chemical exchange. Exchange effects are discussed for various systems including micelles and microemulsions.

COMP 328 Molecular modeling of the oxidized form of nuclear factor κB suggests a mechanism for redox regulation of DNA binding and transcriptional activation
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NF-κB is an important transcriptional regulator of numerous cellular genes, as well as retroviruses such as HIV-1. Paradoxically, oxidative stimuli in the cytosol are associated with nuclear translocation of NF-κB, but in the nucleus, reductive activation by thioredoxin is required for NF-κB to bind to DNA and activate target genes. Experimental structures of the reduced form of NF-κB and its DNA targets are available, from which we modeled the oxidized form of NF-κB homodimer by removal of bound DNA, and modification via a hinge movement of a linker between the dimerization and DNA binding domains of each subunit. Molecular dynamics then enabled the formation of an inter-subunit disulfide bond between the Cys56 residues of each monomer. The resulting model of oxidized, disulfide bridged NF-κB is clearly more compact than the open, reduced form, which may explain why oxidation is necessary for nuclear translocation, through pores in the nuclear envelope. Furthermore, the inter-subunit disulfide blocks DNA from entering the active site of the oxidized dimer, explaining why reduction to the thiol form in the nucleus is essential for transcriptional activation.

COMP 329 Molecular Skeleton Analysis (MoSA) and its application for NMDA/glycine/kynurenic binding complex
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Molecular Skeleton Analysis (MoSA) is a 3D QSAR program. A set of training molecules is required to develop the QSAR model. All training molecules need to be converted to 3D and superimposed. Physical chemical properties of interest, e.g., partial charge, atomic volume, and H-bonding potential, are assigned to each atom of all training molecules. A grid box is constructed for each property included in the study. For any given molecule, property distributions of all atoms on all grid points are calculated using Gaussian function. The accumulated property distributions at grid points are used as descriptors for the given molecule. After the SAR table has been populated, Partial Least Square is used to generate the final QSAR model. Two published sets of data were used to compare the performance of MoSA with CoMFA, which uses...
Program Report

**COMP 330 QSAR studies of high potency sweeteners and novel sweetener discovery**

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Sweetness perception is a very complex phenomenon which is thought to be initiated by the interaction of a sweetener with a receptor. Since the Shallenberger and Acree’s “AH-B” model of 1969, several hypotheses on how this binding occurs have been proposed in an attempt to explain the induction of sweetness. Despite many research efforts in this field, no single sweetener receptor was identified at the time when this work was conducted in the mid 90s.

At The Coca-Cola Company, we have been conducting peptide sweetener research since early 80s. During the mid 90s, we applied computational chemistry in the design and synthesis of new peptide sweeteners. This presentation describes a new sweetener QSAR model using the Comparative Molecular Field Analysis (CoMFA). The model gives significant insights into the steric and electrostatic fields required for activation of the so-called “aspartame receptor”. Further, it has been applied in the discovery and rationalization of a group of novel peptide sweeteners. The synthesis and SAR of these new sweeteners will also be discussed.

**COMP 331 Selective isotopic labeling in macromolecular NMR studies**

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Selective labeling of biologically significant macromolecules was an early tool developed to deal with the spectral complexity of biological macromolecules, and subsequently fell into disuse as photon labeling approaches succeeded neutron labeling. More recently, the approach has a second life as a strategy for dealing with relatively large proteins, for probing conformational transitions, and for addressing specific chemical questions. The results of recent studies utilizing specific labeling with methionine, lysine, and tyrosine to address conformational and chemical questions in DNA polymerase 8 and in other macromolecules will be presented.

**COMP 332 Successful structure-based design of novel protein tyrosine phosphatase inhibitors**

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Through structure-based combination of geometric features from diverse classes of inhibitors crystallized in complex with protein tyrosine phosphatase 1B (PTP1B), we were able to design a novel heterocyclic phosphotyrosine mimic. This designed heterocycle is the basis for a class of extremely potent, competitive, and reversible inhibitors of PTP1B. Crystal structures of PTP1B in complex with these inhibitors show that the phosphotyrosine mimic binds in the active site of the enzyme exactly as designed. This work represents the potential power of structure-based design approaches in targets for which there is a fair amount of structural data available.
COMP 333 Hierarchical representation of protein conformation: Application in flexible receptor docking
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A tree-like representation of protein flexibility, "Flexibility Tree", is implemented to describe the protein conformation at different levels. The sub-space of a protein's conformational space, which contains conformations relevant for the biological activity of the protein, can be applied to protein-ligand docking. Receptors are recursively decomposed into rigid fragments. We implemented a variety of analytical motions (hinge, screw, translation, local perturbation, etc.) and discrete motions such as vibrations obtained from normal mode analysis or essential dynamics, or given by a finite set of conformations. The parameters of the motion objects are part of the search space. A new docking program is built based on the Flexibility Tree and the AutoDock 3.05 force field. Of the 100 previously failed HIV protease cross-docking tests [Proteins: 46, 1, 34], 92 calculations successfully dock the ligands with RMSD less than 1.5 Å from crystal structures.

