COMP 49 Art of the scientific job search

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The average amount of time spent pursuing an advanced degree in science ranges from four to nine years. In addition, many new graduates find that they also must work as a post doctoral fellow for an

additional 1-4 years. The time spent in the academic environment does an excellent job of preparing one for an academic career. Locating an industrial position that is an appropriate fit for your background and research interests requires some advanced planning that is generally not covered by coursework. Landing the position requires a mixture of skills that include scientific training, communication, and marketing. This presentation will look at the process of locating and securing a job as a research scientist in the pharmaceutical industry.

COMP 50 Skills for molecular modeling in industry: observations of a recent emigrant from theoryland to experimentistan

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Among the most important skills of computational chemists working in industry are those that help make computational results understandable and relevant to their experimentalist colleagues. This presentation will draw on the speaker's observations to highlight some of those abilities, particularly those that are less likely to be developed during academic training. Among the skills to be discussed are those needed to communicate effectively with medicinal chemists and biologists and to contribute successfully to projects in their various stages, as well as technical skills which are of particular relevance to modelers in pharmaceutical companies.

COMP 51 Computational chemists in pharmaceutical research

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Industrial and academic career paths emphasize different facets of a scientist's skills. In industry, flexibility, communication, and the ability to identify key issues in the attainment of a practical goal are often emphasized over technical depth and certainly emphasized over publication. The ability to integrate into a project's overall workflow and the ability to work closely and seamlessly with others is critical. However, that is not to say that deep understanding of one's technical and scientific expertise is not critical to personal success. A computational chemist's background should emphasize not knowledge of computer programs, but rather knowledge of the science and theory that the programs attempt to employ. In fact, the most important knowledge required about a computer program is how faithfully and accurately the target science is reproduced. Perhaps even more important is whether and how that science is applicable to the particular applied problem at hand and whether it can be applied in a “timely” manner. Although scientists might first be employed for their scientific knowledge, a scientist's industrial career can take many rewarding paths, not all of them emphasizing daily scientific research. Flow between large companies and small, such as large pharmaceuticals and small biotech, is common and enriching for both the companies and the individual. These issues will be detailed and examples will be given.

COMP 52 Tricks of the drug discovery trade

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Technical and scientific skills obtained during academic training are necessary but not sufficient for a successful career in drug discovery. The (bio)pharmaceutical industry differs from the academic environment in many ways. Being prepared for such differences is important in order to ensure a good transition. The first thing that is obvious when starting a job in (bio)pharma is a new language that contains phrases like pipeline, Go/No-Go decision, portfolio. The next change will be the team experience, where the ability to work in multi-disciplinary teams is a key skill for a successful drug discovery career. Another challenge is the need to deal with several projects simultaneously, which requires skills in time management and prioritization. Since the ultimate goal of (bio)pharma is the delivery of new drugs to market (and not the advancement or teaching of science), the final differences to prepare for are in the decision-making processes and organizational culture.

COMP 53 Career opportunities in the computational chemistry software and services industry for scientists with academic background

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Chemistry/biology software and services industry provides many opportunities to scientists with computer skills. Depending on the skill level in computers (from application users to programmers) there are different opportunities available. In addition, those scientists with business aspirations can find several positions and career paths very attractive. Research & development positions include scientific software developers, project managers, documentation, and quality assurance. Marketing positions include applications scientists, product specialists, and product managers. Services positions include, scientific support, consulting, and custom services. In this presentation, we will review several different career tracks in the [chemistry] software industry.

COMP 54 Preparing for a computational chemistry position in the pharmaceutical industry
Catherine E Peishoff, GlaxoSmithKline Pharmaceuticals, 1250 South Collegeville Road, Collegeville, PA 19426, Catherine.E.Peishoff@gsk.com

WANTED: A highly productive and satisfying computational chemistry position in the pharmaceutical industry.

Computational chemistry is still a relatively small and valuable field, finding a job shouldn't be that hard…or is it? From the perspective of an interdisciplinary chemistry department director at GlaxoSmithKline, learn…

The skills that industry values, technical and otherwise The flavors of computational chemistry positions The balance between depth and breadth of computational chemistry knowledge The pluses and minuses of taking a post doc appointment The benefits of interacting with pharma scientists before graduation …and much, much more!

COMP 55 Academic Entrepreneur: Lessons from N=2
Garland R Marshall, Center for Computational Biology, Washington University, 700 S. Euclid Ave., St Louis, MO 63110, Fax: 314-747-3330, garland@pcg.wustl.edu

The interface between an academic and the world of business is not intuitive. By self-selection, the academic has chosen a profession in which material gains are not a goal. In addition most academics shun administrative and personnel issues for which they are not trained. While each startup opportunity is unique, some generalities regarding the cultural conflicts between academia and business can be drawn. Perhaps, the most disturbing is the extent to which one is dependent on external forces (FDA, IPO market, venture capitalists, etc.) if one needs to raise significant capital. As a startup, the search for capital is ongoing, and any minor delay in meeting milestones can prove disastrous. Academics do not generally have the pressure to be correct in future projections of research results. Personnel needs and the role of research changes as a company matures, and one must have a realistic exit strategy to return to full-time research.

COMP 56 Quantum mechanical modeling of self-reproducible living PNA chip immersed in the lipid bilayer vesicle controlled by quantum computing logic gates
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It was done research of self-assembling of peptide nucleic acid (PNA) chip fragments performing systematic quantum mechanical (QM) ab initio and extended density functional theory (DFT) QM methods including exact evaluations of hydrogen bondings and Van der Waals forces. We compared QM computational energies of self-formation of PNA chips fragments for the performance of elementary acts of PNA computing in water and various lipids phases. The detailed time dependent QM modelings of the molecular electronics and spintronics logical devices are done for controlling electron and proton charge and spin density transfers in the metabolic photo-fragmentation processes that stimulate the PNA-PNA templating and synthesis of other components of protocell. There were implemented molecular logic devices for finding and controlling the new more effective sensitizers, lipid and nucleobases precursors, proton and electron charge and spin density relaxations relays in artificial programmable living protocells modeled by QM methods before they will be done using expensive biochemical experiments. It is continuing building and modeling the lipid bilayer vesicles composed from around 100000 atoms with immersed logically controlled PNA chip possessing artificial photo-synthetic system including various sensitizers, lipid and nucleobases precursors and water molecules. QM and classical dynamics computational experiments of this entire living programmable artificial vesicle are performing using QM ab

initio and DFT, PM3 and NAMD, CHARMM and GROMACS methods.

COMP 57 Multi-scale quantum models for RNA catalysis
Darrin M. York, Department of Chemistry, University of Minnesota, 207 Pleasant Street S.E, Minneapolis, MN 55455, Fax: 612-626-7541, york@chem.umn.edu

Computer simulation methods provide a tool of enormous potential impact in problems of biocatalysis. From a theoretical perspective, ribozymes present several features that make them difficult to model relative to most proteins. Reliable molecular simulations of RNA-catalyzed reactions need to take into account accurate quantum models, complex macromolecular, ionic and solvent environments, and extensive conformational sampling. In order to make accurate predictions about the mechanism and rates of phosphoryl transfer reactions requires theoretical methods that are robust and reliable over a broad range of time and length scales. The present work describes a multi-faceted theoretical approach toward the development of methods that allow simulation of catalytic RNA systems to be performed with increased reliability and predictive capability. The focus here is to outline recent progress in the design of new multi-scale quantum models to study phosphoryl transfer reactions in non-enzymatic and enzymatic environments. Here, ``multi-scale'' implies the integration of a hierarchy of methods that span a broad range of spatial and temporal domains and work together in concert to provide insight into complex problems. Methodological advances presented in this talk will include: 1) linear-scaling electrostatic and generalized solvent boundary methods for hybrid QM/MM simulations, 2) new-generation semiempirical Hamiltonian models for phosphoryl transfer reactions, 3) new models for solvation and prediction of pKa's of phosphates and phosphoranes. Applications to large-scale simulations of ribozyme catalysis in the hammerhead and hairpin ribozymes will be outlined.

