American Chemical Society

Division of Computers in Chemistry
ABSTRACTS

226th ACS National Meeting

New York, NY
September 07-11, 2003 **R. A. Wheeler, W. D. Cornell, Program Chairs**

SUNDAY MORNING

- **Frontiers in DNA Research: An Interdisciplinary Symposium**
J. D. Evanseck, Organizer Papers 1-4

- **Parallel and High-Performance Computing in Chemistry**
D. E. Bernholdt, Organizer, Presiding Papers 5-8

- **Theory and Simulation of Protein Folding Kinetics**
J. Pitera, Organizer Papers 9-14

SUNDAY AFTERNOON

- **Frontiers in DNA Research: An Interdisciplinary Symposium**
J. D. Evanseck, Organizer Papers 15-19

- **Parallel and High-Performance Computing in Chemistry**
D. E. Bernholdt, Organizer; T. L. Windus, Presiding Papers 20-23

- **Theory and Simulation of Protein Folding Kinetics**
J. Pitera, Organizer Papers 24-29

- **Challenges for the Chemical Sciences in the 21st Century: Information and Communication**
P. Gund, Organizer, Presiding Papers 30-35

MONDAY MORNING

- **Frontiers in DNA Research: An Interdisciplinary Symposium**
J. D. Evanseck, Organizer Papers 36-39

- **Parallel and High-Performance Computing in Chemistry**
D. E. Bernholdt, Organizer; R. J. H. Harrison, Presiding Papers 40-42

- **Modeling Spin Forbidden and Open-Shell Processes**
T. Cundari, Organizer Papers 43-46

- **Computational Chemistry in Drug Discovery: Are High Information Content Calculations Better than Low Information Content Calculations**
J. L. Miller, Organizer Papers 47-54

MONDAY AFTERNOON

- **Frontiers in DNA Research: An Interdisciplinary Symposium**
J. D. Evanseck, Organizer Papers 55-59

- **Computational Chemistry in Drug Discovery: Are High Information Content Calculations Better than Low Information Content Calculations**
J. L. Miller, Organizer Papers 60-67

- **Modeling Spin Forbidden and Open-Shell Processes**
T. Cundari, Organizer Papers 68-71

MONDAY EVENING

- **Sci-Mix**
R. A. Wheeler, Organizer Papers 106, 111, 114, 120-121, 126, 132-134, 137-138, 142-144, 146-148, 153, 155, 159, 162-163, 170, 172, 175-176

TUESDAY MORNING

TUESDAY AFTERNOON

TUESDAY EVENING

WEDNESDAY MORNING

WEDNESDAY AFTERNOON

THURSDAY MORNING

THURSDAY AFTERNOON

DIVISION OF COMPUTERS IN CHEMISTRY

1.

G-QUADRUPLEXES: THEIR IMPORTANCE IN GENE SILENCING, AS TARGETS FOR DRUG DESIGN, AND IN THE ETIOLOGY OF COLORECTAL CANCER.
***Laurence H. Hurley**, College of Pharmacy, University of Arizona, 1703 E. Mabel, PO Box 210207, Tucson, AZ 85721, Fax: 520-626-5623, hurley@pharmacy.arizona.edu*

The role of secondary DNA structures in control of gene expression has long been debated. In this presentation I provide direct evidence for a G-quadruplex in a promoter region and its targeting with a small molecule to repress c-MYC transcription. The nuclease hypersensitivity element III1 upstream of the P1 promoter of c-MYC controls up to about 85%of the transcriptional activation of this gene. We have demonstrated that the purine-rich strand of the DNA in this region can form two different intramolecular G-quadruplex structures, only one of which appears to be biologically relevant. This biologically relevant structure is the kinetically favored chair-form G-quadruplex, which when mutated with a single G to A transition is destabilized, resulting in a 3-fold increase in basal transcriptional activity of the c-MYC promoter. The cationic porphyrin TMPyP4, which has been shown to stabilize this G-quadruplex structure, is able to further suppress c-MYC transcriptional activation. These results provide compelling evidence that a specific G-quadruplex structure formed in the c-MYC promoter region functions as a transcriptional repressor element. Furthermore, we establish the principle that c-MYC transcription can be controlled by ligand-mediated G-quadruplex stabilization. The formation of similar G-quadruplexes in other promoters of growth regulatory genes, such as PDGF-A, c-myb, and Ki-ras, suggest that this will be a more general phenomenon in genes associated with growth and proliferation. Furthermore, we have identified the same G to A mutation in the c-MYC repressor element, which results in inactivation of the G-quadruplex repressor element and overexpression of c-MYC in 30%of patients with colorectal cancer.

2.

PROGRAMMED READ-OUT OF THE DNA MINOR GROOVE BY SYNTHETIC LIGANDS. ***Peter B. Dervan**, Department of Chemistry, California Institute of Technology, Mail Code 164-30, Pasadena, CA 91125, dervan@caltech.edu*

Small molecules that specifically bind predetermined DNA sequences would be useful tools in biology, biotechnology and potentially in human medicine. Synthetic ligands are designed to read the DNA double helix in the minor groove by a set of simple chemical principles. Hairpin pyrrole-imidazole polyamides achieve affinities and specificities comparable to DNA-binding proteins. The design of second generation ring pairing rules for distinguishing the four Watson-Crick base pairs will be described.

3.

THREADING POLYINTERCALATION. ***Brent L. Iverson**, Jeeyeon Lee, and Vladimir Guelev, Department of Chemistry & Biochemistry, The University of Texas at Austin, 1 University Station, Austin, TX 78712, Fax: 512-471-8696, biverson@mail.utexas.edu*

Threading intercalators are molecules that insert between the bases of double stranded DNA and place functional groups in both the minor and major grooves. We have been exploring threading polyintercalation in which the threading intercalator 1,4,5,8-naphthalene tetracarboxylic diimide (NDI) is linked in a head-to-tail fashion with a variety of tethers. Using a combinatorial approach, linkers conferring novel sequence specificity to NDI dimers were identified. NMR structural studies revealed that one such dimer bound to its preferred sequence with its linker in the minor groove, while another placed its linker in the major groove. Using these linkers as a model, an NDI tetramer was designed and synthesized. NMR structural analysis of the complex with its preferred 14 base pair sequence has revealed the expected threading mode of polyintercalation, with linkers alternating between the minor and major grooves. Threading polyintercalation represents an interesting DNA binding topology that has the advantage of providing for numerous contacts in both DNA grooves on a relatively low molecular weight scaffold that covers long DNA sequences.

4.

CONTROLLING NUCLEIC ACID STRUCTURAL TRANSITIONS BY INTERCALATION. ***Nicholas V. Hud**, and Swapan Jain, School of Chemistry and Biochemistry, Georgia Institute of Technology, 770 State St., Atlanta, GA 30332, Fax: 404-894-2295, hud@chemistry.gatech.edu*

We are investigating the utility for small molecule intercalation to drive nucleic acid structural transitions. We have recently shown that coralyne, a small crescent-shaped molecule, can cause complete and irreversible duplex disproportionation (Polak & Hud, 2002, Nucleic Acids Res. 30, p983). That is, upon addition of coralyne the strands of duplex poly(dT)·poly(dA) repartition into equal molar equivalents of triplex poly(dT)·poly(dA)·poly(dT) and single stranded poly(dA). We have also discovered that poly(dA) forms a duplex self-structure in the presence of coralyne, which is completely dependant on coralyne intercalation for stability. Similar investigations have now been carried out with homo-dT and homo-dA oligonucleotides of 16 and 32 nucleotides in length. We will show that duplex disproportionation by coralyne is profoundly dependant on oligonucleotide length. For example, disproportionation is reversible with temperature for dT_{16}·dA_{16} over the course of hours, but requires days for dT_{16}·dA_{32}, and is apparently irreversible for poly(dT)·poly(dA). An equilibrium state containing three different secondary structures (i.e. duplex, triplex and the A·A duplex) can also be achieved at certain temperatures, depending upon oligonucleotide length. The interplay we observe between coralyne intercalation, temperature and nucleic acid secondary structure reveals a system of intertwined thermodynamic and kinetic factors.

5.

PARALLELIZATION OF THE EFFECTIVE FRAGMENT METHOD FOR SOLVATION AND EXTENSIONS TO MODEL BULK BEHAVIOR. ***Heather Netzloff**, and M. S. Gordon, Department of Chemistry, Iowa State University, 201 Spedding Hall, Ames, IA 50011, heather@si.fi.ameslab.gov*

As the size of a system grows, ab initio quantum chemistry calculations quickly increase in computational cost. In order to accurately model liquids and solvation effects, a large number of molecules is required. The Effective Fragment Potential (EFP) method for solvation has been developed, in part, to address these concerns. In the method, the system is divided into an ab initio region that contains the solute plus some number of solvent molecules, if desired, and an “effective fragment” region that contains the remaining solvent molecules. Interaction between solvent molecules, represented by effective fragments, and the ab initio part of the system is treated via one- electron terms; fragment-fragment interactions are treated in a similar manner. Thus, the total system Hamiltonian is a sum of the ab initio Hamiltonian and the potential due to the fragment interactions. Even with this simplification of the potential energy, modeling of an increased system size and bulk properties require parallelization of the method and scalable codes. This research considered the fragment-fragment interaction energy and gradient calculation and its parallelization within the GAMESS suite of programs. This is the first time that this part of the potential has been available in parallel code. Results show that reasonable speedup is achieved with a variety of sizes of water clusters and number of processors. The iteratively self-consistent polarization term is treated with a new algorithm to obtain better scalability. Key features of the parallel strategy will be discussed.

6.
LARGE SCALE PARALLELIZATION OF THE PLANE WAVE BASED AB INITIO MD METHOD. ***Glenn Martyna***[1], *Mark Tuckerman*[2], *Laxmikant Kale*[3], *and Ramumar Vadali*[3]. *(1) Physical Science Division, IBM Research, TJ Watson Research Center, PO Box 218, Yorktown Heights, NY 10598, Fax: 914-945-4506, martyna@us.ibm.com, (2) Chemistry, New York University, (3) Department of Computer Science, University of Illinois*

The plane wave based ab initio MD method is widely employed to study systems in which complex processes such as chemical bond making/bond breaking occur or in which the properties of the electronic states are key such as semiconductors and metals. Despite its wide spread use, the standard parallel implementation of the method scales well only when the number of processors is less than the number of electronic states. A new scalable implementation of the method is described followed by an application to a proton transfer reaction in liquid water.

7.
HIGH PERFORMANCE COMPUTING WITH NWCHEM. ***Theresa L. Windus***[1], *Edoardo Apra*[1], *So Hirata*[2], *Eric J. Bylaska*[3], *and T. P. Straatsma*[4]. *(1) Molecular Science Software Group, Pacific Northwest National Laboratory, 902 Battelle Boulevard, P.O. Box 999, MSIN: K1-96, Richland, WA 99352, Fax: 509-375-6631, theresa.windus@pnl.gov, (2) William R Wiley Environmental Molecular Sciences Laboratory, Pacific Northwest National Laboratory, (3) Environmental Molecular Sciences Laboratory, Pacific Northwest National Laboratory, (4) Biological Sciences Division, Pacific Northwest National Laboratory*

With the advent of extremely large computational resources, such as those at PNNL, code efficiency, bottlenecks and algorithms will need to be reexamined to obtain high levels of performance. During this talk, we will describe parallel strategies and computational methodologies that are available within the massively parallel computational chemistry code, NWChem. We will give a brief overview of the NWChem architecture, current parallel algorithms and their evolution with increasing numbers of processors, performance on several architectures, and challenges faced with these large parallel resources. We will also present several science examples that are enabled through massive parallel computations with NWChem.

8.
PARALLELIZATION OF LINEAR-SCALING FOCK MATRIX BUILDS. ***Chee Kwan Gan***, *Valery Weber, and Matt Challacombe, Theoretical Division, Los Alamos National Laboratory, MS B268, Los Alamos, NM 87545, Fax: 505-665-3909, ckgan@lanl.gov*

Linear-scaling electronic structure methods (such as the Fock matrix build and SCF solver) have cost prefactors that are larger than their conventional N^3 counterparts. This fact, coupled with the goal of using linear-scaling methods to attack very large systems, demands their efficient parallelization. However, this is nontrivial because the near-sighted principle (which makes linear scaling possible) leads to highly irregular work load distributions. To obtain a good load balance, we have developed methods that exploit temporal locality in the self-consistent-field calculations. To minimize communication between processors, the relationship between quantum locality and data locality is explored. Speedups obtained with a data parallel approach to the hybrid HF/DFT Fock matrix build will be presented.

9.
FOLDING@HOME: CAN NON-EQUILIBRIUM STATISTICAL MECHANICS AND 100,000 CPUS SIMULATE PROTEIN FOLDING IN ATOMIC DETAIL ON THE MILLISECOND TIMESCALE? ***Vijay S. Pande***, *Department of Chemistry, Stanford University, MS 5080, Stanford, CA 94305-5080, Fax: 650-725-0259, pande@stanford.edu*

While proteins fold quickly on a human timescale (micro to milliseconds), atomistic simulations are typically limited to the nanosecond timescale — a 3 to 6 order of magnitude divide. Starting only from the knowledge of the protein's sequence and by using novel algorithms and tens of thousands of processors in a worldwide grid computing infrastructure, we have been able to bridge this computational divide to simulate the kinetics and thermodynamics of several small, fast folding proteins, yielding successful, quantitative predictions of folding rates, free energies, and native structure. In addition, we have used these powerful computational methods to examine the folded and unfolded states of proteins, making comparisons between ensemble averaged measurements (as one would do in FRET or NMR NOEs) and single molecule characterizations. Our results suggest startling differences between single molecule and ensemble averaged measurements, a novel characterization of the unfolded state, as well as evidence for some universal properties of protein folding.

10.
EFFECTS OF CONFINEMENT IN CHAPERONIN-ASSISTED PROTEIN FOLDING: RATE ENHANCEMENT THROUGH SMOOTHING OF THE FOLDING ENERGY LANDSCAPE. *Andrij Baumketner, Andrew Jewett, and* ***Joan-Emma Shea***, *Department of Chemistry, University of California, Santa Barbara, Santa Barbara, CA 93106, Fax: 805-893-4120, shea@chem.ucsb.edu*

Chaperonins, such as the GroE complex of the bacteria E. Coli, assist the folding of proteins under non-permissive folding conditions by providing a cavity in which the newly translated or translocated protein can be encapsulated. Whether the chaperonin cage plays a passive role in protecting the protein from aggregation, or an active role in accelerating folding rates, remains a matter of debate. We investigate the effects of encapsulation on folding through molecular dynamics simulations of model proteins confined to hydrophilic chaperonin cages. The relationship between the degree of frustration of the substrate protein and the corresponding effect of encapsulation on its folding mechanism and rate will be discussed.

11.
COMPARING SIMULATIONS OF THE KINETICS AND THERMODYNAMICS OF PEPTIDE FOLDING. ***Carlos Simmerling***[1], *Adrian E Roitberg*[2], *and Guanglei Cui*[1]. *(1) Department of Chemistry, State University of New York at Stony Brook, Stony Brook, NY 11790, Fax: 631-632-7960, carlos.simmerling@sunysb.edu, (2) Department of Chemistry, University of Florida*

The nature of the energy landscape for proteins has been the subject of much research. Of particular interest is the process by which single molecules traverse this complex landscape to reach the native basin. Non-equilibrium folding simulations can provide insight into this process, within the limits of the typically small set of observed folding events. Simulations of equilibrium populations can also provide useful descriptions of the folding process. We have carried out both types of simulation for several small model peptides. In each case, we compare the description of the folding process obtained from the two methods. We also discuss the influence on the results from choices required for folding simulations, such as the set of initial (unfolded) structures.

12.
PEPTIDE DYNAMICS FROM MICROSECOND MOLECULAR DYNAMICS SIMULATIONS IN EXPLICIT SOLVENT. *In-Chul Yeh, and* ***Gerhard Hummer***, *Laboratory of Chemical Physics, NIDDK, National Institutes of Health, Building 5, Room 116, 9000 Rockville Pike, Bethesda, MD 20892-0520, Fax: 301-496-0825, icy@helix.nih.gov, hummer@helix.nih.gov*

Molecular dynamics simulation studies of the structure, energetics, and dynamics of small peptides provide unique opportunities for direct comparisons with experiment. Motivated by a series of recent experimental measurements, we study the loop-closure kinetics for several peptides of different lengths in computer simulations using all-atom models in explicit solvent. To provide benchmark comparisons of molecular dynamics simulations with the experiments, we perform multiple simulations for different initial conditions, covering several microseconds in total. The effects of potential parameterizations are quantified by comparing the end-to-end contact-formation kinetics, as well as the structural and dynamic characteristics of the random-coil ensembles determined for different all-atom force fields. We show that two different force fields can give essentially the same rates of end-to-end contact formation, both in good agreement with experiment, and have the same equilibrium constant for the fraction of closed states, yet produce entirely different ensembles of peptide conformations. These results highlight the need for careful comparisons with a broad set of experimental data before conclusions about the validity of the simulations can be drawn.

13.

TBA. ***Cecilia Clementi**, Department of Chemistry, Rice University, 6100 Main street, Houston, TX 77005, Fax: 713-348-5155, cecilia@rice.edu*

Abstract text not available.

14.

PROBING THE PRINCIPLES OF AMYLOID PEPTIDE AGGREGATION. ***John E. Straub**, Department of Chemistry, Boston University, 590 Commonwealth Avenue, Boston, MA 02215, Fax: 617-353-6466*

Amyloid beta-peptide is known to form plaques and fibrils both *in vivo* and *in vitro*. Recently, the possible pathogenic role of low molecular weight aggregates of the peptide has been suggested. Using computational methods we have begun to explore the structure and activity of the wild type, oxidized forms, and naturally occurring mutant variants of the amyloid beta-peptide. A variety of computer simulation methods, including molecular dynamics simulation, are used to probe the structure and energetics of the monomeric peptide. Molecular dynamics and "transition pathway" determination methods are used to explore the initial stages of peptide aggregation and dimer formation. Interpreted in the light of recent experimental studies of the formation of low molecular weight aggregates, our results suggest particular aspects of the peptide structure and dynamics that may be central to its propensity to aggregate.

15.

DNA BULGES: COORDINATES AND FREE ENERGIES. ***B. Montgomery Pettitt**, University of Houston, Houston, TX 77204-5641, pettitt@uh.edu, and Michael Feig, Department of Molecular Biology, TPC-6, The Scripps Research Institute*

Molecular Dynamics simulations have been applied to a DNA octamer which has an adenine bulge at the center to determine the pathway for interconversion between the stacked and extended forms. These forms are known to be important in the molecular recognition of bulges. A variety of distinct conformations and subconformations are found. Stacked and fully looped-out forms are in excellent agreement with experimental data from NMR and X-ray crystallography. Furthermore, in a number of conformations the bulge base associates with the minor groove to varying degrees. Transitions between many of the conformations are observed in the simulations and used to propose a complete transition path way between the stacked and fully extended conformations. The effect on the surrounding DNA sequence is investigated and biological implications of the accessible conformational space and the suggested transition path way are discussed, in particular, for the interaction of the MS2 replicase operator RNA with its coat protein.

16.

MEASURING THE GLOBAL STRUCTURE AND MECHANICAL PROPERTIES OF DNA AND THE RELATION TO PROTEIN-DNA COMPLEXES. ***Donald M. Crothers**, Department of Chemistry, Yale University, P.O. Box 208107, New Haven, CT 06520, Fax: 203-432-6144, donald.crothers@yale.edu, and Yongli Zhang, Department of Molecular Biophysics and Biochemistry, Yale University*

We have developed a high throughput approach to the labor-intensive problems of DNA cyclization, which we use to determine DNA curvature and mechanical properties including bending and torsional flexibilities. The method includes three advances: 1) a combinatorial approach to make the DNA constructs needed, 2) automated real-time measurement of the kinetics using fluorescence, and 3) a new theory for data analysis based on statistical mechanics, replacing Monte Carlo simulation. We illustrate the new approach by determining the properties of sequences involved in indirect recognition by human papiloma virus E2 protein, and using the results to predict variations in the binding constant. We provide an overview of the relation between DNA mechanical properties and protein binding.

17.

DNA BENDING AND FLEXIBILITY IN SIMPLE AND NOT-SO-SIMPLE SYSTEMS. ***L. James Maher III**, Department of Biochemistry and Molecular Biology, Mayo Foundation, 200 First St. SW, Rochester, MN 55905, Fax: 507-284-2053, maher@mayo.edu*

Three questions motivate our experiments: To what extent does backbone charge contribute to DNA stiffness? Can electrostatic effects alone explain some aspects of protein-induced DNA bending? How flexible is DNA in vivo? We will review simple experimental systems where artificial modification of DNA surface charge leads directly to DNA bending, suggesting that local electrostatics can influence DNA shape in dilute solution. We will then turn to the issue of DNA flexibility in vivo, and introduce the topic of "architectural" DNA binding proteins. These proteins cause dramatic DNA bending and flexibility enhancement. We will review our experimental approaches (ensemble, single-molecule, and genetic) to the study of High Mobility Group (HMG) proteins that enhance DNA flexibility both in vitro and in vivo.

18.

DETERMINISTIC PATH SAMPLING OF THE CLOSING CONFORMATIONAL TRANSITION OF DNA POLYMERASE BETA. ***Tamar Schlick**, Department of Chemistry, Courant Institute of Mathematical Sciences, and the Howard Hughes Medical Institute, New York University, 251 Mercer Street, New York, NY 10012, Fax: 212-995-4152, schlick@nyu.edu, and Ravi Radhakrishnan, Department of Chemistry, New York University*

We describe the application of the Transition Path Sampling (TPS) method of Chandler and coworkers for the first time to a complex biomolecular system in explicit solvent, namely the closing conformational transition of DNA polymerase beta occurring on the millisecond time frame. TPS is a general method for sampling slow processes using a combination of dynamics trajectories and Monte Carlo random walks that connect free energy basins in the conformational space; in this way, it produces information on barrier crossing pathways and energies, which collectively can yield a complete reaction profile. Our protocol to adapt TPS to biomolecular systems is based on a divide and conquer strategy for trajectory generation and analysis and to treat the multiple transition states occurring in the free energy landscape. Vital information on biologically interesting regions of conformation space have been gleaned from prior molecular and Langevin dynamics trajectories. To describe the system's reaction profile for the closing motion which preceeds, and is essential for, the chemical reaction of nucleotide incorporation, we compute the free energy (as a function of critical parameters identified in the sampling) using a histogram-based method by employing umbrella sampling. Together, the five identified transition states and associated free energy barriers describe the cooperative dynamics associated with the conformational transition of pol beta, highlight key residues that play a critical role in the enzyme's function, and begin to yield clues into the relation between conformational and chemical barriers.

19.

FUZZY BAR CODE REPRESENTATIONS OF DNA-PROTEIN INTERACTIONS. ***N Sukumar**[1], Curt M Breneman[1], Charles Lawrence[2], Kristin P. Bennett[3], and Inna Vitol[2]. (1) Department of Chemistry, Rensselaer Polytechnic Institute, Cogswell Laboratory, 110 8th Street, Troy, NY 12180-3590, Fax: 518-276-4045, nagams@rpi.edu, (2) Wadsworth Center, (3) Department of Mathematics, Rensselaer Polytechnic Institute*

A new electron density-derived base-pair descriptor scheme is combined with machine learning methodology to uncover the functional relationships between DNA/RNA structure at the genetic level and activity at the physiological level. To this end, electronic property distributions of nucleic acid base-pair sequences are represented through Transferable Atom Equivalent Reconstruction (TAE/RECON) using a base-pair descriptor library designed to provide accurate representations of the electronic environment around base-pairs in DNA and RNA sequences. Using four-letter code descriptors, current bioinformatics techniques are beginning to be able to identify motifs involved in transcription factor binding to DNA, as well as regions important to promoter functions. With the addition of these new, rapidly accessible descriptors that can provide features directly related to the physics of interaction between base-pairs and DNA-binding proteins, a new level of information mining is now available for genomic data.

TAE/RECON descriptors provide over 150 channels of electron density-based property information per base-pair, and take into account its DNA environment. In the present work, base-pair contributions are combined to provide spatially-resolved electronic information about DNA sequences and provide a more accurate - and chemically-relevant - way of representing genomic data. The descriptor patterns for any DNA sequence are thus represented in the form of "fuzzy bar codes" comprised of position-specific DNA pixels ("dixels"). The integration of information from "dixel" maps with data from DNA/protein

co-crystal structures can provide insight into the chemistry of DNA-protein interactions relevant to the regulation of gene expression.

20.
REPORT ON AN EFFICIENT CONFORMATIONAL SPACE SEARCH METHOD USING PARALLEL COMPUTING AND GRID TECHNOLOGY. ***Hitoshi Goto***[1], *Kazuo Ohta*[2], *Mitsuhisa Sato*[3], *Taisuke Boku*[3], *Umpei Nagashima*[4], *and Hiroshi Chuman*[5]. *(1) Department of Knowledge-based Information Engineering, Toyohashi University of Technology, Toyohashi 441-8580, Japan, Fax: 532-48-5588, gotoh@cochem2.tutkie.tut.ac.jp, (2) Conflex Corporation, (3) Center for Computational Physics, University of Tsukuba, (4) National Institute of Advanced Industrial Science and Technology, (5) Faculty of Pharmaceutical Sciences, University of Tokushima*

Among the fundamental problems in elucidation of biomolecular functions with the aid of theoretical and computational chemistry, the first difficulty to overcome is the conformational flexibility problem, especially, related to the folding problem of proteins. To resolve these challenging problems, we have developed of a high-performance conformational space search method by using parallel computing and Grid techniques. In this meeting, we report on a performance of the conformational space search for some small peptides. Some interesting folding processes of them are also demonstrated.

21.
EFFECTIVE VHTS USING COMPUTE GRIDS. ***Chris Crafford****, Engineering, United Devices, 12675 Research Blvd., Bldg. A, Austin, TX 78759, Fax: 512-331-6235, chris@ud.com*

Virtual HTS (VHTS) is being more commonly used in early stage drug discovery to identify possible leads. Compute Grids are ideally suited to running VHTS for both docking and scoring on very large libraries of small molecules. Combining different docking, scoring, ADME and Toxicity applications with consensus scoring methods significantly increases the quality of leads from VHTS. This presentation will show how large-scale Grids can be used to effectively use VHTS to obtain high-quality leads for drug discovery.

22.
SYNTHESIZING HIGHLY OPTIMIZED CODE FOR CORRELATED ELECTRONIC STRUCTURE CALCULATIONS. ***David E. Bernholdt***[1], *Alexander Auer*[2], *Gerald Baumgartner*[3], *Alina Bibireata*[3], *Venkatesh Choppella*[1], *Daniel Cociorva*[3], *Xiaoyang Gao*[3], *Robert J. Harrison*[1], *So Hirata*[4], *Sriram Krishnamoorthy*[3], *Sandhya Krishnan*[3], *Chi-Chung Lam*[3], *Qingda Lu*[3], *Marcel Nooijen*[2], *Russell M. Pitzer*[5], *J. Ramanujam*[6], *P. Sadayappan*[3], *and Alexander Sibiryakov*[3]. *(1) Oak Ridge National Laboratory, P O Box 2008, Bldg 6012, MS 6367, Oak Ridge, TN 37831-6367, Fax: 865-574-0680, bernholdtde@ornl.gov, (2) Department of Chemistry, University of Waterloo, (3) Computer Science, Ohio State University, (4) William R Wiley Environmental Molecular Sciences Laboratory, Pacific Northwest National Laboratory, (5) Department of Chemistry, Ohio State University, (6) Computer Science, Louisiana State University*

Efficient implementations of high-end quantum chemical methods (and many other approaches in computational chemistry) are challenging, complex, and time-consuming. The complexity and variety of modern parallel computing platforms only adds to the challenge. Our "Tensor Contraction Engine" is a tool to automate the synthesis of programs for correlated electronic structure calculations from a natural high-level description of the equations for the method. Techniques similar to those used in compilers are used to optimize the generated code for the target platform, and even for the particular problem. This is a tremendous advantage compared to hand-written code, in which the equivalent decisions are typically made in a far more ad hoc fashion based on the developer's concept of the "average" computer platform and "average" problem for the code. We will describe our approach, the types of optimizations performed, and the results for both sequential and parallel implementations of a variety of methods.

23.
HIJACKING THE PLAYSTATION2 FOR COMPUTATIONAL CHEMISTRY. ***Benjamin Levine****, Department of Chemistry, University of Illinois, Urbana, IL 61801, ben.levine@spawn.scs.uiuc.edu, and Todd J. Martinez, Department of Chemistry and the Beckman Institute, University of Illinois at Urbana-Champaign*

The computing power available to gaming consoles, such as the Sony PlayStation2 (PS2), is rapidly increasing and has at times outstripped that which is available to conventional PCs. For example, the PS2 incorporates two asynchronous vector processing units and a 128-bit data path supporting memory transfer speeds exceeding 6Gb/s. The basic mathematics of the videogames for which these consoles are designed is highly linear algebra intensive, similar to many applications in computational chemistry. The Linux operating system has recently become available on many consoles. Furthermore, the price per unit of consoles is generally quite low as a consequence of the high manufacturing volume, which easily outstrips conventional PCs. These considerations compel us to investigate the possibility of tuning computational chemistry codes for the PS2 and other consoles. We discuss our experiences with hijacking the PS2 console for this purpose, stressing both the obstacles and successes. Prospects for such uses of future game consoles and possibilities for parallelization on clusters of such machines are also discussed.

24.
FOLDING DYNAMICS, STATISTICS AND PATHS. ***Jin Wang****, Department of Chemistry, SUNY, Stony Brook, Stony Brook, NY 11794, jinwang@sprynet.com*

Kinetics of protein folding is studied via energy landscape theory. The kinetic folding time versus temperature (U shape) as well as other environmental variables such as equilibrium constant is obtained. In particular, the low temperature behavior of slow dynamics is explored. The high temperature exponential to low temperature non-exponential kinetics is revealed by the statistics of the folding time distribution from Poisson to power law. The transition temperature is between thermodynamic folding and trapping temperature. The folding dynamics can also be studied via the statistics of the kinetic paths. It is shown that there are multiple folding paths above the transition temperature. Discrete paths emerge below the transition temperature. This reveals the nature of the funneled energy landscape of folding. The connection to single molecule study is revealed.