COMP 334 Homology modeling: Evaluation of loop modeling protocols
Karen A. Rossi, Carolyn A. Weigel, Stanley R. Krystek Jr., and Akbar Nayeem, Computer-Assisted Drug Design, Bristol-Myers Squibb Company, Pharmaceutical Research Institute, P.O. Box 5400, Princeton, NJ 08543-5400, Fax: 609-818-3545, karen.rossi@bms.com

Homology modeling is an integral part of the drug design process. Despite the fact that several techniques are available, a key challenge in this field is the prediction of loops. In this study, four commercially available loop modeling protocols have been evaluated using loops varying in length from 4-12 amino acids. The programs represent a variety of approaches; Monte Carlo searching, database lookup and ab initio methods. Overall comparisons of the modeled loops to the PDB templates were used to determine which method is most accurate. Additionally, a breakdown of the loop lengths was performed to determine the method best suited for short, medium and extended loops. Shorter loop lengths revealed similar results between protocols, however, interesting results were obtained from modeling the extended loops in both accuracy of the loop generation as well as calculation time.

COMP 335 D2Score: A fully automated web server for the dihedral angle based analysis of protein structures
Gungor Ozer, Jonathan Foley IV, Shi Zhong, and Rigoberto Hernandez, School of Chemistry and Biochemistry, Georgia Institute of Technology, 770 State Street, Atlanta, GA 30332-0400, Fax: 404-894-7452, gungor.ozzer@chemistry.gatech.edu

As the number of known protein structures increases, the characterization of these structures becomes more and more important. Beyond the correlations in the \( \phi \) and \( \psi \) values about one residue, the correlations in the \( \psi_{i}\)-\( \phi_{i+1} \) values between 400 different amino acid pairs can play an important role for the dihedral angle analysis. A new scoring function, suggested recently by Hernandez et al., evaluates the degree of structural compatibility with some artificial entropic functions. These so-called D1 and D2 scores might add to the substantial understanding that has already been gained using dihedral angle analysis. A web server, called D2ScoreServer - which gets a user desired PDB file, and outputs these \( \phi-\psi \) and \( \psi_{i}-\phi_{i+1} \) plots, as well as the D1 and D2 scores and the associated residue level color strip - has now been created to make this tool available to the general community.

COMP 336 Assessment of protein structures at the residue level using an entropic score of dihedral-angle correlation
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An entropic score of dihedral-angle correlation proposed for assessing the compatibility of a protein structure to the ensemble of experimentally derived protein structures in the Protein Data Bank (PDB) is used to evaluate the stereochemical quality of a protein structure at the residue level. The origin of the atypical residues has been studied and discussed. A novel color strip is developed to show the degree of the relative atypicality of protein structure along its backbone at the residue level. Such color strips in turn, can be used to investigate structure correlations between distant residues on a protein. As an illustration of its possible utility, the color strip has been used to interpret the structure correlations in the staphylococcal nuclease with structure subject to mutations at a given residue.

COMP 337 Hinge-bending motion in S-adenosyl-L-homocysteine hydrolase: Mutagenesis, fluorescence and modeling
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S-adenosyl-L-homocysteine hydrolase (SAHH) is a homotetrameric enzyme involved in transmethylation reactions. SAHH:inhibitor complexes populate a closed structure, with ligand engulfed by 18° domain reorientation relative to the open, substrate-free conformation. We present mutagenesis, fluorescence and modeling studies to characterize SAHH domain reorientations, with the long-term goal of developing specific antiparasitic SAHH inhibitors. In wild type, substrate-free SAHH fluorescence anisotropy experiments revealed domain reorientations on time scale of 10-20 ns. Mutagenesis and fluorescence studies showed that reorientations involve a crucial hinge region, and that both binding and oxidation of the ligand are needed to shift the equilibrium from open to closed form. Molecular dynamics simulations of SAHH showed domain reorientations in excellent agreement with experiments. Interestingly, the trajectory motions occurred both along and perpendicular to the conformational transition. A normal mode analysis revealed coupled domain/subunit motions, suggesting a mechanism for enzyme cooperativity.

**COMP 338 Molecular modeling of the C-terminal end of human intestinal mucin (MUC2) predicts a cysteine-knot tertiary structure**

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Secretory mucins are the principal determinants of the viscoelastic properties of intestinal mucus, the major barrier to absorption of many drugs. Although mucin is known to play a significant role in inhibition of drug transport and in diseases such as Cystic Fibrosis, its structure remains mostly unknown. A cysteine-rich region (92 residues) exists within the mucin C-terminal domain and is involved in dimer formation. Taking advantage of complete genome sequences in diverse organisms, the present study was undertaken to determine a detailed structure of the C-terminal end of human intestinal mucin (MUC2) via homology modeling. Based on sequence-structure alignments and three-dimensional modeling, a cysteine-knot tertiary structure homologous to that of human chorionic gonadotropin is predicted. The model displays a highly conserved cysteine-knot characteristic, thus providing strong evidence for the existence of the cysteine-knot and novel insight into mucin structure. A comparative experimental study is carried out to validate the model.

**COMP 339 Prediction of Human DP Receptor Structure and Binding mode for prostanoid compounds**

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We perform the structure prediction for the human DP receptor using the MembStruk, first principles prediction method, starting from its amino acid sequence. Using HierDock ligand docking method, we predict the binding mode for endogenous agonist PGD2 and other prostanoid compounds. PGD2 is predicted to locate among TM1237 region and be covered by ECII loop. The residues involved in the predicted binding mode correlate very well with available mutation experiments on DP, IP, TP, FP, and EP subtypes. The predicted binding mode of PGD2 in hDP explains the conservations of prostanoid compounds and receptors. It also leads to good understanding of the selectivity of prostanoid receptors. In the predicted binding mode, PGD2 disrupts TM1-N, TM2-D, TM7-XXXXP hydrogen bond network, which is conserved among rhodopsin superfamily and believed to keep rhodopsin in dark state, and leads to rotation of TM7, which is coupling to activation. The predicted DP structure and binding mode improves our understanding of prostanoid receptors and offers a basis for structure based drug design.