COMP 58 Coupling between protein and solvent dynamics: microscopic insights from molecular dynamics simulations
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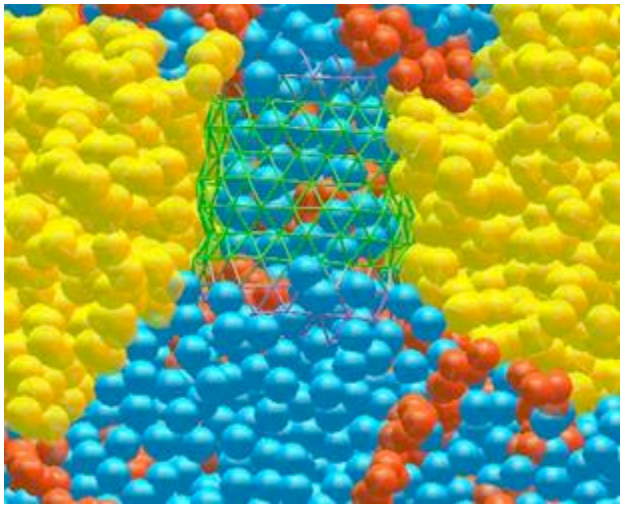
The rate at which biological agents like proteins denature is a determining factor for the shelf-life of protein/enzyme based pharmaceuticals. Thus, the dynamics of the protein has a direct influence on the shelf-life of the formulation. It has been shown that the dynamics of a protein is controlled by the dynamics of the surrounding solvent (slaving) and that the dynamics of the denaturation process can be suppressed by the careful selection of the solvents used (enhanced bio-preservation). Two solvents have proven to be very efficient in the suppression of the dynamics of proteins: glycerol and trehalose. In this talk I will focus on molecular mechanisms that lead to the slaving and suppression of the protein dynamics in these solvents. Our study suggests that the hydrogen bonding network present in the system controls the slaving and suppression of the protein dynamics. For example, in the case of slaving, the physical properties of the hydrogen bonds between the solvent and the surface of the protein control the structural relaxation of the whole protein. Other results will be discussed.

COMP 59 Water Diffusion Across Nano-Bio-Assemblies of Block Copolymers: A Coarse-grain Simulation Study
Goundla Srinivas, department of Chemistry, Center for Molecular Modeling, Department of Chemistry, University of Pennsylvania, 231S, 34th Street, Philadelphia, PA 19104, srini@cmm.upenn.edu, Dennis E. Discher, Department of Chemical and Biomolecular Engineering, University of Pennsylvania, and Michael L. Klein, Department of Chemistry, University of Pennsylvania

Self-assembling block-copolymer amphiphiles present a robust and functionalizable alternative to soft, biological assemblies. Protein pore insertion and nano-tubule features of block copolymer membranes are examined with a focus on chain flexibility. In coarse-grain molecular dynamics, thick-membrane bilayers not only accommodate small protein-like channels but also tend to regulate transport. The hydrophilic chains prove key, leading to a demonstration of the accuracy of corona density profiles. Lastly, flexible triblocks that exploit “hairpin-” and “straight”-chain conformations assembles into novel nanotube-like structures.



COMP 60 Ab initio simulations of folding pathways by molecular dynamics with the united-residue model of polypeptide chains
Mey Khalili, Dept of Chemistry & Chemical Biology, Cornell University, Baker Lab of Chemistry, Ithaca, NY 14853-1301, Fax: 607-254-4700, Adam Liwo, Faculty of Chemistry, University of Gdansk, and Harold A. Scheraga, Dept Chemistry & Chemical Biology, Cornell University

Langevin dynamics was applied to our physics-based united-residue (UNRES) force field, and the algorithm was tested on proteins of different sizes and structural classes (containing from 28 to 75 amino-acid residues). The α-helical proteins folded to the native-like structures. For most of the α+β and β-proteins, non-native α-helical structures were obtained, even though the native-like structures are located as the lowest in energy by global optimization. This is due to neglecting the entropy factor while parameterizing UNRES. Average folding times are three orders of magnitude smaller than the experimental ones due to the removal of the fast degrees of freedom. Folding simulations required 2 to 10 CPU hours, depending on the size, with a single processor. With parallel processing, thousands of folding pathways can be explored, and folding scenarios and kinetic and thermodynamic characteristics can be predicted, as demonstrated with staphylococcal protein A.

COMP 61 Consensus pose prediction
Mark McGann, Principal Developer, Docking Software, OpenEye Scientific Software, 222 3rd Street Suite 3211, Cambridge, MA 02142, mcgann@eyesopen.com

Many docking programs can reliably produce a set of potential poses in which at least one pose can be considered correctly docked. Reliably picking this single correct pose out of the entire set with a scoring function is often more problematic. This work examines the effect of using multiple scoring functions to pick out the correctly docked pose. This "consensus structure" method is distinct from what is generally called "consensus scoring" because the former is used to determine the docked structure while the latter is used for enrichment.

COMP 62 Prediction of Binding Affinities for Structure-Based Drug Design
Scott Brown and Steven W. Muchmore, Abbott Laboratories, Depts. R42T and R46Y, Bldg. AP10, 100 Abbott Park Rd., Abbott Park, IL 60064

The ability to calculate accurate, computationally tractable protein-ligand binding free-energies across large compound libraries is desirable in a drug discovery setting, as it has the potential for accelerating the process of finding novel therapeutic compounds in a systematic way. We present here preliminary data towards development of a general physics-based scoring methodology for obtaining accurate estimates of relative differences in protein-ligand binding free energies across compound libraries. This method is based on Molecular Mechanics with Poisson-Boltzmann Surface Area (MM-PBSA) methodology. This presentation will focus on both proof-of-concept calculations as well as prospective analysis, and prediction of binding affinities of compounds whose crystal structures are unknown.

COMP 63 Improved protein mapping for fragment based drug design

Sandor Vajda[1], Michael Silberstein[2], Spencer C. Thiel[2], and David Lancia[1]. (1) Department of Biomedical Engineering, Boston University, 44 Cummington St, Boston, MA 02215, Fax: 617-353-6766, vajda@bu.edu, (2) Bioinformatics Program, Boston University

Computational solvent mapping methods place molecular probes - small molecules or functional groups - on a protein surface in order to identify the most favorable binding positions. We have developed a mapping algorithm that generally eliminates the spurious local minima, and finds the bound positions of small organic probe molecules in good agreement with x-ray or NMR data. This efficient and highly accurate mapping algorithm is used as the first step of a fragment-based drug design procedure, at this point with restricted fragment libraries derived from known drug molecules. We describe preliminary applications to drug targets that are known to be difficult, including peroxisome proliferator activated receptors (PPARs), protein tyrosine phosphatase 1B (PTP1B), and protein kinases. These results suggest that the mapping can provide very useful information for drug design.

COMP 64 Protein ensemble docking: An effective strategy for enhanced lead docking

Luciano Mueller, Department of Macromolecular Structure, Bristol Myers Squibb Pharmaceutical Research Institute, Route 206 & Provinceline Road, P. O. Box 4000, Princeton, NJ 08543-4000, luciano.mueller@bms.com, and Daniel L. Cheney, Structural Biology and Modeling, Bristol-Myers Squibb

Accurate lead docking remains an elusive task in molecular modeling. Sampling scoring, solvation, (structural waters), and protonation states are among the many aspects of ligand / protein binding that must be addressed in any comprehensive lead docking protocol. Our previously reported results in lead docking using protein conformational ensembles in place of a single protein were promising, and prompted further investigations. High quality ligand datasets are generated from crystal complexes spanning 6 targets (130 ligands total) and docked into a conformationally diverse ensembles of protein crystal structures. Substantial improvements are observed in pose sampling for all targets. Ranking of retained docked poses can be significantly enhanced by minimizing docked complexes with OPLS-AA in the presence of the SGB continuum model (Schrodinger, Inc). Overall average success rates is more than doubled, and the average RMSD of top-ranked poses was cut in half. Alternative scoring techniques are also examined.

COMP 65 Accurate prediction of binding modes and binding affinities of protein-ligand complexes

Richard A. Friesner, Department of Chemistry, Columbia University, 3000 Broadway, MC 3110, New York, NY 10027, Fax: 212-854-7454

Over the past several years, we have developed novel methods and models for the prediction of binding modes and binding affinities of protein-ligand complexes. These methods include qualitatively improved empirical scoring functions for hydrogen bonding and hydrophobic interactions, the use of polarized charges in lead docking calculations, and rapid, robust computational methods for induced fit calculations. The talk will focus on the optimization and validation of these methods using large test suites of protein-ligand complexes (including a wide variety of series generated by medicinal chemistry), as well as challenging individual applications such as modeling of the binding of ligands to the HERG ion channel. Preliminary results indicate that the new methods are able to address not only virtual screening and enrichment, but also lead optimization, in an effective fashion.