25.
LEARNING FOLDING & DOMAIN SWAPPING FROM ALL-ATOM STRUCTURES AND SIMPLE PARAMETES. *Apichart Linhananta, Hongyi Zhou, Chi Zhang, and* ***Yaoqi Zhou****, Department of Physiology/Biophysics, State University of New York at Buffalo, 124 Sherman Hall, Buffalo, NY 14214, Fax: 716-829-2344, yqzhou@buffalo.edu*

Topology, commonly referred to the arrangement of the secondary structures of a protein, has been extensively studied for its role in protein folding. Recent work shows that topology alone can not account for all the variety of folding behavior found for the proteins within the same structural family. A question naturally arises: can the atomically-detailed native structure of a protein improve the prediction of folding mechanism? Here, we examined the effect of sidechain packing on the folding mechanisms of a beta-hairpin and a three-helix bundle protein. This is done by using a recently developed all-atom Go model and discontinuous molecular dynamics techniques. The results further lead to the development of a simple loop-contact-distance parameter that qualitatively captures the dual folding behavior of a loop. Moreover, it was showed that there is an intimate connection between folding and domain swapping, a possible cause of misfolding and aggregation.

26.
BREAKING NON-NATIVE HYDROPHOBIC CLUSTERS IS THE RATE-LIMITING STEP IN THE FOLDING OF AN ALANINE-BASED PEPTIDE. *Shibasish Chowdhury, Wei Zhang, Chun Wu, Guoming Xiong, and* ***Yong Duan****, Department of Chemistry and Biochemistry, University of Delaware, Newark, DE 19716, Fax: 302-831-6335, yduan@udel.edu*

The formation mechanism of an alanine-based peptide has been studied by all-atom molecular dynamics simulations with a recently developed all-atom point-charge force field and the Generalized Born continuum solvent model at an effective salt concentration of 0.2M. Thirty-two simulations were conducted Each simulation was performed for 100 ns. A surprisingly complex folding process was observed. The development of the helical content can be divided into three phases with time constants of 0.06-0.08, 1.4-2.3, and 12-13 ns, respectively. Helices initiate extreme rapidly in the first phase similar to that estimated from explicit solvent simulations. Hydrophobic collapse also takes place in this phase. A folding intermediate state develops in the second phase and is unfolded to allow the peptide to reach the transition state in the third phase. The folding intermediate states are characterized by the two-turn short helices and the

transition states are helix-turn-helix motifs-both of which are stabilized by hydrophobic clusters. The equilibrium helical content, calculated by both the main-chain Phi-Psi torsion angles and the main-chain hydrogen bonds, is 64-66%, which is in remarkable agreement with experiments. After corrected for the solvent viscosity effect, an extrapolated folding time of 16-20 ns is obtained that is in qualitative agreement with experiments. Contrary to the prevailing opinion, neither initiation nor growth of the helix is the rate-limiting step. Instead, the rate-limiting step for this peptide is breaking the non-native hydrophobic clusters in order to reach the transition state. The implication to the folding mechanisms of proteins is also discussed.

27.

CONFORMATIONAL CHANGES AND FOLDING PATHWAYS OF PROTEINS COMPUTED USING THE STOCHASTIC DIFFERENCE EQUATION. ***Alfredo E. Cardenas**, and Ron Elber, Computer Science, Cornell University, 4130 Upson Hall, Ithaca, NY 14853, Fax: 607-255-4428, alfredo@cs.cornell.edu*

A boundary value algorithm is used to compute approximate classical trajectories using a length parameterization. The approximation in the algorithm consists in the filtering out of high frequency motions due to the use of large step sizes. The filtering of high frequency motions (faster than the corresponding length step) and the boundary formulation make the algorithm very stable and suitable to study slow processes in the microsecond (or longer) time regime. Here we describe the algorithm and show examples of their numerical implementation for the following molecular systems: conformational changes in valine dipeptide, helix formation of a small alanine-rich peptide and folding pathways of cytochrome c.

28.

EXTRACTING DYNAMICAL INFORMATION ABOUT PROTEIN FOLDING FROM TIME SERIES ANALYSIS. ***Konstantin Kostov**[1], Mikito Toda[2], Yasuhiro Matsunaga[3], and Tamiki Komatsuzaki[3]. (1) Department of Chemistry, University of Chicago, 5735 S. Ellis Ave Room 169, Chicago, IL 60615, Fax: 773-702-0805, (2) Department of Physics, Nara Women's University, (3) Department of Earth and Planetary Sciences, Kobe University*

We use local principle component analysis (LPCA) and embedding nonlinear time-series analysis to study the folding and unfolding processes of the simplest realistic protein models: 22-mers and 46-mers containing three types of "beads" representing hydrophobic, hydrophilic, and neutral aminoacids. These proteins are studied over a range of temperatures by simulating T-jump experiments from an initial unfolded state to the folded state and vice versa. The LPCA is able to extract features of dynamics that takes place in multiple potential wells and is used to characterize the pathway diversity and distinguish between folding and unfolding pathways of these protein models. We also analyze time series of the potential energy fluctuations (PEF) and PCs for a modified Go-type model 46-mer protein with a funnel energy landscape. This model exhibits stronger nonstationary behavior of the PEF at the folding temperature than the original frustrated energy landscape, with a significant 1/f noise structure.

29.

CONSTRUCTING MASTER EQUATION MODELS OF PROTEIN DYNAMICS FROM PARALLEL TEMPERING SIMULATIONS. ***John D. Chodera**, Graduate Group in Biophysics, University of California, San Francisco, UCSF Mission Bay, Box 2240, 600 16th Street, San Francisco, CA 94143-2280, Fax: 415-502-4222, jchodera@ugcs.caltech.edu, and Ken A. Dill, Department of Pharmaceutical Chemistry, University of California at San Francisco*

Dynamical processes in proteins, such as folding, are often studied by computer simulations, using all-atom models. Computing transition rates between conformational substates can be difficult; transitions may be infrequent at the temperatures and timescales accessible by molecular dynamics (MD) simulations, and importance sampling is hindered by the potentially large number of intervening saddle points. While an efficient way to sample the thermodynamics is to use parallel tempering MD (or replica exchange among temperatures), dynamical information cannot be extracted directly from such simulations because individual replica trajectories represent unphysical walks in temperature. We describe a method for reweighting these trajectories to reflect their proper contribution to the dynamics at the temperature of interest. The method allows for the efficient estimation of observables that are functionals of the trajectories, such as transition rates between regions of configuration space, or time correlation functions, even when the energy hypersurface is complicated or transitions at the temperature of interest require thermal activation. Examples will illustrate the construction of master equation models of protein dynamics from a single replica exchange simulation using a molecular mechanics potential.

30.

PURPOSES OF THE NRC REPORT, "CHALLENGES FOR THE CHEMICAL SCIENCES IN THE 21ST CENTURY". ***Douglas J. Raber**, Board on Chemical Sciences & Technology, National Research Council, 2101 Constitution Ave. NW, Washington, DC 20418, Fax: 202-334-2154, draber@nas.edu*

Abstract text not available.

31.

CHALLENGES FOR THE CHEMICAL SCIENCES IN THE 21ST CENTURY: A WORKSHOP REPORT. ***Mark Ratner**, Chemistry Dept, Northwestern Univ, Evanston, IL 60208, Fax: 847-491-7713, ratner@chem.nwu.edu, and Richard C. Alkire, Department of Chemistry, University of Illinois*

As part of the challenges for the chemical sciences study, the National Research Council is issuing a series of six reports. One of these reports is on information and communications, and will be overviewed in this presentation.The report contains sections on discovery, interfaces, challenges and infrastructure. It also presents a series of findings, and points out major issues that should be confronted for the chemical sciences to take maximal advantage of improvements in information technology.

32.

ADVANCING CHEMICAL SCIENCE AND TECHNOLOGY THROUGH INFORMATION TECHNOLOGIES. ***Thom H. Dunning Jr.**, Joint Institute for Computational Science, University of Tennessee, Oak Ridge National Laboratory, Oak Ridge, TN 37831, Fax: 865-574-6076, dunning@jics.utk.edu*

We are presently in the midst of a revolution in computing and communications with an order of magnitude increase in capability being realized every three to four years. The most pressing question now is: what must we do to harness the power of high-performance computers and networks to solve the most critical problems in chemistry and chemical engineering? In this presentation we will discuss opportunities and challenges in using advanced information and communications technologies to model molecular and chemical systems and to manage chemical data and instruments.

33.

HOW SCIENTIFIC COMPUTING, KNOWLEDGE MANAGEMENT, AND DATABASES CAN ENABLE ADVANCES AND NEW INSIGHTS IN CHEMICAL TECHNOLOGY. ***Anne M. Chaka**, Computational Chemistry Group, National Institute of Standards and Technology, 100 Bureau Drive, Stop 8380, Gaithersburg, MD 20899-8380, Fax: 301-869-4020*

Global competition is driving industry to reduce the time and cost of developing and manufacturing new products in the chemical, materials, and biotechnology sectors. But discovery and process optimization are limited by a lack of property data and a lack of mechanistic insight. For most applications, particularly mixtures and complex systems, evaluated property data do not exist and are difficult to obtain. Hence we have seen an explosion in combinatorial, data mining, and simulation technologies to supplement and guide experimentation. The greatly increased pace of science and engineering, however, is already beginning to outstrip our ability to produce needed data. The key questions are: How do we develop the capability to supply massive amounts of evaluated data in a timely manner? How do we generate models and simulation methods for quantitatively predicting properties and physical phenomena? How do we

transform data and information into knowledge and wisdom to enable better technical decision-making? Recent advances in computing and scientific algorithms have created the opportunity to begin to address these issues.

34.
DRUG DISCOVERY, A GAME OF 20 QUESTIONS. ***Dennis J. Underwood**, Infinity Pharmaceuticals, 760 Memorial Dr, Cambridge, MA 02139, dennis.underwood@ipi.com*

A key objective in the post-genomic era is to understand the relationship between protein sequence, structure and function. Proteins which share a high level of sequence and/or structural similarity are likely to have similar functional significance, although dissimilar biological sequences may still show functional similarity. Once the function of a therapeutic target is revealed, numerous drug discovery technologies can be used to focus lead discovery and optimization efforts. While the amount of data gathered dramatically increases through the application high throughput technologies, finding a drug remains inordinately challenging. This is due partly to our lack of detailed understanding of the behavior of biological systems to drug-like compounds. It is also due to difficulties integrating different kinds of data and information to provide context and meaning. A corollary to this is, as with the game of 20 questions, simple yes-no responses to key experiments provides dramatic reduction of the size of "possible solution" space. This has dramatic implications for the process of drug discovery.

35.
MODELING OF COMPLEX CHEMICAL SYSTEMS RELEVANT TO BIOLOGY AND PHARMACEUTICAL RESEARCH: PROBLEMS AND PROSPECTS. ***Richard A. Friesner**, Department of Chemistry, Columbia University, 3000 Broadway, MC 3110, New York, NY 10027, Fax: 212-854-7454, rich@chem.columbia.edu*

Over the past decade, a great deal of progress has been made with regard to the ability to carry out molecular simulations of complex systems. Exponential increase in affordable computing power, coupled with improvements in models, algorithms, and software, have enabled realistic treatment of problems such as protein structural refinement and protein-ligand binding. We will discuss both the underlying fundamental technologies necessary for such calculations (force fields, sampling algorithms, and models for aqueous solvation) as well as applications in the context of the pharmaceutical industry, with a particular focus on high throughput docking and homology modeling. The key issues that must be addressed to bring the technology to the next level will then be discussed.

36.
STUDIES TOWARDS THE ARTIFICAL CONTROL OF GENE EXPRESSION. ***Steven M. Firestine**[1], Na Lin[1], David Bednarski[1], Jaipal Hooda[1], Sarah Mueller[2], Jeffrey D. Evanseck[3], and Anne Loccisano[4]. (1) Graduate School of Pharmaceutical Sciences, Duquesne University, 600 Forbes Avenue, Pittsburgh, PA 15282, Fax: 412-396-5599, firestine@duq.edu, (2) Department of Chemistry and Biochemistry, Duquesne University, (3) Department of Chemistry & Biochemistry and Center for Computational Sciences, Duquesne University, (4) Center for Computational Sciences, Duquesne University*

Our research groups are interested in the potential to control gene expression. To accomplish this feat, we have engineered a synthetic transcriptional protein that is regulated by binding to a molecule that induces dimerization. This system has been shown to regulate genes involved in arabinose metabolism in bacteria. We are also investigating the design and synthesis of DNA bending agents for their ability to regulate gene expression. Our design utilizes the polyamide molecules as a sequence-specific carrier of "bending loci". These "bending loci" are typically bulky molecules that are designed to widen the minor groove of DNA by steric interactions. We have designed and synthesized a series of molecules based upon either the 1:1 or 2:1 binding mode of the polyamides. Studies on DNA binding of the molecules indicate that these molecules bind weaker to DNA and one of the compounds has shown a gel shift consistent with DNA bending.

37.
TOWARDS A MOLECULAR PICTURE OF GENE EXPRESSION: MAPPING THE REGULATORY SURFACES OF THE TRANSCRIPTIONAL MACHINERY. ***Anna K. Mapp**[1], Aaron R. Minter[1], Jenifer K Lum[2], Garrette belanger[3], Brian B. Brennan[1], Zhiqian Wu[1], Annette Plachetka[1], and Steven P. Rowe[1]. (1) Department of Medicinal Chemistry and Department of Chemistry, University of Michigan, 930 N University, Ann Arbor, MI 48109-1055, Fax: 734-615-8553, amapp@umich.edu, (2) Department of Medicinal Chemistry, University of Michigan, (3) Department of Chemistry, University of Michigan*

A growing number of human diseases are characterized by aberrant patterns of gene expression that are often correlated with malfunctioning transcriptional regulators. This has spurred renewed interest in developing a detailed picture of the protein-protein interactions that regulate transcription so that effective intervention approaches can be designed. Towards that end, we developed an approach for selecting molecules from synthetic combinatorial libraries that interact with individual proteins from the eukaryotic transcriptional machinery in order to 'map' key protein binding events. The first-generation ligands were used to identify binding sites within the Mediator complex that are used for gene up-regulation. The binding site location and functional potency of these novel activators can be tuned by simple functional group changes. These results provide evidence that transcriptional machinery assembly can be mediated by targeting a relatively small binding surface area, suggesting that constructing a small molecule transcriptional regulator is a feasible goal.

38.
DESIGNER POLYDACTYL ZINC FINGER PROTEINS: DEVELOPMENT OF A UNIVERSAL SYSTEM FOR GENE ADDRESSING AND REGULATION. ***Carlos F. Barbas III**, The Skaggs Institute for Chemical Biology and the Department of Molecular Biology, The Scripps Research Institute, 10550 North Torrey Pines Road, La Jolla, CA 92037, Fax: 858-784-2583, carlos@scripps.edu*

In order to create a universal system for the targeting of any given DNA sequence and the control of gene expression, we have developed methods for the construction of novel polydactyl zinc finger proteins that recognize extended DNA sequences. We have created a large family of zinc finger domains that may be recombined to specifically recognize most DNA sequences. Construction of polydactyl proteins containing 6 defined zinc finger domains and recognizing 18-bp of DNA sequence has allowed for the targeting of unique DNA addresses within the human genome. We have used this strategy to regulated endogenous genes for the first time in cell culture and later in transgenic organisms. More recently we have incorporated this technology in a genome-wide gene activation and repression strategy. Application of our transcription factor approach to both disease and discovery will be presented.

39.
TERNARY COMPLEX OF DNA, CAP, AND LAC REPRESSOR: MULTI-SCALE STRUCTURAL MODEL AND SIMULATION PERSPECTIVES. ***Alexander Balaeff**, IBM T.J.Watson Research Center, 1101 Kitchawan Rd., Rt. 134, Yorktown Heights, NY 10598, balaeff@us.ibm.com, L. Mahadevan, Department of Applied Mathematics and Theoretical Physics, UInversity of Cambridge, and Klaus Schulten, Department of Physics and Beckman Institute, U. of Illinois at Urbana-Champaign*

Catabolite gene activator protein (CAP) and lactose operon (lac) repressor are two celebrated transcriptional regulators from E. Coli. A structure of the ternary complex between the two proteins and a 76 base pair-long DNA loop is built on the basis of all-atom structures of the proteins and an elastic rod model of the DNA loop. Two alternative structures of the complex are compared; the model is used to explain the cooperative DNA binding by CAP and lac repressor. Perspectives for multi-scale simulations of the protein-DNA complex are discussed.

40.
APPLICATION OF PARALLEL PROCESSING METHODS IN MONTE CARLO SIMULATIONS OF MOLECULAR CLUSTERS. ***Kenneth D. Jordan**, Dept of Chemistry and Center for Molecular and Materials Simulations, University of Pittsburgh, Pittsburgh, PA 15260, Fax: 412-624-8611, jordan@pitt.edu*

The parallel tempering Monte Carlo method is ideally suited for parallel processing environments. In this talk, the results of parallel tempering MC simulations will be presented for $(H_2O)_n$ clusters, described using both two-body and

polarizable force fields, $(H_2O)_{n^+}$ clusters, employing an MS-EVB description of the interactions, and $(H_2O)_{n^-}$ clusters, using a novel Drude oscillator approach in which the dispersion interactions between the excess electron and the water molecules are described within the context of a one-electron model. Finally, an n-body decomposition procedure for carrying out MP2-level parallel tempering Monte Carlo simulations on molecular clusters will be described.

41.

PARALLEL COMPUTATIONAL CHEMICAL CALCULATIONS FOR AIR FORCE MATERIAL PROJECTS. ***Jean-Philippe Blaudeau**, ASC/HP, High Performance Computing Inc, Building 676, 2435 5th Street, Wright-Patterson Air Force Base, OH 43235, Fax: 937-255-4585, blaudejp@asc.hpc.mil, Douglas S. Dudis, AFRL/MLBP, Wright-Patterson AFB, A. Todd Yeates, Materials & Manufacturing Directorate, Air Force Research Laboratory, and Thomas M. Cooper, Materials and Manufacturing Directorate, Air Force Research Laboratory*

We will report results on two chemical systems of interest to the Air Force: C122 complexes and Pt-containing oligomers. The former are excellent electron acceptors, while the latter have interesting non-linear optical properties. It is known that C122 complexes, which are two buckminsterfullerene (C60) balls connected by an acetylene bridge, are good electron acceptors: the AM1 electron affinity is of the order of 8 eV. In order to characterize these molecules more fully, we have performed calculations, at the generalized gradient approximation level of DFT, studying the bridging found in these compounds. These can be characterized as vertex, 5-6 edge, or 6-6 edge bridging. We have characterized the HOMO and LUMO orbitals for the various neutral confromations, as well as for anionic species. trans-bis(acetylene phenyl)bis(tri n-butyl phosphine)Pt has been synthesized in our laboratories. Several derivative oligomers have also been synthesized and their visible spectrum has been caharacterized. We have performed ab initio DFT calculations to try to provide insight on the ground state and the low lying excited states in order to provide insight onto the non-linear optical properties of these molecules.

42.

NUMERICAL METHODS FOR TIME-DEPENDENT SCHROEDINGER EQUATIONS IN THE NONLINEAR-NONPERTURBATIVE REGIME OF LASER-MOLECULE INTERACTIONS. ***A. D. Bandrauk**, and HuiZhong Lu, Laboratoire de Chimie théorique, Faculté des sciences, Université de Sherbrooke, Sherbrooke, QC J1K 2R1, Canada, Fax: 819-821-8017, Andre.Bandrauk@USherbrooke.ca*

Current laser technologies allow for the generation of ultashort (now attosecond) pulses and intense pulses with fields exceeding that inside molecules. At such intensities dissociative ionization occurs necessitating numerical solutions of TDSEs (Time Dependent Schroedinger Equations) beyond Born-Oppenheimer approaches and extending into the nonlinear-nonperturbative regime of laser-molecule interaction.We have developped for this purpose moving adaptive grid methods which we are currently extending to include nuclear motion, ie, to go beyond the Born-Oppenheimer method. In particular we are developping a new numerical method involving high order split-operator methods combined with Fourier-Finite Difference methods in order to circumvent Coulomb singularities inherent in any numerical grid method. The present method has exponential convergence in the angular coordinates, reduces to one-dimension in radial coodinates and is always unitary. The present approach should be particularly useful for methods such as TDDFT where nonlocal potentials are reduced to local potentials.

43.

SPIN-ORBIT INTERACTION AND CONICAL INTERSECTIONS. A NEW LOOK AT AN OLD PROBLEM. ***David R. Yarkony**, Department of Chemistry, Johns Hopkins University, 3400 N. Charles Street, Baltimore, MD 21218, Fax: 410-516-8420, yarkony@jhuvms.hcf.jhu.edu*

For the nonrelativistic (Coulomb) Hamiltonian a conical intersection has a branching space, the space in which the conical topography is evinced, of dimension 2. For a molecule with an odd number of electrons, including the spin-orbit interaction changes the dimension of the branching space to 5. The implications of this result are analyzed and illustrated.

44.

VERY-LARGE-CORE RELATIVISTIC EFFECTIVE POTENTIALS FOR CALCULATIONS OF ELECTRONIC SPECTRA. ***Walter C. Ermler**, and Maria M. Marino, Department of Chemistry, The University of Memphis, Computational Research on Materials Institute, Memphis, TN 38152, Fax: 703-292-9046, wermler@memphis.edu*

A relativistic pseudopotentional (RPP) is defined. It extends the usual core and valence definitions of atomic electrons used for standard effective core potentials (RECPs) to three spaces - core, outer core and valence. The RPP is defined at runtime and is specific to the molecular environment. Nonlocal effects, core/valence polarization, multi-center interactions, and relativistic effects are discussed. In the context of an RPP a single Am 5f7/2 electron defines the valence space of Am+2, while its six 5f5/2 electrons are relegated to the outer core. Calculations of spectra and of AmCl+ using small-core RECPs and very-large-core RPPs are presented. Components of the Dirac Hamiltonian that correspond to spin-orbit coupling are incorporated into the RPP and states are defined according to Hund's coupling case c. The electronic spectra calculated using spin-orbit averaged RECPs with the addition of the spin orbit operator as a first-order perturbation are shown to be grossly inadequate.

45.

ULTRAFAST CAGE-INDUCED SPIN FLIP PROCESSES IN MOLECULAR PHOTODISSOCIATION IN MATRICES AND CLUSTERS. ***R. Benny Gerber**[1], M. Y. Niv[2], and A. Cohen[2]. (1) Department of Chemistry, University of California, Irvine, Irvine, CA 92697, Fax: 949-824-8571, benny@fh.huji.ac.il, (2) Department of Physical Chemistry, The Hebrew University of Jerusalem*

Photodissociation of diatomic molecules,inluding F2 aqnd HCl, in rare gas solids and clusters was studied by semiclassical Molecular Dynamics simulations.A whole manifold of excited electronic states plays a role in these processes.The potential energy surfaces (36 for the case of F2@Ar)and the nonadiabatic couplings were modelled by DIM,and a surface hopping algorithm was use to treat the nonadibatic transitions.Aspects explored include the time dependence of the electronic state populations and the dynamics of spin-forbidden and other nonadiabatic processes.One of the main findings is the occurence of very effecient,femtosecond timescale singlet-to triplet conversions induced by the cage. For F2 in Ar,initially excited to a singlet Pi state,substational population builds up in a weakly-bound triplet Pi state within about 60fs.This effect was confirmed experimentally by pump- probe femtosecond laser experiments by N.Schwenter and group (Berlin).Similar ultrafast spin flip effects are predicted for HCl in Ar.The mechanism revealed by the calculations suggests that the cage-induced ultrafast spin-flip effect should be very common in matrix photochemistry.Interesting propensities are found for the dependence of these processes on the electronic quantum numbers.

46.

RELATIVISTIC POTENTIAL ENERGY SURFACES AND LASER CONTROL OF CHEMICAL REACTIONS. ***Shiro Koseki**, Department of Material Science, CIAS, Osaka Prefecture University, 1-1 Gakuen-cho, Sakai 599-8531, Japan, Fax: +81-72-254-9702, shiro@ms.cias.osakafu-u.ac.jp*

The dissociation potential energy curves of low-lying spin-mixed states in Group 5 hydrides, VH, NbH, and TaH, are obtained using both effective core potential (ECP) and all-electron approaches. Both approaches are based on the multi-configuration self-consistent field (MCSCF) method, augmented by second order configuration interaction (SOCI): the first method employs SBKJC basis sets augmented by a set of polarization functions, and spin-orbit coupling effects are estimated with a one-electron approximation using effective nuclear charges. The second method employs MIDI basis sets and three sets of p functions are added to both transition element and hydrogen and one set of f functions is also added to transition element. The relativistic-elimination-of-small-components (RESC) scheme and full Breit-Pauli Hamiltonian are employed in order to estimate relativistic effects in the hydrides. The details of the relativistic effects will be discussed. In addition, our recent study will be also presented on laser control of chemical reactions: dissociation potential energy surfaces are calculated for neutral molecules and their cations (and their dications) under instantaneous electric field conditions. The relationship will be discussed between ionization/dissociation processes and the polarization direction of laser field.

47.

ARE HIGH INFORMATION CONTENT CALCULATIONS BETTER THAN LOW INFORMATION CONTENT CALCULATIONS? FROM 2D/3D DESCRIPTORS TO SCORING FUNCTIONS, PHARMACOPHORES AND MOLECULAR ORBITALS. ***Alexander A. Alex**, James E. J. Mills, and Marcel J. de Groot, Molecular Informatics, Structure and Design, Pfizer Global Research and Development, Sandwich Laboratories, Ramsgate Road, Sandwich, United Kingdom, Fax: 01304-658463, alexander_alex@sandwich.pfizer.com*

High information content and low information content calculations both have their place in Computational Chemistry and make valuable contributions towards state-of-the-art Drug Discovery. This is highlighted with applications to Drug Discovery programs, including structure-based drug design, structure-based and ligand-based virtual screening, pharmacophore database searching, ADMET predictions and molecular orbital calculations on reaction mechanisms. This paper emphasises the importance of applying the most suitable method to give the most relevant results within a time frame that is compatible with the pace of modern Drug Discovery programs.

48.

INTEGRATING VHTS INTO COMBINATORIAL LIBRARY DESIGN. ***R.D. Clark**, D.S. Baker, L. Akella, and F. Soltanshahi, Research, Tripos, Inc, 1699 South Hanley Road, St. Louis, MO 63144, Fax: 314-647-9241, bclark@tripos.com*

OptDesign is an extension of optimizable k-dissimilarity(OptiSim)selection that supports efficient construction of multiblock and sparse combinatorial libraries. At the method's heart is evaluation of a series of small reactant subsamples drawn alternately from each reagent pool, with the "best" candidate drawn from the subsample chosen at each iteration. When the criterion for "best" is structural dissimilarity with respect to products selected at preceding iterations, the libraries produced are diverse and representative. An additional, reagent-based objective function can be accommodated by biasing the selection of reagents for inclusion in the subsample - by reagent cost, for example. Here we describe a more generalized approach for incorporating other product-based criteria for what consitutes "best" that complement structural diversity. In particular, CombiFlexX will be used to create a structurally diverse combinatorial library likely to exhibit an interesting pattern of binding affinity toward a selected target protein.

49.

COMPARING COMPUTATIONAL APPROACHES TO SCREENING LIBRARY SELECTION. ***Erik Evensen**, Hans Purkey, Ken Lind, and Erin K. Bradley, Computational Sciences, Sunesis Pharmaceuticals Inc, 341 Oyster Point Blvd., South San Francisco, CA 94080, Fax: 650-266-3501, ee@sunesis.com*

Screening compound collections has long been a method for finding starting points in the drug discovery process. Modern automation techniques make it possible to screen increasingly large numbers of compounds. Nevertheless, the numbers of compounds and size of chemical space represented in corporate collections or accessible via convenient chemistries involving commercially available compounds exceeds the cost time, cost, and practical limitations of even the largest high throughput screening effort. Moreover, such screening is largely unproductive. It would be useful, therefore, to have a method for prioritizing or triaging compounds for acquisition and/or screening. We present a comparison of a number of computational approaches to such triage, including docking with scoring functions of varying complexity, searching for pharmacophore complementarity to the target, and prioritizing compounds to reveal shape or feature preferences of the site.

50.

ASSESSING THE EFFECT OF LIBRARY DESIGN CHOICES ON MODEL PERFORMANCE. ***Kiko Aumond**[1], Hans Wolters[1], and Jennifer L. Miller[2]. (1) CADD, Signature BioScience, 475 Brannan Street, San Francisco, CA 94107, (2) Signature Biosciences*

The development of a productive virtual assay is critically dependent upon the data points used to train the model. Given the same type of compound descriptor (pharmacophores), we examine the size and objective function effects of the "library design" problem. Specifically, we will characterize the generalization ability of a classifier as a function of the number of compounds picked by two different library design techniques: informative and diverse.

51.

HTSVIEW: SOFTWARE WHICH LEADS TO LEAD IDEAS. *Marc Zimmermann[1], Sally Ann Hindle[2], Thorsten Naumann[3], Hans Matter[3], Gerhard Hessler[3], Karl-Heinz Baringhaus[3], Christian Lemmen[4],* ***Marcus Gastreich**[4], and Matthias Rarey[5]. (1) SCAI, Fraunhofer Gesellschaft, Schloss Birlinghoven, Sankt Augustin 53757, Germany, Fax: 0049-2241-14-2656, (2) Chemoinformatics, BioSolveIT GmbH, (3) Molecular Modelling, aventis pharma Deutschland GmbH, (4) BioSolveIt GmbH, An der Ziegelei 75, 53757 Sankt Augustin, Germany, Fax: 0049-2241-973-6688, marcus.gastreich@biosolveit.de, (5) Zentrum fuer Bioinformatik, Univ. Hamburg*

The pursuit of innovative drug candidates has driven technological progress in the field of high throughput screening (HTS). However, the HTS process generates vast amounts of data often plagued with noise. There is increasing demand for approaches that sensibly interpret such data and to this end we have developed a novel tool called "HTSview". The software combines data mining techniques with pharmacophoric concepts. Based on the Feature Trees descriptor and lacking the necessity of 3D alignments, HTSview is extremely fast. Clustering algorithms and classification methods quickly facilitate the focussing of data. Extraction of SAR information to form biophore models optimized in conjuction with machine learning techniques is also a central capability of the tool. We tested the tool on data available from both in- house sources and the literature. Virtual screening studies with biophore models demonstrated the scaffold hopping potential of HTSview – an important concept in lead idea generation.