**COMP 340 Structural model of CCR5 for the discovery of entry inhibitors for the therapeutic intervention of HIV-1 infection**

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There are many challenges in determining a robust structure of G-protein coupled receptors by either experimental or computational techniques alone. CCR5 belongs to the family of G-protein coupled receptors and is an attractive target for therapeutic intervention of HIV-1 infection. We characterized the structural and molecular interactions of CCR5 with multiple CCR5 inhibitors active against R5 HIV-1 including a potent in vitro and in vivo CCR5 inhibitor apilavroc. The structural interactions were elucidated by combining the results of site directed mutagenesis experiments, homology modeling, and docking that accounted for the flexibility of the receptor side chains. The quality of the structural model was evaluated by carrying out new saturation binding experiments by mutating CCR5 residues predicted to be important by the model. The structural model enabled us to precisely define the binding site of CCR5 inhibitors within CCR5 and elucidated the key binding site interactions responsible for the anti-viral activity the inhibitors. We will discuss the results of virtual screening of compound libraries based on our model and highlight the importance of combining experiments.
with homology modeling for determining robust GPCR structures.

**COMP 341 Improved docking method for organics adsorbed in zeolite catalysts**  
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A molecular docking method has been developed to improve the identification of preferred sites of adsorbates in zeolite catalysts that are widely used in petroleum cracking. The newly developed method has been used to explore the configurational space of benzene in supercages of protonated zeolite faujasite using Monte Carlo minimization algorithm coupled with radius-based sampling and the Compass force field. The simulations confirmed previous theoretical and experimental findings of multiple adsorption sites of benzene at proton and window sites in the faujasite supercage cavity. Additionally, the simulations predicted a new lowest energy minimum in some supercages having appropriate charge distribution of the zeolite structure. These results demonstrate the suitability for this method to be a complementary tool in understanding reactions and separations of organics adsorbed in porous crystalline materials at a molecular level.

**COMP 342 Integration of in-silico filters and computational quantum chemistry for structure based COX-II specific drug design and screening**  
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In this work we investigated the molecular recognition of the interacting molecules with the chemical structure of active sites as a rational approach towards pharmaceutical drug design. The structure of target protein is known a priori. Considering the biological activity, the information gained from this study can be used as a method for virtual screening of drugs in the final stages of pre-clinical development and for design of new or improved drugs. We have employed a computational quantum chemistry approach using Gaussian 98, and the Jaguar software packages integrated with in-silico drug screening tools. Primary considerations during this investigation were geometrical characteristics, and protein–inhibitor interaction energy considerations. Various candidate molecules were developed as analogues of a known COX-II specific inhibitor. Molecular Mechanics and ab-initio calculations were performed on the candidate molecules for structure and energy optimization. First set of lead compounds were selected after passing them through empirical filters which assed their drug-like properties. Empirical filters such as Lipinski's rule of five were used which uses molecular properties like LogP, hydrogen bond donor and acceptor and molecular weight. Group-contribution method was used to obtain a variety of molecular properties. For each successful candidate molecule, protein-ligand docking calculations were performed and free energy was estimated using the DOCK program. The candidate molecules were reported as lead compounds depending upon the value of the Free Energy. This method not only accelerates the drug discovery process but also allows development of novel compounds which might be better than existing COX-II inhibitor. The computational results were compared with established experimental results to benchmark our study. The study was further extended to new drugs and candidate drugs were screened based on the protein-ligand binding energy. The study revealed results, which can aid in screening the drugs based on their binding ability to the target protein.

**COMP 343 Modeling fragmentation reactions of gas-phase peptide-ions**  
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Investigations of the structural and energetic properties of molecules in the gas phase represent an important new direction for scientific research. The proliferation of mass spectrometry in the field of proteomics has led to the regular study of gaseous, ionized peptides. Modeling such molecules using the majority of contemporary empirical force fields for proteins would prove problematic as these have been optimized for the study of proteins in condensed phases. Furthermore, these molecules carry charges in nonstandard places, such as on atoms along the peptide backbone. Motivated by these limitations, we have developed and validated parameters for ionized peptides in the gas phase. Specifically, we are studying the conformations of protonated peptides. As the first step toward successful modeling of peptide ions in the gas phase, force field parameters for the protonated peptide backbone, based on the CHARMM22 protein force field, are being developed. We also compare results of modeled fragmentation reactions with mass spectral data.

**COMP 344 Molecular modeling of chemical warfare agents**  
Ganesh K Kamath, Department of Chemical Engineering and Materials Science, Wayne State University, Detroit, MI 48201, 5050, Anthony Wayne Dr, Detroit, MI 48202, g_kamath@wayne.edu, and Jeffrey J. Potoff, Department of Chemical Engineering and Materials Science, Wayne State University
Molecular-level understanding of the adsorption process of chemical agents onto surfaces and/or porous media is necessary for the design of improved sensors, filters and catalytic materials. Due to the toxic nature of such agents, the majority of experimental adsorption studies have been performed with relatively non-toxic simulators. Simulants are non-toxic analogs that contain the functional group thought to be most important, but lack other moieties that would cause them to be toxic. Molecular simulation is well suited to the study of toxic materials provided an accurate molecular model or "force field" is available. In this work, we present recently developed force fields for the chemical agent sarin and its non-toxic analog dimethylmethylphosphonate (DMMP). These force fields are based on a Lennard-Jones plus fixed point charge functional form and utilize a united-atom representation for the methyl, methylene and methine moieties. Partial charges are determined from a CHelpG analysis of ab initio calculations performed at the HF/6-31g+(d,p) level. Lennard-Jones parameters for the -O, =O, CH, and CH3 functional groups are taken from the Transferable Potentials for Phase Equilibria United-Atom (TraPPE-UA) series of force fields. Lennard-Jones parameters for the remaining phosphorous atom are tuned to reproduce the vapor pressure of DMMP from 325-408 K as well as the liquid densities at 373 K and 303 K at 1 bar. With no additional parameterization, the liquid density at 298 K and normal boiling point for sarin are predicted to within 1% of experimental values. Additional calculations were performed to determine the adsorption isotherms for DMMP and sarin in graphite slit pores. While both DMMP and sarin exhibit type I adsorption isotherms, significant quantitative differences are found.