COMP 66 Applications of electronic structure theory at the teraflop level and beyond

David A Dixon, Department of Chemistry, University of Alabama, Box 870336, Shelby Hall, Tuscaloosa, AL 35487-0336, Fax: 205-348-4704, dadixon@bama.ua.edu, Wibe A. de Jong, W. R. Wiley Environmental Molecular Sciences Laboratory, Pacific Northwest National Laboratory, Theresa L. Windus, Environmental Molecular Sciences Laboratory, Pacific Northwest National Laboratory, and Kirk A. Peterson, Department of Chemistry, Washington State University

With the confluence of advances in theory, algorithms, software, and high performance computer architectures, it is now possible to calculate reliably the thermodynamics of a range of compounds at a level of accuracy only dreamed about even a decade ago. This talk will explore applications of computational chemistry electronic structure techniques at the teraflop level to predict the properties of compounds such as the heats of formation of octane and the xenon fluorides as well as those of alkoxy

radicals. The talk will not only highlight successes in these areas but will also describe continuing challenges in terms of the limitations of electronic structure methods given current resources. Challenges include the prediction of vibrational zero point energies, accuracies of the correlation treatment, open shell systems, and relativistic effects.

COMP 67 Quantum Monte Carlo: An ab initio molecular computational methodology for terascale computing

Alan Aspuru-Guzik[1], Romelia Salomon-Ferrer[2], Brian Austin[2], Dominik Domin[1], David Skinner[3], Ricardo Oliva[4], and **William A. Lester Jr.**[2]. (1) Kenneth S. Pitzer Center for Theoretical Chemistry, Department of Chemistry, University of California, Berkeley, Berkeley, CA 94720-1460, alan@aspuru.com, (2) Kenneth S. Pitzer Center for Theoretical Chemistry, Department of Chemistry, Chemical Sciences Division, Lawrence Berkeley National Laboratory, Berkeley, CA 94720-1460, WALester@lbl.gov, (3) National Energy Research Supercomputer Center, Lawrence Berkeley National Laboratory, (4) Computing Division, Lawrence Berkeley National Laboratory

Quantum Monte Carlo for the electronic structure of molecules is an ab initio method. In the diffusion MC (DMC) form, the method is capable of very high accuracy. In addition, it can be used on computers with thousands of processors for a wide range of biological, chemical, and physical problems. This talk will describe some of issues encountered in the application of DMC to a system of biological interest.

COMP 68 Achieving sustained teraflop performance with the NWChem coupled cluster module

Wibe A. deJong, W. R. Wiley Environmental Molecular Sciences Laboratory, Pacific Northwest National Laboratory, PO Box 999, Richland, WA 99352, bert.dejong@pnl.gov, and Karol Kowalski, WR Wiley Environmental Molecular Sciences Laboratory, Pacific Northwest National Laboratory

Over the years advances in hardware and software have enabled computational chemistry to reach the point where it can be used to properties of small molecules to chemical accuracy using high accuracy ab initio methods. Obtaining the same level of accuracy for molecules consisting of tens of atoms pushes current terascale computers and the application software to their limits, and requires computational chemistry codes to fully utilize the teraflops available. In this paper we will discuss our efforts to enhance the NWChem coupled cluster module in order to achieve sustained teraflop performance on the supercomputer at the Molecular Science Computing Facility (MSCF) at the Environmental Molecular Science Laboratory (EMSL).

This work was supported through the U.S. Department of Energy by the MSCF in EMSL at the Pacific Northwest National Laboratory, operated by Battelle Memorial Institute. The MSCF and EMSL are funded by OBER in the U.S. Department of Energy.

COMP 69 Scalable correlated electronic structure theory: Strategies and applications

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Two strategies for extending the size of molecular systems that are amenable to accurate theoretical study will be addressed. The first of these is the application of parallel computational strategies to correlated electronic structure theory. New parallel approaches for MCSCF wave functions, MCSCF analytic second derivatives, and coupled cluster methods will be discussed. The second strategy is to develop accurate potentials for the study of processes that do not involve explicit breaking of covalent bonds. Such a method, the effective fragment potential (EFP) method is being developed in our laboratory. New developments of the EFP method, and applications to problems in nanotechnology will be presented.

COMP 70 Full configuration interaction (FCI) method in Teraflop computing: Implementation and application

Zhengting Gan, The University of Tennessee, Oak Ridge National Laboratory, PO Box 2008 MS6367, Oak Ridge, TN 37831-6367, ganz@ornl.gov

In this talk we present an efficient parallel and vector implementation of FCI method on supercomputers. By exploiting the structure of Hamiltonian matrix using the N-2 electron space, the original sparse matrix-vector multiplication is efficiently performed using dense matrix-matrix multiplication with the help of

vector gather and scatter operations. The new implementation avoids the explicit computing of Hamiltonian matrix elements and incurs minimum overhead of memory movement and communication cost, thus removes the major parallel scalability bottlenecks. We will also present in this talk an automatically adjusted single-vector iterative diagonalization method developed to alleviate the memory constraint and avoid the I/O bottleneck in large-scale benchmark calculations. The parallel scalability and the capability of our implementation will be demonstrated by benchmark calculations. We will also compare the parallel performance of different FCI algorithms, and analyze the implementation strategies suitable for teraflop computers. Finally, we report the application of our FCI code on Teraflop computers by presenting the new benchmark results on series of open-shell systems and systems of strong multi-reference characters.

COMP 71 Importance-sampling coupled-cluster theory
Micah Abrams, Department of Chemistry, Virginia Tech, 107 Davidson Hall, Blacksburg, VA 24061-0001, Fax: 540-231-3255, abramsm@vt.edu

A general-order, general-configuration determinant-based program is extended to locate the most important coupled-cluster amplitudes. Different algorithms for locating the important coupled-cluster amplitudes will be described. Several applications will show that accurate spectroscopic constants and potential energy surfaces can be computed with a fraction of the total number of amplitudes.

COMP 72 Recent developments in the linear scaling Coulomb problem for first principles DFT calculations with Gaussian functions
Laszlo Fusti-Molnar, Jing Kong, and Shawn T. Brown, Q-Chem Inc, Q-Chem Inc, 5001 Baum Blvd, Pittsburgh, PA 15213, fusti@q-chem.com

Coulomb interaction is one of the major time-consuming components of a DFT calculation. In the last decade, dramatic progresses have been made to improve the efficiency of Coulomb calculation, including Continuous Fast Multipole Method (CFMM) and J-Engine technique. The most recent development is the Fourier Transform Coulomb (FTC) method which replaces the least efficient part of previous Coulomb methods with an accurate numerical integration scheme. A unique combination of these three techniques has been recently implemented in Q-Chem. The FTC technique has a much smaller slope in the linear scaling with respect to the molecular size and we will demonstrate through a series of benchmark calculations that it speeds up, without loss of accuracy, the calculation of Coulomb portion by several (4-6) fold over the most efficient existing code, i.e. the combination of CFMM and J-engine. Furthermore, we will show that the FTC technique is complementary to the CFMM and together the three methods offer the best performance for Coulomb problem. Results of modern parallel implementation for both energies and gradients are also discussed in detail.

COMP 73 Interpolating density values on a cartesian grid: Improving the efficiency of Lebedev based numerical integration in Kohn-Sham density functional algorithms
Shawn T. Brown, László Füsti-Molnár, and Jing Kong, Q-Chem Inc, The Design Center, 5001 Baum Blvd, Pittsburgh, PA 15213, stbrown@psc.edu

Most modern density functional theory algorithms utilize numerical techniques to solve integrals that arise from the complicated forms of the functionals employed. Various radial quadrature schemes have been used, and by far the most popular method for handling the angular portions of the integration is to use Lebedev spheres. In an effort to take advantage of the smoothness of diffuse Gaussian functions, density values are computed on a Cartesian grid the atom-centered grid are determined via divided difference interpolation. Since an algorithm to evaluate the density and its gradient on a Cartesian grid can be written in much more efficient way than Lebedev spheres, great savings in the time necessary to evaluate the electron density can be achieved. It is shown there is error control based on the point density of the Cartesian grid, and that the vast majority of the basis function pairs can be evaluated in this way.