52.

PROBING INFORMATION CONTENT IN QSAR ANALYSES USING THE SIGNATURE MOLECULAR DESCRIPTOR. ***Jean-Loup Faulon**[1], Shawn Martin[1], Donald P Visco[2], and Archana Kotu[2]. (1) Computational Biology, Sandia National Laboratories, P.O. Box 969, MS 9951, Livermore, CA 94551, Fax: 925-924-3020, jfaulon@sandia.gov, (2) Department of Chemical Engineering, Tennessee Tech. University*

The signature molecular descriptor, recently introduced (JMGM 2002 and JCICS 2003) is based on extended valence sequence and belongs to the class of fragmental descriptors including holograms, molecular subgraphs, and tree fingerprints. Like other fragmental descriptors, signature performs well in QSAR analyses. Yet, signature appears to be the only descriptor from which molecular structures can be reconstructed. In opposition to other 2D descriptors, we find that degeneracy can fully be controlled with signature, or, in other words, the number of molecular structures matching a given descriptor value can be limited by varying the signature height. Thus, signature is particularly suited for studying information content in QSAR analyses. We present here the effect of increasing the signature information content, via increasing the signature height, in two series of QSAR analyses; one for log P prediction and a second for HIV-1 protease inhibitors binding affinities calculations.

53.

MODELING THE MU-OPIOD RECEPTOR AFFINITY OF SYNTHETIC 8-AMINOCYCLAZOCINE ANALOGUES USING TAE, PEST AND PAD DESCRIPTORS AND MACHINE-LEARNING METHODS. ***Lingling Shen**[1], Curt M Breneman[2], N Sukumar[2], Mark P. Wentland[2], and Mark J. Embrechts[3]. (1) Chemistry, Rensselear Polytechnic Institute, 110 8th St, Troy, NY 12180, Fax: 518-276-4887, shenl@rpi.edu, (2) Department of Chemistry, Rensselaer Polytechnic Institute, (3) Decision Sciences and Engineering Systems, Rensselaer Polytechnic Institute*

Cyclazocine was studied in the early 1970's as an analgesic, however, clinical research ceased in this area because of the short duration of analgesic action as well as undesirable side-effects. Cyclazocine is currently being tested in humans to determine if it is a potential treatment for cocaine abuse. More recently, a series of 8-aminocyclazocine analogues was synthesized that could retard this metabolic inactivation with an associated increased duration of action. To predict the mu-opiod receptor affinity of these new cyclazocine analogues, three sets of descriptors have been used, including Transferable Atom Equivalents (TAEs), Property-Encoded Surface Translator (PEST) descriptors, and PEST Autocorrelation Descriptors (PAD), where the latter two types (PEST and PAD) incorporate hybrid shape/property information. Both partial least squares (PLS) regression and kernel partial least squares (KPLS) regression were used to develop predictive models, with feature selection being accomplished using a genetic

algorithm approach. The best results were obtained using PEST descriptors with GA feature selection and a linear bootstrap-PLS model, where the q2 for the validation set was found to be 0.94 and the q2 for the blind test set was seen to be 0.97.

54.
FLESHING-OUT PHARMACOPHORES WITH VOLUME RENDERING OF MOLECULAR CHARGE DENSITIES AND HYPERWALL VISUALIZATION TECHNOLOGY. ***Preston J. MacDougall**, Department of Chemistry, Middle Tennessee State University, 1301 E. Main St., Murfreesboro, TN 37132, pmacdougall@mtsu.edu, and Christopher E. Henze, Data Analysis Group, NASA Ames Research Center*

Pharmacophores are an important consideration in the drug discovery process, particularly during computational screening of molecular libraries. Typically, these key elements are represented by little more than a type-label and coordinates. We present images of pharmacophores generated by interactive, and parallel, computational "screening" of molecular libraries on a 7x7 hyperwall. We utilize volume rendering of the Laplacian of the total charge density computed for a homologous series of antibiotic compounds (penicillin derivatives and peptido-mimetic drug candidates). The rendering is done interactively so as to optimally image characteristic features of multiple pharmacophores within a single molecule. The rendering is also done in parallel, so that corresponding pharmacophores in related drug molecules can be visually compared and contrasted in exquisite detail. The hyperwall has seven rows of seven high-resolution monitors, and associated processors, networked synchronously. Each column of screens on the hyperwall corresponds to one type of pharmacophore in the drug molecules, while the rows of screens on the hyperwall correspond to different drug molecules in the homologous series. The technical requirements for this powerful visualization technique will be outlined, and its potential contribution to the drug discovery process will be discussed.

55.
INTERNAL COORDINATE MOLECULAR DYNAMICS (ICMD) MODELING OF DNA UNDER LIMITED HYDRATION. ***Alexey K. Mazur**, Laboratoire de Biochimie Theorique, Institut de Biologie Physico-Chimique, Paris 75005, France, Fax: 01.58.41.50.26, alexey@ibpc.fr*

Internal coordinate molecular dynamics (ICMD) is a recent efficient method for modeling polymer molecules. It treats them as chains of rigid bodies rather than ensembles of point particles as in Cartesian MD. The double helical DNA can be modeled with rigid bases, but free all torsion and some bond angle degrees of freedom. This simplifies the free energy landscapes and makes possible larger time steps. In addition, we are looking for the possibility to reduce the burden of explicit hydration in MD simulations of nucleic acids. A combination of these two approaches allows us to study longer DNA fragments over longer time periods. Recent simulations of double helical DNA under limited explicit hydration shed new light upon the role of free solvent counterions, the mechanisms of static intrinsic curvature, and the transitions between the A and B-forms.

56.
AZOLE CARBOXAMIDE NUCLEOBASES AS PROBES OR NUCLEIC ACID POLYMERASES. ***Vincent Jo Davisson**, Medicinal Chemistry and Molecular Pharmacology, Purdue University, 575 Stadium Mall Dr, West Lafayette, IN 47907-2091, Fax: 765-494-1414, vjd@pharmacy.purdue.edu, and Donald E. Bergstrom, Medicinal Chemistry and Molecular Pharmacology, Purdue University and Walther Cancer Institute*

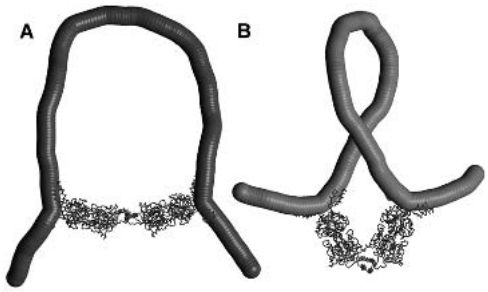
The development of novel artificial nucleobases and detailed x-ray crystal structures for primer/template/DNA polymerase complexes provide opportunities to assess DNA-protein interactions that dictate specificity. Historically, the major contributions were assigned to Watson-Crick base pairing preferences (and shapes) of the substrate and DNA template bases. However, the contributions of electrostatics to the non-bonding interactions that influence specificity have not been adequately assessed. The isosteric azole carboxamide nucleobases offer a new perspective for analyzing the molecular principles governing substrate-template interactions in DNA polymerases. These compounds differ only in the number and placement of nitrogen atoms within a common shape and therefore, present unique electronic distributions. The results with these compounds as both template and substrates for thermostable DNA polymerases demonstrate how subtle changes in electrostatics can translate into significant changes in the selectivity. Electrostatic interactions in polymerase recognition and processing contribute another perspective on the molecular basis for fidelity of replication.

57.
COMPUTATIONAL STUDIES OF BASE FLIPPING IN DNA ALONE AND BOUND TO THE CYTOSINE-5-METHYLTRANSFERASE FROM HHAI. ***Alexander D. MacKerell Jr.**, School of Pharmacy, University of Maryland, Baltimore, 20 N. Pine Street, Baltimore, MD 21201, Fax: 410-706-0346, alex@outerbanks.umaryland.edu*

Base flipping represents a simple, but biologically important conformational change in DNA. Flipping events are essential for a number of DNA repair and modification enzymes and have been implicated as initial steps in DNA opening associated with transcription and replication. Potential of mean (PMF) calculations were performed on the DNA dodecamer, GATAGCGCTATC, alone and in the presence of the cytosine-5-methyltransferase from HhaI (M.HhaI) to obtain free energy profiles that encompass flipping though both grooves and for the fully flipped states. Results, in good agreement with experimental data based on NMR imino proton exchange, show that base flipping is feasible through both the minor and major grooves in DNA alone. When bound to M.HhaI, flipping of the target C is facilitated by the enzyme through the major groove pathway. Atomic details from the PMF calculations suggest a mechanism for sequence dependent effects of base flipping in DNA and the mechanism by which M.HhaI facilitates base flipping.

58.
ANALYSIS AND CONTROL OF PROTEIN-DNA LOOPS. ***Jason D. Kahn**, Laurence M. Edelman, Raymond Cheong, and Ruchi A. Mehta, Department of Chemistry and Biochemistry, University of Maryland, College Park, College of Life Sciences, Chemistry Bldg. 091, College Park, MD 20742-2021, Fax: 301-405-9376, kahn@adnadn.umd.edu*

DNA looping increases the efficiency of transcriptional repression and activation. Efficient looping requires that two DNA binding sites be on the same face of the helix, but efficiency is surprisingly independent of DNA length. Model DNA substrates for Lac repressor looping that include sequence-directed phased A tract bends flanked by *lac* operators were constructed. The resulting loops are hyperstable in EMSA competition assays. Depending on the operators' helical phasing with respect to the bend, loops can be forced into "open" (A) or "closed" (B) conformations, as shown by DNA cyclization kinetics, loop-induced DNA topology changes, and steady-state and time-resolved FRET between fluorophores 130 bp apart. The conformation is determined by a balance between bending and twisting free energies. Monte Carlo simulations of cyclization suggest that Lac repressor intrinsically prefers the open form. Its flexibility presumably allows it to adapt to different ionic conditions and to the presence of other DNA bending proteins in the loop region.



59.
ANOMALOUS MIGRATION OF INTRINSICALLY CURVED DNA. ***udayan Mohanty**, and Aleksander Spasic, Department of Chemistry, Boston College, Chestut Hill, Newton, MA 02467, Fax: 617-552-2705, mohanty@bc.edu*

We have explicitly solved the long standing problem of a quantitative predictive model that describes the electrophoretic mobility patterns of circularly-permuted oligomeric DNA molecules, all having the same length but with the bend positioned differently in each, in polyacrylamide gel of various concentration. The bends are due to short stretches of adenines (A-tracts) which were repeated in phase with the helical repeat. The model takes into account in an approximate way polyelectrolyte effects such as condensed and screened counterions,

coulombic end effects, salt concentration, pH of the buffer, screening of the hydrodynamic interactions, flexibility of the molecule, concentration of the gel, as well as the characteristics of the interactions of the gel with the curved DNA. The predictions are in excellent agreement with the experimental data of Crothers and coworkers and of Thompson and Landy. We have generalized our model to a description of the dynamics of phased A-tracts.

60.
MERGING TETHERED BINDING DATA AND INFORMATIVE DESCRIPTOR ANALYSIS TO IDENTIFY POTENTIAL SITES OF SMALL MOLECULE BINDING. ***Erin K. Bradley***[1], *Erik Evensen*[1], *Hans Purkey*[1], *Ken Lind*[1], *Andrew C. Braisted*[2], *and Michelle R. Arkin*[3]. *(1) Computational Sciences, Sunesis Pharmaceuticals Inc, 341 Oyster Point Blvd., South San Francisco, CA 94080, Fax: 650-266-3501, ebradley@sunesis.com, (2) Chemistry, Sunesis Pharmaceuticals Inc, (3) Biology, Sunesis Pharmaceuticals Inc*

Protein-protein binding interfaces are considered improbable sites for high-affinity small molecule ligands; yet this target class represents the majority of therapeutically relevant targets. Until recently, understanding the binding properties at protein-protein interfaces has been limited to structural and mutational analysis. We will present a computational method, that when combined with tethering data, can be used to identify sites to exploit for small molecule binding. The method uses simple descriptors and informational data mining techniques, and produces a ranking of binding sites (and in most cases initial selection of anchoring fragments). We will compare this technique to high-throughput virtual screening, and demonstrate the utility on several targets, including IL2.

61.
ENRICHMENT FACTORS IN MOLECULAR DOCKING: COMMON MISCONCEPTIONS. ***Anton Filikov***, *Informatics and Modeling, ArQule Inc, 19 Presidential Way, Woburn, MA 01801, Fax: 781-376-6019, afilikov@arqule.com*

Following docking of a database of compounds in virtual screening, the next step is to decide what fraction of the database should be selected for experimental testing. This decision can best be made if an enrichment factor for the database can be estimated. Very often a number of known binders are mixed with random compounds, then this database is docked, scored and sorted, and the enrichment factor is calculated by computing the ratio of the density of the binders to their average density throughout the database. However, this approach ignores conformational changes of the receptor. Known binders must recognize the protein, but they do not have to recognize a particular structure of it. An alternative approach is to use only the ligands from the crystal structures for the calculations. We will present an examination of the methods performed on multiple protein structures. The effect of coarseness of the receptor representation will be discussed also.

62.
WITHDRAWN.

63.
MOLECULAR DYNAMICS SIMULATIONS STUDIES ON HUMAN COAGULATION FACTOR VA. ***Tivadar Orban***, *Valentin Gogonea, and Michael Kalafatis, Department of Chemistry, Cleveland State University, Euclid Avenue at East 24th Street, Cleveland, OH 44115, Fax: 216-687-9298, t.orban@csuohio.edu*

Factor Va is the cofactor required for prothrombinase complex to achieve physiologically relevant rates for conversion of prothrombin to ?-thrombin. There are no structural informations on the cofactor. The current factor Va model based on its homology with ceruloplasmin lacks 46 amino acid residues from the carboxyl-terminal portion of the heavy chain (Arg664 to Arg709). We were not able to find any homologous peptide for the missing 46 amino acid residue sequence. Consequently, we used computer simulation techniques to obtain a three dimensional structure for this sequence. After insertion of the missing residues in the entire molecule, we allowed the cofactor to relax using molecular dynamic techniques. We have obtained a structure that allowed us to study the distance and location of the amino acids representing the factor Xa binding site, and those representing the prothrombin binding site. Those are key residues regulating the formation of prothrombinase complex. A detailed presentation of the structure is provided.

64.
LEAD OPTIMIZATION: USING MD TO IMPROVE POTENCY AND SELECTIVITY IN PTP-1B INHIBITORS. ***Christopher I. Bayly***[1], *Cheuk K. Lau*[1], *J.Y. Gauthier*[1], *Chun Li*[2], *Michel Thérien*[1], *Ernest Asante-Appiah*[3], *W Cromlish*[1], *Yves Boie*[3], *Farnaz Forghani*[3], *S Desmarais*[4], *Qingping Wang*[3], *K Skorey*[4], *D Waddleton*[4], *Paul Payette*[3], *C Ramachandran*[4], *B Kennedy*[1], *and Giovana Scapin*[5]. *(1) Department of Medicinal Chemistry, Merck Frosst Centre for Therapeutic Research, 16711 TransCanada Highway, Kirkland, QC H9H 3L1, Canada, bayly@merck.com, (2) Medicinal Chemistry Department, Merck Frosst Canada & Co, (3) Department of Biochemistry and Molecular Biology, Merck Frosst Centre for Therapeutic Research, (4) Merck Frosst Canada Inc, (5) Department of Medicinal Chemistry, Merck Research Laboratory*

Structure-based design encompasses a range of methods from fast and cheap through to slow and expensive. Applying the latter needs to be “worth it” in the context of medicinal chemistry priorities and timeliness. The usefulness of full-scale molecular dynamics using periodic boundary conditions and explicit water will be demonstrated in the context of the lead optimization of small-molecule phosphotyrosine phosphatase 1B (PTP-1B) inhibitors to improve PTP-1B potency and introduce modest selectivity against the highly similar anti-target T-cell phosphotyrosine phosphatase.

65.
COSMO-RS: A NOVEL BRIDGE FROM QUANTUM CHEMISTRY TO FLUID PHASE THERMODYNAMICS. ***Andreas Klamt***, *COSMOlogic GmbH&CoKG, Burscheider Str. 515, Leverkusen 51381, Germany, Fax: 49-2171-731689, andreas.klamt@cosmologic.de*

Due to the rapid developments of methods and computers, reliable quantum chemical calculations on molecules of up to 50 - 100 atoms can nowadays be performed within the time-scale of a day on cheap computer hardware. Thus quantum chemistry, and here especially the density functional theory (DFT), has become an efficient source of information for molecular properties. Nevertheless, the traditional quantum chemistry is restricted to the calculation of single molecules in vacuum or to small clusters. Hence it cannot be directly used for the calculation of properties of molecules in liquids or even for fluid phase equilibrium properties.

In this situation, the dielectric continuum solvation method COSMO and its combination with statistical thermodynamics COSMO-RS provides an efficient link between quantum chemistry and fluid phase thermodynamics. COSMO-RS opens a wide area of applications in all areas of computational chemistry, i.e. in drug design and in materials and synthesis modelling, as well as in chemical engineering. In the latter area it is an ideal supplement to the well accepted group contribution methods like UNIFAC, overcoming most of the deficiencies of these methods and giving a detailed molecular understanding of the systems under consideration. In contrast to group-contribution methods COSMO-RS is very well able to handle intramolecular interactions (proximity effects) resulting from electronic effects and from intramolecular hydrogen bonds. In addition, it can treat multi-comformations, taumerisation, and it can resolve differences between isomers.

Finally, COSMOtherm can be applied to calculate important properties for drug design and development, as water solubility, physiological partition coefficients, pKa, etc. Last year COSMO-RS has proven its outstanding capabilities for fluid phase simulations by winning the First Industrial Fluid Properties Simulation Challenge organized by NIST and COMSEF.

66.

FIRST PRINCIPLES CALCULATION OF DRUG SOLUBILITY, PARTITIONING, AND PKA WITH DFT/COSMOTHERM: GETTING INSIGHT, NOT JUST NUMBERS. ***Andreas Klamt**, COSMOlogic GmbH&CoKG, Burscheider Str. 515, Leverkusen 51381, Germany, Fax: 49-2171-731689, andreas.klamt@cosmologic.de*

Continuum solvation models like COSMO (Conductor-like Screening Model) have proven to be efficient and reliable tools for the approximate treatment of solvents in quantum chemical calculations. The combination of density functional theory with such continuum models gives good qualitative results at moderate computation time. A much more general and powerful access to the problem is provided by the COSMO-RS method. This uses the output of COSMO calculations, i.e. energies and screening charge densities on the molecular surface, as basis for a statistical thermodynamics treatment.This new method is much more efficient and probably more accurate than MD- or MC-simulations which are used for liquid systems by many computational chemists. In addition it provides much physical insight into the problem of solvation. On the other hand it is much more general applicable than group contribution methods like CLOGP or UNIFAC, which is state of the art in chemical engineering.

Based on DFT/COSMO calculations COSMO-RS has been parameterized for all elements relevant in organic chemistry, yielding remarkable accuracy for vapor pressures, Ghydr and partition coefficients. Even more, solubilities, miscibilities, and phase diagrams are well described. For the use in life science modelling such direct property calculations may be of considerable value. All properties are calculated by surface integrals and hence logarithmic partition coefficients and hydration energies can be visualised on the molecular surface. The ability to calculate solubility of drug-like compounds is of special importance. In addition, COSMO-RS offers a set of linear descriptors for arbitrary partition behaviour, which may be of great use in any QSAR study which has to do with more complicated partition problems like blood-brain, intestinal absorption, BCF, etc. Very recently, even the pKa prediction based on COSMO-RS has been validated.

An outlook will be given to application to large molecules and to docking questions, based on an semi-empirical COSMO-RS parameterisation, combined with linear scaling semi-empirical codes. Fast shortcuts of COSMO-RS, which may be useful for HTS-studies will be discussed as well.

67.

ACCURATE PREDICTION OF PROTEIN – LIGAND BINDING ENERGY IN THE QCPFF APPROACH. *Nikolay A. Anikin, Vladimir V. Bobrikov, Vladislav L. Bugaenko, Alexey M. Andreyev, and **Victor M. Anisimov**, Quantum Biochemistry Group, Konstantina Fedina-3 / 24, Moscow, Russia, aanikin@swf.chem.ac.ru, victor@quantumbiochem.org*

Application of force fields to drug screening is complicated by unpredictable variability of chemical space of potential drugs and complex nature of atomic interactions. The Quantum Chemically Polarizable Force Field (QCPFF) increases parameter transferability by combining the classical force field function with quantum mechanical (QM) density matrix and describing the polarization effect at the quantum mechanical level. The QCPFF first order density matrix is rapidly evaluated from hybrid atomic orbitals and it is parameterized to reproduce internal details of electronic density matrix and electronic field as predicted by the B3LYP/aug-cc-pVDZ method. This assures accurate and rapid calculations for the wide range of molecular structures. The model is tested on calculation of electrostatic, van-der-Waals and total intermolecular interaction energy maps for protein – ligand complexes with varied geometry of the complexes. High speed and accuracy of the QCPFF prediction make practical in silico high-throughput screening of unknown drug candidates without a need to involve expensive full QM methods to improve the screening efficiency.

68.

ROLE OF THE MINIMUM ON THE SEAM OF CROSSING (MSX) BETWEEN DIFFERENT SPIN STATES IN SPIN-FORBIDDEN REACTIONS. ***Keiji Morokuma**, Cherry L. Emerson Center for Scientific Computation and Department of Chemistry, Emory University, 1515 Pierce Drive, Atlanta, GA 30322, Fax: 404-727-7412, morokuma@emory.edu*

In chemical reactions in which the reactant and the product have different spin states, non-adiabatic transition at the minimum of the seam of crossing (MSX) potential hypersurface in 3N-7 (N: the number of atoms) dimension between different spin states plays a key role as a "transition state". The spin-orbit matrix elements as well as the slopes at the crossing determine the probability of transition. We have been determining such MSXs for a variety of reactions, and will present several examples of such studies, covering from gas-phase ion-molecule reactions and photodissociation reactions to reactions of transition metal complexes.

69.

SPIN-FORBIDDEN REACTIONS IN ORGANOMETALLIC CHEMISTRY: HOW FAST DO THEY REALLY GO? ***Jeremy N. Harvey**, School of Chemistry, University of Bristol, Bristol BS8 1TS, United Kingdom, jeremy.harvey@bris.ac.uk, and Rinaldo Poli, Laboratoire de Synthèse et d'Electrosynthèse Organométalliques, Université de Bourgogne*

Transition metal compounds and intermediates often have several close-lying electronic states. Reactions therefore often involve a change in spin, which is formally forbidden. There has been much discussion as to the effect that this might have on the corresponding reaction rate. In this contribution, I will use several examples to show that rates can be understood in terms of the individual potential energy surfaces of the different spin states, and in particular, of the relative energies of the relevant minimum energy crossing points (MECPs) between surfaces. For some reactions (e.g. addition of CO to $(C_5H_5)Co(CO)$), the rate is unaffected by spin-state changes. For others (e.g. addition of CO to $Fe(CO)_4$), spin change does cause a reduced rate. It will also be shown that non-adiabatic transition state theory can be used to compute rate coefficients, and the accuracy of different DFT and *ab initio* methods for describing energetics of different spin states of transition metal compounds will be discussed.

70.

CATALYSIS BY PARAMAGNETIC CHROMIUM COMPLEXES: RATIONAL DESIGN OF CATALYSTS IN SPIN-FORBIDDEN REACTIONS. ***Douglas J. Doren**[1], Danesha R. Fitzgerald[1], and James S. Hess[2]. (1) Department of Chemistry and Biochemistry, University of Delaware, Newark, DE 19716, Fax: 302-831-6335, doren@udel.edu, (2) Gaussian, Inc*

Reactions that involve a change of spin state depend on the potential energy surfaces of two electronic states. In principal, the rate-limiting step may be an activated process on either potential surface, or the non-adiabatic crossing between those surfaces. This talk will illustrate these issues through density functional theory studies of oxidation reactions catalyzed by a family of organometallic Cr complexes, such as Cp*CrOCl2. The mechanisms for epoxidation of C-C double bonds and hydrogen abstraction reactions will be explored. The effects of ligand substitution and changes in the substrate on the rates of these reactions will be discussed and comparisons will be made to experimental tests of these predictions.

71.

MODELING OF OPEN-SHELL SPECIES. ***Thomas R. Cundari**, Department of Chemistry, University of North Texas, Denton, TX 76203, Fax: 940-565-4318, tomc@unt.edu*

Modeling of open-shell transition metal complexes brings with it special challenges above and beyond those normally encountered for their closed-shell congeners. A variety of examples of modeling the chemical structure and reactivity involving open-shell transition metal species are presented. Density functional and non-density functional methods are employed on problems involving transition metals from all three transition series.

72.

NATURAL PRODUCTS AND NATURE'S LESSONS: FIVE SOLUTIONS TO THE SEQUENCE SELECTIVE RECOGNITION OF DUPLEX DNA. ***Dale Boger**, Department of Chemistry, The Scripps Research Institute, 10550 North Torrey Pines Road, La Jolla, CA 92037, Fax: 858-784-7550, boger@scripps.edu*

Recent studies on the synthesis and examination of biologically active natural products and their analogues which derive their properties through sequence selective binding to duplex DNA will be described including: (1) CC-1065, the duocarmycins, and yatakemycin, (2) bleomycin A_2, (3) sandramycin, luzopeptins, quinoxapeptins, and thiocoraline, (4) distamycin A, and (5) isochrysohermidin.

73.

CHARACTERIZING THE MOLECULAR RECOGNITION OF WATSON-CRICK AND T/G MISMATCHED BASE PAIRS BY STACKED POLYAMIDES. ***Moses Lee**[1], Minh Le[1], Jessica Grandillo[1], Karen Buchmueller[1], Sarah Horick[1], W. David Wilson[2], Andrew Staples[1], Eilyn Lacy[2], Binh Nguyen[2], Caroline O'Hare[3], and John A. Hartley[3]. (1) Department of Chemistry, Furman University, 3300 Poinsett Highway, Greenville, SC 29613, Fax: 864-294-3559, moses.lee@furman.edu, (2) Department of Chemistry, Georgia State University, (3) Department of Oncology, Royal Free & London Medical School*

Many polyamides analogues of distamycin prefer to bind as anti-parallel and side-by-side dimers within the minor groove. In this binding motif, a side-by-side Py/Py pair recognizes A/T or T/A, Py/Im recognizes C/G, and Im/Py recognizes G/C. To these rules we have added an additional recognition motif, in which the Im/Im pair preferentially recognizes a T/G or G/T mismatched base pair, as well as lower affinity recognition of G/C or C/G matched pairs. In this presentation, complete biochemical and biophysical (kinetic and thermodynamic) characterization of Watson-Crick and T/G mismatch base pair recognition will be described using results obtained from DNase I footprinting, Surface Plasmon Resonance (SPR), circular dichroism, and isothermal calorimetry (ITC) studies. Results from SPR studies are complementary to those obtained from footprinting analyses, and we now have a detailed structural and thermodynamic understanding of the molecular recognition of T/G mismatched base pairs by polyamides.

74.

HYBRIDIZATION OF COMPLEMENTARY AND HOMOLOGOUS PEPTIDE NUCLEIC ACID PROBES TO FOLDED DNA TARGETS. ***Bruce A. Armitage**[1], Stuart A. Kushon[2], Bhaskar Datta[1], Christoph Schmitt[1], and Jason P. Jordan[3]. (1) Department of Chemistry, Carnegie Mellon University, Carnegie Mellon University, 4400 Fifth Avenue, Pittsburgh, PA 15213-3890, Fax: 412-268-1061, army@cyrus.andrew.cmu.edu, (2) Department of Chemistry - Armitage Group, Carnegie Mellon University, (3) Division of Chemistry and Chemical Engineering, California Institute of Technology*

Folding of natural DNA and RNA sequences imposes thermodynamic barriers to hybridization by antisense agents. This lecture will focus on the thermodynamics of hybridization in two model folded structures: a DNA hairpin and a DNA quadruplex. The hairpin forms when two complementary sequences are separated by a short noncomplementary region. DNA quadruplexes can arise from folding of guanine-rich sequences. The basic unit of the quadruplex is a guanine tetrad, in which four guanines are simultaneously hydrogen bonded into a square array. Stacking of G-tetrads is facilitated by cation binding. Complementary peptide nucleic acid (PNA) probes were synthesized to target these structures and the thermodynamics of hybridization were measured using temperature-dependent UV absorbance experiments. In addition, a quadruplex-forming DNA was targeted using a homologous, rather than complementary, PNA probe. The PNA successfully recognized the G-rich DNA and formed a hybrid PNA2-DNA2 quadruplex, representing the first demonstration of homologous hybridization.

75.

QUANTITATIVE REPRESENTATION OF DNA-LIGAND INTERACTIONS. ***Wilma K. Olson**, Department of Chemistry, Rutgers, The State University of New Jersey, 610 Taylor Road, Piscataway, NJ 08854-8087, Fax: 732-445-5958, olson@rutchem.rutgers.edu*

The ionic character of the sugar-phosphate backbone makes DNA especially sensitive to its local environment, with the association of ligands frequently leading to a change of conformational state. The role of solvent, drugs, and proteins in these processes is suggested by the arrangements of amino acids and other ligand fragments in high resolution structures. Sets of elastic functions suitable for quantitative characterization of such behavior have been extracted from the observed positions of water molecules and amino acid atoms that come into close contact with the bases, sugars, and phosphates in high resolution DNA crystal structures. The distributions of ligand coordinates accumulated around the different moieties have been transformed to ellipsoidal densities, and the elastic functions that underlie the derived spatial representations have been tested against the known positions of drugs in the B-DNA minor groove. Computations which allow for rigid-body displacement of designed polyamides with respect to the DNA scaffold, i.e., primitive docking, are consistent with mechanisms by which minor-groove binding ligands are though to discriminate among DNA sequences and with preferred drug binding sites on nucleosomal DNA. The ellipsoidal functions thus appear promising as mathematical tools for the study of drug-DNA and protein-DNA interactions and for gaining new insights into DNA binding mechanisms.

76.