**COMP 345 Rapid and accurate evaluation of the electromagnetic response properties of noble metal nanoparticles**

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The discrete dipole approximation (DDA) is a widely-used numerical method for investigating the electromagnetic response properties of metallic nanoparticles; the method models a nanoparticle as an array of polarizable subunits. Although the subunit polarizabilities are often chosen to be defined by the Clausius–Mossotti (CM) relation, recent work [Rahmani et al., Astrophys. J. 607, 873 (2004)] suggests that subunits near the nanoparticle's surface should be assigned different polarizabilities to account for the near-surface local environment. We use the DDA method to compute the response of nanoscale prolate metal spheroids to a static uniform external electric field, employing either the conventional CM polarizabilities or the surface-corrected polarizabilities. We find that simulations based on CM polarizabilities can exhibit serious errors, particularly for high-aspect-ratio spheroids that are of interest in surface-enhanced Raman spectroscopy and other nanoscale photonics applications. If time permits, we will also present some preliminary DDA simulations of high-aspect-ratio nanoparticles using non-cubic subunits and compare these simulations with those using cubic subunits.

**COMP 346 Reactive molecular dynamic approach to thermal decomposition of kerogen**

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Kerogen, the insoluble fraction of sedimentary organic matter, is a complex mixing of organic macromolecules, the structure of which evolves during geological times as a function of temperature mainly. The thermal evolution of kerogen is at the origin of hydrocarbon deposits in sedimentary basins. Understanding and quantifying the physicochemical processes associated to this transformation is therefore important to improve the evaluation of petroleum systems. To date, thermal transformations in kerogen are represented by empirical equations that are not theoretically justified, leading to uncertainties in predicting hydrocarbon volumes. This work attempts to derive physicochemically constrained kinetic models of kerogen cracking directly from molecular dynamics (MD) using the ReaxFF reactive force field whose parameters are derived from quantum mechanics. We report the molecular model for algalenan, a geopolymer, from ReaxFF MD, and compare it to experimental pyrolyses of algalenan. Gaps and similarities between the model and the data will be discussed during the presentation.

**COMP 347 Structural characterization of n-octanol and 3-octanol interfaces using molecular dynamic simulations**

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The structurally isomeric octanol interface systems, water/vapor, 3-octanol/vapor, n-octanol/vapor, 3-octanol/water, n-octanol/water, mixture of 3-octanol, n-octanol/vapor and mixture of 3-octanol, n-octanol/water were studied at 298 K using molecular dynamics simulation techniques. The present study is intended to investigate strongly associated
liquid/liquid interfaces and probe the atomistic structure of these interfaces. Our results supports the hypothesis of an ordered interface only 1 or 2 molecular layers deep before bulk properties are reached for the 3-octanol and water systems. However, in contrast to most other systems studies by molecular dynamics simulations, the n-octanol interface extends for several molecular layers. The octanol hydroxyls form a hydrogen bonded network with the water which orders the surface molecules into a preferred direction and produces a hydrophilic/hydrophobic layering. The ordered n-octanol produces an oscillating low-high density of oxygen out of phase with a high-low density of carbon atoms, consistent with an oscillating dielectric. In contrast, the isomeric 3-octanol has only a single carbon rich layer directly proximal to the interface, as a result of the different molecular topology. Both octanols roughen the water interface with respect to the water/vapor interface. Water within the octanol phases breaks up the ordering of the interface and reduces the distance of the octanol/water interface perturbations. The "wet" octanol phases, in the octanol/water systems reaches bulk properties in a shorter distance then the "dry" octanol/vapor interfaces.

COMP 348 Optimization of ROMP poly(norbornene) as a catalyst support using molecular simulations
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ROMP poly(norbornene) (PNB) is currently being examined as a possible catalyst support for an immobilized organometallic catalyst. Because it has a number of configurations, it may be possible to synthesize a conformation of PNB that is more elongated and helical, and therefore more accessible to the reactants, giving an increase in the reaction rate. Molecular modeling techniques were used to find the low-energy conformations. From previous work with poly(norbornane), it is theorized that a polymer that will form an elongated helix needs alternating rotatable/non-rotatable bonds, cis across the non-rotatable bonds, and a bulky side group that alternates sides of the polymer backbone. Therefore, it was expected that the only configuration of PNB that would result in an elongated helical structure would require racemic dyads, cis across the double bond, and a side group. While the cis racemic version did have a somewhat helical structure, both of the meso dyadic configurations also remained in helices.