COMP 74 Formulation, parametrization and performance appraisal of the analytic and variational Xα method
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We have formulated a fully analytic and variational density-functional method based on Slater's Xα approximation to Hartree-Fock theory. It uses linear combination of atomic orbitals to express both the molecular orbitals and the Kohn-Sham potential. The method allows arbitrary scaling of the exchange-correlation potential around each atom. Being analytic, it is free from numerical integration and delivers machine-precision, basis-set-dependent energies that are stationary in all respects. One choice of scaling uses the α's that give exact atomic energies. This choice gives total molecular electronic energies that are precisely the sum of atomization energies and experimental atomic energies. We assess the performance of this method by calculating the atomization energies and total energies of the G2 and extended G2 sets of molecules. The MAE in total energies for the G2 set of molecules is 17 kcal/mol. This is comparable to or better than almost all pure and hybrid density functional models. This error is reduced by a factor of one third by finding the α's that minimize the G2-set MAE, but this improvement comes at the expense of no longer having a quantum-mechanical energy that dissociates to exact atomic energies.

COMP 75 Identifying and extracting the sources of errors in the calculation of binding energies of van der Waals clusters of aromatic molecules

Ines Gonzalez[1], Carlos A. Gonzalez[2], and Edward C. Lim[1]. (1) Chemistry, University of Akron, 319 Knight Chemical Laboratory, Akron, OH 44325, igonzalezarraga@yahoo.com, (2) Computational Chemistry Group, National Institute of Standards and Technology

Moeller-Plesset second order perturbation theory (MP2) has proven to be one of the most cost-effective methodologies for calculating the intermolecular potentials of clusters of aromatic molecules. Despite its popularity, there remains considerably uncertainty regarding the reliability of MP2 in the prediction of thermochemical properties of weakly bound complexes such as van der Walls clusters of aromatic molecules. This situation gets complicated by the fact that binding energies computed by the supermolecular approach, tend to overestimate the true binding energy due to the so-called basis set superposition error (BSSE), which arises from an unbalance in the monomers' basis sets. In this work, we discuss a systematic procedure to extract the different source of errors in the calculation of binding energies for aromatic clusters by MP2 theory. We apply this procedure to the case of benzene dimer and discuss its application in the study of other types of clusters.

COMP 76 Energy landscapes of bimolecular nucleophilic substitution (SN2) reactions: A comparison of density functional theory and coupled cluster methods

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One of the key features of the structure of DNA comprises the hydrogen bonds between the different DNA base pairs, that are strong and specific and well understood by high-level theoretical calculations (JACS 2000, 122, 4117; JACS 2004, 126, 16718). The process of DNA replication occurs with high fidelity, the origin of which is still under debate (ACIE 2002, 41, 2092). The basic reaction taking place in the DNA replication process is an SN2 nucleophilic attack at the incoming nucleotide triphosphate, which we aim to study with Density Functional Theory (DFT). The choice of the DFT functional can however have a large impact on the potential energy surface, as shown in a recent preliminary study (Mol. Phys. 2004, 102, 2467). In the current contribution, we report a systematic study of the performance of DFT functionals for the potential energy surface of SN2 reactions of model systems for which high-level CCSD(T) reference data are available. It will be shown that recent DFT functionals perform well for the barrier, well-depth and exothermicity of the reactions.

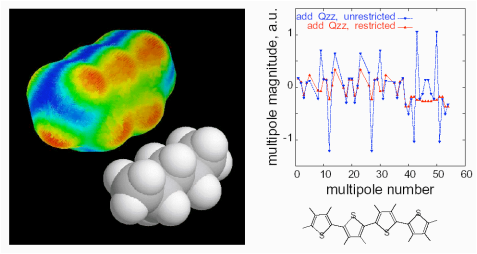
COMP 77 Minimal atomic multipole expansion (MAME): controlling redundancies in distributed multipole expansion of molecular fields

Eugene V. Tsiper, George Mason University and Naval Research Laboratory, NRL Code 6390, 4555 Overlook Ave. S/W, Washington, DC 20375, etsiper@gmu.edu, and Kieron Burke, Department of Chemistry and Chemical Biology, Rutgers

Accurate, efficient and intuitive representation of molecular fields is important for understanding intermolecular forces. Evaluation of polarization forces, hydrogen bonding, pi-pi interactions etc. all require quantitative representation of molecular electrostatic potentials (MEPs) that a molecule exerts upon the

neighboring molecules or the solvent. Representation of MEPs in terms of atomic partial charges is appealing and has drawn significant attention in recent years. Potential-derived (PD) charges, such as CHelpG or Merz-Kollman are defined directly through the best fit to the MEP. Most PD schemes suffer from a multitude of issues, all having the redundancy problem as a common source, inherent in the distributed multipole analysis.

We have developed a scheme that selects a special "minimal" set of atomic multipoles, thus eliminating redundancies before they appear. A few simple rules based on the Lewis structure of the molecule determine the minimal set, which normally consists of a single atomic multipole (not necessarily a charge) per atom, and a few extra multipoles to describe lone pairs or pi-clouds. The MAME code builds the minimal set automatically, while allowing for hand-tuning, then computes the multipole values by fitting the MEP on an isodensity surface. The isodensity surface fitting is essential, as it eliminates sampling errors and rectifies deficiencies imposed by the Poisson's equation in the region where molecular density is not negligible. We demonstrate the performance of the MAME scheme on several molecules of interest, which include a peptide, an alcane, alpha-quaterthiophene and water.



COMP 78 Path integral thermochemistry
Kurt R. Glaesemann, Chemistry and Materials Science Directorate, Lawrence Livermore National Laboratory, L-268, P. O. Box 808, Livermore, CA 94551, glaesemann1@llnl.gov, and Laurence E. Fried, Chemistry and Material Science, University of CA at LLNL

The calculation of thermochemical data relies upon accurate molecular energies. The rotational and vibrational effects must be accounted for, in order to obtain the needed accuracy. These effects are generally calculated using a normal mode analysis. Such an analysis assumes perfect harmonicity. We present a path integral Monte Carlo method for going beyond the traditional harmonic analysis. This method includes all thermal, vibrational, and rotational effects a priori. The underlying classical potential is calculated using ab initio methods, such as CCSD(T) and MBPT2. This approach explicitly includes electronic-vibrational coupling. Results for several chemical systems are presented and anharmonic effects are found to be significant.

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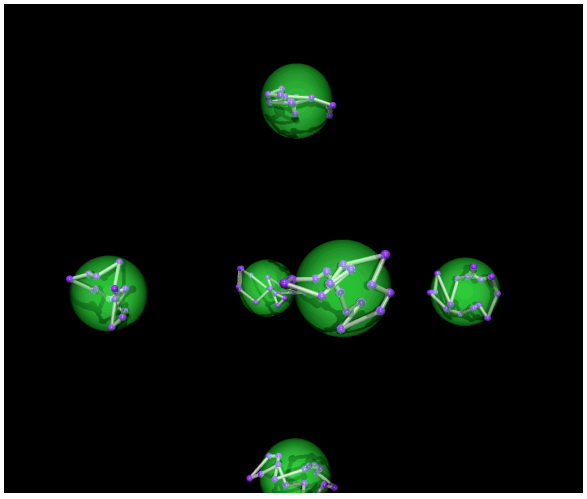

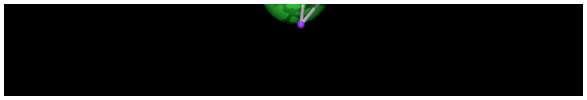

COMP 79 Partial averaging theories for the path integral in curved spaces
Emanuele Curotto, Chemistry & Physics, Arcadia University, 450 S. Easton Rd, Glenside, PA 19038, Fax: 215 572 7595, curotto@arcadia.edu, and Michael W Aviles, Chemistry, Arcadia University

We present a set of methods that allows us to compute the imaginary time path integral in curved spaces. Our formalisms is derived from the DeWitt Path integral formula. The significance of this recent advance in quantum Monte Carlo methods to chemistry is explained. For example, we are able to simulate the thermodynamics of rigid tops, and clusters containing small covalent molecules at cold temperatures. Once a primitive algorithm is established, we are able to develop and test three different partial averaging theories for the stereographic projection path integral in curved spaces. Results are presented for simple test systems that demonstrate the convergence properties in the asymptotic region. Additionally, we adapt and test the centroid virial estimator for the kinetic energy in curved spaces.We verify that the centroid virial estimator converges to the kinetic energy for both confining and non-confining potentials for the particle in a ring.