CONFORMATIONAL TARGETING OF ABL KINASE USING SMALL MOLECULE INHIBITORS. ***William G. Bornmann**, and Darren Veach, Molecular Pharmacology and Chemistry Program, Memorial Sloan-Kettering Cancer Center, 1275 York Avenue, New York, NY 10021, Fax: 212-717-3655, w-bornmann@ski.mskcc.org*

The 2-phenylaminopyrimidines (e.g. GleevecTM) and pyrido[2,3-d]pyrimidines are potent inhibitors of the oncogenic BCR-Abl tyrosine kinase. Molecular modeling of these inhibitors has been an integral part of our research towards improving existing therapies for CML and other cancers. The crystal structure of Abl kinase in two distinct conformations is known. Pyridopyrimidines favor the active-like conformation, while phenylaminopyrimidines seem to favor the inactive-like conformation. To explore this phenomenon, a number of inhibitors of each class have been evaluated in silico, synthesized and evaluated in vitro. The impact of inhibitor design and subtle changes in functionalization on Abl conformational preference and inhibitory potency will be discussed. Selective targeting of one conformation of a kinase over another is yet another important factor to consider when designing and evaluating kinase inhibitors.

77.

DEVELOPMENT OF A CURATIVE TREATMENT PROGRAM FOR CHRONIC MYELOGENOUS LEUKEMIA (CML). ***Bayard Clarkson**, Darren Veach, and William G. Bornmann, Molecular Pharmacology and Chemistry Program, Sloan-Kettering Institute, 430 East 67th Street - Room 401C-RRL - Box #96, New York, NY 10021, Fax: 212-717-3053 (shared), b-clarkson@ski.mskcc.org*

CML is caused by inadvertent fusion of two genes in a hematopoietic stem cell, resulting in p210bcr-abl, a fusion protein with constitutively increased tyrosine kinase activity. Imatinib is the best example yet of a selective drug for human cancer treatment, inducing complete remissions in most patients with early-stage CML with little toxicity. However, mutations in the kinase and other domains of p210bcr-abl and additional cytogenetic abnormalities are frequently observed, and residual leukemic cells are detected in all treated patients. PD173955, a pyrido[2,3-d]pyrimidine developed as an inhibitor of c-Src kinase, was found to be ~20-fold more inhibitory to p210bcr-abl than Imatinib; subsequently 30 analogs were synthesized, 4 of which are ~80- to 150-fold more inhibitory. Because neither Imatinib nor any of the pyridopyrimidines are capable of killing dormant CML stem cells at clinically permissive concentrations, additional selective drugs will be required. A possible curative treatment strategy has been proposed.

78.

CRYSTAL STRUCTURE OF UNPHOSPHORYLATED C-SRC IN COMPLEX WITH AN ANALOGUE OF GLEEVEC™ REVEALS RELATIVE ORIENTATIONS OF THE SH3, SH2 AND KINASE DOMAINS IN THE ACTIVE CONFORMATION. ***Sandra W. Cowan-Jacob**, Gabriele Fendrich, Janis Liebetanz, Doriano Fabbro, and Paul W. Manley, Novartis Institutes for Biomedical Research, CH-4002 Basel, Switzerland, sandra.jacob@pharma.novartis.com*

Gleevec™ (STI571) is a drug targeted against Bcr-Abl kinase for the treatment of chronic myelogenous leukemia (CML). Whereas most chronic phase CML patients respond well under treatment, many in late phases of CML develop

resistance to STI571 and relapse. A potential approach to treat or circumvent such resistance is to target a down-stream component of the Bcr-Abl intracellular signaling pathway, such as c-Src kinase. 4-[(4-methyl-1-piperazinyl)methyl]-N-[3-[[4-(3-pyridinyl)-2-pyrimidinyl]amino]phenyl]-benzamide (**1**) is an analogue of STI571 that lacks the methyl substituent on the central diaminophenyl ring. Compounds such as **1** are relatively unselective inhibitors of protein kinases, whereas introduction of the methyl group imparts considerable potency and selectivity towards c-Abl. In order to clarify this behaviour and understand the requirements for selectivity in kinase inhibition on a molecular basis, the crystal structure of **1** in complex with c-Src was determined by X-ray crystallography and compared to the structure of STI571 in complex with Abl kinase. The structure has been determined at 1.9 Å resolution and confirms that **1** adopts a different binding mode which requires co-planarity of the pyridinyl, pyrimidinyl and diaminophenyl rings. This is a less favorable binding mode for STI571 due to steric clashes with the methyl group. A novel feature of this crystal structure is that it reveals the relative orientations of the SH3, SH2 and kinase domains of c-Src in the unphosphorylated state. All known c-Src structures to date have been of the inactive state in which the phosphorylated C-terminal tail binds to the SH2 domain, locking it into an inactive conformation. The unphosphorylated structure adopts an active conformation, in which the activation loop containing Tyr416 is relatively exposed and available for phosphorylation. This is a step forward in the understanding of the regulation mechanism of Src family kinases.

79.

STRUCTURE-BASED METHODS TO DESIGN POTENT AND SELECTIVE SRC/ABL DUAL INHIBITORS AND THEIR DEVELOPMENT AS ANTILEUKEMIC AND ANTIMETASTATIC AGENTS. ***Chester Metcalf III***[1]*, Yihan Wang*[1]*, William Shakespeare*[1]*, Raji Sundaramoorthi*[1]*, Terence Keenan*[1]*, David Dalgarno*[1]*, Regine Bohacek*[1]*, Kimberly Burns*[1]*, Jonathan Roses*[1]*, Marie Rose van Schravendijk*[1]*, Mary Ram*[1]*, Jeff Keats*[1]*, Shuenn Liou*[1]*, Susan Adams*[1]*, Joseph Snodgrass*[1]*, Victor Rivera*[1]*, Manfred Weigele*[1]*, John Iuliucci*[1]*, Tim Clackson*[1]*, Margaret Frame*[2]*, Valerie Brunton*[2]*, and Tomi Sawyer*[1]*. (1) ARIAD Pharmaceuticals, Inc, 26 Landsdowne St., Cambridge, MA 02139, Fax: 617-494-8144, chet.metcalf@ariad.com, (2) The Beatson Institute for Cancer Research, University of Glasgow*

c-Src kinase has been implicated in a number of processes important for growth of malignant tumors, including growth factor-driven cell proliferation, VEGF-dependent angiogenesis, and metastasis. In the latter case, recent studies have elucidated the critical role that enhanced expression of Src plays in the spread of colon cancer, specifically disrupting proper assembly of E-cadherin-dependent cell-cell contacts leading to cancer-cell migration. We have focused on Src as a therapeutic target for cancer, with the expectation that Src inhibitors could have direct antitumor effects and also potently inhibit metastasis. In addition, dual inhibitors of Src and Abl tyrosine kinases have shown utility against clinically relevant mutated isoforms of Bcr-Abl that are known to result in resistance to Bcr-Abl kinase-targeted inhibitors, such as imatinib, used to treat patients with chronic myelogenous leukemia (CML). In this presentation, we describe the discovery of potent dual inhibitors of Src and Abl kinases, using SMART drug design (i.e., ARIAD's structure-based, proprietary drug discovery technology), that are highly active in both Src and Abl-specific assays of tumor growth and tumor metastasis. Such potent and selective inhibitors of Src and Abl have the potential utility for the treatment of the progression and spread of solid tumors, such as colon cancer, as well as the treatment of CML, including refractory CML.

80.

STRUCTURE OF APO, UNACTIVATED INSULIN-LIKE GROWTH FACTOR 1 RECEPTOR KINASE AT 1.5Å RESOLUTION. ***Sanjeev Munshi****, Structural Biology, Merck & Co. Inc, WP44-K, Sumney Town pike, West Point, PA 19438, Fax: 215-652-9051, sanjeev_munshi@merck.com*

Crystal structure of the unactivated kinase domain of insulin-like growth factor-1 receptor (IGFRK-0P) has been determined to 1.5Å resolution. IGFRK-0P is composed of two lobes connected by a hinge region. The N-terminal lobe of the kinase is a twisted beta-sheet flanked by a single helix, and the C-terminal lobe comprises eight alpha-helices and four short beta-strands. The ATP binding pocket and the catalytic center reside at the interface of the two lobes. Despite the overall similarity to other receptor tyrosine kinases, three notable conformational modifications are observed — 1. This kinase adopts a more closed structure, with its two lobes rotated further towards each other; 2. The conformation of the proximal end of the activation loop (residues 1121 to 1129) is different; 3. The orientation of the nucleotide-binding loop is altered. Collectively, these alterations lead to an ATP-binding pocket that is different from that of Insulin receptor kinase domain. These structural differences might impact on inhibitor designs for IGFRK-0P. Two molecules of IGFRK-0P are seen in the asymmetric unit, associated as a dimer. Two types of dimers, with either the ATP binding clefts of the two monomers, facing towards or away from, each other, are observed. The ordered N-terminus of the monomer suggests the autoinhibitory role for Tyr 957 in the juxtamembrane region.

81.

EGF RECEPTOR KINASE DOMAIN A-LOOP IS POISED FOR CATALYSIS WITHOUT TYROSINE PHOSPHORYLATION. ***Charles Eigenbrot***[1]*, Jennifer Stamos*[1]*, and Mark X. Sliwkowski*[2]*. (1) Department of Protein Engineering, Genentech, Inc, 1 DNA Way, South San Francisco, CA 94080, (2) Department of Molecular Oncology, Genentech, Inc*

The crystal structure of the kinase domain from the epidermal growth factor receptor (EGFRK), including forty amino acids from the carboxy-terminal tail, has been determined to 2.6 Å resolution, both with and without an EGFRK-specific inhibitor currently in Phase III clinical trials as an anti-cancer agent, erlotinib (OSI-774, CP-358,774, Tarceva™) . The EGFR family members are distinguished from all other known receptor tyrosine kinases in possessing constitutive kinase activity without a phosphorylation event within their kinase domains. Despite its lack of phosphorylation, we find the EGFRK activation loop adopts a conformation similar to that of the phosphorylated, active form of the kinase domain from the insulin receptor. Surprisingly, key residues of a putative dimerization motif lying between the EGFR kinase domain and carboxy-terminal substrate docking sites are found in close contact with the kinase domain. Significant intermolecular contacts involving the carboxy-terminal tail or the amino-terminal alpha-helix are discussed with respect to receptor oligomerization and the activity of mutant receptors.

82.

ENERGY SPLITTINGS OF DIFFERENT SPIN STATES: A CHALLENGE FOR MODERN QUANTUM CHEMICAL METHODS IN TRANSITION METAL CHEMISTRY. ***Markus Reiher****, Theoretische Chemie, University of Erlangen-Nuremberg, Egerlandstrasse 3, Erlangen D-91058, Germany, Fax: +49-(0)9131-85-27736, Markus.Reiher@chemie.uni-erlangen.de*

The accurate calculation of relative energies of different spin states is crucial for the study of reactions, which involve first-row transition metal complexes. DFT is currently the only quantum chemical method which is capable for the calculation of structures and energetics of large transition metal complexes. However, we found that standard density functionals are not able to reliably reproduce energies of different spin states for Fe(II)-sulfur complexes and suggested a simple modification of the standard B3LYP functional to cure this problem. This failure of standard density functionals was found to be systematic for pure and hybrid functionals. Our simple modification of the popular B3LYP functional turned out to be a general improvement on the standard B3LYP functional.

We demonstrate the reliability of our reparameterized hybrid density functional for complexes like first-row metallocenes and spin-crossover complexes. Due to the significance and the general applicability of reduced exact exchange in hybrid density funtionals, contrary findings for transition barriers appear less important, which was shown by Harvey and Aschi. With our modified B3LYP functional we are, for instance, able to study spin states and spin barriers occuring in the dinitrogen coordination and reduction process at biomimetic Fe(II)-sulfur complexes.

83.

REDUCTION OF OXOMANGANESE (V) PORPHYRINS BY BROMIDE IONS: A DFT STUDY. ***Filippo De Angelis**, Roberto Car, Ning Jin, and J. T. Groves, Department of Chemistry, Princeton University, Princeton, NJ 08544, fde@princeton.edu*

Spin-singlet Oxo-Mn(V) porphyrins easily transfer the oxo ligand to bromide resulting into spin-quintet Mn(III) complexes and hypobromite. The reaction rate depends strongly on the axial ligands protonation and on the porphyrin meso-substituents, with the more electron-rich 4-N-methylpyridyl (4-Pyp) isomer approximately 1000 times more reactive than the 2-N-methylpyridyl (2-Pyp) isomer, in marked contradiction with reactivity correlations. To understand the origin of this surprising experimental result, we investigated the correlation of electronic structure and acid-base chemistry of axial ligands with reactivity of isomeric oxo-Mn(V) porphyrins with 2-Pyp and 4-Pyp substituents. We find that two effects contribute to the higher reactivity of the latter: the 4-Pyp isomer is more easily protonated than the 2-Pyp isomer, so that at a given pH, the reactive diprotonated oxo-aquo species is present in larger concentration; low-lying quintet spin-states are more easily accessible for the 4-Pyp isomer, which shows a significantly smaller singlet-quintet gap than the 2-Pyp isomer.

84.

STRUCTURAL PREDICTION OF TRANSITION METAL TETRACHLORIDES BY SEMIEMPIRICAL AND DFT METHODS. ***Corneliu Buda**, Chemistry, University of North Texas, Denton, TX 76203, cbuda@unt.edu, and Thomas Cundari, University of North Texas, Department of Chemistry*

Prediction of the ground state geometries and multiplicities for 33 transition metal tetrachlorides has been carried out using two different levels of theory: semiempirical (PM3(tm)) and DFT (BP86). All data regarding geometry and spin state provided by both computational methods were compared with experimental data when these were available. The calculations were performed for all possible spin multiplicities and the most common geometries for coordination number four (tetrahedral, square planar, dodecahedral, and cis-divacant) were used for initial guesses. A match between both computational methods in terms of predicted ground state multiplicity and geometry was found for 26 species, which translated into almost 80%agreement. For the remaining 7 species, multiplicity and/or geometry prediction were dissimilar. Even though the PM3(tm) geometry prediction protocol involved more steps for isolating a feasible global minimum, the aggregate of these calculations was still considerably faster than DFT calculations using extended basis sets.

85.

BEYOND THE TWO-STATE CONICAL INTERSECTIONS: THREE-STATE CONICAL INTERSECTIONS IN THE ALLYL RADICAL. ***Spiridoula Matsika**, Department of Chemistry, Johns Hopkins University, 3400 N. Charles St., Baltimore, MD 21218, Fax: 410-516-8420, smatsika@jhu.edu, and David R. Yarkony, Department of Chemistry, Johns Hopkins University*

Conical intersections of two states of the samesymmetry play a key role in nonadiabatic processes. For molecules with nospatial symmetry and four or more atoms, conical intersections of three statesare possible but difficult to locate. We have developed an algorithm to locatethree-state conical intersections that uses analytic gradient, and Lagrangemultiplier, techniques with multireference configuration interaction wavefunctions.Using the above algorithm we studied the excited states of the allyl radical. Three-stateconical intersections are reported for the spectroscopically observed $B(^2A_1)$,$C(^2B_1)$ and $D(^2B_2)$ states which arereassigned to the 4,5,6 ^{2}A states. Three-state intersections are also reported for the 3,4,5 ^{2}Astates. The minimum energy 4,5,6 ^{2}Athree-state conical intersection is predicted to be 1.1 eV above theD^2B_2 state at its equilibrium geometry. This seam ofthree-state degeneracies is connected to two, two-state seams of conicalintersection, the 4,5 ^{2}A and 5,6 ^{2}A conicalintersections.

86.

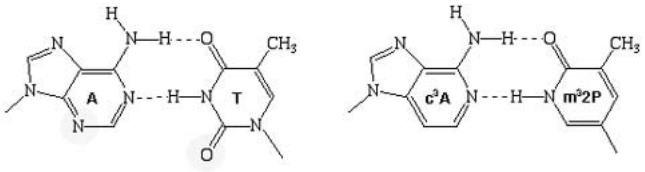
STABILITY OF PYRIMIDINE NUCLEIC ACID BASES WITH RESPECT TO INTRA- AND INTERMOLECULAR PROTON TRANSFER REACTIONS INDUCED BY EXCESS ELECTRONS. ***Maciej Gutowski**[1], Iwona Dabkowska[2], Maciej Haranczyk[2], Janusz Rak[2], Kit H. Bowen Jr.[3], Shoujun Xu[3], J. Michael Nilles[3], Dunja Radisic[3], and Sarah Stokes[3]. (1) Fundamental Science Division, Pacific Northwest National Laboratory, 902 Battelle Blvd., P.O. Box 999, MS K1-96, Richland, WA 99352, maciej.gutowski@pnl.gov, (2) Department of Chemistry, University of Gdansk, (3) Department of Chemistry, Johns Hopkins University*

Chemically transformed nucleic acid bases are considered as sources of point mutations in genetic material. Our computational results and photoelectron spectra provide information about chemical transformations of pyrimidine bases induced by excess electrons. The isolated pyrimidine bases as well as their complexes with X (X=amino acid, carboxylic acid, alcohol, purine base) have been studied with the B3LYP and MPW1K density functionals, as well as at the second order Moller-Plesset level of theory. The photoelectron spectra of some anionic complexes reveal broad features with maxima around 2 eV. These features cannot be associated with the anion of an intact pyrimidine base solvated by X and indicate occurrence of chemical transformations. Our main findings are: (i) the excess electron attachment can induce a barrier-free proton transfer (BFPT) from X to the O8 atom of uracil, thymine or cytosine, (ii) the instability of neutral rare tautomers of uracil or thymine can be significantly suppressed due to the interaction with zwitterionic amino acids.

87.

IMPACT OF MINOR GROOVE FUNCTIONAL GROUPS ON DNA STRUCTURE. ***Larry W. McLaughlin**, Tao Lan, Dongli Chen, and Andrew Fraley, Department of Chemistry, Boston College, Merkert Chemistry Center, 2609 Beacon St, Chestnut Hill, MA 02467, Fax: 617-552-2705*

The role of DNA minor groove functional groups can be probed by preparing DNA sequences with analogue residues in which the functional groups have been deleted without altering other properties such as interstrand Watson Crick hydrogen bonding. DNA sequences containing dA and dT minor groove deletion analogues exhibit significantly reduced duplex stabilities. Increasing numbers of analogue residues also result in a conformational shift form a B-form helix to one that is more A-like. Minor groove deletion analogues can also be use to probe the binding of minor groove ligands to DNA. The absence of minor groove functional groups can have significant effects on the activity of some enzymes such as DNA polymerases.



88.

MOLECULAR DYNAMICS SIMULATIONS OF PAPILLOMA VIRUS E2 DNA SEQUENCES: DYNAMICAL MODELS FOR OLIGONUCLEOTIDE STRUCTURES IN SOLUTION. ***K. Suzie Byun**, Department of Chemistry, Wesleyan University, Middletown, CT 06459, kbyun@wesleyan.edu, and David L. Beveridge, Department of Chemistry and Molecular Biophysics Program, Wesleyan University*

Specificity of Papillomavirus E2 protein-DNA binding depends critically upon the sequence of a DNA region not in direct contact with the protein and is one of the simplest known examples of indirect readout. In the crystalline state, the E2 DNA oligonucleotide, d(ACCGAATTCGGT), exhibits three different structural forms. We report the solution structure E2 DNA based on MD simulations. The predicted structure is in close accord with two of the three crystal structures, and indicates that a significant kink in the double helix at the central ApT step in the third molecule may be a packing effect. To study the role of structural adaptation in the binding process, a simulation on the E2 protein-dna complex was initiated from the crystallographic coordinates. The MD results for the E2 DNA complex and the E2 DNA oligonucleotide sequences will be presented.

89.

DNA QUADRUPLEXES: STRUCTURES AND THEIR RECOGNITION. ***Stephen Neidle**, Gary N Parkinson, Michael Lee, Gianni Chessari, and Shozeb Haider, Cancer Research UK Biomolecular Structure Group, School of Pharmacy, University of London, 29-39 Brunswick square, London WC1N 1AX, United Kingdom, Fax: 44-207-753-5970, stephen.neidle@ulsop.ac.uk*

The structures of guanine quadruplexes formed from telomeric DNA repeats are determined by strand orientation, the nature of the loop sequences, and the stabilising cation. Recent structural studies have shown that quadruplexes involving human telomeric DNA have a preference in physiological conditions for all the strands to be parallel. The resulting structures have grooves in which the TTA loops are partially embedded. This results in complex morphologies for the grooves.

There is much current interest in exploiting G-quadruplexes as targets for selective therapeutic agents that can interfere with telomere maintenance and have antitumour activity. Rational design of small molecules that stabilise G-quadruplexes yet disfavour binding to genomic duplex DNA has been aided by several crystal structures that show that ligand binding utilises both the planar surface of a terminal G-quartet, and surface/charge features of the grooves. Recent structures determined in this laboratory will be discussed, together with molecular modelling and simulation studies that have explored the dynamics of ligand, solvent and cation binding to quadruplexes. Features of loop and groove architecture will also be discussed.

90.

STRUCTURAL CHARACTERIZATION OF N-ACETYL-2-AMINOFLUORENE (AAF) GUANINE AND DEOXYGUANOSINE ADDUCTS VIA A MOLECULAR MECHANICS, SEMI-EMPIRICAL, AND DENSITY FUNCTIONAL THEORY CASCADE METHOD. ***Timothy A. Isgro**, Department of Physics, University of Illinois at Urbana-Champaign, Loomis Laboratory of Physics, 1110 West Green Street, Urbana, IL 61808-3080, isgro@uiuc.edu, Nitin Mathew, Department of Chemistry, Cooper Union for the Advancement of Science and Art, and Robert Q. Topper, Department of Chemistry, Medical Technology and Physics, Monmouth University*

Hepatic activation of N-acetyl-2-aminofluorene (AAF) produces major (C8) and minor (N^2) guanine adducts to DNA. The N^2 adduct may be important in mutagenesis due to its persistence in vivo but its structure has not been determined experimentally. The present study seeks to elucidate both adduct structures via quantum-mechanical study of small complexes of AAF bonded to guanine (G) or deoxyguanosine(dG). A computational cascade of MMFF94 conformer searches followed by AM1 and subsequent density-functional theory BP/DN, BP/DN* , and BP/DN** geometry optimizations was used to predict the low energy conformer distributions. C8 adducts reveal a preference for one of two orientations, with G or dG oriented either ~180° or ~45° with respect to the fluorenyl rings. N^2 adducts similarly exhibit two general conformer classes, one of which is characterized by H-bonding between the acetyl O and N^2 of guanine. The dG-N^2 adduct differs somewhat from G-N^2 due to attractive AAF-ribose interactions.

91.

STEP-WISE ASSEMBLY OF DNA TILINGS AND THEIR APPLICATIONS. ***Sang Jung Ahn**[1], Sung Ha Park[2], Hao Yan[1], John H. Reif[1], and Thomas H. LaBean[1]. (1) Department of Computer Science, Duke University, P.O. Box 90129, Durham, NC 27708, Fax: 919-660-6519, sjahn@duke.edu, (2) Department of Physics, Duke University*

Self-assembling nanostructures composed of DNA molecules have recently been demonstrated to be highly useful as material for constructing periodically patterned structures, mechanical devices with nanometer-scale feature resolution, and the structure of molecular computing systems with massive parallelism. Here we present a novel method for step-wise formation of DNA tiles (4x4), supertiles, and lattices by sticky-end association-dissociation. The structures are studied via AFM analysis to monitor self-assembly as a function of temperature and counterion concentration. The novelty of the 4x4 structure includes a square aspect ratio with helix stacking and sticky-end connections in four directions (north, south, east, and west) within the lattice plane. The final size of resulting lattice has been controlled using only slight reprogramming of the sticky-ends. The 4x4 lattice structure provides an excellent scaffold for production of uniform nano-dot lattice via metal deposition and the basic mechanism of sticky-end association-dissociation enlarges the application of DNA nanostructures.

92.

DESIGN OF MAP KINASES INHIBITORS FOR THE TREATMENT OF INFLAMMATORY DISEASES. ***Francesco G. Salituro**, Medicinal Chemisty, Vertex Pharmaceuticals, 130 Waverly Place, Cambridge, MA 02139, Salituro@vpharm.com*

JNK3 and p38 are members of the MAP Kinase family which regulate signal transduction in response to stress factors. Specific inhibitors of p38 are known to block the production of TNF-alpha and IL-1beta, and are effective in animal models of inflammatory disease both in the periphery and in the CNS. Activation of the JNK pathway in the brain has been associated with neuronal apoptosis, thus inhibition of JNK may also play a role in the treatment of neurological diseases. We have discovered several structurally novel classes of specific p38 inhibitors, two of which have advanced into clinical development. Additionally, we have designed brain permeable dual inhibitors of JNK3 and p38, which could inhibit both apoptotic and inflammatory processes in stroke. Details on the discovery, structure and pharmacological activity of these novel MAP Kinase inhibitors will be discussed in this presentation.

93.

BINDING MODES OF KNOWN CLASSES OF P38 MAP KINASE INHIBITORS. ***Neil Moss**, Boehringer Ingelheim Pharmaceuticals, Inc, 900 Ridgebury Road, P.O. Box 368, Ridgefield, CT 06877-0368, nmoss@rdg.boehringer-ingelheim.com*

Inhibition of p38 MAP kinase has become a popular strategy for the potential development of anti-inflammatory agents, and many pharmaceutical companies have disclosed structurally unique classes of inhibitors. With the growth of kinase inhibitor research in general has come a strong commitment to structure based design and lead optimization. This presentation will discuss and compare known binding modes of p38 MAP kinase inhibitors with attention to likely key structural features responsible for binding affinity. Key aspects of these binding modes will be related to non p38 kinase inhibitors recently approved or in advanced clinical trials.

94.

HUMAN MAP KINASE KINASE 1 (MEK1): DE NOVO CRYSTAL STRUCTURE DETERMINATION AND STRUCTURE-BASED DRUG DESIGN. ***Jeffrey F. Ohren**[1], Christopher E. Whitehead[1], Erli Zhang[1], Alexander Pavlovsky[1], Huifen Chen[1], Peter Kuffa[2], Chunhong Yan[1], Patrick McConnell[1], Amy Delaney[3], Nickolay Y. Chirgadze[1], and Charles Hasemann[1]. (1) Discovery Technologies, Pfizer Global Research and Development, Ann Arbor Labs, 2800 Plymouth Rd, Ann Arbor, MI 48105, Fax: 734-622-2782, Jeffrey.Ohren@Pfizer.com, (2) Department of Chemistry, University of Michigan, (3) Cancer Pharmacology, Pfizer Global Research and Development, Ann Arbor Labs*

Mitogen-Activated Protein Kinase Kinase 1 (MEK1) is a critical component of the cell signaling pathway. The Pfizer clinical candidate CI-1040 is a potent inhibitor of MEK1 and may represent a non-cytotoxic agent for the treatment of proliferative and inflammatory diseases. In order to elucidate the structural basis for the activity of CI-1040 - like inhibitors, the de novo crystal structure of human MEK1 was determined to 2.4 Å resolution as a ternary complex with an inhibitor and MgATP. The crystal structure revealed that, in contrast to all other known protein kinase - inhibitor co-complex structures, the CI-1040 - like MEK1 inhibitors achieve exquisite selectivity and high potency by interacting with both the protein and ATP to lock the enzyme into an inactive conformation. Based on the structural information, a highly predictive CoMFA model was developed using a subset of compounds with known IC50 activity. The CoMFA model was then used to prioritize the synthesis and testing of novel compounds.

95.

STRUCTURE-BASED DESIGN OF HIGHLY POTENT AND SELECTIVE CDK4 INHIBITORS. ***Teruki Honma**, Kyoko Hayashi, Takashi Yoshizumi, Chinatsu Ikeura, Mari Ikuta, and Ikuko Suzuki-Takahashi, Banyu Tsukuba Research Institute in collaboration with Merck Research, Okubo-3, Tsukuba 300-2611, Ibaraki, Japan, Fax: 81-298-77-2027, honmatr@banyu.co.jp*

D-type cyclins and Cdk4/6 play an important role in the G1/S transition of the cell cycle. Because loss of function or deletion of p16 (endogeneous Cdk4/6 specific inhibitor protein) frequently occurs in clinical cancer cells, selective

Cdk4 inhibitors are expected to be a new class of non-cyctotoxic antitumor agents. Identification of selective inhibitors for a particular protein kinase without inhibition of other kinases is very difficult because there are hundreds of homologous kinases and their kinase domains including the ATP binding pocket have a common folding pattern. To obtain highly potent and selective Cdk4 inhibitors, we performed a structure-based design consisting of the following two steps: (1) lead generation of a new class of Cdk4 inhibitors based on a Cdk4 homology model and (2) enhancement of Cdk4 selectivity of lead compounds over Cdk1/2 and the other kinases based on the binding modes and locations of Cdk4 specific amino acid residues. As a result, we developed a novel diarylurea class of potent and selective Cdk4 inhibitors.

96.

IMPORTANCE OF CATION-π INTERACTIONS FOR MOLECULAR RECOGNITION OF ATP IN ATP-BINDING PROTEINS. ***Lisong Mao***, *Yanli Wang, Yuemin Liu, and Xiche Hu, Department of Chemistry, The University of Toledo, 2801 W. Bancroft St., Toledo, OH 43606, Fax: 419-530-4033, lmao@utoledo.edu*

Adenosine 5′-triphosphate (ATP) plays an essential role in all forms of life. Molecular recognition of ATP in ATP-binding proteins is a subject of great importance for understanding enzymatic mechanism and drug design. We have carried out a large scale data mining of the Protein Data Bank (PDB) to analyze the molecular determinants for recognition of ATP, in particular, the adenine base, by proteins at the level of intermolecular interactions. In addition to confirming the importance of the widely known hydrogen bonding, we found out that cation-π interactions between adenine and positively charged residues are also crucial for ATP binding in proteins. An interesting distribution pattern of charged residues around the adenine base was discovered: lysine residues tend to occupy the major groove N7 side of the adenine ring, and the arginine residues situate preferentially above or below the adenine bases. Cation-π interaction energies were subsequently analyzed using the supermolecular approach at the MP2/6-311++G** level, and the effects of solvation were treated using the SM5.42R model.

97.