COMP 349 Computational chemistry with "MULTIMODE" and new strategies for ab initio potential energy surface
Joel M. Bowman1, Bastiaan Braams2, Stuart Carter3, Xinchuan Huang1, Zhong Jin1, and Zhen Xie1. (1) Department of Chemistry and Cherry L. Emerson Center for Scientific Computation, Emory University, Atlanta, GA 30322, jmbowma@emory.edu, (2) Department of Mathematics and Computer Science and Cherry L. Emerson Center for Scientific Computation, Emory University, (3) Department of Chemistry, University of Reading, UK, Cherry L. Emerson Center of Scientific Computation and Department of Chemistry, Emory University

I will describe the code MULTIMODE which calculates rovibrational energies of polyatomic molecules using full dimensional potential energy surfaces. Advances in creating potential energy surfaces that explicitly exploit the permutational symmetry of like atoms will also be reviewed briefly. This approach is used to fit of the order of 104-105 high quality ab initio energies to obtain global potentials that also dissociate correctly.

I will describe applications to a variety of molecular systems, eg. CH3+, H5+, H2O2+, H3O2−, CH3OH, etc.

COMP 350 Structural features of hairpin triloops in rRNA in light of global conformational changes upon ligand binding
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RNA structure can be considered as being a flexible polymer of various structural motifs that is substantially influenced by its environment. By using the 3D structures of 4 free rRNAs and 38 large ribonucleoligand complexes as the starting point, all rRNA residues in contact with ligands as well as regions of considerable conformational changes upon complex formation are identified. The behavior, influenced by ligand binding, of 73 hairpin triloops with closing g-c and c-g base pairs is investigated using root-mean-square deviation (RMSD) approach and PRIMOS-pseudotorsional (n, θ) convention at the nucleotide-by-nucleotide level. A possible classification of the interior triloops, based on the 2D n-θ unique path, is established. The pseudotorsion analysis is suggested to be a possible way of resolving ambiguities of the sugar-phosphate backbone in the 2.5-3 Å resolution range, typically attained for large biologically relevant nucleic acids. The present work sheds more light on the particular conformations involved in function of the ribosomal machinery.

COMP 351 Molecular docking and analysis of interactions between vascular endothelial growth factor (VEGF) and SPARC protein
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The extracellular module of SPARC/Osteonectin binds to vascular endothelial growth factor (VEGF) and inhibits VEGF-stimulated proliferation of endothelial cells. In an attempt to identify the binding site for SPARC on VEGF, we hypothesized that this binding site could overlap at least partially the binding site of VEGF receptor 1 (VEGFR1), as SPARC acts by preventing VEGF-induced phosphorylation of VEGFR1. To this end, a docking simulation was carried out using a predictive docking tool to obtain modeled structures of the VEGF-SPARC complex. The predicted structure of VEGF-SPARC complex indicates that the extracellular domain of SPARC interacts with the VEGFR-1 binding site of VEGF. Following molecular dynamics, side-chain interactions were identified at the protein interface that are predicted to contribute a large fraction of binding free energy. The identified interactions will be used for directing further mutagenesis studies to investigate their effect on the binding activity. The docking model obtained will provide us with a detailed understanding of the protein-protein interactions and can be used as a basis for guiding future studies aimed at identifying VEGF receptor antagonists.

COMP 352 New NMR approaches to the structure of carbohydrates bound to proteins
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Recognition of cell-surface carbohydrates by proteins plays an important role in processes that range from virus infection, to immune response, to fertilization, to cell development, to metastasis of malignant cells. The development of drugs that can regulate any of these processes would be greatly facilitated by structural information on bound state geometries of carbohydrate ligands. NMR has historically been able to provide much of this information, but new types of data, including residual dipolar couplings (RDCs), promise to greatly improve the quality of information provided. We describe some new methods for enhancing the contributions of RDCs to measurements made when carbohydrate ligands are exchanging between protein-bound and solution forms. These allow application to carbohydrates without the need of isotope labeling and they allow structural analysis of carbohydrates that show few trans-glycosidic NOE interactions. Illustrations using the lectin Galectin-3 interacting with simple saccharides will be presented.

COMP 353 Recent developments and applications of the ONIOM Method
Keiji Morokuma, Cherry L. Emerson Center for Scientific Computation and Department of Chemistry, Emory University, 1515 Dickey Dr, Atlanta, GA 30322, Fax: 404-727-7412, morokuma@emory.edu

The ONIOM method, a flexible hybrid method allowing integrating different quantum mechanic (QM) and molecular mechanic (MM) theoretical methods, is now being widely in many applications of computational chemistry. We will discuss some recent developments of the ONIOM method, and its applications to nanostructures, homogenous catalyses and enzymatic reactions.

COMP 354 Tautomerization states of pteridine analogs: Quantum mechanics calculations and $^{13}$C NMR studies
J. Phillip Bowen and Haizhen Zhong, Center for Drug Design, Department of Chemistry and Biochemistry, University of North Carolina at Greensboro, 400 New Science Building, PO Box 26170, Greensboro, NC 27402-6170, Fax: 336-334-5402, jpbowen@uncg.edu

Understanding tautomeric preferences in pteridine ring systems is important, particularly for protein-ligand interactions when pteridine analogs are bound to dihydrofolate reductase (DHFR). Previous studies were focused on keto-enol equilibrium under various pH conditions. $^{13}$C NMR spectroscopy has been a convenient way of studying the keto-enol tautomerization. In this presentation, we present our studies on the tautomeric changes of pteridine analogs under various solvents, using quantum mechanic calculations and $^{13}$C NMR. Our data show that the keto tautomer is energetically more favorable. As the solvent dielectric constant increase (i.e., the solvent becomes more polar), the energetic preference of the keto form becomes more apparent. The molecular dipole moments become larger as the solvent polarity increases, and the keto tautomer shows larger dipole moments than the enol tautomer.