COMP 80 Quantum Monte Carlo estimation of properties of novel nanoscale compounds
John A.W. Harkless and **Floyd Fayton Jr.**, Department of Chemistry, Howard University, 525 College St., NW, Washington, DC 20059, Fax: 202-806-5442, jharkless@howard.edu

Quantum Monte Carlo (QMC) refers to a set of ab initio methods that use a stochastic simulation to solve the many-body Schrodinger equation. We plan to apply QMC to the problem of accurately predicting and elucidating the electronic and thermodynamic properties of novel molecular clusters within size regimes smaller than those typically explored in solid-state applications. Thermodynamic characterization of reactions of binary compounds and atoms, and larger clusters of carbon, nitrogen and oxygen. Anticipated results include quantum mechanical predictions of potentially new, novel materials and syntheses.

COMP 81 Quantum wavepacket ab initio molecular dynamics: An approach to perform simultaneous dynamics of electrons and nuclei in large systems
Srinivasan Iyengar, Department of Chemistry, Indiana University, 800 E. Kirkwood Ave, Bloomington, IN 47408, Fax: 812-855-8300, iyengar@indiana.edu

Abstract text not available.

COMP 82 Symmetry, form and shape: Guiding principles for robustness in macromolecular machines
Charles L. Brooks III and Florence Tama, Department of Molecular Biology, TPC6, The Scripps Research Institute, 10550 N. Torrey Pines Rd, La Jolla, CA 92037, Fax: 858-784-8688, brooks@scripps.edu

Investigations of the functional dynamics of macromolecular machines such as the ribosome, myosin and viral capsids with multi-resolution elastic network normal mode analysis have revealed general insights into the role of symmetry, shape and form in controlling these motions. During this lecture, examples from each of these systems will be used to illustrate how robustness of functional modes is encoded in shape and symmetry of the underlying molecular structure. Simple models for the role of specific modes in achieving functional objectives will be described and questions of dynamics will be discussed.

COMP 83 Mixed level coarse-graining of protein structures for dynamics
R.L. Jernigan, Baker Center for Bioinformatics and Biological Statistics, Iowa State University, Ames, IA 50011-3020, jernigan@iastate.edu, and Pemra Doruker, Department of Chemical Engineering, Bogazici University

Representation of molecular structures as networks of interacting elements is useful for simulating the large domain motions of large structures, not computationally accessible with atomic molecular dynamics. Normal modes are obtained from the eigenmodes of the connectivity matrix. By utilizing only one representative point per residue, or less, and connecting the close residues to one another with identical

springs, the normal modes of motion can be obtained. The largest scale motions, which are the most important, are the most reliable since these depend principally on the overall shape. This simple model reproduces crystallographic B factors, and a combination of the slow modes of motion corresponds closely to known transitions. In a number of cases the level of detail required to reproduce the slowest motions is well below 1 point per residue. We find that 1 point per 10 residues and often 1 point per 40 residues is sufficient.

COMP 84 The multi-scale simulation of biomolecular assemblies
Gregory A. Voth, Department of Chemistry and Center for Biophysical Modeling and Simulation, University of Utah, 315 S. 1400 E. Rm 2020, Salt Lake City, UT 84112-0850, Fax: 801-581-4353, voth@chem.utah.edu

A multi-scale computational methodology will be presented for simulating biomolecular assemblies across multiple length- and time-scales. The approach provides an interface between atomistic molecular simulations, mesoscale dynamics, and continuum mechanics. The underlying methodology relies on a closed feedback loop in which information from atomistic-level simulations can be coupled with mesoscale simulations which, in turn, can be coupled to continuum-level modeling. A new and systematic coarse-graining strategy for linking the atomistic-scale interactions to the mesoscale will also be presented. An illustrative application of the approach will be given for biological membranes. It will further be demonstrated how the multi-scale simulation methodology can be extended to treat membrane-bound protein systems that are embedded within long wavelength mesoscopic membrane motions and domain structures. Extensions of the approach to describe filaments relevant to the cellular cytoskeleton will be described if time allows.

COMP 85 Simulating, Modeling and Refining Supramolecular Complexes at Multi-resolution and Multi-length Scales
Jianpeng Ma, Biochemistry and Molecular Biology, Baylor College of Medicine, One Baylor Plaza, BCM-125, Houston, TX 77030, Fax: 713-796-9438, jpma@bcm.tmc.edu

A set of new computational methods has been developed for simulating, refining, and modeling supermolecular complexes at multi-resolution and multi-length scales.

COMP 86 Coarse grained to atomistic mapping algorithm: a tool for multiscale simulations
Steven O. Nielsen, Department of Chemistry, University of Texas at Dallas, 2601 North Floyd Road, Richardson, TX 75083-0688, Fax: 215-573-6233, snielsen@cmm.upenn.edu, and Michael L. Klein, Department of Chemistry, University of Pennsylvania

A key component to the success of multiscale modeling approaches is the ability to switch between molecular representations involving different levels of detail. In particular, the transition from a coarser to a finer representation is challenging because it requires the creation of information. To address this challenge, an algorithm is presented to fill in the detail when a coarse grained representation of a molecular system is replaced by an atomistic representation. The algorithm consists of minimization on the Lie group SO(3) for every coarse grained site, using the components of the atomistic force field that operate between atoms belonging to different coarse grained sites. This method is maximally efficient because the optimization is done at the coarser level using frozen atomistic library structures corresponding to each kind of coarse grained unit. The algorithm can be applied to any system since its input requirements are simply the force fields and molecular structures of both levels. The efficacy of the algorithm is demonstrated through its implementation to liquid dodecane.

COMP 87 Computational modeling for kinase inhibitor discovery
Y. Zhu, Informatics, Plexxikon Inc, 91 Bolivar, Berkeley, CA 94710, ylzhu@plexxikon.com

Protein kinases have become a major family of drug targets and are being explored for a wide range of indications. The catalytic domain of kinases has proven to be tractable for structure-based design of small molecule inhibitors. Nonreceptor tyrosine kinase BRAF is involved in the pathogenesis of many malignant cancers. Somatic mutations of BRAF are associated with 60% of malignant melanoma and occur with moderate to high frequency in colorectal, ovarian, and papillary thyroid carcinomas. To aid in the optimization of our novel inhibitors of BRaf-V599E, the predominant oncogenic form of the protein, we

wished to utilize molecular dynamics simulations to study the interactions between potential inhibitors and the protein. We first modeled BAY43-9006 analogs based on the published BRaf-V599E/BAY43-9006 complex structure (PDB 1uwj) and correlated MMPBSA-based binding energies of the compounds with their measured IC50s. These results have provided validation of the basic approach for analysis of the energetic of BRaf/inhibitor complexes, and this methodology has subsequently been extended to our proprietary class of inhibitors.

COMP 88 Docking Studies on inhibitors of GSK-3Beta Kinase

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We present molecular docking studies on the inhibitors of GSK-3beta Kinase in the enzyme binding sites as available in the X-ray complexes (1H8F, 1PYX, 1O9U, 1Q4L, 1Q5K and 1UV5). The X-ray ligands in these 6 complexes have been docked in all the active sites. In addition, both active and weakly active compounds from patent literature have been docked into these binding sites using the standard and extra precision docking algorithms in Glide. In cases of cross docking experiments that produce docked poses which are distinctly different from the corresponding X-ray poses, flexible induced fit docking has been carried out to obtain poses similar to those in experimental structures. Specifically, the active site of 1O9U has been induced to fit the ligands in 1Q4L, 1Q5K and 1UV5. Also, the active site of 1Q4L has been induced to fit the X-ray ligands in 1Q5K and 1UV5. Correlation between docked poses and experimental IC50 values has been obtained using the fitting algorithms in Liaison. Docking modes of reported ligands of 1H8F have been compared with the docking modes of highly active patented ligands.