STRUCTURE-BASED DRUG DESIGN WITH PDK1. ***Daan M. F. van Aalten***, *School of Life Sciences, University of Dundee, Dow Street, Dundee DD1 5EH, United Kingdom, Fax: + 44 1382 345768, dava@davapc1.bioch.dundee.ac.uk*

PDK1 plays a key role in regulating signalling pathways by activating AGC kinases such as PKB/Akt and S6K. The 2.0 Å crystal structure of the PDK1 kinase domain in complex with ATP will be described. The structure defines the hydrophobic pocket termed the 'PIF-pocket' which plays a key role in mediating the interaction and phosphorylation of certain substrates such as S6K. Using a combination of co-crystallography, enzymology and virtual screening, several interesting scaffolds have been identified and their merits will be discussed.

98.

MINING MOLECULAR DYNAMICS DATA FOR MOLECULAR PROPERTIES. ***Ralph A. Wheeler***, *Department of Chemistry & Biochemistry, University of Oklahoma, 620 Parrington Oval, Norman, OK 73019, Fax: 405-325-6111, rawheeler@chemdept.chem.ou.edu*

The continuing surge in computer power, combined with new algorithms allowing molecular dynamics (MD) simulations to span enormous time and length scales, has led to an explosion of MD data. Although the need for new algorithms to analyze the wealth of MD data is critical, most algorithms for estimating molecular properties are rooted in the classical statistical mechanics of the mid-20th century. This contribution describes the adaptation of data-mining techniques used extensively in multivariate statistical analysis, signal processing, pattern recognition, chemometrics, and bioinformatics to mine MD data sets for vibrational frequencies and modes. The method, given various names including principal component analysis (PCA) and the Karhunen-Loeve expansion, is optimal and gives more accurate vibrational frequencies (in a mean-square sense) than Fourier transform-based methods, maximum entropy algorithms, and conventional quantum chemistry. Numerical tests presented include water, water oligomers, and liquid water, models for the peptide bond, and metalloporphyrins. The method is also general and may be used as a more accurate alternative to Fourier analysis to calculate spectra other than vibrational spectra, as well as transport properties.

99.

SUPER-LINEAR MINIMIZATION SCHEME FOR THE NUDGED ELASTIC BAND METHOD. ***Jhih-Wei Chu***[1], *Bernhardt Trout*[1], *and Bernard R. Brooks*[2]. *(1) Department of Chemical Engineering, Massachusetts Institute of Technology, Cambridge, MA 02139, (2) Laboratory of Biophysical Chemistry, National Heart, Lung and Blood Institute, National Institutes of Health*

In this work, we demonstrate a superlinear minimization schemedipep for the Nudged Elastic Band (NEB) method, which determines a minimum energy path (MEP) of a reaction via connecting intermediate replicas given the reactant and the product. New features are added such that the distances between the replicas can be defined in the RMS best-fit space with flexible weighting options, including mass weighting. The minimization scheme is based on a quasi-Newton method: the adopted basis Newton-Raphson (ABNR) minimization. The key feature of the scheme is the self-consistent solution at of the tangent directions in the subspace of ABNR expansion. This procedure is performed at each step of ABNR minimization. The superlinear convergence of our scheme is demonstrated via three nontrivial test cases: isomerization of an alanine tide, a helix to p helix transition of an alainie docta paptide, and the oxidation of dimethyl sulfide. The MEP can also be combined with restrained molecular dynamics (MD) or Monte Carlo sampling to obtain the free energy profile. The acceleration of obtaining MEPs enables applications to large and complex systems such as enzymatic reactions and allosteric transitions of proteins.

100.

PEPTIDE TO NON-PEPTIDE: A REAL BREAKTHROUGH IN VIRTUAL SCREENING. *Jeremy G. Vinter,* ***Timothy J. Cheeseright****, and Mark D. Mackey, Cresset BioMolecular Discovery, Spirella Building, Bridge Rd, SG 6 4ET, Letchworth, United Kingdom, Fax: +44 1462 476329, tim@cresset-bmd.com*

Peptide inhibitors of proteases and receptors are well known and relatively easy to find. However, poor ADMET properties limit their widespread use. To mimic a peptide with a small orally bioavailable drug remains the goal of most medicinal chemistry programs. A new description of inhibitors of biological targets will be presented. The surface and shape properties of a molecule are described as 'field points'. These descriptors can be encoded as a 1D vector, which when combined with a similarity metric allows molecules' field properties to be rapidly compared. Population of a database with commercially available compounds and comparison of a known active to the database allows virtual screening using fields to be applied to lead discovery. Validation on a GPCR target returned a 30%hit rate (activity > 10uM) with molecules that had no structural similarity to any known inhibitor. Peptide to non peptide becomes a reality.

101.

IMPLEMENTATION AND DEVELOPMENT OF THE SELF-CONSISTENT CHARGE DENSITY FUNCTIONAL TIGHT-BINDING METHOD. ***Maciej Gutowski***, *Fundamental Science Division, Pacific Northwest National Laboratory, 902 Battelle Blvd., P.O. Box 999, MS K1-96, Richland, WA 99352, maciej.gutowski@pnl.gov*

We will discribe our implementation of the Self-Consistent-Charge Density Functional Tight-Binding model (SCC-DF TB). This method aims to model directly quantum effects in very large systems (~ 10^4 atoms). Examples are the intrinsic quantum effects in nano-engineered systems, the reactivity at solid-adsorbate-solution interfaces, as well as the reactivity of biological macromolecules. The SCC-DF TB method is parameterized on the basis of modern Density Functional Theory (DFT). The self-consistent charge feature of this method is anticipated to be a crucial factor in the success of the model (in contrast to traditional approximate tight-binding approaches, which ignore self-consistent redistribution of electronic charge in the molecular or crystalline system). The method will be validated and its power will be illustrated in a prototypical study of multiply damaged nucleotides.

102.
PREDICTION AND CLASSIFICATION OF PROTEIN BINDING SITES. ***Matthias Keil***[1], *Thomas Exner*[2], *and Jürgen Brickman*[2]. *(1) Discovery Informatics, Tripos, Inc, 1699 South Hanley Road, St. Louis, MO 63144, Fax: 314-647-9241, mkeil@tripos.com, (2) Department of Physical Chemistry, Darmstadt University of Technology*

An algorithm for the identification of possible binding sites of biomolecules, which are depicted as regions of the molecular surface will be presented. The algorithm is based on the segmentation of the molecular surface into overlapping patches. The properties of these patches(calculated on the basis of physical and chemical principles) are used for the analysis of the molecular surfaces of 7821 proteins and protein complexes. Special attention is drawn to known protein binding sites. A binding site identification algorithm is realized on the basis of the calculated data using a neural network strategy. The neural network is able to classify surface patches as protein-protein, protein-DNA, protein-ligand- or non-binding sites. In order to show the capability of the algorithm, results of the surface analysis and the predictions will be presented and discussed with representative examples.

103.
QSAR-BASED DATABASE MINING: A SUCCESS STORY OF THE DISCOVERY AND EXPERIMENTAL VALIDATION OF NOVEL ANTICONVULSANT COMPOUNDS. ***Min Shen***[1], *Cecile Beguin*[2], *Alexander Golbraikh*[1], *Harold Kohn*[2], *and Alexander Tropsha*[1]. *(1) Laboratory for Molecular Modeling, School of Pharmacy, University of North Carolina, CB # 7360, Beard Hall, School of Pharmacy, Chapel Hill, NC 27599-7360, Fax: 919-966-0204, mshen@email.unc.edu, (2) Department of Medicinal Chemistry and Natural Products, School of Pharmacy, University of North Carolina at Chapel Hill*

We have developed a drug discovery strategy that employs variable selection QSAR models for chemical database mining. In contrast to the traditional methods, our approach is based on the use of rigorously validated and predictive QSAR models obtained with the variable selection k nearest neighbor (kNN) method. Also unique to our approach is that the similarity search is conducted in the descriptor pharmacophore (selected variables) space as oppose to the full descriptor space. This approach was applied to the discovery of anticonvulsant agents in the Maybridge and NCI databases that contain ca. 285,000 compounds combined. 34 compounds were predicted to be active; of those 11 were synthesized and tested, and 9 were confirmed to be active. These results are reassuring in terms of our computational strategies, which can be exploited as a general tool for the discovery of active lead compounds.

104.
STOCHASTIC PROXIMITY EMBEDDING – METHODS AND APPLICATIONS. *Huafeng Xu, and* ***Dimitris K. Agrafiotis****, Research Informatics, 3-Dimensional Pharmaceuticals, Inc, 8 Clarke Drive, Cranbury, NJ 08512, Fax: 609-655-6930, hxu@3dp.com, dimitris@3dp.com*

We present stochastic proximity embedding (SPE), a novel self-organizing algorithm for producing meaningful underlying dimensions from proximity data. SPE attempts to generate low-dimensional Euclidean embeddings that best preserve the similarities between a set of related observations. The embedding is carried out using an iterative pairwise refinement strategy that attempts to preserve local geometry while maintaining a minimum separation between distant objects. Unlike previous approaches, our method can reveal the underlying geometry of the data without intensive nearest neighbor or shortest-path computations, and can reproduce the true geodesic distances of the data points in the low-dimensional embedding without requiring that these distances be estimated from the data sample. More importantly, the method scales linearly with the number of points, and can be applied to very large data sets that are intractable by conventional embedding procedures. SPE can be applied to any problem where nonlinearity complicates the use of conventional methods such as principal component analysis and multidimensional scaling, and where a sensible proximity measure can be defined. Because it seeks an embedding that is consistent with a set of upper and lower distance bounds, SPE can also be applied to an important class of distance geometry problems including conformational analysis, NMR structure determination, ligand docking etc. To that effect, the basic self-organizing algorithm is extended to preserve not only inter-atomic distance bounds but also chiral constraints that enforce the planarity of conjugated systems and correct chirality of stereocenters, as well as other types of constraints specific to the problem at hand. When applied to conformational analysis, we show that this approach produces excellent starting geometries that minimize to more diverse and energetically favorable conformations at a fraction of the time required by kindred techniques. Ongoing efforts in other applications in structural chemistry and biology will be discussed.

105.
AUTOMATIC SYNTHESIS OF HIGH-PERFORMANCE PARALLEL PROGRAMS FOR ELECTRONIC STRUCTURE METHODS. ***P. Sadayappan***[1], *Alexander Auer*[2], *Gerald Baumgartner*[1], *David E. Bernholdt*[3], *Alina Bibireata*[1], *Daniel Cociorva*[1], *Venkatesh Choppella*[3], *Xiaoyang Gao*[1], *Robert J. Harrison*[3], *So Hirata*[4], *Sriram Krishanmoorthy*[1], *Sandhya Krishnan*[1], *Chi-Chung Lam*[1], *Qingda Lu*[1], *Marcel Nooijen*[2], *Russell M. Pitzer*[5], *J Ramanujam*[6], *and Alexander Sibiryakov*[1]. *(1) Computer Science, Ohio State University, 2015 Neil Avenue, Columbus, OH 43210, saday@cis.ohio-state.edu, (2) Department of Chemistry, University of Waterloo, (3) Oak Ridge National Laboratory, (4) William R Wiley Environmental Molecular Sciences Laboratory, Pacific Northwest National Laboratory, (5) Department of Chemistry, Ohio State University, (6) Louisiana State University*

The development of high-performance implementations for advanced electronic structure methods like coupled cluster and configuration interaction is an arduous task. The particular algorithm chosen can affect memory access and communication overhead in ways that are extremely complex for the programmer to estimate and optimize.

We are developing a program synthesis system called the Tensor Contraction Engine (TCE) that can generate state-of-the-art, high performance, parallel programs in an automated fashion, starting from a high-level specification of the computation as a set of tensor contraction expressions. The synthesized programs are optimized to minimize memory/disk access costs and interprocessor communication costs. Moreover, the algorithms are designed to minimize operation costs, subject to the memory and disk space constraints of the target machine.

The TCE project is interdisciplinary and involves chemists and computer scientists from multiple institutions (PNNL, Ohio State, Princeton University, ORNL, and Louisiana State). The computational methods that can be handled range from high accuracy CCSDT and CCSDTQ methods to localized-orbital CCSD schemes. Analytical energy gradients and excited state methods in the context of coupled cluster theory, as well as multireference coupled cluster methods will be considered in the future.

106.
THEORETICAL INVESTIGATIONS OF SYSTEMS RELEVANT IN THE CHEMISTRY OF THE ATMOSPHERE. ***Marzio Rosi****, Marzo Di Stefano, and Antonio Sgamellotti, Istitute of Molecular Science and Technologies (ISTM), Italian National Research Council (CNR), c/o Department of Chemistry, Via Elce di Sotto 8, 06123 Perugia, Italy, Fax: 01139 075 5855605, marzio@thch.unipg.it*

Nowadays, atmospheric chemistry represents a large field of investigations, both from the experimental and theoretical point of view. Many new experimental techniques allow investigations on different regions of the atmosphere and the characterization of their chemical composition. In the last few years, for instance, astronomical spectra have revealed the presence of aromatic and polyaromatic molecules in extraterrestrial environments, as carbon stars, molecular clouds and meteorites. Moreover, the recent observation of benzene in interstellar clouds has increased the interest in this class of molecules and in their chemical behavior. We have focussed our attention in the reaction between N^+ and benzene, in collaboration with the experimental research group of the University of Trento (Italy). In particular we have analyzed the reactive mechanism by which the reactants are converted in several cations containing at least one C-N bond, according to this general scheme:

$$C_6H_6 + N^+ = H_mC_nN^+ + C_xH_y$$

where $H_mC_nN^+$ could be one of the following cations: $H_2C_5N^+$, HC_5N^+, $H_3C_4N^+$, $H_2C_3N^+$, $H_2C_2N^+$ and H_2CN^+. All these species have been studied using the DFT formalism with the B3LYP hybrid functional in conjunction with the 6-31G* basis set. We have characterized all the possible isomers of the previous systems and the reactive channels which might contribute to their synthesis, through the survey of their potential energy surfaces. Thermochemical calculations, and the comparison with experimental values, allow to distinguish between exoergonic and endoergonic processes and, therefore, to have a detailed description of the investigated systems. Since the entire class of

molecules containing carbon and nitrogen atoms plays an important role in the chemistry of biological systems, an understanding of the mechanism by which aromatic hydrocarbons can be converted into cyano and amino molecules, the building blocks of amino acids, may partially contribute to the controversy concerning the possible interstellar origin of biological molecules.

107.
LOW LYING ELECTRONIC STATES OF HOCL CATION: AB INITIO CALCULATIONS AND SIMULATIONS OF THE HE I PHOTOELECTRON SPECTRUM. ***Daniel K. W. Mok***[1], *Alex K. T. Yeung*[1], *Dianxum Wang*[2], *and Foo-tim Chau*[3]. *(1) Department of Applied Biology and Chemcial Technology, The Hong Kong Polytechnic University, Hung Hom, Hond Kong, Hong Kong, Fax: +852 23649932, bcdaniel@polyu.edu.hk, (2) Institute of Chemistry, Chinese Academy of Sciences, (3) Department of Applied Biology and Chemical Technology, The Hong Kong Polytechnic University*

High level molecular orbital calculations were performed on the ground state and the low lying electronic states of HOCl+ in order to obtain their near equilibrium potential energy functions. For the lowest state of a given symmetry, RCCSD(T)/cc-pVQZ was used, for excited states, MRCI/cc-pVQZ was then used. Spectral simulations based on Franck-Condon factor calculations including the Duchinsky effect with the inclusion of anharmonicity were performed for the first four bands of the He I photoelectron spectra of HOCl to assign the experimental spectra. Iterative Franck-Condon analyses were also carried out by systematically comparing the simulated and observed spectra to derive a more accurate geometry for the cationic ground state.

108.
DYNAMICS OF METHYLENE NITRAMINE DECOMPOSITION FROM REACTION PATH CALCULATIONS. *Chris Stopera, Dave Thweatt, and* ***Michael Page****, Department of Chemistry, North Dakota State University, Fargo, ND 58105, Fax: 701-231-8831, Christopher.Stopera@ndsu.nodak.edu, mike.page@ndsu.nodak.edu*

Methynene Nitramine (H2CNNO2) decomposes unimolecularly both by simple NN bond rupture to H2CN and NO2 and by a concerted reaction through a five-center cyclic transition state yielding HCN and HONO. We have performed steepest descent reaction path calculations to map out the minimum energy path for the concerted decomposition. Using reaction path information, we perform semiclassical dynamics calculations based on a mixed quantum-classical treatment using the Reaction Path Hamiltonian formalism. Not surprisingly, we find significant vibrational excitation of incipient HONO OH bond. What is surprising to us is that our calculations predict significant excitation of the in-plane HCN bending vibration in the product. The results will be discussed in the context of the relevant features of the potential energy surface.

109.
NEW MECHANISM FOR PHOTODESORPTION: SELF-TRAPPING OF SURFACE EXCITONS. ***Margaret A. Gabriel****, William Stier, Fernando D. Vila, Graeme Henkelman, and Hannes Jonsson, Department of Chemistry 351700, University of Washington, Seattle, WA 98195-1700*

We have carried out theoretical calculations that demonstrate how a photo-induced exciton at a quartz surface can lead to desorption of weakly bound adatoms such as Xe. The calculations were carried out with plane wave based density functional theory and classical dynamics (Car-Parrinello simulations). The formation of an exciton in SiO2 is accompanied by a large structural relaxation where atoms can be displaced by more than an Ångstrom as the exciton self traps. At the surface, this can lead to an outward relaxation of atoms which, in turn, can collide with an adatom, leading to desorption. The dynamics simulations predict the kinetic energy of desorbed xenon atoms to be 0.2 eV on average, while the largest value observed in 29 successful trajectories was 0.4 eV.

110.
SCREENING TOOLS FOR THE DESIGN OF MOLECULAR DIODES. ***Steven K Pollack****, Center for Bio/Molecular Science and Engineering, Naval Research Laboratory, Code (6950), 4555 Overlook Ave., Sw, Washington, DC 20375, Fax: 202-767-9594, Steven.Pollack@nrl.navy.mil*

The challenge in designing molecules for use in molecular electronics is to be able to predict their linear and non-linear conduction behavior in advance of their synthesis and characterization. We have observed that asymmetric shifts in frontier orbital energies as a function of an applied field are a marker for experimentally observable rectification. For such an orbital to be important in electron transport, it must have contiguous orbital density from one electrode to the other. We have developed a series of tools to rapidly identify orbitals which have the required properties stated above. We present our results for a series of molecules that have been experimentally studied and make predictions for several new materials.

111.
ELECTRONIC STRUCTURE OF 1 TO 2 NM DIAMETER SILICON CORE/SHELL NANOCRYSTALS: SURFACE CHEMISTRY, OPTICAL SPECTRA, AND DOPING. ***Zhiyong Zhou****, Louis Brus, and Richard A. Friesner, Department of Chemistry, Columbia University, 3000 Broadway, New York, NY 10027, Fax: 212-854-7454, zhiyong@chem.columbia.edu*

The electronic structure of small Si nanocrystals is explored by all-electron, hybrid functional DFT calculations with unrestricted geometry optimization. We study surface passivation, P and Al doping, optical excitation, and charge transfer properties of nanocrystals based upon Si_{35}, Si_{66}, and Si_{87} cores. Our result of different passivation explains the experimental observation that hydrogen passivated Si nanocrystals luminesce in the blue, while oxide passivated Si nanocrystals luminesce in the yellow-red. The calculation of incompletely passivated doped nanocystal Si_{65}(internal P)H_{63} suggests electron transfer from a P atom dopant to the surface dangling bond, creating a lone pair which does not show an ESR signal or trap the optically excited electron. This result explains the recent experimental findings of the effect of P doping on PL and ESR of Si (also SiGe alloy) nanocrystals embedded in SiO_2 matrices.

112.
SEMI-DFT APPROACH TO CALCULATION OF PROTEIN SYSTEMS. *Nikolay A. Anikin, Vladislav L. Bugaenko, and* ***Victor M. Anisimov****, Quantum Biochemistry Group, Konstantina Fedina-3 / 24, Moscow, Russia, aanikin@swf.chem.ac.ru, victor@quantumbiochem.org*

A grid free exchange-correlation potential has been developed for the molecular fragment partitioning approach to solution of the Kohn-Sham equation for protein systems. The whole molecule is partitioned on small transferable molecular fragments determining the full exchange correlation potential via a sum of fragment potentials and the inter-fragment polarization. The exchange-correlation energy is obtained from contributions of the individual fragments plus a correction on variation of electron density proportional to the X-C potential. The accuracy of the approach is verified on small peptides in comparison with conventional solution of the Kohn-Sham task.

113.
STUDY OF CHEMICAL STABILITY OF NOVEL, POTENT INHIBITORS OF DPP-IV. ***Doree Sitkoff***[1], *David Magnin*[2], *Jeff Robl*[2], *Richard B. Sulsky*[2], *David J. Augeri*[3], *Yanting Huang*[2], *Prakash Taunk*[2], *David A. Betebenner*[2], *Ligaya M. Simpkins*[2], *James G. Robertson*[4], *Ashish Khanna*[5], *Benoni Abboa-Offei*[4], *Aiying Wang*[4], *Michael Cap*[4], *Li Xing*[6], *Li Tao*[6], *Mary Malley*[7], *Jack Z. Gougoutas*[8], *Qi Huang*[4], *Song-Ping Han*[4], *Rex A Parker*[4], *and Lawrence G. Hamann*[2]. *(1) Department of Computer Aided Drug Design, Bristol-Myers Squibb Company, P. O. Box 5400, Princeton, NJ 08543-5400, Fax: 609-818-3545, (2) Discovery Chemistry, Bristol-Myers Squibb Company, (3) Discovery Chemistry, Bristol-Myers Squibb, (4) Department of Metabolic Research, Bristol-Myers Squibb Company, (5) Department of Preclinical Candidate Optimization, Bristol-Myers Squibb Company, (6) Department of Exploratory Pharmaceutics, Bristol-Myers Squibb Company, (7) Department of Crystallography, Bristol-Myers Squibb Company, (8) Division of Analytical Research and Development, Pharmaceutical Research Institute, Bristol-Myers Squibb*

DPP-IV is a sequence-specific serine protease that catalyses the cleavage of dipeptides from the N-terminus of proteins with the sequence H-X-Pro-Y or H-X-Ala-Y. Inhibition of the enzyme has shown clinical benefit as a novel mechanism for treatment of type 2 diabetes. Some previously studied proline-based DPP-IV inhibitors have been shown to be chemically unstable. Here we present two novel methanoproline classes: the cis-4,5-methanoprolinenitrile and the cis-3,4-methanoprolinenitrile dipeptides and show that cis-4,5-methanoprolinenitriles with increased β-branching in the N terminal aminoacid provide unique chemical stability and inhibitory potency. The interactions associated with

the enhanced chemical stability are probed using computational techniques including quantum chemistry calculations.

114.

IN SILICO STRUCTURAL MODELS FOR THE END STATES OF ATP HYDROLYSIS IN THE MOTOR PROTEIN MYOSIN. ***Sonja M. Schwarzl***, *Jeremy C. Smith, and Stefan Fischer, IWR - Computational Molecular Biophysics, University of Heidelberg, Im Neuenheimer Feld 368, 69120 Heidelberg, Germany, Fax: 0049-6221-548868, sonja.schwarzl@iwr.uni-heidelberg.de*

The ATP-driven molecular motor myosin exists in a variety of different structural states. Conventional muscle myosin II has been crystallized in both OPEN (post-powerstroke) and CLOSED (pre-powerstroke) conformations. Only the CLOSED conformation, in which both ATP analogs and transition state analogs have been crystallized, is competent for ATP hydrolysis. However, the structural basis for catalysis of the hydrolysis step is not well understood. This is particularly true for the product state, after nucleotide cleavage but before the phosphate has been released, for which no structural information is available. In the present study, structural ensembles for both pre-hydrolysis (ATP.H2O) and post-hydrolysis (ADP.Pi) states have been determined using combined quantum mechanical / molecular mechanical modelling techniques.

115.

FUNCTIONS OF THE COPPER(I)-THIOLATE CLUSTER IN COPY. ***Melinda A. Harrison***, *Department of Chemistry and Biochemistry , Center for Computational Sciences, Duquesne University, 600 Forbes Avenue, Pittsburgh, PA 15282, Fax: 412-396-5683, harriso760@duq.edu, Jeffrey D. Evanseck, Department of Chemistry & Biochemistry and Center for Computational Sciences, Duquesne University, and Charles T. Dameron, Department of Chemistry and Biochemistry, Duquesne University*

Copper homeostasis in the Gram-Positive bacterium *Enterococcus hirae (E. hirae)* is controlled by the cop operon which encodes four genes: *copY, copZ, copA* and *copB*. The metal binding site of the CopY repressor in *E. hirae* is the key to metal regulation of a copper uptake and resistance pathway. Although the structure of the protein has not been elucidated previous research has shown that the copper-protein stoichiometry is two Cu(I) per monomer. Computational work has been undertaken to evaluate the Cu_4S_8 cysteinyl thiolate cluster. An appropriate level of theory is selected by comparing computed and experimental data on the Cu_4S_6 system. The Cu(I) systems have been modeled using the Gaussian 98 program. Density functional theory (DFT) calculations, at the B3LYP/6-31G(d) level of theory, have been used to study the structure, energy and vibrations of this hypothesized thiolate cluster and model systems.

116.

DFT INVESTIGATION OF THE REMARKABLE REACTIVITY OF THE GEM-DIZINC (IZN)2(CHI CARBENOID AS A CYCLOPROPANATION REAGENT COMPARED TO THE MONO ZINC IZNCHI2 CARBENOID. ***Dong-qi Wang***, *Cunyuan Zhao, and David Lee Phillips, Department of Chemistry, University of Hong Kong, Pokfulam Road, Hong Kong, Hong Kong, Fax: 852-2857-1586, wangd@hkusua.hku.hk*

Density functional theory computations for the cyclopropanation reactions of several mono zinc carbenoids and their corresponding gem-dizinc carbenoids with ethylene are presented. The mono zinc carbenoids react via an asynchronous attack on one CH2 group of ethylene with a barrier to reaction in the 20-25 kcal/mol range similar to other Simmons-Smith type carbenoids previously examined. In contrast, the gem-dizinc carbenoids react with ethylene via a synchronous attack on both CH2 groups of ethylene with lower barriers to reaction (about 15 kcal/mol) compared to their corresponding mono zinc carbenoid. Both mono zinc and gem-dizinc carbenoid cyclopropanation reactions can be accelerated by addition of ZnI2 groups as a Lewis acid and this lowers the barrier by another 1-5 kcal/mol for addition of one ZnI2 group. Our results indicate that gem-dizinc carbenoids react with C=C bonds with noticeably lower barriers to reaction than thier corresponding mono zinc carbenoids. The three gem-dizinc carbenoids examined have a larger positive charge distribution than those in the mono zinc carbenoids and thus there is a stronger electrophilic character for the gem-dizinc carbenoids.

117.

REACTIVITY AND SPECTRA OF MODEL CYTOCHROME P450 INTERMEDIATES. ***John C Hackett***, *Division of Medicinal Chemistry and Pharmacognosy, The Ohio State University, 500 W 12th Ave, Columbus, OH 43210, Fax: 614-292-2435, hackett.35@osu.edu, Robert W. Brueggemeier, Division of Medicinal Chemistry & Pharmacognosy, College of Pharmacy, The Ohio State University, and Christopher M. Hadad, Department of Chemistry, Ohio State University*

The cytochromes P450 are a family of cysteinato-heme ligated enzymes with the ability to catalyze many monoxygenation reactions. In addition to the high-valent P450 compound **I**, the rate-limiting reduction of ferrous dioxygen P450 produces another reactive intermediate, the reduced ferrous dioxygen P450. Optimized geometries, vibrational frequencies, and natural population analyses were determined for the ferrous dioxygen, $[(Porphyrin)(Fe)(O_2)(SH)]^{1-}$ and reduced ferrous dioxygen $[(Porphyrin)(Fe)(O_2)(SH)]^{2-}$ bound model systems using the BPW91 density functional. These calculations accurately predicted the ground state of the ferrous dioxygen to be a singlet, with a low-lying triplet state in the gas phase and chlorobenzene. This result is consistent with available electron paramagnetic resonance data for the native enzyme with O_2 bound. Geometric parameters for the ferrous dioxygen model are in close agreement with the recent X-ray crystallographic data of CYP101 with O_2 bound. These calculations have accurately predicted the ground state of the reduced ferrous dioxygen to be a doublet. Single electron reduction of the ferrous dioxygen model resulted in lengthening of the O-O, Fe-O, and Fe-S bonds in both media. The chlorobenzene polarizable continuum results in shift of the electron affinity of the ferrous dioxygen species from +43 to –38 kcal/mol. Proton affinities of the proximal and distal oxygen atoms of the reduced species were determined and provide insight into the possible proton-assisted pathway to Compound **I** formation or dysfunctional decoupling resulting in the formation of H_2O_2. The distally twice-protonated species is not a minimum, rather optimizes directly to a Van der Waals complex of Compound **I** and water.The proton affinity of the proximal oxygen lie 23 and 25 kcal/mol above the distal oxygen in the gas phase and chlorobenzene, respectively. Time-dependent BPW91 calculations are ongoing to study excited states of these model cytochrome P450 species for comparison with available UV/Visible spectra. We are also applying density funtional theory methods to study the role of the reduced ferrous dioxygen species in the transformation of small molecules.

This work was supported by Ohio Supercomputer Center Grant PAS0091.

118.

AB INITIO STUDIES OF THE ENERGIES, STRUCTURES AND ELECTRONIC PROPERTIES OF MYO-INOSITOL MONO-PHOSPHATE IN-VACUO AND WATER. ***Ping Yang***, ***Xin Bai***, *Pushpalatha P.N. Murthy, and Richard EDWIN Brown, Department of Chemistry, Michigan Technological University, 1400 Townsend Dr, Houghton, MI 49931, pyang@mtu.edu*

Symmetric myo-inositol-2-mono-phosphate, $(Ins(2)P_1)$ is an important member of the inositol phosphate family of compounds that are involved in signal transduction. This work involved performing ab initio HF, MP2 and DFT calculations with the 6-31G(d) and 6-311G(d) basis sets to determine the important thermally accessible conformations and the transition state structure for the ring inversion for the neutral $InsP_1$ and its anions, $InsP_{1-1}$ and $InsP_{1-2}$. All of the calculations show that the minimum prefers a 1ax/5eq structure where the phosphate group is in the axial position with all OH groups in the equatorial positions. These results agree with those that were determined from NMR data. Depending on the level of theory, an activation energy of 12.24 to 15.52 kcal/mol was obtained for the neutral species in the gas phase. However when the effect of solvent was included using the polarized continuum model (PCM), the activation energy dropped from ~14kcal/mol to 4.3kcal/mol.