COMP 355 Using shape, chemistry and electrostatics to identify bioisosteric fragments
A. Geoffrey Skillman, Robert Tolbert, and Anthony Nicholls, OpenEye Scientific Software, 3600 Cerrillos Rd, Suite 1107, Santa Fe, NM 87507, skillman@eyesopen.com

A common task in medicinal chemistry is to modify a molecular structure in a minor way to modulate a biological or chemical property without destroying biological activity. Bioisosteric replacement is one of the most powerful tools available to medicinal chemists for this lead optimization. We will present computational methods that identify and characterize known bioisosteres. We use shape, functional group, flexibility and electrostatic similarity to analyze the bioisosteric pairs. This method is suitable for suggesting potential bioisosteric fragments from a database of over 2.5 million unique chemical entities. We will present the results of applying this technology to examples from the medicinal chemistry literature.
COMP 356 A new way to find the needles in a haystack: Identify promising HTS hits in SAR-bearing clusters

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Modern drug discovery usually starts from screening large compound libraries in order to identify interesting starting points for medicinal chemistry. Despite the great advance in HTS technologies, the productivity in the pharmaceutical industry has not yet been noticeably improved as hoped. Primary HTS hit selection is the very first step of a drug discovery project and has fundamental far-reaching effects to the entire process; yet, it is the least reviewed step in a typical hit-to-lead procedure. Oftentimes, the hits are selected naively using a single activity cutoff, depending largely on the follow-up capacity. Due to the noisy nature of HTS, such "top X" approach unavoidably generates many false positives. To overcome this limitation, statistical approaches have been developed, e.g., the RP-based SCAM method. However, these methods still heavily rely on the individual compound activities and knowledge-based analysis is rarely integrated into the hit-picking process. For example, it is often more desirable to select a cluster of compounds with relatively lower but related activities than a singleton with higher activity, as it is clearly advantageous to further explore those SAR-conserved hits from a medicinal chemist's point of view. No existing hit-picking methods have been suggested to carry out such scaffold-based, intelligent selection in an automatic and statistically rigorous way. Here we proposed a novel knowledge-based statistical approach, driven by the hidden SAR within a screening library, for primary HTS hit generation. We applied this method to an in-house HTS campaign and demonstrated it could directly identify active, diverse scaffolds containing valuable SAR information with a significantly improved confirmation rate compared to the "top X" approach (from 55% to 85%). This new HTS hit selection paradigm can facilitate the identification of high-quality lead series in the hit-to-lead phase and may contribute to the overall success rate of the multi-step drug discovery process.

COMP 357 QSAR Data cleansing with independent component analysis

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Independent Component Analysis (ICA) has recently been successfully applied to challenging signal processing applications for noise suppression and mixed signal separation. ICA has now been used for the first time in a similar spirit as a general data cleansing filter. This methodology was applied to several QSAR data sets, and shows the effectiveness of ICA filtering before applying other modeling techniques such as Partial Least Squares (PLS), Kernel-PLS or Support Vector Machine methods.

Independent Component Analysis can be considered as a nonlinear extension of Principal Component Analysis (PCA) and in that sense is a "better PCA". ICA and PCA can also be considered as methods for unsupervised preprocessing of the data, while the PLS algorithm can be considered to be a related but supervised procedure for data preprocessing. In this presentation we will outline how ICA, PCA, and PLS are different views of a more general canonical correlation analysis theory. We will also show how ICA, PCA, and PLS can be efficiently implemented by slight variations of Herman Wold's NIPALS algorithm.

COMP 358 Reverse fingerprinting, multiple seed similarity searching and fingerprint bit importance

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Recent research has demonstrated that using /data fusion /rules to combine fingerprint-based similarity scores from different sources can improve results over more traditional approaches, which typically use one reference molecule and one similarity score. Combining similarity scores from multiple reference compounds has in particular been shown to be effective. In this paper a new collection of 2D typed triangle fingerprints based on the MOE pharmacophore annotation points, PCH+, is introduced, and these new fingerprints are used along with other 2D typed atom fingerprints (TGT and GpiDAPH) and the MACCS keys to investigate the general effectiveness of using multiple reference compounds, or /seed pods/, in similarity searches. The average recall over 36 biological targets was computed while varying the number of compounds in the seed pod. Internal statistics of the seed pod, such as average, maximum and minimum pair-wise similarity were also computed and related to the recall rates. The fingerprints bits themselves were further investigated by implementation of /reverse /versions of the fingerprinting systems, which allows retrieval of the molecular fragment responsible for any given fingerprint bit. Seed pod bits were ranked by the rate of bit occurrence in the seed pod, or /coverage /(C_{k} ), and by the /bit likelihood/, /T_{k} , a ratio of bit occurrence in the seed pod over bit occurrence in a broader chemical space. The coverage and likelihood values were used to isolate bits for visualization and coarse pharmacophore elucidation. The general correspondence between 2D and 3D fingerprinting typed atom polygon systems is discussed. Scaffold-hopping abilities using compounds active against two phosphodiesterase isoforms (PDE4 and PDE5) are also investigated. Similarity of PDE4/PDE5 active compounds to known biological substrates (cAMP/cGMP ) is used to examine the relative chemical space of these ligands.
COMP 359 Computational target validation based on 3-D QSAR for antiparasitic leads
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Pentamidine has been known to be active against a range of parasitic diseases including the malarial parasite which causes millions of deaths per year. There are two separate schools with regard to the primary target involved with the activity of this compound in P. falciparum - DNA minor groove, ferritoporphyrin IX (FPIX). This study aims at working with available pentamidine analogs in our database that are active against malaria to develop a probabilistic model that will be able to computationally evaluate target complementarity. Our protocol to develop such a model is to use GASP for conformational analysis and develop pharmacophore hypothesis followed by 3D QSAR to assist in target validation. Usage of pentamidine against diseases is prone to problems with respect to toxicity and oral availability. Target validation would open new pathways in terms of developing effective leads against Malaria and/or guide the synthesis of other scaffolds.