COMP 89 Structure-based design of acylguanidine BACE1 inhibitors

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Alzheimer's Disease (AD) is a progressive, neurodegenerative disease without a known cure, and is the leading cause of dementia in the elderly. Although the cause of AD is still unclear, deposition of β-amyloid peptide (Aβ) in the brain is a hallmark of AD pathogenesis, and it is believed that therapeutic agents that lower Aβ will be beneficial in the treatment of AD. β-secretase or BACE (β-site APP Cleaving Enzyme) is a membrane-associated aspartic acid protease, and is one of the enzymes responsible for production of Aβ by proteolytic cleavage of APP (Amyloid Precursor Protein). In particular, BACE1 (EC 3.2.23.46) activity generates a membrane-bound C-terminal APP fragment containing the amino terminus of Aβ, which is subsequently cleaved by γ-secretase to produce Aβ, with BACE1 activity as the rate-limiting step in the process. Therefore, BACE1 is an attractive therapeutic target for AD. We will discuss the optimization of a relatively weak (micromolar) BACE1 high-throughput screening hit to a lead series with nanomolar potency. This series contains an acylguanidine moiety that forms a novel interaction with the catalytic aspartic acid side chains, and displaces the BACE1 flap region up to nearly 8Å relative to what has been observed for peptidomimetic-bound complexes. The optimization approach included structure-based combinatorial libraries as well as the design of specific molecules, utilizing in-house x-ray crystal structures, biological assay data, and calorimetric measurements, in conjunction with computational techniques such as protein-ligand docking, quantum chemical conformational analysis, and MM/PBSA calculations to account for solvent effects. Efforts in identifying small molecule BACE1 inhibitors may lead to the identification of disease-modifying therapeutics for AD.

COMP 90 Structure-based Drug Design for Nuclear Hormone Receptors

Stanley Krystek Jr.[1], Lawrence G. Hamann[2], Mark E. Salvati[3], Aaron Balog[3], Jack Hunt[3], James Li[2], Mark Manfredi[2], Rogelio Martinez[3], Akbar Nayeem[1], Alexandra Nirschl[2], Dacia Pickering[3], Dora Schnur[1], Weifeng Shan[3], Chongqing Sun[2], Donna Wei[3], and Hong Zhu[3]. (1) Computer-Assisted Drug Design, Bristol-Myers Squibb, Pharmaceutical Research Institute, P.O. Box 5400, Princeton, NJ 08543-5400, Fax:

609-818-3545, stanley.krystek@bms.com, (2) Discovery Chemistry, Bristol-Myers Squibb Company, (3) Oncology Chemistry, Bristol-Myers Squibb Pharmaceutical Research Institute

Structure-based drug design encompasses a number of technologies that provide the drug discovery process with rapid and unique approaches to ligand discovery and optimization. The aim of structure-based design is optimization of ligand potency and selectivity. However, drug design requires optimization of many properties including absorption, metabolic stability, distribution, plasma protein binding, toxicology and other pharmaceutical properties. In this talk we will highlight aspects of ligand design for members of the nuclear hormone receptor family.

COMP 91 Structure-based prediction of drug binding to human serum albumin

Jian Li, Brett A. Tounge, and Charles H. Reynolds, Molecular Design and Informatics, Johnson & Johnson Pharmaceutical Research and Development L.L.C, Welsh and McKean Roads, PO Box 776, Spring House, PA 19477, jli@prdus.jnj.com

Human serum albumin (HSA) is the most abundant protein in serum plasma. Binding of drug compounds to serum albumin is one of many factors that affect the pharmacokinetic and pharmacodynamic properties of drugs, such as drug distribution and disposition. In this study, we combined induced-fit docking with linear interaction energy (LIE) calculations to investigate the binding modes and affinities of drug compounds bound to the IIA and IIIA sites of HSA. The crystal structure binding modes for several compounds (warfarin, propofol, thyroxine) were reproduced by this docking protocol. The binding affinities for a series of drug compounds were correlated to the calculated van der Waals (ΔvdW) and electrostatic (Δele) terms in the interaction energies. As a test of this methodology, we computed the HSA binding affinities of several diflunisal analogues and compared to them with experimental results.

COMP 92 Folding@Home: Using desktop grid computing to overcome fundamental barriers in biomolecular simulation

Vijay S. Pande, Department of Chemistry, Stanford University, MS 5080, Stanford, CA 94305-5080, Fax: 650-725-0259, pande@stanford.edu

One of the great challenges of a physical approach to computational biology is the vast complexity of biological systems and the long timescales involved (from the point of view of simualtions). Indeed, atomistic simualtions on the millisecond timescale would currently require millions of CPU days, putting them far beyond what one can typically do, even with the fastest traditional supercomputers. I will discuss new paradigms for scientific computation to break this fundamental computational barrier; in particular, I will discuss novel methods to efficiently utilize a loosely coupled grid of 200,000 actively participating CPUs ("Folding@Home") in order to reach timescales thousands to millions of times longer than typically examined. We apply these methods to study the thermodynamics and kinetics of protein self-assembly or folding. Our methods allow us, for the first time, to reach experimentally relevant timescales to observe folding and our simulations are in quantitative agreement with experiment. While our applications are primarily suited to biomolecular simulation, these algorithms should be broadly applicable to many areas of simulation and theory and conclude with a discussion of further applications.

COMP 93 Molecular Modeling of Complex Biological Systems: Microbial Membranes

T. P. Straatsma, Computational Sciences and Mathematics Division, Pacific Northwest National Laboratory, Richland, WA 99352, Fax: 509-375-6631, tps@pnl.gov

Gram-negative microbes such as Pseudomonas aeruginosa and Shewanella oneidensis are of particular interest to the US Department of Energy because of the specific role that these bacteria play in the environment. The microbial outer membrane is believed to play a key role in processes that govern microbial metal binding, microbial adsorption to mineral surfaces, and microbe mediated oxidation/reduction reactions at the bacterial exterior surface. At Pacific Northwest National Laboratory a computational modeling capability is developed for the study of geochemical reactions at the outer bacterial envelope of these Gram-negative bacteria. The major constituent of the outer membrane of Gram-negative bacteria are lipopolysaccharides. Molecular models have been designed for the rough lipopolysaccharides of P. aeruginosa and S. oneidensis based on available experimentally determined structural information. Electrostatic models have been developed based on Hartree-Fock SCF calculations of the complete LPS molecules. Molecular dynamics simulations have been carried out and analyzed for

the rough LPS membranes of these microbes. Results are presented of the initial investigations of the interaction of the P. aeruginosa membrane with the mineral goethite, and the role of the membrane on the stability and dynamics of embedded proteins.

PNNL-SA-44989

COMP 94 Distributed computations for biomolecular structure, dynamics and folding
Adrian E Roitberg, Department of Chemistry, University of Florida, Quantum Theory Project, Gainesville, FL 32611

My group is developing a number of techniques with the following three goals: 1. To sample the conformational space of peptides/proteins as well as possible. 2. To design simulations setups that close resemble the experiments. 3. To compute primary experimental observables from the sampling.

This overall design allows us to not only directly compare with experimental averages, but also to look at fluctuations, conformational substates and a number of other properties not easily accesible to experiments.

The overall idea is set under a distributed computational environment, where the

underlying assumption is that very large numbers of processors are available, if they are needed only for relatively short times.

Details of the algorithms and some applications to free energy calculations and folding rates will be shown.

COMP 95 Fast Multipole Communications Scaling
B. Montgomery Pettitt, Chemistry, University of Houston, 4800 Calhoun, Houston, TX 77204-5003, pettitt@uh.edu, and Jakub Kurzak, Computer Science, University of Houston

A major limitation of fast summation methods in the form of fast multipole algorithms has been the number of particles required to break even against other more traditional methods to handle long range forces in particle simulations. We present a new load balanced parallel implementation of a non-adaptive version of Greengard and Rokhlin's fast multipole method for distributed memory architectures with focus on applications in molecular dynamics. We introduce a novel load balancing and communication overlapping scheme. Our implementation includes periodic boundary conditions calculations with Ewald and facilitates multiple time stepping techniques without sacrificing determinism of computation and scales to hundreds of processor for systems of only O(10 k) atoms.