119.

PREDICTING AQUEOUS SOLUBILITY: A FUNDAMENTAL APPROACH. ***Jason D. Thompson***[1], *Christopher J Cramer*[1], *and Donald G. Truhlar*[2]. *(1) Department of Chemistry, University of Minnesota, 207 Pleasant St SE, Minneapolis, MN 55455, thompson@pollux.chem.umn.edu, (2) Department of Chemistry and Supercomputing Institute, University of Minnesota*

Solubility is a fundamental physical property, and there is a great need, especially in environmental, pharmaceutical, and industrial chemistry, for accurate predictions of solubilities that have not been measured and even of

solubilities of compounds that have not yet been synthesized. A method of predicting solubility that utilizes the thermodynamic relationship between solubility, free energy of solvation and solute vapor pressure will be described. Using a test set of 75 liquid solutes and 15 solid solutes, the utility of this relationship for predicting aqueous solubilities from experimental aqueous free energies of solvation and experimental vapor pressures of pure substances will be presented. In addition, the use of a continuum solvation model to predict solubility will be discussed, in particular the SM5.42R model, which can predict aqueous free energies of solvation and free energies of self-solvation.

120.
CONTRIBUTION OF ORDERED WATER MOLECULES TO BINDING THERMODYNAMICS. ***Zheng Li**, and Themis Lazaridis, Department of Chemistry, City College of CUNY, Convent Ave & 138th St., New York, NY 10031*

Binding between biomolecules is usually accompanied by the formation of direct interactions with displacement of water from the binding sites. In some cases, however, the interactions are mediated by ordered water molecules, whose contribution to binding affinity and the other thermodynamic functions is unclear. In our work we compute the contribution of such water molecules to the thermodynamic properties using statistical mechanical formulas for the energy and entropy. The requisite correlation functions are obtained by molecular dynamics simulations, and the thermodynamic contribution of specific regions of space to the solvation properties is determined. Applying this approach to the HIV-1 protease-inhibitor complex, we find that the entropic penalty of ordering is large but is outweighed by the favorable water-protein interactions. We also find a large negative contribution from this water molecule to the heat capacity. This approach is also applied to cancanavalin A-carbohydrate complexes. The thermodynamic consequences of displacement of an ordered water molecule by ligand modification are calculated and compared to experimental data. Our approach is also applicable to less ordered water molecules and could be useful in rational drug design by providing a method to estimate when the displacement of ordered water molecules is favorable.

121.
THE SOLUBILITY OF CO_2 IN BRINES THROUGH FEP/MC SIMULATIONS. ***Thomas J. Dick**, Department of Chemistry and Biochemistry, Duquesne University, 308 Mellon Hall, 600 Forbes Ave., Pittsburgh, PA 15282, Fax: 412-396-5683, dick251@duq.edu, and Jeffry D. Madura, Department of Chemistry and Biochemistry, Center for Computational Sciences, Duquesne University*

One proposed method of CO_2 sequestration is mineral trapping in brine aquifers. In mineral trapping, CO_2 dissolves into the brine, is converted to CO_3^{-2}, and associates ionically with metal ions in solution to form insoluble metal carbonates. The first step in mineral trapping is the thermodynamically unfavored conversion of gaseous CO_2 to an aqueous phase. CO_2 solubility in aqueous solution is influenced by ion concentration, but experimental studies have usually been in simple salt solutions, not complex brines. This research will give insight into the conversion of CO_2 from gas to solution in brines using FEP/MC simulations. Several CO_2 models have been designed and tested to find the best model of CO_2 and this model of CO_2 was used to calculate the solubility of CO_2 in several salt solutions to validate the methods. The solubility of CO_2 in different brine solutions has also been undertaken.

122.
PRIORI PKA PREDICTIONS: INVESTIGATION OF STERIC EFFECTS ON THE BASICITY OF SUBSTITUTED PYRIDINES VIA MC/FEP CALCULATIONS. ***Theresa M. Lyons**, Ivan Tubert-Brohman, and William L. Jorgensen, Department of Chemistry, Yale University, New Haven, CT 06520, Theresa.Lyons@yale.edu*

Density Functional Theory (DFT) and Monte Carlo Free Energy Perturbation (MC FEP) calculations, using explicit solvent, were performed to determine the basicity of a series of substituted pyridine molecules in a 50 %(by volume) aqueous ethanol solution. This method furnishes pK_a values for 2,6-di-*tert*-butylpyridine (DTBP), 2,6-dimethylpyridine (DMP), 2-*tert*-butylpyridine (TBP), 2-methylpyridine (MP), and pyridine (P) in good agreement with experimental data. The use of explicit solvent allows for insight into the steric reasoning as to why 2,6-di-*tert*-butylpyridine is less basic than pyridine. Additional Monte Carlo simulations reveal the factors that influence hydrogen bonding and solute-solvent energy pair distributions of the neutral and protonated pyridine series.

123.
SOLVATED VS. DIPOLE-BOUND ELECTRON FROM THE POINT OF VIEW OF ATOMS-IN-MOLECULE THEORY. ***Qadir K. Timerghazin**, Centre for Research in Molecular Modeling, and Department of Chemistry & Biochemistry, Concordia University, 1455 de Maisonneuve Blvd. W, Montreal, QC H3G 1M8, Canada, Fax: 514-848-2868, qadir@cermm.concordia.ca, and Gilles H. Peslherbe, Centre for Research in Molecular Modeling and Department of Biochemistry & Chemistry, Concordia University*

An electron can interact with a cluster of polar neutral molecules in two ways: it can either reside outside the cluster, trapped in the field of the cluster dipole moment (dipole-bound electron), or inside the cluster (solvated electron). Studies of both species are of great importance to further our understanding of the bulk solvated electron phenomenon and, from a more general perspective, the interaction of electrons with molecules. In this contribution, we will discuss the dipole-bound vs. solvated electron in the framework of the Atoms-In-Molecules (AIM) theory, which is based on the topological analysis of the electronic density. Generic topological patterns by which the dipole-bound or solvated electron manifests itself in polar solvent cluster anions will be presented, and numerical parameters to characterize the nature of electron binding will be proposed. We also will try to apply the insight gained from the present cluster studies and extrapolate it to the solvated electron problem in bulk solvents.

124.
THEORETICAL STUDY ON THE ROLES OF DIVALENT METAL IONS IN GTP HYDROLYSIS. ***Yan-Ni Wang**, Jack R. Collins, and Stanley K. Burt, Advanced Biomedical Computing Center, NCI-Frederick, SAIC, Frederick, MD 21702, Fax: 301-846-5762, yanniw@ncifcrf.gov*

Phosphate hydrolysis by GTPases plays an important role as a molecular switch in signal transduction and as an initiator of many other biological processes. In spite of the centrality of this ubiquitous reaction, the process is still poorly understood. To understand the mechanisms of GTP hydrolysis and the roles of metal ions in the reaction, GTP hydrolysis pathways catalyzed with divalent metal ions Mg^{2+}, Mn^{2+}, Zn^{2+}, and Ca^{2+}, were studied using density functional methods. Results show that in the GTP hydrolysis process, negative charge is transferred from the γ-phosphate to β-phosphate through the bridging ester oxygen, and the divalent metal ions play important roles in GTP hydrolysis process by neutralizing the transition states. The activation barriers of GTP hydrolysis catalyzed with the divalent metal ions were lower than that of the corresponding non-metal catalyzed reaction. Effects of dielectric force field on the energetics of the reactions were also studied in this work.

125.
ROLE OF SECOND SPHERE ZN^{2+} LIGANDS IN *AEROMONAS PROTEOLYTICA* AMINOPEPTIDASE. ***Petra Munih**, Department of Chemistry, The Center for Molecular Modeling, University of Pennsylvania, 231 S. 34th St., Philadelphia, PA 19104-6323, Fax: 215-573-6233, munih@cmm.chem.upenn.edu, and Michael L. Klein, Department of Chemistry, University of Pennsylvania*

Aeromonas proteolytica aminopeptidase (AAP) is a hydrolytic metalloenzyme with a quasi symmetrical active site which contains two Zn^{2+} cations. The complete first coordination spheres of the two metals include a terminal glutamate/aspartate and a histidine ligand each, besides an aspartate and a solvent molecule bridging between them.

Dynamical treatment of the system was achieved ab-initio Car-Parinello molecular dynamics (CPMD) and hybrid quantum-classical (CPMD/AMBER) methodologies. In addition, CPMD was used to obtain optimized minimal geometries of selected active site models and along with the NWChem package to derive any relevant electronic properties.

Our QM model contained metals and their first coordination spheres, several solvent molecules and some second sphere ligands. The role of second sphere ligands in the stability and modulation of the active site as well as in the qualitative aspects of the mechanism were determined. Two such residues (Glu151 and Asp99) were singled out.

126.
VARYING LEWIS ACIDITY IN IONIC LIQUIDS WITH NEW FORCE FIELD PARAMETERS. ***Orlando Acevedo**, Center for Computational Sciences, Duquesne University, Department of Chemistry and Biochemistry, 600 Forbes Avenue, Pittsburgh, PA 15282, Fax: 412-396-5683, acevedo323@duq.edu, and Jeffrey D. Evanseck, Department of Chemistry & Biochemistry and Center for Computational Sciences, Duquesne University*

Molecular factors that endow room temperature ionic liquids with the ability to enhance the rate and stereoselectivity on a vast range of organic reactions are largely unknown. A new force field has been created for the liquid phase of the 1-ethyl-3-methyl-imidazolium (EMI^+) chloroaluminate ionic liquid, which takes advantage of the Lewis acid variability in acidic or basic melts. The ions that form ($AlCl_4^-$, $Al_2Cl_7^-$ and EMI^+) depend on the proportion of the melt. Our parameters allow for the first time, the ability to construct boxes of ionic liquids at different acidic and basic melt ratios. These ionic liquid boxes will allow systems under investigation, such as the Diels-Alder reaction between cyclopentadiene and methyl acrylate, to be explored using the differing melt ratios. Using experimental x-ray and infrared data reported and our quantum mechanical calculations, new parameters have been developed and tested to describe the relationship of chemical structure to energy.

127.
PDDG/PM3 AND PDDG/MNDO: EXTENSION TO THE HALOGENS. ***Ivan Tubert-Brohman**, Cristiano Ruch Werneck Guimarães, Matthew P. Repasky, and William L. Jorgensen, Department of Chemistry, Yale University, New Haven, CT 06520, Ivan.Tubert-Brohman@yale.edu*

The new semiempirical methods, PDDG/PM3 and PDDG/MNDO, have been parameterized for halogens. The original MNDO and PM3 were also reoptimized for the halogens using the same training set, giving the methods referred to as MNDO' and PM3′. For 442 halogen-containing molecules, the smallest mean absolute error (MAE) in heats of formation was found for PDDG/PM3 (5.6 kcal/mol), followed by PM3′ (6.1 kcal/mol), PDDG/MNDO (6.6 kcal/mol), PM3 (8.1 kcal/mol), MNDO' (8.5 kcal/mol), AM1 (11.1 kcal/mol), and MNDO (14.0 kcal/mol). For small haloalkanes, the PDDG methods give heats of formation that are better than both B3LYP and B3PW91 using large basis sets. PDDG/PM3 and PM3′ also give improved binding energies for complexes involving halide anions, which are competitive with B3LYP/6-311++G(d,p) results. Among the semiempirical methods studied, PDDG/PM3 generates the best agreement with high-level ab initio G2 and CCSD(T) intrinsic activation energies for S_N2 reactions involving methyl halides and halide anions.

128.
RATIONAL DEVELOPMENT OF A LONE PAIR INCLUSIVE FORCE FIELD. ***Sarah M Tschampel**, Department of Chemistry, Complex Carbohydrate Research Center, 220 Riverbend Road, Athens, GA 30602, tschampe@chem.uga.edu, and Robert J. Woods, Complex Carbohydrate Research Center, University of Georgia*

In 2001, the TIP5P water model demonstrated that inclusion of lone-pairs resulted in better reproduction of cluster and bulk water properties than its predecessors without lone-pairs. At present, models for solute and solvent have developed parameters for lone-pairs utilizing different methodologies. Therefore, it is not clear that they are compatible and the development of a transferable model is advantageous. Quantum electrostatic-potentials were calculated utilizing the CHELPG scheme for a test-set of molecules. Using RESP, partial-charges were then computed while varying the LP-O length, leading to the best fit between classical and quantum electrostatic potentials. Notably, all structures yielded a best fit at an LP-O distance of about 0.70Å, which agrees with the LP-O distance used in the current version of the TIP5P model. Therefore, the modified charge fitting scheme is consistent with the empirical TIP5P lone-pair arrangement and will be used to generate partial charges for biomolecular simulations with AMBER.

129.
CH/π INTERACTIONS BETWEEN ETHENE AND AROMATIC AMINO ACIDS. ***Alba T. Macias**, School of Pharmacy, University of Maryland, 20 North Pine Street, Baltimore, MD 21201, Fax: 410-706-0346, alba@outerbanks.umaryland.edu, and Alexander D. MacKerell Jr., School of Pharmacy, University of Maryland, Baltimore*

Cation-π and CH/π interactions have been shown to be important interactions between aromatic amino acids and unsaturated lipids. High level ab-initio calculations have been carried out in order to study the weaker CH/π interactions. The binding energies between ethene (and 2-butene) with a series of model compounds representing the amino acids (benzene, indole, imidazole, phenol) have been calculated in a variety of orientations using the MP2/cc-pVTZ level of theory. Binding energy profiles as a function of distance have been calculated and compared to the binding energy profiles obtained with CHARMM.

130.
DEVELOPMENT OF NEW CHARMM FORCE FIELD PARAMETERS FOR NOVEL DNA BENDING AGENTS. ***Anne Loccisano**, Center for Computational Sciences, Duquesne University, Department of Chemistry and Biochemistry, 600 Forbes Avenue, Pittsburgh, PA 15282, Fax: 412-396-5683, aloccisano@hotmail.com, Steven M. Firestine, Graduate School of Pharmaceutical Sciences, Duquesne University, and Jeffrey D. Evanseck, Department of Chemistry & Biochemistry and Center for Computational Sciences, Duquesne University*

Bending of DNA by external agents has been attributed previously to groove widening or contraction either by steric or ionic interactions. We are interested in the development of sequence-specific agents that bind to and bend DNA by minor groove distortions. These agents are polyamide-based drugs that bind in a 1:1 or 2:1 complex with DNA, and they contain sterically bulky groups that widen the minor groove of DNA. In order to evaluate the sequence specificity and the ability to bend DNA, force field parameters for the new molecules have been created for the CHARMM force field in order to perform molecular dynamics simulations with DNA and the bending agents. The new parameters have been created by comparing available experimental data and computed quantum mechanical information. The information gained from simulations of these molecules with DNA will provide a detailed picture of how these molecules bend DNA.

131.
DNA BENDING BY UNNATURAL GUANINE NUCLEOTIDES. ***Sarah A. Mueller-Stein**, Department of Chemistry and Biochemistry, Center for Computational Sciences, Duquesne University, 600 Forbes Avenue, Pittsburgh, PA 15282, Fax: 412-396-5683, mueller971@duq.edu, Steven M. Firestine, Graduate School of Pharmaceutical Sciences, Duquesne University, and Jeffrey D. Evanseck, Department of Chemistry & Biochemistry and Center for Computational Sciences, Duquesne University*

A computational and experimental approach has been undertaken to investigate the hypothesis that small but sterically bulky molecules cause DNA bending. A 24-bp oligonucleotide has been generated using the CHARMM program. One internal guanine residue has been covalently modified with a bulky group such as adamantanamine, t-butylamine, and methylamine. Parameters for the covalently modified guanine residues were developed. Four 1 ns trajectories have been collected. Starting positions and velocities have been varied in order to sample aggressively the conformational space of modified and unmodified oligonucleotides. Helical parameters have been determined using the Curves program. Important conformational changes related to bending in the modified oligonucleotides have been determined using multivariate analysis methods such as principal coordinate analysis. Experimentally, the oligonucleotides have been synthesized and bending will be analyzed through gel migration assays and fluorescence studies.

132.
MOLECULAR DYNAMICS SIMULATION OF RETINOIC ACID RECEPTORS/RETINOIDS. ***Amy Marie Waligorski**, Center for Computational Sciences, Duquesne University, Department of Chemistry and Biochemistry, 600 Forbes Avenue, Pittsburgh, PA 15282, Fax: 412-396-5683, waligor805@duq.edu, Wilson S. Meng, Division of Pharmaceutical Sciences, Duquesne University, and Jeffrey D. Evanseck, Department of Chemistry & Biochemistry and Center for Computational Sciences, Duquesne University*

Retinoic acid (RA) and some synthetic retinoids (Vitamin A derivatives) have shown promise for the treatment and prevention of several cancers. Retinoic acid receptors (RARs), and cellular retinoic acid-binding proteins (CRABPs) are two classes of proteins that play roles in mediating the biological effects of retinoic acid (RA). The exact mechanism by which these proteins interact with retinoids in order to invoke an immune response is not known. The CHARMM program was used in order to conduct molecular dynamics simulations of these complexes. First, new force field parameters were developed which are consis-

tent with structural, vibrational, and energetic data of retinoids. Molecular dynamics simulations were then carried out which involved CRABP I/RA in a periodic water box. Several key interactions have been identified and found to be responsible for the differential binding between RA and fenretinide.

133.
CALCULATION OF THE BINDING AFFINITY OF β-SECRETASE INHIBITORS USING THE LINEAR INTERACTION ENERGY METHOD. ***Brett A. Tounge***, *and Charles H. Reynolds, Computer Assisted Drug Discovery, Johnson & Johnson Pharmaceutical Research and Development, L.L.C, Welsh & McKean Roads, P.O. Box 776, Spring House, PA 19477, Fax: 215-628-4985, btounge@prdus.jnj.com*

It has been shown that the rate-limiting step in the production of β-amyloid peptide (Aβ) is the proteolytric cleavage of the membrane-bound β-amyloid precursor protein (APP) by β-secretase (BACE). Since the accumulation of Aβ has been implicated as one of the key events in the progression of Alzheimer's disease, BACE has become an important therapeutic target. Recently, two crystal structures of BACE co-crystallized with the inhibitors OM99-2 and OM00-3 were published by Tang and coworkers. In addition, the Ghosh group has published binding data on a series of inhibitors based on their initial lead, OM99-2. Using this set as a basis, we have developed a model for the binding affinity of these ligands to BACE using the Linear Interaction Energy (LIE) method. The best binding affinity model for the full set of ligands had a RMSD of 1.10 kcal/mol. The best model excluding the two charged ligands had a RMSD of 0.87 kcal/mol.

134.
STRUCTURE-BASED DESIGN OF STATINE ANALOGS AS BACE1 INHIBITORS. ***Kristi Yi Fan***[1]*, Baihua Hu*[1]*, Derek Cole*[1]*, Kristie Bridges*[1]*, Rajiv Chopra*[1]*, Eric S Manas*[1]*, Alan Katz*[1]*, Juan C. Alvarez*[1]*, Frank E. Lovering*[1]*, Ping Zhou*[1]*, Guixian Jin*[1]*, Rebecca Cowling*[1]*, and Jonanthan Bard*[2]*. (1) Chemical and Screening Sciences, Wyeth Research, CN8000, Princeton, NJ 08543, Fax: 732-274-4292, fank@wyeth.com, (2) Neurosciences, Wyeth Research*

beta-secretase (BACE) is a membrane-associated aspartic acid protease that cleaves the beta-amyloid precursor protein (APP) and generates the amino-terminus of Abeta, a key step in the pathogenesis of Alzheimer's disease. BACE1 is generally considered one of the promising targets for an Alzheimer's therapy. We describe a structure-based peptidomimetic approach to identify novel structural scaffolds. Based on the available and in-house X-ray structures of BACE1 in complex with peptide inhibitors, we have explored the BACE1 active site using the GRID computer program, as well as virtual screening. As a result, we have obtained insights into the structural requirements that are essential for binding. This information was used in the generation of PEPSCAN (Spot Synthesis) libraries that identified an initial lead with an IC50 of 0.5 uM in the BACE1 FRET assay. Further modification via both conventional medicinal chemistry and a structure-based combinatorial approach produced a new lead with an IC50 of 21 nM. Further drug design efforts were carried out to improve the drug-like properties of this lead.

135.
BIOINFORMATICS AND STRUCTURAL BIOINFORMATICS ANALYSES OF GALECTIN LIGAND BINDING SPECIFICITIES AND ITS IMPLICATION IN DEVELOPING TARGET SPECIFIC PHOTODYNAMIC THERAPY AGENTS. ***Ting-Hsiu Liu***[1]*, **Tin-Chun Chu***[1]*, Masayuki Shibata*[1]*, Thomas J. Dougherty*[2]*, and Ravindra K. Pandey*[3]*. (1) Biomedical Informatics, University of Medicine and Dentistry of New Jersey - School of Health Related Professions, 65 Bergen Street, SSB-Rm350, Newark, NJ 07107-3001, Fax: 973-972-1054, (2) Photodynamic Therapy Center, Roswell Park Cancer Institute, (3) PDT Center and Department of Nuclear Medicine, Roswell Park Cancer Institute*

Specific recognition of a variety of carbohydrate moieties by various proteins is the foundation for many biological processes including the blood type specificity, immunological responses and regulation of cell growth. Better understanding of the molecular mechanisms responsible for the specificity of carbohydrate binding proteins is one of the active research area in emerging glycomics. The galectins are the family of animal lectins, which bind specifically to β- galactoside moiety of oligo-saccharides. Both standard bioinformatics approach through the multiple sequence analyses and the phylogenetic analyses of galectins, as well as, structural bioinformatics approach including multiple structure alignments of available crystal structures are applied to examine molecular basis of specific recognition process. The results lead to the similarity/difference in sequences and 3D structures of galectins, which will be exploited for the design of the target specific photodynamic therapy agents. We gratefully acknowledge the National Institutes of Health (NIH CA 55791) for financial support of this research.

136.
CURARIFORM ANTAGONISTS BIND IN DIFFERENT ORIENTATIONS TO ACETYLCHOLINE BINDING PROTEIN. ***Fan Gao***, *Bren Nina, Alicia Little, Hai-Long Wang, and Steven M. Sine, Dept. of Physiology & Biophysics, Mayo Clinic, Receptor Biology Lab, Mayo Clinic, Rochester, MN 55905, gao.fan@mayo.edu*

Acetylcholine binding protein (AChBP) recently emerged as a prototype for studying structure and function of the ligand binding domain of nicotinic acetylcholine receptors (nAChRs). To understand interactions of competitive antagonists at the atomic structural level, we studied binding of the curare derivatives d-tubocurarine (d-TC) and metocurine to AChBP using computational methods, mutagenesis and ligand binding measurements. To account for protein flexibility, we employed a 2 ns molecular dynamics simulation of AChBP by using AMBER 7 to generate multiple snapshots of the equilibrated dynamic structure to which optimal docking orientations were determined by AUTODOCK 3.0.3. Our results predict a predominant docking orientation for both d-TC and metocurine, but unexpectedly, the bound orientations differ fundamentally for each ligand. Mutagenesis of binding site residues in AChBP, combined with measurements of ligand binding, confirms the different docking orientations. Thus structurally similar ligands can adopt distinct orientations at receptor binding sites, posing challenges for interpreting structure-activity relationships for many drugs.

137.
STRUCTURE-BASED DRUG DESIGN USING KNOWLEDGE-BASED POTENTIALS. ***Brian N. Dominy***, *Department of Chemistry and Chemical Biology, Harvard University, 12 Oxford Street - Box 79, Cambridge, MA 02138, dominy@fas.harvard.edu, and Eugene I. Shakhnovich, Chemistry and Chemical Biology, Harvard University*

An intense debate on the rigor of knowledge-based potentials has resulted in both demonstrations and derivations showing that pairwise potentials of mean force can't be extracted from the Protein Data Bank (PDB). In this study, we attempt to address the theoretical limitations of knowledge-based potentials and develop a method to extract approximate potentials of mean force from the PDB. The method utilizes an information theoretic approach to define particle types within the PDB in order to generate a canonical-like distribution from which approximate potentials of mean force may be extracted. This technique optimally balances the amount of information extracted from the data bank with the precision of the resulting potential. The method has been integrated into the SMoG drug design package, resulting in an improved approach for the rapid and accurate estimation of binding affinities from structural information.

138.
CONSTRUCTION AND SIMULATION MODELING OF *MYCOBACTERIUM TUBERCULOSIS* CELL WALLS. ***Xuan Hong***, *and A.J. Hopfinger, Laboratory of Molecular Modeling and Design, MC/781, College of Pharmacy, University of Illinois at Chicago, 833 South Wood Street, Chicago, IL 60612-7231, Fax: 312-996-7107, xhong1@uic.edu*

Mycobacterium tuberculosis is the leading cause of death worldwide from an infectious agent. Data suggests that intrinsic drug resistance is in part due to the low permeability of the cell wall. The mycobacterial cell wall is composed of an asymmetric lipid bilayer. The inner leaflet contains mycolic acids that are tightly packed and covalently linked to arabinogalactan. This inner leaflet is believed to have the lowest permeability of the overall cell wall. In this study, by using conformational search and molecular dynamics simulation, we (1) studied the conformation and physical organization of the mycolic acid – arabinogalactan complex, (2) built an inner leaflet model and (3) investigated the permeability of the inner leaflet, using a variety of organic solutes. The results show that more consideration should be given to the shape, size and polarity of molecules for inner leaflet transport in the future design of antituberculosis drugs.

139.

MOLECULAR MODELING OF INTEIN STRUCTURE. *Eric Storm,* ***Parbati Biswas****, Shekhar Garde, and Georges Belfort, Department of Chemical Engineering, Rensselaer Polytechnic Institute, 110 8th Street, Troy, NY 12180-3590, storme@rpi.edu, biswap@rpi.edu*

Inteins are autocatalytic self-splicing proteins that naturally occur as internal interruptions in a variety of host proteins. Following translation of the host protein-intein precursor sequence, the intein excises itself and ligates the flanking host protein segments to form the native host protein and the released intein segment. The underlying principles of this splicing reaction are complex and are determined by various reaction conditions such as temperature, pH as well as the amino acid residues in the vicinity of the splice junction. The three-dimensional structure and dynamics of the amino acids are crucial in understanding the molecular mechanism and energetics of this reaction. The crystal structure of intein is thus a critical input for molecular modeling and molecular dynamics calculations. To this end, we model a plausible structure for the Cleavage Mutant (CM) intein that is of considerable experimental interest. Crystal structures for three different inteins are available to date. In an attempt to establish the structure of the CM intein, we propose a model of the intein structure based on sequence overlaps among the available structures. This is performed with BLAST sequence search method. We then perform sequential and rational mutation of the homologue to obtain the likely structure. As MxeGyrA intein is similar to CM intein in sequence space, we simulate MxeGyrA intein in water. Using molecular dynamics, we mutate the selected sites and relax the mutated structure in water. This process is sequentially performed till the correct sequence of the CM intein is obtained. The molecular dynamics simulation of MxeGyrA intein in water may also provides some insight into the splicing mechanism.

140.

COMPREHENSIVE PHARMACOPHORE ANALYSIS: APPLICATION TO HIV NNRTI. ***Kenichi Torikoshi***[1]*, Shirley Louise-May*[1]*, Gerald Vigliotti*[2]*, Christopher Marlor*[2]*, Douglas Buechter*[2]*, Milind Deshpande*[3]*, and Atul Agarwal*[1]*. (1) Computational Chemistry and Informatics, Achillion Pharmaceuticals, Inc, 300 George Street, New Haven, CT 06511, Fax: 203-752-5454, ktorikoshi@achillion.com, (2) Exploratory Biological Screening, Achillion Pharmaceuticals, Inc, (3) Chemistry, Achillion Pharmaceuticals, Inc*

Pharmacophore analysis is the method of choice for drug design and three-dimensional data mining in situations where target:ligand complex structure is yet to be determined. A pharmacophore analysis program is desired that can efficiently analyze a flexible and congeneric or non-congeneric set of ligands and present a common binding motif. We have developed a method focusing on pre and post processes while retaining the fundamental concept of pharmacophore analysis. Our method utilizes explicit three dimensional structures including conformational flexibilities of ligands. Potential target:ligand interaction sites are marked in the conformational libraries and used to enumerate a combinatorial set of pharmacophore hypotheses. The biologically relevant pharmacophore(s) are identified by systematically applying a sequence of local and global properties criteria to the pharmacophore hypotheses. We demonstrate our comprehensive pharmacophore analysis method by using the HIV NNRTI data set and discuss several key steps in the sequence of our post processing analysis.

141.

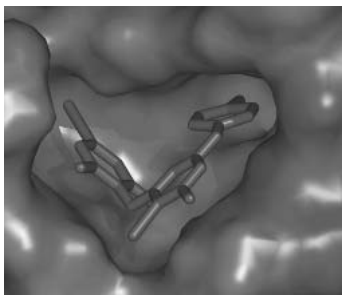
COMBINATION OF RECEPTOR-BASED AND LIGAND-BASED DRUG DESIGN: APPLICATION IN 3D-QSAR OF HIV-1 RT NON-NUCLEOSIDE INHIBITORS. ***Zhigang Zhou****, and Jeffry D. Madura, Department of Chemistry & Biochemistry, Center for Computational Sciences and Duquesne University, 600 Forbes Av, Mellon Hall 320, Pittsburgh, PA 15282, Fax: 412-396-5683, zhou7454@duq.edu*

3D-QSAR is normally constructed from the structural and/or physic properties (3D) of ligands. The ligand-based approach provides important information on ligand design. Meanwhile receptor-based modeling provides an insight of interaction model of a ligand in it receptor. They both benefit rational drug design. In this work, we combined receptor-based modeling with ligand-based modeling to study 3D-QSAR of a set of non-nucleoside RT inhibitors: TIBO derivatives. The "active" conformation of ligands in RT and molecular alignment were performed using flexible docking according the binding site of RT and the 3D-QSAR models which demonstrate good ability to predict activity of studied compounds, were constructed using CoMFA. The results demonstrate that combination of ligand-based and receptor-based modeling is a powerful approach to build 3D-QSAR models.