COMP 360 Spectrophore technology for fast and reliable virtual screening
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We will describe the application of a proprietary chemoinformatics technology, called Spectrophores™, developed by Silicos[1], Belgium. This new technology allows to rapidly convert three-dimensional molecular properties into one-dimensional molecular fingerprints. Typical molecular properties that can be converted into Spectrophores™ include electrostatic potentials, atomic lipophilicities, and hard- and softness potentials. Molecules with similar 3D-properties, and as such similar biological activities, will always yield similar Spectrophores™. Therefore this technology is well-suited as a rapid and accurate virtual screening tool. To illustrate the power of Spectrophores several examples of applications in the fields of virtual screening and database characterization will be provided.

COMP 361 Structure and binding of glycopeptide antibiotics to bacterial cell wall analogs: Solvent and dimerization effects
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HF and DFT studies of the binding of vancomycin, avoparcin, teicoplanin, and ristocetin aglycons with dipetides, Ac-D-Ala-X, where X = D-Lac, D-Ser, D-Ala, Gly and a model "methylated D-Ala" CH2CH(CH3)CO2- have been carried out in liquid as well as in gas phase. The gas-phase ordering of the binding of vancomycin, from strongest to weakest, is; Gly, D-Ala, D-Ser, CH2CH(CH3)CO2- and D-Lac. The order of the Gly and D-Ala binding is reversed in solution [1], which agrees with the experimental result [2]. Also, the cooperative binding effect of vancomycin dimer has been analyzed by HF and DFT calculations.


COMP 362 Molecular design: The biomimetic paradigm
WITHDRAWN

The predominant paradigm of drug development has consisted of the screening/testing of large numbers of substances for a desirable biological activity in model systems, followed by systematical chemical modification of the lead compound to optimize its properties. Rational design of pharmaceuticals has been continually being enhanced by the better understanding of the molecular basis of recognition in the biological world. Thus, the biomimetic paradigm - the architectural principles observed in nature are applied to the invention of novel synthetic compounds that can achieve the same goals - has become an increasingly attractive direction for structure-based drug design. Here, we highlight recent successful design of small molecules that are capable of mimicking protein surfaces recognized by other macromolecules, transition states of enzymatic reactions, and active sites of enzymes as illustrative examples to address the challenge and potential of such an approach.

COMP 363 STIMD: A grid-based method for accelerating the calculation of differences in binding free energies and its application to the binding of peptides to Src SH2 protein domains
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Although methods exist for calculating free energies of binding, their use has been hampered by the time it takes to compute a single value. We shall describe a novel method, steered thermodynamic integration using molecular dynamics...
(or STIMD), that uses an intercontinental high performance computational grid to accelerate this process. This method reduces from months to less than one week the time taken to calculate differences in binding free energies.

We have applied STIMD to study the binding of a series of peptides to a v-Src SH2 protein domain. We achieve very good agreement between the calculated and experimental values of the differences in binding free energies, entropies and enthalpies. The amino acids that are predicted to contribute to the binding via a component analysis have been previously shown to be important by mutagenesis experiments. We conclude by discussing the role of water in the binding of the peptides.

**COMP 364 An application of QM-QSAR to predict and rationalize the refractive index of a wide variety of simple organic/organosilicon molecules**

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the refractive index(RI) is a basic optical property of organic matter. in our research on dental restorative materials, RI values of monomers are important, since they affect the penetration of initiating light pulses into the forming matrix. This paper addresses the development of a general quantum-mechanically based quantitative structure-activity relationship (QM/QSAR) for the RI of small molecules. SAM1 is the semiempirical method used to calculate molecular properties. a training set of 75 varied molecules was used to derive the final QSAR model, which include descriptors quantifying the contributions of the relative numbers of carbon atoms and the alpha-polarizability of the molecule. the coefficient of correlation was R2=0.924, and the other indicators of quality were within acceptable limits. the model demonstrated extensibility beyond the training set by predicting the refractive index of 29 molecules with an R2=0.913. the signed error, unsigned error and RMSE are -0.0049, 0.01412, and 0.0167 respectively. comparison was made to existing models in the literature.

**COMP 365 Quantum mechanical structure-activity relationship to predict volume shrinkage**

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Volume shrinkage is an undesirable side effect of many polymerization reactions, often decreasing the quality of composite dental restoratives and precision castings. In addition, internal stresses created during the polymerization affect the mechanical properties of the final product. The ability to predict shrinkage for monomers with qualitative structure activity relationship (QSAR) models would benefit the development of new polymer products, but has been unsuccessful due to the limited availability of data collected using a standardized experimental procedure. Recently, mercury dilatometry measurements have been collected for a series of epoxides and methacrylates using a systematic approach, and QSAR models were developed for the two types of compounds with descriptors relating reactivity to volume shrinkage. It is hypothesized that the reactivity descriptors are largely due to the relationship between monomer conversion and shrinkage. This was tested with models developed for densitometer data undergoing experimental conditions which ensured maximum conversion. The hypothesis appears to be confirmed by this result.