COMP 96 Scalable molecular dynamics simulation of cellular processes
Emad Tajkhorshid, Theoretical and Computational Biophysics Group, University of Illinois at Urbana Champaign, Beckman Institute, 405 N. Mathews, Urbana, IL 61801, Fax: 217-244-6078, emad@ks.uiuc.edu

The fundamental processing units in the living cell that mediate and control biochemical processes are often huge in size and/or complex in nature. Furthermore, they function in an even larger complex environment. Striking progress has been achieved in characterizing the immense machines of the cell, such as the ribosome, at the atomic level. Advances in understanding the mechanism of function of these machines, however, demand special tools and computational resources allowing to model these machines in their natural environment and for time scales relevant to the biochemical process at hand. Molecular dynamics simulations have been successfully applied to a variety of biological problems, ranging from transmembrane traffic of materials to mechanical properties of macromolecules. In this talk I will present some examples of recent molecular dynamics simulations of cellular processes that have been made possible due to the availability of extensive clusters of computers and algorithms that exploit them in the most efficient manner possible. The talk will focus mainly on one of the most advanced molecular dynamics codes, NAMD, in terms of parallel computing, and will address technically important features of the program as well as prospective applications of the technique.

COMP 97 Use of NASA's Columbia teraflop supercomputer to study DNA damage by charged

particles

Galina M. Chaban[1], Winifred M. Huo[1], Dunyou Wang[2], and Christopher E. Dateo[2]. (1) NASA Ames Research Center, Mail Stop T27B-1, NASA Ames Research Center, Moffett Field, CA 94035-1000, Fax: 650-604-1095, chaban@nas.nasa.gov, (2) Eloret Corporation

Using the high end computing facility Columbia at NASA Ames Research Center, we have simulated the damage of guanine-cytosine base pair by charged particles using first principles calculations. The calculation established the formation of tandem double lesions to be a multi-step process. Guanine is first ionized by the charged particle. If the ionized electron originates from an orbital with significant charge density along the N(1)-H bond, it leads to breaking of this bond (first lesion), releasing a proton. If the proton is produced with energy above ~2.5 eV, its interaction with the neighboring cytosine leads to cytosine ring opening resulting in a second lesion. The present result shows that, analogous to the hydroxyl radical, charged particles interaction can also lead to tandem base damages.

COMP 98 Calculations to determine the experimental conformation of a cyclic insect pheromone using a novel multi-faceted ab initio approach

Frank A. Momany, Plant Polymer Research, National Center for Agricultural Utilization Research, ARS, USDA, 1815 N. University St., Peoria, IL 61604, Fax: 309-681-6362, momanyfa@ncaur.usda.gov, Robert J. Bartelt, Crop Bioprotection Research Unit, USDA, REE, Agricultural Research Service, National Center for Agricultural Utilization Research, and Wayne B. Bosma, Department of Chemistry, Bradley University

A new pheromone from Galerucella calmariensis L. has recently been identified and has the chemical formula; 12,13-dimethyl-5,14-dioxabicyclo[9.2.1]tetradeca-1(13),11-dien-4-one. The structure was determined by mass spectrometry, NMR, and UV spectroscopy. The ring is flexible, and the preferred conformation difficult to deduce from NMR data. A molecular mirror image symmetry exists of the same energy as the original structure. The DFT(GIAO) calculated isotropic 1H and 13C chemical shifts for different conformations of low energy were compared with experiment. Two conformations of low energy were found within ~0.5 kcal/mol of each other, with small rms deviations from observed chemical shift values. Transition state barriers between energy minima were obtained using an eigenvalue following routine and new minimum energy conformations obtained by energy optimization from the transition states. Dihedral angle driving methods were used to examine how driving individual dihedral angles through mirror image values changes the low energy conformations. Quantum dynamics was carried out at the 4-31G* level of theory and many transitions to other conformations were observed.

COMP 99 Investigations of Light Harvesting Complexes

Ian R. Gould, department of chemistry exhibition road, Imperial College, imperial college london, exhibition road, london sw7 2ay, United Kingdom, Fax: 44 207 5945809, i.gould@imperial.ac.uk

We present here a comprehensive investigation of the Light Harvesting Complexes (LHC II) in Rs. molischanum and Rs. molischanum using Ab Initio excited state calculations. We contrast the results obtained with CIS and TD DFT methods and the implication for QM/MM calculations on such systems.

COMP 100 Substituent effects on hydrogen bonding in Watson-Crick base pairs

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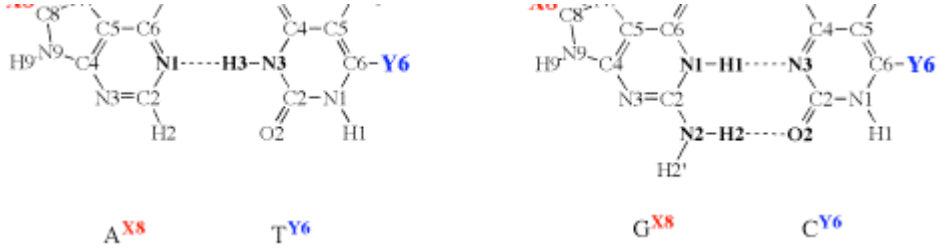
We have theoretically analyzed Watson-Crick AT and GC base pairs in which purine C8 and/or pyrimidine C6 positions carry a substituent X (see illustration) using the generalized gradient approximation (GGA) of density functional theory at BP86/TZ2P. The purpose is to study the effects on structure and hydrogen bond strength if X = H is substituted by a halogen atom. Furthermore, we wish to explore the relative importance of electrostatic attraction versus orbital interaction in the above multiply hydrogen bonded systems, using a quantitative bond energy decomposition scheme. We find that replacing X = H by charged and neutral substituents from groups 15 - 17 has characteristic effects on hydrogen bond lengths, strengths and bonding mechanism. This is interpreted in terms of the substituent-induced attenuation or amplification of the hydrogen-bond-accepting and hydrogen-bond-donating capabilities of a DNA base.



COMP 101 Coupled cluster methods including non-iterative approximate quadruple excitation corrections . A new alternative for thermochemistry
Yannick J. Bomble, Institute for Theoretical Chemistry-Departments of Chemistry and Biochemistry, The University of Texas at Austin, 1 University Station A5300, austin, TX 78712-0165, Fax: 512-471-8696, ybomble@mail.utexas.edu, John F. Stanton, Institute for Theoretical Chemistry, Departments of Chemistry and Biochemistry, University of Texas, Austin, TX 78712, Mihály Kállay, Department of Physical Chemistry, Budapest University of Technology and Economics, and Juergen Gauss, Institut für Physikalische Chemie, Universität Mainz

The addition of non iterative quadruple excitations to the CCSDT method (CCSDT(Q)) based on the application of perturbation theory on the CCSDT state is investigated. This method is thoroughly tested on a large set of atoms and molecules and is compared to CCSDT, CCSDTQ, CCSDTQP and the addition of quadruple excitations obtained by applying perturbation theory on the HF-SCF state (CCSDT[Q]). The studied method performs well and its correlation energy is extremely close to the one calculated with both CCSDTQ and CCSDTQP methods; the mean absolute deviation is less than 0.100 mH and 0.055 mH, respectively. This new method is well-balanced and is size-consistent. For a large set of small open-shell and closed-shell systems the calculated enthalpies of formation are within 0.30 kJ/mol of the best known experimental values.

COMP 102 Efficient SCF method for large systems of weakly interacting components
Rustam Z. Khaliullin, Department of Chemistry, University of California, Berkeley, Berkeley, CA 94720, rustam@berkeley.edu, Alexis T. Bell, Department of Chemical Engineering, University of California, Berkeley, CA, and Martin Head-Gordon, Department of Chemistry, University of California

An efficient method for removing the SCF diagonalization bottleneck is proposed for systems of weakly interacting components. The method is based on the locally projected SCF for molecular interactions equations (LP SCF MI) of Gianinetti et.al. [E. Gianinetti, I. Vandoni, A. Famulari, M. Raimondi, Adv. Quantum Chem. 31, 1998 251]. A generalization of the DIIS method for non-orthogonal molecular orbitals is formulated to increase the rate of convergence of the LP SCF MI. A fast scalable second-order single-excitation perturbative correction is developed to improve the LP SCF MI energies. The resulting energies closely reproduce the conventional counterpoise corrected SCF energy. Extensive test calculations are performed on large water clusters up to several hundred molecules. Compared to conventional SCF, speed-ups of the order of $(N/O)^2$ have been achieved for the diagonalization step, where N is the size of the AO basis, and O is number of occupied molecular orbitals.