142.

VALIDATION OF A MODEL FOR THE COMPLEX OF HIV-1 REVERSE TRANSCRIPTASE WITH NON-NUCLEOSIDE INHIBITOR TMC125. ***Marina Udier-Blagovic****, Julian Tirado-Rives, and William L. Jorgensen, Department of Chemistry, Yale University, P.O.Box 208107, New Haven, CT 06520, Fax: 203-432-6144, marina.udier@yale.edu*

The structure for the complex of non-nucleoside inhibitor TMC125 and HIV-1 reverse transcriptase has been determined and validated through computation of resistance profiles using Monte Carlo/Free Energy Perturbation calculations. The good quantitative agreement between the computed and experimental anti-HIV activities for TMC125, nevirapine and efavirenz with wild-type RT and four commonly selected mutants (L100I, K103N, Y181C, and Y188L) confirms the correctness of the predicted structure and provides insights into the improved potency of this novel NNRTI. Balanced flexibility, which permits an inhibitor to accommodate changes in the binding pocket by small conformational adjustments, while retaining favorable specific interactions, is key to the design of antiviral therapeutics that remain active against microbial mutants.



143.

TARGETING THE DISRUPTION OF HIVGP41 MEDIATED CELL MEMBRANE FUSION: DOCKING AND MM-GB/PBSA STUDIES. ***Robert C. Rizzo****, Miriam Gochin, and I.D. Kuntz, Department of Pharmaceutical Chemistry, University of California at San Francisco, Genentech Hall, 600 16th Street, Box 2240, San Francisco, CA 94143-2240, rizzo@francisco.compchem.ucsf.edu*

Cell membrane fusion events during HIV infection are mediated by viral envelope proteins gp120 and gp41. Crystallographic studies of the core domain of HIVgp41 have revealed a hairpin structure (fusion-active) in which three outer C-helices loop and wrap around three inner N-helices. Peptides based on the outer C-helices have been reported which target a proposed pre-hairpin intermediate and disrupt formation of the fusion-active state thereby inhibiting cell membrane fusion. We are using the DOCK suite of programs to virtually screen compounds from the National Cancer Institute, targeting a highly conserved hydrophobic pocket formed at the interface of the gp41 N-helices. For each docked compound, the fifty best scoring complexes are ranked, clustered, and re-ranked using MM-PBSA and MM-GBSA calculations to include estimates of desolvation. The most favorable re-ranked compounds will be tested for the ability to bind to a gp41 pre-hairpin model using fluorescence and NMR-based assays.

144.

EVALUATION OF STRATEGIES FOR MOLECULAR DOCKING. ***Daniel Cheney****, and* ***Luciano Mueller****, Department of Macromolecular Structure, Bristol Myers Squibb Pharmaceutical Research Institute, Princeton, NJ 08543-4000, Fax: 609-818-3545, cheneyd@bms.com, luciano.mueller@bms.com*

Flexible docking is a critically important tool for hit identification, and binding mode prediction. Moreover, flexible docking is expected to play an increasing role in de novo drug design and lead optimization. Multiple docking programs have been developed in various laboratories, each employing strategies of varying uniqueness in terms of sampling and scoring. While considerable improvements in several docking programs have been reported, problems persist in scoring energies, inclusion of solvation effects and conformational flexibility, as well as ligand-induced pKa shifts in protein residues. In this study, the relative performance of several docking programs is examined across a range of proteins and ligand chemotypes. Specifically, the effects of ligand

induced variations in the binding site structure is investigated by performing ensemble docking against representative ensembles of protein structures. The effects of crystal water molecules and variation of ionization states of polar residues in the ligand binding cavities are assessed.

145.
RESCALING OPTIMIZATION: APPLICATIONS TO FLEXIBLE LIGAND DOCKING. ***Ebru Demet Akten***, *Chemistry, Scripps Research Institute, San Diego, CA 92121, and Jianwei Che, Computational Discovery, Genomics Institute of the Novartis Research Foundation*

We apply a newly developed rescaling optimization method to flexible ligand docking on a set of receptor ligand complexes with known binding sites. The receptor field is modeled by energy grids consisting of electrostatic, hydrogen bonding, and van der Waals interactions. Ligand molecules are represented by hierarchical clusters using internal coordinates. Each ligand conformation is generated by Monte Carlo sampling of torsion angles and then minimized in the receptor field using our rescaling optimization method. With bond lengths and angles held as constants during optimization, we are able to obtain successful docking results as a result of improved efficiency and accuracy of the optimization method.

146.
ENRICHMENT OF HIGH-THROUGHPUT DOCKING RESULTS USING NAIVE BAYES. ***Anthony E. Klon***[1], *Meir Glick*[1], *Mathis Thoma*[2], *Pierre Acklin*[1], *and John W. Davies*[1]. *(1) Lead Discovery Center, Novartis Institutes for Biomedical Research, 100 Technology Square, Cambridge, MA 02142, anthony.klon@pharma.novartis.com, (2) Information and Knowledge Management, Novartis Institutes for Biomedical Research*

The technique of high-throughput docking (HTD) is commonly utilized in the drug discovery process. However, the ability to accurately rank compounds using a scoring function remains problematic. Here we show that by employing a simple machine learning method (Naïve Bayes) it is possible to significantly improve the ranking of compounds. Four protein targets were docked using three software packages; Dock, FlexX and Glide. For each target, known active compounds and the Available Chemical Database (ACD) were evaluated. In cases where HTD alone was able to produce enrichment of known actives, the application of Naïve Bayes was able to significantly improve upon the enrichment. The application of the Naïve Bayes classifier to enrich HTD results can be carried out without any a priori knowledge about the active compounds. The methodology results in superior enrichment of known actives compared to the use of HTD scoring or consensus scoring methods alone.

147.
MOLECULAR DOCKING FOR GENERATING PEPTIDES AND PEPTIDO-MIMETICS INHIBITORS FOR THROMBIN AND FACTOR XA. ***Cristina C. Clement***, *Chemistry Department, City University of New York, Lehman College, 365 Fifth Avenue, New York City, NY 10016, cclement_us@yahoo.com, Manfred Philipp, 365 Fifth Avenue, City University of New York, Lehman College, and Julian Gingold, New Rochelle High School*

This investigation is focused on discovery of peptides and peptido-mimetics that reversibly inhibit thrombin and Factor Xa. The experimental approach combines molecular docking using "Sculpt" provided by "MDL" and chemical synthesis of the candidate compounds using standard F-moc chemistry and an automatic solid phase synthesizer. Initial molecular docking experiments were used to generate a candidate group of compounds (with both L- and D- amino acids) that were characterized by a predicted free energy of interaction with thrombin or Factor Xa ranging from -20 to -100 kcal/mol. The thrombin candidate inhibitors were selected from two classes of sequences 1-DPhe-Pro-Arg-dPro-P2′-P3′- and 2-dPhe-Pro-dArg-P1′-P2′). Both the use of D-Pro in the P1′ Position and the use of D-Arg instead of Arg in the P1 Position is expected to inhibit the hydrolysis of peptides, allowing these sequences to function as inhibitors for thrombin. Peptido-mimetics were designed by maintaining constant the P2, P1, and P1′ in the leads but varying P3 position with Phe analogs like trans-cinnamic acid and dihydrocinnamic acid. Similar docking experiments were performed for generating peptide libraries with inhibitory potential for Factor Xa, were peptides were selected from the sequence space Ile-Glu-DArg-X. The results are discussed with respect to the structural determinants that are involved in predicting the best binding affinity between peptides and thrombin or Factor Xa.

148.
OPTIMIZATION OF DOCK FOR RNA TARGETS. ***P. Therese Downing***[1], *Veena L. Thomas*[2], *Thomas L. James*[3], *and I.D. Kuntz*[3]. *(1) Chemistry and Chemical Biology, UCSF, Genentech Hall, 600 16th Street, San Francisco, CA 94143, terry@francisco.compchem.ucsf.edu, (2) Pharmaceutical Sciences and Pharmacogenomics, University of California at San Francisco, (3) Department of Pharmaceutical Chemistry, University of California at San Francisco*

With the identification of RNA molecules as potential therapeutic targets, there is a need to develop, optimize, and apply theoretical techniques that will help facilitate the drug design process. As a class, RNA presents a difficult computational challenge because of its high charge density. Therefore, we are optimizing the portions of the procedure in the DOCK suite of programs that calculate electrostatics, including solvation, partial charges, and scoring function. The utility of each of these modifications is examined for the ability to recreate experimental structures using a test set of RNA-ligand complexes. If successful, these procedural modifications will be applied to designing novel inhibitors of RNA targets.

149.
DOCKING STUDIES OF PEPTIDE/HLA-A2.1 COMPLEXES. ***Tugba Gul Kucukkal***[1], *Wilson S. Meng*[2], *and Jeffrey D. Evanseck*[1]. *(1) Department of Chemistry & Biochemistry and Center for Computational Sciences, Duquesne University, 600 Forbes Avenue, Pittsburgh, PA 15282, Fax: 412-396-5683, tugbakucukkal@yahoo.com, (2) Division of Pharmaceutical Sciences, Duquesne University*

HER2/neu is a transmembrane glycoprotein that is overexpressed in many tumors, including ovarian and breast cancers. The HER2/neu peptide IISAVVGIL (GP2) is recognized by tumor-specific cytotoxic T lymphocytes in the context of the human class I major histocompatibility complex (MHC) molecule HLA-A2.1. One limiting-factor for using this peptide as a tumor vaccine is its poor affinity for HLA-A2.1. Although it has the correct peptide-binding motif, it still binds poorly. The aims of this computational research are to develop a practical and accurate docking method to investigate the binding of GP2 and other ligands to HLA-A2.1, and to predict the new mutations for GP2 that could lead to new tumor vaccines. The docking calculations have been performed on peptide/HLA-A2.1 complexes utilizing Autodock3.0 and GOLD. The efficiencies of these docking programs for peptide/HLA-A2.1 complexes have been compared. In addition, the effects of different parameters on the docking results have been investigated systematically.

150.
DOCKING STUDIES OF THE ORPHAN NUCLEAR RECEPTOR LRH-1 : A POTENTIAL TARGET FOR TISSUE SPECIFIC CANCER THERAPY. ***Tiba Aynechi***, *Graduate Group in Biophysics, University of California, San Francisco, Genentech Hall, 600 16th Street, N474, Box 2240, San Francisco, CA 94143-2240, Fax: 415-476-1410, tiba@francisco.compchem.ucsf.edu, Holly A. Ingraham, Department of Physiology, Univeristy of California, San Francisco, and I.D. Kuntz, Department of Pharmaceutical Chemistry, University of California at San Francisco*

Estrogen synthesis from C19 steroids is catalyzed by the aromatase cytochrome P450 enzyme encoded by the CYP19 gene. Elevated levels of estrogen, aromatase activity, and CYP19 expression have been found in breast cancer adipose tissue. The liver receptor homologue-1 (LRH-1), an orphan nuclear receptor, is a known transcription factor for CYP19 and is expressed in high levels in undifferentiated human adipose tissue. Thus, regulation of LRH-1 can serve as a tissue specific mechanism for regulating CYP19 in breast cancer cells. We are using DOCK and other computational structure-based design tools to screen a database of 1200 hormone and steroid analogs, assembled from the Available Chemicals Directory, to find ligands compatible with the LRH-1 receptor. Favorably docked compounds are rescored using the MM-PB/SA method to account for desolvation. Compounds are clustered and the top 50 cluster heads will be ordered for experimental assay.

151.
ANALYSIS OF CONFORMATIONAL FAMILIES OF ANALOGS OF GBR 12909.
*Carol A. Venanzi[1], **Deepangi Pandit**[1], Milind Misra[1], Kathleen M. Gilbert[1], Dorota Matecka[2], Thomas Prisinzano[2], and Kenner C. Rice[2]. (1) Department of Chemistry and Environmental Science, New Jersey Institute of Technology, 323 King Boulevard, Newark, NJ 07102, Fax: 973-596-3596, venanzi@adm.njit.edu, dnp5@njit.edu, (2) Laboratory of Medicinal Chemistry, NIDDK, DHHS, National Institutes of Health*

GBR analogs are an important class of dopamine reuptake inhibitors that appears to be useful in the treatment of cocaine abuse. As the first step in the modeling of a pharmacophore for binding to the dopamine transporter, we carry out random search conformational analysis to locate local minima on the potential energy surface of the molecules. We explore various ways of identifying conformational families with the long-term goal of using a representative conformer from each family as a template for Comparative Molecular Field Analysis of a series of GBR analogs. Here we compare the conformational potential energy surface of four GBR 12909 analogs in order to investigate the effect of side chain length and piperazine versus piperidine ring on the accessible molecular conformations. Similarities to methylphenidate conformations are identified.

152.
CONFORMATIONAL ANALYSIS OF METHYLPHENIDATE.
*Carol A. Venanzi[1], **Kristina A. Paris**[1], Neelam H. Naik[1], Kathleen M. Gilbert[1], William J. Skawinski[1], and Howard M. Deutsch[2]. (1) Department of Chemistry and Environmental Science, New Jersey Institute of Technology, 323 King Boulevard, Newark, NJ 07102, Fax: 973-596-3596, venanzi@adm.njit.edu, kaparis22@yahoo.com, (2) School of Chemistry and Biochemistry, Georgia Institute of Technology*

Methylphenidate binds to the cocaine binding site on the dopamine transporter and prevents reuptake of dopamine, but does not appear to have the same abuse potential as cocaine. This study, part of a comprehensive effort to identify a drug treatment for cocaine abuse, investigates the effect of solvent on the conformational energy of methylphenidate. Conformational analysis was carried out by the AM1, AM1/SM5.4, molecular mechanics, and ab initio methods. Both neutral and protonated methylphenidate and rigid analogues of methylphenidate were studied. Graphical analyses of the conformational energies suggest a more significant effect of solvent on the protonated analogues and on analogues in which the nitrogen is in close proximity to the phenyl ring. This work was supported in part by NIH grant DA11541.

153.
APPLICATION OF A COARSE-GRAINED DYNAMICAL METHOD TO EXPLORE THE CONFORMATIONAL SPACE OF SMALL MOLECULES.
***Yudong Wu**[1], Philip S. Hammond[2], Todd J. Minehardt[3], Jeffrey D. Schmitt[2], and Roberto Car[1]. (1) Department of Chemistry, Princeton University, Washington Road and William street, Princeton, NJ 08540, yudongwu@princeton.edu, (2) Molecular Design, Targacept, Inc, (3) Department of Chemistry, The University of Colorado at Denver*

Understanding the conformational potential energy surface (PES) of small organic molecules is of interest to numerous research disciplines. Laio and Parrinello have recently devised a coarse-grained dynamical method that can be used to explore global PES. (A. Laio and M. Parrinello, PNAS 2002, 99:12562-12566) This formalism - metadynamics - relies on identifying key order parameters that are used to guide the microdynamics of the system. If the PES for a small organic system is described as a function of a limited number of torsional degrees of freedom, the resulting PES is relatively smooth and may be explored in an efficient manner. We have employed metadynamics (the Cornell et al. 1994 AMBER force field was utilized for microdynamics) to quantify the accessible conformational space of nicotine and methylphenidate, both compounds of biological importance. Our results demonstrate that this coarse-grained method can explore conformational space efficiently.

154.
HOW THE MEMBRANE RETENTION OF IN VITRO PERMEABILITY AFFECTS PRECISION/ACCURACY OF IN SILICO PERMEABILITY PREDICTION.
*Saeho Chong[1], **Litai zhang**[2], Stephen R Johnson[2], and Terry R Stouch[2]. (1) Discovery Chemistry and Metabolic and Cardiovascular Drug Discovery, Bristol-Myers Squibb Pharmaceutical Research Institute, Princeton, NJ 08543-5400, saeho.chong@bms.com, (2) Computer-Assisted Drug Design, Bristol-Myers Squibb, Box 4000, Princeton, NJ 08543, litai.zhang@bms.com*

Two of the most popular in vitro permeability/absorption models used today are Caco-2 cells and PAMPA (artificial lipid membrane). Caco-2 cells are derived from a human colon carcinoma and undergo spontaneous enterocytic differentiation in cell culture and resemble small intestinal epithelial cells. PAMPA is a non-cell based lipid membrane filter also mimicking intestinal epithelium. Permeability calculated by the rate of passage of compounds through either the Caco-2 cell monolayer or lipid membrane layer can be related to the extent of in vivo absorption in man. Computational modeling of in vitro permeability data has been difficult despite the seeming simplicity of these in vitro systems. This presentation will focus on these assays and discuss potential sources of experimental error which may contribute to the difficulty correlating computational prediction to experimental results. Particularly, the role of extensive membrane retention (viz.: poor recovery) will be discussed in detail.

155.
MOLECULAR MODELING OF THE CHEMOKINE RECEPTOR CCR5 AND ITS SMALL MOLECULE ANTAGONISTS AS ANTI-AIDS THERAPEUTICS.
***Minghu Song**, Curt M Breneman, and N Sukumar, Department of Chemistry, Rensselaer Polytechnic Institute, 110 8th Street, Troy, NY 12180, Fax: 518-276-4887, songm@rpi.edu*

Recent studies have shown that the CC Chemokine receptor CCR5 plays a critical role in the invasion of HIV-1 virus into white blood cells. This discovery has motivated intensive efforts for the development of small molecule CCR5 antagonists as a new class of anti-HIV therapeutics. To further explore the receptor-antagonist interaction at the atomic level, in the present study, a three-dimensional (3D) model of the CCR5 receptor was initially constructed by means of a homology modeling approach. Molecular dynamics (MD) simulation was then performed to obtain a set of refined 3D coordinates for the CCR5 receptor. Recently published CCR5 antagonists with potent anti-HIV activity were chosen as sample ligands for the subsequent docking studies. The final protein coordinates of the CCR5 receptor could then be obtained by removing the bound ligand from the energy-minimized complex. Once the homology-based receptor models are validated experimentally using site-directed mutagenesis or other approaches, they could be used as structure-based targets to virtually screen a library of potential candidate compounds. In addition to the above structure-based drug design approach, 3D Quantitative Structure-Activity Relationship (QSAR) studies were also conducted on a series of piperidine-based CCR5 antagonists using comparative molecular field analysis (CoMFA) and comparative molecular similarity indices analysis (CoMSIA) techniques. These ligand-based 3D QSAR models as well as a derived 3D structural model of CCR5 can provide new insights into the physicochemical factors crucial for CCR5 receptor-antagonist binding, and in turn can be used to guide the rational design of potential anti-viral drugs.

156.
SODIUM CHANNEL DESIGN LIBRARIES FROM MINING TO NOVEL COMPOUNDS: A PHARMACOPHORE-BASED APPROACH.
***Toan B. Nguyen**, Informatics and Modeling, ArQule, Inc, 19 Presidential Way, Woburn, MA 01801, Fax: 781-376-6019, tnguyen@arqule.com*

Sodium channels are players in signal transduction and amplification, and are the targets of anaesthetic drugs and neurotoxins. To identify and expand Sodium channel-motif in ArQule's corporate database a mining strategy based upon pharmacophore approach was pursued to confirm 11.5 percent hit rates. Novel chemotypes were designed and tested in vitro and in vivo studies.Results will be presented.

157.

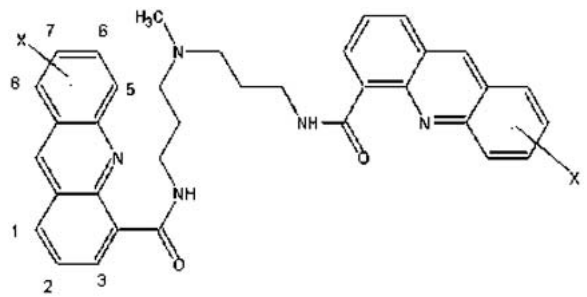
PRELIMINARY PHARMACOPHORE MODEL FOR METHYLPHENIDATE CLASS OF DOPAMINE REUPTAKE INHIBITOR. *Carol A. Venanzi[1], **Milind Misra[1]**, **Kathleen M. Gilbert[1]**, Ronald A. Buono[1], Margaret M. Schweri[2], Qing Shi[3], and Howard M. Deutsch[3]. (1) Department of Chemistry and Environmental Science, New Jersey Institute of Technology, 323 King Boulevard, Newark, NJ 07102, Fax: 973-596-3596, venanzi@adm.njit.edu, mxm0528@njit.edu, kxg2248@njit.edu, (2) School of Medicine, Mercer University, (3) School of Chemistry and Biochemistry, Georgia Institute of Technology*

Methylphenidate (MP) affects the reuptake of dopamine by binding to the cocaine binding site on the dopamine transporter (DAT), but does not appear to have the same abuse potential as cocaine. Data from structure-activity studies of methylphenidate analogues may be useful in identifying a pharmacophore for DAT binding, and, ultimately, a drug that could be useful in the treatment of cocaine abuse. Random search conformational analysis was carried out on both neutral and protonated MP to locate conformational minima. These were divided into 10 conformational families and a template conformer from each was selected for Comparative Molecular Field Analysis (CoMFA). Separate CoMFA studies were carried out on both neutral and protonated MP and 29 analogues with phenyl ring substituents. Most of the CoMFA studies gave predictive models with q**2 greater than 0.5. To distinguish between these models, a rigid analogue of methylphenidate (R-MP) was synthesized and shown to have the same binding affinity for the DAT as MP. By superimposing each of the template structures on the various invertamers of R-MP, three template conformers were identified that best fit the rigid analogue. It is hypothesized that these may be related to the bioactive conformer. A preliminary pharmacophore for DAT binding was defined from these conformers. This work was supported in part by NIH grant DA11541.

158.

COMPUTATIONAL MODELING STUDIES ON ANTI TUMOR ACTIVITY OF BIS-ACRIDINES AGAINST MURINE P388 LEUKEMIA CELLS, MURINE LEWIS LUNG CELLS (LLC) AND HUMAN JURKAT LEUKEMIA WILD-TYPE CELLS(JLC): A GRAPH THEORETICAL APPROACH. ***Nitin Sapre**, School of Chemical Sciences, DA University, 3/6 Manoramaganj, Indore 452001, India, Fax: 91-731-2523352, nitinssapre@yahoo.com*

Computational modeling studies were performed on the Bis-acridine systems to understand their anti-tumor activity using graph theoretical indices for 2D QSAR. Topological indices namely Wiener, Randic and Balaban were used as the descriptors to be correlated with the binding ability (association constant). Genetic function algorithm (GFA) and multiple linear regression (MLR) techniques were used to perform 2D QSAR studies. The results from 2D QSAR studies against Murine P388 leukemia cells indicate that GFA proved to be better in predicting the binding (r^2=0.832, q^2=0.788) while MLR showed extremely poor result with very less significant correlation (r^2=0.682, q^2=0.467). To study the effect of substitution at 5-position an indicator parameter was used and the results show that substituent at that position will enhance the biological activity of compounds. The results for Murine Lewis Lung cells (LLc) also gave better results with GFA (r^2=0.939, q^2=0.924) while MLR gave very less significant results (r^2=0.571, q^2=0.243), in this case also the substituent effect was studied and has indicated that substitution at 5-position will enhance activity Even in case of Human Jurkat Leukemia Wild-type Cells (JLc) GFA performed better (r^2=0.704, q^2=0.635) while the results from MLR were inferior (r^2=0.725, q^2=0.399), also the results have shown that substitution at 5-position should enhance the activity.



159.

USING A KOHONEN SELF - ORGANIZING MAP TO GENERATE REPRESENTATIVE TRAINING, CROSS VALIDATION AND PREDICTION SETS FOR QSAR MODELLING. ***Rajarshi Guha[1]**, Jon R. Serra[2], and Peter C. Jurs[1]. (1) Department of Chemistry, Pennsylvania State University, 152 Davey Laboratory, University Park, State College, PA 16802, rajarshi@presidency.com, (2) Chemistry Department, Pennsylvania State University*

This study investigated the use of a Kohonen self-organizing map to generate representative training, cross validation and prediction sets for QSAR model generation. The assumption is that sets whose composition correspond more closely to that of the overall dataset should lead to better predictive models. The methodology starts by using the KSOM to classify the data set into two classes using an external descriptor set. The QSAR sets are then generated making sure that the relative populations of the two classes are maintained in each of the sets. This procedure was repeated for several combinations of Dragon descriptors as the external descriptor set, and the respective training, cross validation and prediction sets were used to generate QSAR models to predict the log IC50 for dihydrofolate reductase inhibitors. The procedure generated several models with prediction set errors equivalent to those found using the standard methodology. In addition, the size of the best model was found to be half the size of the best published model.

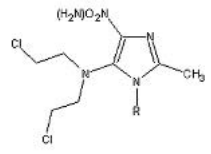
160.

STUDY OF SAR FOR 5-[BIS(2CHLOROETHYL)AMINO]-2-METHYL-4-NITRO(AMINO)-N-SUBSTITUTED IMIDAZOLE USING SEMIEMPIRICAL CALCULATION BY HYPERCHEM PROFESSIONAL. ***Iwona Weidlich**, and Stanis[3]aw Sobiak, Department of Chemical Technology of Drugs/Faculty of Pharmacy, University of Medical Sciences, Grunwaldzka 6, 68-780 Poznañ, Poland, Fax: 865-9566, iweidlic@amp.edu.pl*

A specific ability of nitroimidazoles are recognized to accumulate in the hypoxic anticancer cells. We synthesized some phenacyl derivatives of 5-bromo-4-nitroimidazoles which showed promising inhibition of the growth of HeLa cancer cell lines. The derivatives of 5-[bis(2-chloroethyl)amino]-2-methyl-4-nitro(amino)-N-substituted imidazole were subjected to detailed analysis by molecular modelling using the program HyperChem Professional (scheme1). The calculations were performed for the vacuum by the semiempirical method PM3. Analysis of the chemical structure of each studied compound was made on the basis of the following results: optimization of the molecule geometry to find a local minimum, energy and thermodynamic properties of an isolated point in a multidimensional energy surface, conformation analysis determination of local minima in order to find a global one. The results of the calculations were correlated with the screening study for 5-bromo(piperidino, morpholino,pyrrolidino)-1-(4-halogenophenacyl)-2-methyl-4-nitroimidazole.

Scientific research was supported by Center of Committee of Scientific Investigations (Poland) –project # 0321/P05/2002/23.

Scheme 1



R = CH_3, C_2H_5, CH_2CN, CH_2COOEt, CH_2COOH, CH_2CH_2COOEt, CH_2CH_2COOH, $COOCH_3$, $CH_2COC_6H_5F$, $CH_2COC_6H_5Cl$, $CH_2COC_6H_5Br$, $CH_2COC_6H_5I$

161.

PREDICTING THE GENOTOXICITY OF POLYCYCLIC AROMATIC COMPOUNDS FROM MOLECULAR STRUCTURE WITH DIFFERENT CLASSIFIERS. ***Linnan He[1]**, Peter C. Jurs[1], Laura Custer[2], Stephen K. Durham[2], and Greg M. Pearl[2]. (1) Department of Chemistry, The Pennsylvania State University, 152 Davey Laboratory, Box 27, Univeristy Park, PA 16802, lyh103@psu.edu, (2) Bristol-Myers Squibb*

Classification models were developed to provide accurate prediction of genotoxicity of 277 polycyclic aromatic compounds (PACs) directly from their molecular structures. Numerical descriptors encoding the topological, geometric, elec-

tronic, and polar surface area properties of the compounds were calculated to represent the structural information. Each compound's genotoxicity was represented with IMAX values measured by SOS Chromotest with/without S9 rat liver homogenate. The compounds' class identity was determined by a cutoff IMAX value of 1.25. Several binary classification models were generated to predict genotoxicity: k-nearest neighbor (k-NN), linear discriminant analysis (LDA), and probabilistic neural network (PNN). The study showed k-NN to provide the highest predictive ability among the three classifiers with a training set classification rate of 93.5%. A consensus model was also developed that incorporated the three classifiers and correctly predicted 81.2%of the 277 compounds. It also provided a higher prediction rate on the genotoxic class than any other single model.

162.
COMBINATORIAL QSAR: HUNTING FOR PREDICTIVE MODELS. ***Patricia de Cerqueira Lima***[1], *Assia Kovatcheva*[2], *Alexander Golbraikh*[1], *Yun-De Xiao*[3], *Scott Oloff*[4], *and Alexander Tropsha*[1]. *(1) Laboratory for Molecular Modeling, School of Pharmacy, University of North Carolina at Chapel Hill, CB # 7360, Beard Hall, School of Pharmacy, Chapel Hill, NC 27599-7360, Fax: 919-966-0204, lima@email.unc.edu, (2) Institute of Pharmaceutical Chemistry, University of Vienna, Austria, (3) Targacept, East First Street Suite 300, Winston-Salem, NC 27101-4165, (4) Department of Pharmacology, University of North Carolina at Chapel Hill*

QSPR models are typically generated with a single modeling technique. We have developed a combinatorial QSAR approach which explores all possible combinations of various descriptor sets and optimization methods coupled with external model validation. We explore this approach using two datasets: 195 substrates of P-glycoprotein (P-gp) and 98 ambergris fragrance compounds. Descriptor sets included Topological Indices (TI), MOE, and Atom Pairs. Optimization methods included kNN classification, binary QSAR, and Support Vector Machines (SVM). The models were considered acceptable if they had both high internal accuracy for the training set and external prediction power for the test set. The best model for P-gp substrates had internal and external accuracy of 92%and 78%, respectively. Corresponding values for the best model for ambergris fragrances were 74%and 85%. The combinatorial QSAR approach is automated, efficient, and affords selection of robust models with validated prediction power.

163.
PRINCIPAL CURVES ANALYSIS AND SELF-ORGANIZING MAPS IN QSAR: A COMPARATIVE STUDY. ***Yun-De Xiao***, *Josef Klucik, Rebecca Harris, and Jeffrey D. Schmitt, Molecular Design Group, Targacept, Inc, 200 East First Street, Suite 300, Winston-Salem, NC 27101-4165, Fax: 336-480-2107, yxiao@targacept.com*

The drug design and QSAR community are becoming increasingly aware of the merits of nonlinear pattern recognition techniques. We recently demonstrated that one such technique, the supervised variant of Kohonen self-organizing maps, shows considerable promise in modeling and decoding complex structure-activity and structure-property relationships. Since the nonlinear projection method of discretized principal curves has been shown to be analytically equivalent to self-organizing maps, we have undertaken a comparative study of these two methodologies using QSAR/QSPR benchmark datasets. A comparative statistical analysis, using linear mapping techniques as a reference, is provided. Finally, the relative ability of these methods to supply chemically and/or physically meaningful information is also discussed.