**COMP 366 Effect of electron donating and withdrawing substituents on the ring stability of cyclobutadiene**

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Recent work has shown that the energy difference between the rectangular and square forms of cyclobutadiene is on the order of ~25kJmol\(^{-1}\). In addition, the effect of electron correlation must be taken into account to obtain the correct experimental geometry of a \(D_{2h}\) rectangular singlet ground state. Given the very small energy differences between the two forms and that the \(p\)-system electrons play such a significant role, it is of interest to investigate the effect of electron withdrawing or donating substituents on the symmetry and energy of the ring structure. The influence of standard electron donors such as -NH\(_2\) and acceptors such as -NO\(_2\), as well as donor/acceptor strength will be examined.
COMP 367 On the delocalization of electrons in donor-acceptor molecules
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The fact that the chemistry of various classes of molecules is a physical consequence of the behavior of electrons is beyond dispute. Many previous studies done on simple donor-acceptor (DA) complexes have failed to provide quite a detailed picture on the behavior of electrons. Thus, a rigorous treatment of the delocalization of electrons in the DA complexes BH$_2$NH$_2$, BC$_3$N$_3$H$_3$, AlH$_2$NH$_3$, AlCl$_3$NH$_3$ and GaCl$_3$NH$_3$ is carried out by use of the MP2/6-311+G(2df,p) state-of-the-art quantum chemical computations. Three distinct standpoints of the analysis can be singled out: 1) the nature of the DA interactions with respect to the electronic charge considerations, 2) the determination of electron delocalization by means of the basin-basin bond indices, and 3) the extent of sharing of electrons between the groups making the DA molecules. Because the analysis is rooted in the first-order density matrix, no reference to orbitals has been invoked. This work provides a new insight into the electronic basis of the DA interactions.

COMP 368 Potential energy surface of cation-pi interaction: Quantum chemical studies
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Cation-pi interaction is one of the non covalent interactions between aromatic ring systems and cationic groups of side chains, metal cations that influence the protein-ligand and protein-protein interactions. The strength is dependent on the angle of cations that makes with the aromatic ring systems. Despite angular dependent nature, the distance between cations and net pi-electron cloud is also important in determining its strength. In this study, potential energy surface and stability of this interaction between adenine and arginine were explored. For this purpose, quantum chemical calculations at HF, MP2 and B3LYP level of calculations were done with a 6-311G** basis set using Gaussian 03 program. The energy of cation-pi interaction was computed for every 0.25 increment step starting from 3.0A upto 7.0A. To analyze the stability of the cation-pi interaction in solvent, the adenine-arginine complex was modeled using Polarizable Continuum Model. The results will be discussed during the presentation.

COMP 369 On the accuracy of density functional theory for iron-sulfur clusters
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A powerful wave function manipulation method is introduced utilizing ionic fragments that allows for systematic mapping of the wave function space for complex, multi-spin systems with antiferromagnetic coupling. The use of this method is demonstrated for developing ground state electronic wave function for [2Fe-2S] and [Mo-3Fe-4S] clusters. Using well-defined ionic wave functions for iron, sulfide, and thiolate fragments, the accuracy of various density functionals and basis sets including effective core potentials are evaluated on a [4Fe-4S] cluster by comparing the calculated geometric and electronic structures to crystallographic geometry and experimental atomic spin densities from X-ray absorption data, respectively. We find that the basis set seems to saturate only at the triple-zeta level with polarization and diffuse functions and the most reasonable geometry is obtained by a hybrid functional with 10% HF exchange and 90% density functional exchange supplemented with Perdew’s 1986 correlation functional.

COMP 370 Quantum Monte Carlo studies of S4 conformer energetics
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We apply the quantum Monte Carlo method to the problem of conformer energetics of S4. 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 the atomization energy of S4. The overall effectiveness and accuracy of the method is compared against other available theory and experiment.

COMP 371 To achieve stable spherical clusters: General principles and experimental confirmations
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Highly symmetrical and chemically (quasi)inert clusters have long been sought since they may serve as ideal building blocks for tailored nanomaterials. Clusters with closed shells of electrons are good prospects, several insightful electron counting rules such as jellium model, Wade's 2n+2 skeletal electron rule and Hirsch's (2n+1)^2 rule[1] have offered us a strong predictive power. Close atomic packing is another important factor determining stability whereby clusters with 13, 55, 147, n atoms would be magic.[2] Actually both geometric and electronic considerations must be taken into account in order to achieve a stable cluster. However, despite their physical and chemical insights, these two guidelines are oversimplified. We now present general principles for the design of stable highly symmetrical clusters, which take advantage both of the extra stability of cage aromaticity[3] and of good geometrical balance between the outer cage and the endohedral dopant. Experimental confirmations are provided. The applicability was confirmed by the designed experiments on group 14 element cages with endohedral Al's, as well as by many literature findings.


**COMP 372 Role of oxygen vacancies on growth of 1B (Au, Ag and Cu) particles on TiO_2(110)**

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Nanometer sized metal clusters dispersed on oxide supports often exhibit much higher activity than single-component metal catalysts. Their catalytic performance markedly depends on cluster size, shape, and size distributions, along with support materials and support preparation methods. Supported metal nanoclusters can also easily rearrange and sinter during the course of thermally activated catalytic reactions (even at moderate temperatures). An accurate assessment of the effects of cluster-support interactions on the growth, structure, and chemistry of supported metal clusters, as well as the adsorbate-induced structural changes is therefore necessary to understand their catalytic performance under realistic operating conditions. It is also important to understand these behaviors in order to develop a new and reliable way to control their structural catalytic properties on the atomic scale. As a part of the effort to gain this atomic level understanding, we present our recent findings from density functional theory calculations, including: electronic structure of a reduced TiO_2(110) surface and interactions between oxygen vacancies, with a brief introduction to the dynamics of oxygen molecules on the reduced surface; role of oxygen vacancies and oxygen adspecies in the nucleation of Au, Ag, and Cu clusters.