COMP 103 Electronic structure of "difficult" systems: Quantum Monte Carlo estimates of transition metal IP and EA
John A.W. Harkless, Ainsley Anthony Gibson, and Gordon Taylor, Department of Chemistry, Howard University, 525 College St., NW, Washington, DC 20059, Fax: 202-806-5442, jharkless@howard.edu

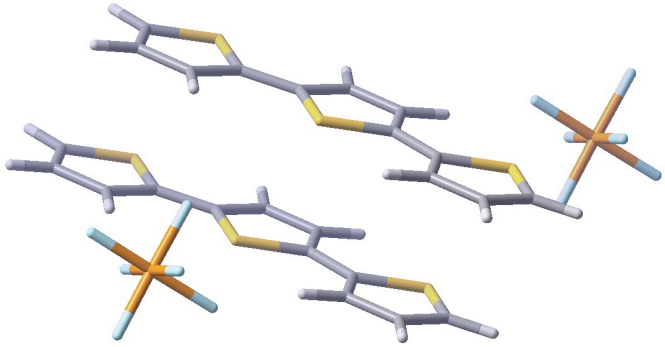
One way to characterize a system as considered difficult for electronic structure methods is to determine if the system may be effectively described by a common variant of a given theory. In other words, if the implementation of a particular theory is one that is used in 90-95% of all cases cannot effectively describe the system, then that particular system may be considered “difficult.” In common practice, systems that are considered difficult tend to have unique features that make them interesting and relevant to a number of novel applications: open shells, metastable radical states, multireference character, and accessible excited electronic states, are all examples of features that can contribute to a “difficult” system. The research to be presented here will cover the use of quantum Monte Carlo methods in addressing some “difficult” systems of potential interest in nanomaterial science and characterization of metallic systems' electronic properties.

A discussion of QMC methods in general, and factors contributing to a lack of “difficult” systems for the method will also be included.

COMP 104 Charge-transfer effects and counterions in electroactive polymers

Nicholas E. Miller, Damian Scherlis, and Nicola Marzari, Department of Materials Science and Engineering, Massachusetts Institute of Technology, 77 Massachusetts Ave, 13-4066, Cambridge, MA 02139, nedward@mit.edu

Conducting polymers such as oligothiophenes can pair through π-stacking interactions under the appropriate electrochemical conditions. Such mechanisms have been recently proposed as a driving force in the design of molecular actuators. We investigate here by means of extensive quantum-chemistry and first-principles molecular dynamics calculations the driving force behind π-stacking. Density functional theory calculations are carried out at the PBE and hybrid B3LYP levels of theory. Particular attention is payed to the role of the solvent, calculating within the polarized continuum model. Furthermore, the common counterion hexafluorophosphate is explicitly included in the calculations. The attachment of these counterions to the oligothiophene backbone, and the resulting charge transfer, are examined in detail. In particular, the dielectric environment is found to be crucial in determining both the stacking interactions between oxidized oligomers and interactions between oligomers and their counterions.



COMP 105 Hydronium on Pt (111) surface and their roles in O_2 reduction

Liang Qi[1], Joshua Fujiwara[2], and **Ju Li**[1]. (1) Department of Materials Science and Engineering, Ohio State University, 494 Watts Hall, 2041 College Road, Columbus, OH 43210, Fax: 614-292-1537, qi.36@osu.edu, li.562@osu.edu, (2) Honda Research Institute USA, Inc, 1381 Kinnear Road, Columbus, OH 43212

DFT study of a series of hydronium-water complexes on (111) Pt surface is performed. Different surface hydronium $H^+(H2O)_n$, n=1..4, configurations are considered to obtain the preferred adsorption geometry and energy. The bonding and charge-transfer processes during adsorption are analyzed by charge integration, density difference map and orbital analysis. The roles of water-hydronium complexes in the reduction of O_2 on Pt (111) surface are then investigated. Both the nudged elastic band and the dimer methods are used to find the transition states in the elementary steps of O_2 reduction. Our model helps to refine a reaction pathway catalog for the complex reactions occuring on the PEM fuel cell cathode, where there is a three-phase interface of gas, water-swollen membrane and metal catalyst.

COMP 106 Mechanism of the Rh(I)-catalyzed asymmetric hydrogenation of unprotected enamines: A density functional theory study

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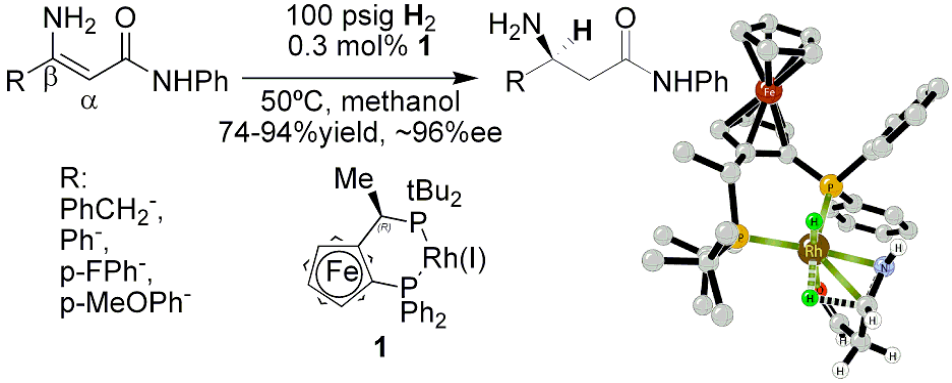
The mechanism of the Rh(I)-catalyzed hydrogenation of unprotected enamines, shown following, has been investigated, using density functional theory (B3LYP) and 6-31+G* (C, H, O, N, and P) and LANL2DZ+ECP (Rh and Fe) basis sets. Various pathways were first scanned with PH_3 model ligands, while the actual ligand (Josiphos, **1**) used in the Merck process [Hsiao *et al. JACS*, **2004**, *126(32)*, 9918-9919] was applied to investigate the origin of the observed enantioselectivity. It has been confirmed theoretically that the N=C double bond of imine tautomers, instead of the C=C of the enamines, is reduced by the Rh-hydride complex. The stereochemistry of the reduction is controlled by electronic effects of substituted phosphines and ferrocenyl groups of the Josiphos ligand.



COMP 107 Mechanistic explorations of the vinylcyclobutane-cyclohexene and sceptrin-ageliferin rearrangements using density functional theory

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The rearrangements of vinylcyclobutane to cyclohexene and of sceptrin to ageliferin, which represents the first vinylcyclobutane rearrangement of a natural product, have been studied computationally with density functional theory. Both rearrangements proceed through a stepwise diradical mechanism and share many structural similarities. The shapes of their respective potential energy surfaces, however, differ quite strongly. In addition, the minimum energy pathway for the rearrangement of vinylcyclobutane is shown to be suprafacial with inversion of configuration at the migrating carbon while rearrangement of sceptrin to ageliferin occurs suprafacially with retention. Mechanistic details and factors governing product stereochemistries for both rearrangements will be discussed.

COMP 108 Rational design of organocatalysts using quantum mechanical calculations - towards new catalytic proline derivatives for the diastereoselective intermolecular aldol and Mannich reactions

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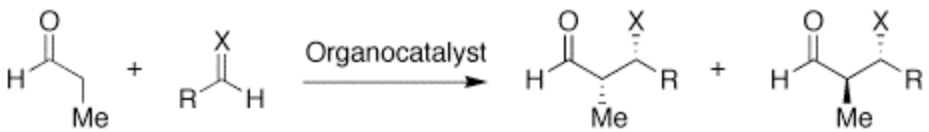
Quantum Mechanical calculations have been used to elucidate the origins of diastereoselectivity in proline-derivative catalyzed intermolecular aldol and Mannich reactions. New proline derivatives are predicted to be useful catalysts. Some are expected to show greater diastereoselectivity than proline, while others are predicted to give the anti-Mannich and the syn-aldol products, which are unattainable using proline or chiral imidazolidinone catalysis.



Syn Product
Anti Product
X = NPh, O