164.
APPLICATION OF THE QM-QSAR METHOD TO PREDICT REFRACTIVE INDEX OF THE DENTAL RESIN COMPOSITE. *Andrew J. Holder*[1], ***Lin Ye***[2], *J. David Eick*[3], *Cecil Chappelow*[4], *and Paul Knox*[1]. *(1) Department of Chemistry, University of Missouri, 5009 Rockhill Rd., Kansas City, MO 64110, Fax: 816-235-6543, holdera@umkc.edu, (2) Department of Chemistry, University of Missouri-Kansas City, 5100 Rockhill Rd, Kansas City, MO 64110, ly041@umkc.edu, (3) School of Dentistry, Dept. of Oral Biology, University of Missouri, (4) Midwest Research Institute*

The refractive index (RI) is a basic optical property of polymers that measures how light scatters within the material. Light scatter is important in the cure procedure of dental composites since better light scatter enhances polymerization laterally, but inhibits depth of cure. Also, refractive index is one of the indices of great aesthetic concern with respect to dental restoratives. In our study, the RI information is collected for a training set of monomers, and the dimer structures of those monomers are optimized using quantum mechanics. Using those results, we develop and employ a QM-QSAR model for prediction of RI for the dental composite monomers. This QM-QSAR model is validated with an external test set and then used to screen potential composite monomers for RI. The QM-QSAR results, statistical analysis, and initial screening results will be reported.

165.
APPLICATION OF 3D-QSAR TO THE STUDY OF METALLOCENE-BASED CATALYST POLYMERIZATION. ***Victor L. Cruz***[1], *Javier Ramos*[2], *Antonio Muñoz-Escalona*[2], *and Javier Martinez-Salazar*[2]. *(1) Department of Computational Chemistry, Centro Tecnico de Informatica - C.S.I.C, Calle Pinar, 19, 28006- Madrid, Spain, Fax: +34-91-5616193, victor@cti.csic.es, (2) Department of Macromolecular Physics, Instituto de Estructura de la Materia*

Single site olefin polymerization catalysts are suitable candidates for modeling purposes. The well defined structure and the almost complete elucidation of the polymerization mechanisms make these organometallic complexes appropriate for Quantitative Structure-Activity Relationship (QSAR) studies. Although QSAR is an extensively used technique in drug design, very few papers have appeared on its application to metallocene-based polymerization catalysis. The difficulties inherent to the control of the experimental conditions during the polymerization process could be the cause of this situation. In the present study, a number of zirconocene catalysts under carefully controlled experimental conditions,i.e., keeping all variables constant except the catalyst structure, were used. Catalytic activity as well as molecular weight of the resulting polyethylenes were experimentally determined. The 3D-QSAR methodology was used to explain the experimental data in terms of three dimensional field descriptors, all of them associated to the metallocene catalyst structure. Useful correlations between experimental ethylene polymerization activities and steric, LUMO and local softness fields of the catalysts were found. In terms of molecular weight calculation, good correlation was obtained with models including the LUMO and local softness fields. Based on the proposed models, steric and electronic factors affecting the polymerization performance will be further discussed.

166.
QUANTITATIVE STRUCTURE-BASED DESIGN: FORMALISM AND APPLICATION OF RECEPTOR-DEPENDENT (RD) 4D-QSAR ANALYSIS TO A SET OF GLUCOSE ANALOG INHIBITORS OF GLYCOGEN PHOSPHORYLASE. ***Dahua Pan***, *Yufeng Tseng, and Anton J Hopfinger, Department of Medicinal Chemistry and Pharmacognosy, Uinversity of Illinois at Chicago, 833 S. Wood St., Rm 539, M/C 781, Chicago, IL 60612, pandahua@hotmail.com*

A method for performing quantitative structure-based design has been developed by extending the current receptor-independent (RI) 4D-QSAR methodology to include receptor geometry. The resultant receptor-dependent (RD) 4D-QSAR approach employs a novel receptor-pruning technique to permit effective processing of ligands with the lining of the binding site wrapped about them. Data reduction, QSAR model construction and identification of possible pharmacophore sites are achieved by a three step statistical analysis consisting of genetic algorithm optimization followed by backward elimination multidimensional regression and ending with another genetic algorithm optimization. The RD-4D-QSAR method is applied to a series of glucose inhibitors of glycogen phosphorylase b, GPb. The statistical quality of the best RI and RD-4D-QSAR models are about the same. However, the predictivity of the RD- model is quite superior to that of the RI-4D-QSAR model for a test set. The superior predictive performance of the RD- model is due to its dependence on receptor geometry. There is a unique induced-fit between each inhibitor and the GPb binding site. This induced-fit results in the sidechain of Asn-284 serving as both a hydrogen bond acceptor and donor site depending upon inhibitor structure. The RD-4D-QSAR model strongly suggests that quantitative structure-based design cannot be successful unless the receptor is allowed to be completely flexible.

167.
G PROTEIN-COUPLED RECEPTORS (GPCRS)-DIRECTED MINING: A PHARMACOPHORE-BASED APPROACH. ***Toan B. Nguyen***, *Informatics and Modeling, ArQule, Inc, 19 Presidential Way, Woburn, MA 01801, Fax: 781-376-6019, tnguyen@arqule.com*

G Protein-Coupled Receptors (GPCRs) have proven to be a highly amenable target class to successful therapeutic intervention with a market margin of about

60 billion. This explains 40 percent of the pharmacological targets being evaluated by drug companies are related to GPCRs. To identify and expand GPCR-motif in ArQule's corporate database a mining strategy based upon pharmacophore approach was pursued to confirm 24 percent hit rates for 6 GPCR targets. These targets were initially selected based on their therapeutic importance consisting of biogenic amines and peptide-receptor ligands, i.e, adenosine (A1), serotonin (5HT2A), histamine (H1), cholecystokinin (CCKA), orphinan (ORL1), and neuropeptide (Y1). In addition, we were able to validate the design libraries of novel chemical compounds whose property space overlaps with that of the GPCR ligands.

168.
MODELLING TRANSMEMBRANE PEPTIDES. ***durba sengupta****, interdisciplanary computational science (IWR), univ. heidelberg, germany, INF 368, 69120 heidelberg, Germany, durba.sengupta@iwr.uni-heidelberg.de*

Transmembrane peptide sequences do not have a large structural database. Hence we need computational methods to explore the energy landscape and model these structures. In this work we use both explicit and implicit membrane function to understands the relationship between structure and function of these helices.

169.
KINETIC AND THERMODYNAMIC ASPECTS OF RECOGNITION IN A MULTIPROTEIN ENVIRONMENT. ***Garegin A. Papoian****, and Peter G. Wolynes, Department of Chemistry and Biochemistry, University of California, San Diego, 9500 Gilman Drive, La Jolla, CA 92093-0371, gap5@cornell.edu*

We analyze signal transduction using an energy landscape theory for modeling heterogeneous intracellular environment. Many signaling pathways are kinetically controlled. We describe a generalization of energy landscape theory to nonequilibrium systems applicable for multistep signaling pathways, emphasizing the effects of cross-talk between pathways and stochastic effects on amplification.

170.
TESTING SIMPLE MODELS OF PROTEIN FOLDING WITH COMPUTER SIMULATION. ***Laura L. Thomas***[1]*, Jed Pitera*[2]*, Julia Rice*[2]*, Jeffry D. Madura*[1]*, and William Swope*[2]*. (1) Department of Chemistry and Biochemistry, Center for Computational Sciences, Duquesne University, 308 Mellon Hall, 600 Forbes Avenue, Pittsburgh, PA 15282, Fax: 412-396-5683, littlewonderlt@hotmail.com, (2) IBM Almaden Research Center*

The goal of the IBM Blue Gene project is to develop large-scale computational resources and apply them to study protein folding. Aside from hardware advances and development, this includes the development of software to perform molecular simulations. The large datasets that will result from these simulations will necessitate the development of new software tools for their analysis. In particular, analysis of many observed quantities produced from protein folding simulations by molecular dynamics is being done to ascertain possible patterns that can be related to folding kinetics. Using hundreds of nanosecond timescale constant energy trajectories of a 16 amino acid hairpin that were started from various starting states, dozens of properties of each conformation have been measured. The analysis is oriented to the discovery of combinations of these properties that are appropriate for describing the kinetics of folding. Some of the software developed and preliminary results obtained from the analysis will be presented.

171.
PHI VALUES AND THE FOLDING TRANSITION SATE OF PROTEIN G: UTILIZATION AND INTERPRETATION OF EXPERIMENTAL DATA THROUGH SIMULATION. ***Isaac A. Hubner****, Jun Shimada, and Eugene I Shakhnovich, Department of Chemistry and Chemical Biology, Harvard University, 12 Oxford Street, Cambridge, MA 02138, hubner@fas.harvard.edu*

We expand and refine a method for determining a protein's transition state ensemble (TSE,) which utilizes phi value data from protein engineering studies as restraints in all-atom Monte Carlo simulations in order to deepen our understanding of the folding process and the interpretation of experimental phi value. We conclude that the simplistic interpretation of phi, as the fraction of native contacts made by each residue in the TSE, is incomplete and misleading without simulation and detailed analysis of individual structures. Pfold analysis, a measure of the transmission coefficient of a structure, was included to test the validity of including each structure in the TSE. We also show that inferring TSE structural information from phi values is incomplete without consideration of the folding mechanism of protein G, which follows multiple pathways that converge through the formation of a specific nucleus of six hydrophobic residues.

172.
ENERGETIC DETERMINANTS OF THE STRUCTURE OF TRANSMEMBRANE HELIX DIMERS. ***Madhusoodanan Mottamal****, Jin-Ming Zhang, and Themis Lazaridis, Department of Chemistry, City College of CUNY, Convent Ave & 138th St., New York, NY 10031, madhu@miles.sci.ccny.cuny.edu*

The function of many integral membrane proteins depends upon the formation of oligomers through interactions between their transmembrane alpha-helices. The forces that drive oligomerization and the influence of the membrane environment on the structure of these oligomers is not entirely clear. Here we use a recently developed implicit membrane model to obtain insights into these questions. Our system of choice is the dimeric transmembrane domain of Glycophorin A, whose structure in both detergents and bilayers is known. From an initial configuration of two parallel, uncoiled alpha-helices inserted vertically in the membrane, a large number of conformations are generated by rotating each helix at 20 intervals around its axis. Each conformer is subjected to simulated annealing followed by energy minimization with a distance constraint between the centers of mass of five C-alpha carbons from each monomer at the helix crossing point. Different crossing points are considered. We examine the ability of the energy function to discriminate the native configuration of Glycophorin A and the contributions of van der Waals, electrostatic, and solvation terms as well as side-chain entropy to the stability of right-handed and left-handed configurations.

173.
PROTEIN LOOP PREDICTIONS USING LOW BARRIER MOLECULAR DYNAMICS. ***Raphaël Geney***[1]*, Viktor Hornak*[2]*, and Carlos Simmerling*[1]*. (1) Department of Chemistry, State University of New York at Stony Brook, Stony Brook, NY 11794-3400, Fax: 631-632-7942, (2) Center for Molecular Medicine, SUNY Stony Brook*

Homology modeling allows the structural determination of a protein using the structure of a sequentially related protein. However the accuracy of homology models drops in low sequence identity segments, like surface loops. Surface loops are often associated with intermolecular recognition events, often involved in key biological processes, hence their localization deserves a precise treatment.

Low-barrier molecular dynamics (LBMD) simulations were conducted by combining a softcore interatomic potential with a locally enhanced sampling (LES) of the protein loops of interest. The softcore potential, applied to LES particles, was necessary to reduce infinite energy barriers arising from atomic overlap, thus expanding the sampling basin to otherwise inaccessible regions.

LBMD simulations led to near-native loop structures, starting from distorted and random conformations, in the case of antibody loops. In the particular case of the DB3 anti-progesterone antibody H3 loop, most final LBMD conformations converged to the unbound crystallographic geometry while a minority converged to the bound form, suggesting this "induced-fit" is intrinsically related to the flexibility of the loop.

174.
FOLDING KINETICS OF A ß-HAIRPIN: A MOLECULAR DYNAMICS STUDY. ***Asim Okur***[1]*, Daniel R. Roe*[1]*, Guanglei Cui*[2]*, Viktor Hornak*[3]*, and Carlos Simmerling*[2]*. (1) Department of Chemistry, Stony Brook University, Stony Brook University, Chemistry Dept, Stony Brook, NY 11794, aokur@csb.sunysb.edu, droe@ic.sunysb.edu, (2) Department of Chemistry, State University of New York at Stony Brook, (3) Center for Molecular Medicine, SUNY Stony Brook*

Protein folding is a very complex process. Due to high number of local minima it is virtually impossible to simulate folding from random initial structures for large proteins. Short peptides allow extensive conformational searches and simulations but only a few show properties similar to large proteins experimentally. In this study extensive analysis of folding and unfolding was performed on a short â-hairpin. Approximately 50 independent folding trajectories and 50 unfolding trajectories were created at the melting temperature. The folding and unfolding pathways were analyzed and compared. Kinetic analysis of the

pathways was performed. The trajectories were also analyzed thermodynamically by projecting the data on the free energy landscape generated from an equilibrium ensemble.

175.
ANALYSIS AND PREDICTION OF THE OLIGOMERIC STATE OF COILED COILS. ***Jorge Ramos***, *and Themis Lazaridis, Department of Chemistry, City College of CUNY, Convent Ave & 138th St., New York, NY 10031, jorge@miles.sci.ccny.cuny.edu*

The coiled coil is one of the simplest and best-studied protein folding motifs, consisting of two, three, four, or five helices wound around each other. Empirical rules have been established on the tendency of different core sequences to form a certain oligomeric state but the physical forces behind this specificity are unclear. In this work we model a number of core sequences into the structures of dimer, trimeric, tetrameric, and pentameric coiled coils. We examine the ability of an effective energy function (EEF1) to discriminate the correct oligomeric state for a given sequence and analyze the contribution of the core residues to the stability of a given oligomeric state.

176.
COMPUTER-AIDED PREDICTION OF NEW PHARMACOLOGICAL ACTIONS IN LAUNCHED DRUGS. ***Denis V. Akimov***, *Dmitrii A. Filimonov, and Vladimir V. Poroikov, Lab. for Structure-Function Based Drug Design, Institute of Biomedical Chemistry of Rus. Acad. Med. Sci, Pogodinskaya st., 10, Moscow 119121, Russia, Fax: 7-095-245-0857, adv@ibmh.msk.su*

Computer-aided prediction of biological activity spectra by computer program PASS (http://www.ibmh.msk.su/PASS) was applied to the set of active substances from the list of Top 200 medicines. Known pharmacological effects were found in the predicted activity spectra in more than 90%of cases. The probability of some new effects was also found to be significant, including angiogenesis inhibition, bone formation stimulation, multiple sclerosis treatment, etc. These predictions, if confirmed experimentally, may become a reason for a new application of pharmaceuticals from the Top 200 list. Most of known side and toxic effects were predicted by PASS in about 80%of cases. PASS predictions provide the basis for finding new leads among the launched drugs. PASS applications to about 10.000 drug substances provide the basis for clustering and focusing of this set according to the particular pharmacotherapeutic fields.

177.
ESTIMATING THERMODYNAMIC PROPERTIES FOR CHEMICAL PROCESS DESIGN. ***Martin Schiller***, *DuPont Engineering Technology, E.I. du Pont de Nemours and Company, Inc, B-8428, 1007 Market Street, Wilmington, DE 19898, Fax: 302-774-2457, martin.schiller@usa.dupont.com*

Reliable values of properties of chemicals and materials are necessary for the design of efficient and safe chemical processes. A large amount of physical, chemical, and transport property data has been published and correlated over the years. However, ever new products, processes, and technologies seem to be responsible for maintaining a significant gap between demand and availability. During chemical process design, it is virtually impossible to not having to use different methods for predicting properties. For the area of chemical process design, this talk attempts to describe what kind of properties are important, when prediction methods can be used, what kind of prediction methods are currently used, and where computational chemistry methods could be helpful filling current gaps. Certainly, this talk will not be able to cover every aspect of properties for chemical process design, but rather will focus on certain unit operations that are typical for handling fluids.

178.
TOWHEE: A MONTE CARLO MOLECULAR SIMULATION PROGRAM FOR INDUSTRIAL APPLICATIONS. ***Marcus G. Martin***, *Computational Materials and Molecular Biology, Sandia National Laboratories, P.O. Box 5800, Mail Stop 0316, Albuquerque, NM 87185-0316, Fax: 505-284-5451, marmart@sandia.gov*

Towhee is a freely available Monte Carlo molecular simulation code that works with a variety of classical force field potential functions. This talk first provides an overview of the applications that are possible using this simulation package. Then results using Towhee to compare the Amber, Charmm, Compass, Gromos, TraPPE, and OPLS force fields for liquid density and vapor-liquid coexistence are discussed. Finally, recent work on automatic force field fitting is presented with particular emphasis on Germanium, Telurium, and Antimony alloys.

179.
CRITICAL ISSUES IN THE APPLICATION OF QUANTUM CHEMISTRY IN COMPUTATIONAL KINETICS. ***Carlos A. Gonzalez***, *Computational Chemistry Group, National Institute of Standards and Technology, 100 Bureau Drive Stop 8380, Gaithersburg, MD 20899-8380, Fax: 301-869-4020, carlos.gonzalez@nist.gov*

Despite the success of quantum chemistry methods in the prediction of physical and thermochemical properties of a large variety of molecular systems, the use of such methods in the area of computational kinetics has remained an obscured science being used most of the time by experts in the field. There is no doubt that the application of quantum chemistry calculations in comput-taional kinetics will have a significant impact. In order for this to happen, however, it is critical that the state-of-the-art methodologies be properly validated and widely available to the scientific community. In this talk, a critical assessment of the performance of modern quantum chemistry methodologies in computational kinetics will be presented. In addition, a brief summary of the efforts in their validation currently under way at NIST will also be discussed.

180.
COUPLING DETAILED KINETICS AND TRANSPORT. ***Anthony M. Dean***[1], *Hans-Heinrich Carstensen*[1], *Robert J. Kee*[2], *Chad Sheng*[1], *Kevin M. Walters*[2], *and Huayang Zhu*[2]. *(1) Chemical Engineering Dept, Colorado School of Mines, 1613 Illinois St., Golden, CO 80401, Fax: 303-273-3730, amdean@mines.edu, (2) Engineering Division, Colorado School of Mines*

The integration of a validated detailed kinetic mechanism into a realistic flow model has the potential to markedly improve our ability to describe “real world” systems of commercial interest. We will illustrate this approach of coupling kinetics and transport by using solid oxide fuel cells as an example. Solid-oxide fuel-cell (SOFC) systems are currently in development for use in a number of applications, including distributed power generation. These systems offer the potential for direct electrochemical oxidation of hydrocarbons, without the requirement for upstream fuel reforming. However, at nominal operating temperatures of 600-1000°C, fuel stability and carbonaceous deposits within the fuel channels and porous anode structures present potential limitations to cell performance. The theoretical analysis of the kinetics occurring in fuel cells under typical operating conditions provides an important tool to explore this issue as part of the development process. To do so we are using a plug-flow model that is modified to accommodate the effects of oxygen ion flux through the electrode-electrolyte assembly and into the fuel channel. Fuel pyrolysis and oxidation is modeled using a detailed elementary reaction mechanism, which includes a large number of reactions that lead to deposit formation. We have used high-level electronic structure calculations to generate “kinetically accurate” potential energy surfaces and used these as the basis for a detailed chemical-activation analysis to predict the effect of temperature and pressure on the branching ratios. Calculating the cell’s ohmic resistance, operating voltage, Nernst potential, and activation overpotentials enables a determination of the oxygen-ion flux through the electrolyte into the anode. The oxygen ions are electrochemically oxidized in the anode, producing an electric current and delivering the stoichiometric equivalent of steam and carbon dioxide to the fuel channel. The presence of substantial quantities of these species has the potential to significantly influence the deposition kinetics by dilution, decrease in residence time and gasification. The power density and composition profiles predicted by the model can be used to evaluate system performance in terms of operating temperature, fuel composition, flow rates, and fuel-channel dimensions, thus assisting cell design and identifying favorable operating conditions.

181.
COMPUTATIONAL STUDIES OF MOLECULAR RECOGNITION: APPLICATIONS TO THE BINDING SPECIFICITY OF SIGNALING DOMAINS. ***Barry Honig***, *Department of Biochemistry and Molecular Biophysics, Howard Hughes Medical Institute, Columbia University, 630 W. 168 St., New York, NY 10032, bh6@columbia.edu*

The factors that determine the affinity and specificity of protein-protein, protein-DNA and protein-membrane interactions will be discussed. Particular emphasis will be placed on features that are common to members of entire protein families and to features that are unique to individual family members. It

is shown that a combination of computational tools including multiple structure and sequence alignments of family members, homology modeling and the calculation of binding free energies can elucidate the factors that drive association phenomena as well as the contribution of individual amino acids to binding specificity. Applications to the binding determinants of SH2 domains and a number of other domain families will be described.

182.
PHYLOGENOMIC STUDIES OF MOLECULAR SIGNALING. ***Olivier Lichtarge**, Human and Molecular Genetics, Baylor College of Medicine, One Baylor Plaza, BCM 225, Houston, TX 77030, Fax: 713-798-5386, lichtarge@bcm.tmc.edu*

A major problem in biology is that the functions of most genes remain unknown even when there is ample evolutionary information on their sequence and structural information on their protein product. We will discuss how these distinct data can be integrated to identify canonical determinants of structure and function. Experiments show that these determinants identify ligand binding sites and can be manipulated to alter functional specificity along the G protein signaling pathway. Other results show that this approach, called the Evolutionary Trace, is scalable. Thus, it will soon be possible to determine functional sites and thereby focus studies of molecular recognition, protein-protein interactions and drug design on a structural proteomic scale.

183.
CHARACTERIZATION OF PROTEIN BINDING SITES USING COMPUTATIONAL SOLVENT MAPPING. ***Sandor Vajda**, Department of Biomedical Engineering, Boston University, 44 Cummington Street, Boston, MA 02215, Fax: 1-617-353-6766, vajda@bu.edu, and Michael Silberstein, Program in Bioinformatics, Boston University*

Computational solvent mapping is a powerful tool for the identification and characterization of binding sites on proteins. The method moves molecular probes - small organic molecules containing various functional groups – around the protein surface, finds favorable positions using empirical free energy functions, clusters the conformations, and ranks the clusters on the basis of the average free energy. The mapping procedure reproduces the available experimental solvent mapping results, eliminating the problem of spurious local minima associated with previous computational methods. A very important result is that using at least six different solvent as probes, the consensus sites found by the mapping are always in the major subsites of the functional site, and as a result, the amino acid residues that interact with the probes also bind the specific substrates of the enzyme. Thus, computational mapping provides detailed and reliable information on the functional sites of proteins. In this talk we focus on the applications of the method to kinases and phosphatases, including the design of phosphatase inhibitors, and the analysis of interfaces in transitional protein-protein complexes formed in signal transduction pathways.

184.
KINASE BINDING AND SELECTIVE INHIBITOR DESIGN. ***William L. Jorgensen**, Yale University, New Haven, CT 06520-8107, william.jorgensen@yale.edu, and Yukio Tominaga, Dainippon Pharmaceutical Co*

Kinase-ligand binding is being studied via Monte Carlo simulations with statistical perturbation theory and linear response approaches. The OPLS-AA force field is used to describe the intermolecular and intramolecular interactions and the solvent is explicitly represented with the TIP4P water model. Thermodynamic and structural results will be presented for complexes of multiple kinases including CDK2, p38, and Lck. The calculations provide detailed insights into factors that control binding affinities and kinase selectivities. An accurate scoring function has been developed for kinase inhibition using the de novo design program GenMol; this allows rapid generation of libraries of novel kinase inhibitors that have also been filtered for desirable ADME characteristics with QikProp.

185.
STRUCTURE-DRIVEN LEAD DISCOVERY AND OPTIMIZATION. ***Jeffrey M. Blaney**, Computational Chemistry, Structural GenomiX, 10505 Roselle St, San Diego, CA 92121, Fax: 858-558-0642, jeff_blaney@stromix.com*

SGX has integrated high-throughput gene-to-structure technology with medicinal and computational chemistry to accelerate the discovery and optimization of kinase inhibitors. We will present an overview of our kinase inhibitor discovery strategy, focusing on the application of docking and MM/PBSA approaches for discovering and optimizing new leads.

186.
MULTISCALE SIMULATIONS OF PROTEIN KINASE. ***Yingkai Zhang**, Howard Hughes Medical Institute, University of Carlifornia at San Diego, 9500 Gilman Drive, La Jolla, CA 92093-0365, Fax: 858-534-7042, yzhang@mccammon.ucsd.edu, Yuhui Cheng, Department of Chemistry and Biochemistry, University of Carlifornia at San Diego, and J Andrew McCammon, Howard Hughes Medical Institute and Department of Chemistry and Biochemistry and Department of Pharmacology, University of California, San Diego*

The phosphorylation of protein residues catalyzed by kinases plays an essential role in cellular regulation and signal transduction. To understand the reaction mechanism and the structural origin of catalytic efficiency, we have been studying cAMP-dependent protein kinase with molecular dynamics simulations and pseudobond ab initio QM/MM calculations. Our calculations take account of protein dynamics, and determine the catalytic reaction pathways within a realistic enzyme environment.

187.
ROLE OF PREDICTIVE ADME AND TOXICITY MODELING IN DRUG DISCOVERY. ***Alan G.E. Wilson**, Pharmacia, 800N Lindbergh Blvd, St. Louis, MO 63167, Fax: 314-694-2517, alan.g.e.wilson@pharmacia.com*

Toxicity and ADME/PK issues remain important hurdles in reducing drug candidate failure and improving productivity. This has strengthened the importance of early screening for ADME/PK and toxicity properties. An increasingly important component of this screening strategy is the use of computer–based predictive models (in silico). Global and local (quantitative and qualitative) models are being applied to library design, to help prioritize synthetic programs, and to identify structural features which may contribute to undesired effects. Searchable databases and database engines are available for data storage and retrieval. Predictive modeling, in conjunction with other screening technologies, has the potential to significantly impact the drug discovery paradigm. This presentation will discuss the current status of in silico systems for ADME and toxicity prediction and present examples of the application of ADME and toxicity prediction. In addition, the future challenges and opportunities on in silico prediction will be discussed.

188.
STRUCTURAL ALERTS FOR HEPATOTOXICITY. ***William J. Egan**, Modeling Methods, Vertex Pharmaceuticals, 130 Waverly Street, Cambridge, MA 02139, Fax: 617-444-6688, bill_egan@vrtx.com*

One review calculated that approx. 26%of drug withdrawls in the period 1960-1999 were initiated due to hepatotoxicity. We have created a structural database of hepatotoxic drugs and chemicals containing over 230 molecules, including 54 drugs which were withdrawn or whose use was abandoned due to hepatotoxicity. Besides name and structure, the database contains information on marketing status, type of injury, mechanism of injury, metabolism, and pertinent references. Analysis of the structural features, clinical and biochemical literature, and routes of metabolism shows that there are a number of structural features that are definitely or possibly associated with hepatotoxicity in humans. The presentation will summarize the database, review some of the identified structural features, and discuss the challenges involved in extracting useful alerts and rules applicable to the complex processes of liver toxicity.

189.
BOOSTING THE LIMITS IN EARLY ADME PREDICTION. *Marco Pintore[1], Nadège Piclin[1], Han van de Waterbeemd[2], and **Jacques R. Chretien**[1]. (1) BioChemics Consulting, Centre d'Innovation, 16, rue Leonard de Vinci, Orleans cedex 2 45074, France, Fax: 33-238417221, marco.pintore@univ-orleans.fr, jacques.chretien@univ-orleans.fr, (2) PDM, Department of Drug Metabolism, Pfizer Global Research and Development*

Early ADMET remains high amongst current challenges. The slow progress observed despite huge efforts, is due to the poor or imprecise quality of the information content of the commonly available data. To circumvent this crucial drawback and to boost the limits of ADME early prediction, we will address here the quality assessment of the database mining strategy. It is supported by an

innovative Adaptive Fuzzy Partitioning (AFP) algorithm, which was applied to different bioactivities and to ADME data. Progresses up to 10 to 25%have been observed in the predictions with particular cases. Different key points will be considered and presented with examples: (i) open selection and permutation of molecular descriptors issued from large sets; (ii) impact of surface molecular descriptors using Volsurf; (iii) robustness of derived models; (iv) degree of validity of model inside the drug space; (v) estimation of the raw data noise.

190.
CHALLENGES IN PREDICTIVE ADMET: IMPERFECT DATA IN AN IMPERFECT WORLD. ***Stephen R Johnson**, Computer-Assisted Drug Design, Bristol-Myers Squibb, P.O. Box 4000, Princeton, NJ 08543-4000, stephen.johnson@bms.com*

Great effort is being allocated to the in silico and in vitro prediction of ADMET related activities. There is a growing industry consensus, however, that these efforts fall somewhat short in quantitative predictive ability. This presentation presents an overview of the factors contributing to these problems, including biological complexity, assay reproducibility, and in vitro-in vivo relationships. We will present a simple method to understand the extent to which a model can be expected to be predictive based on the underlying data used to generate it. Finally, an example of a model generated using noisy data will be used to illustrate many of these points. The relative utility of the model will be demonstrated for use in compound design.

191.
CLASSIFYING THE MUTAGENICITY OF TWO DIVERSE SETS OF ORGANIC COMPOUNDS USING AMES TEST DATA FOR *SALMONELLA TYPHIMURIUM* TA100 AND TA98. ***Brian E. Mattioni**[1], Peter C. Jurs[1], and David T. Stanton[2]. (1) Department of Chemistry, The Pennsylvania State University, 152 Davey Laboratory, Box 43, University Park, PA 16802, Fax: 814-865-3314, bem172@psu.edu, (2) Central Research Chemical Technology Division, Procter & Gamble*

Classification models are constructed for mutagenicity assessment using Ames test data with two diverse sets of organic compounds. The models are developed for two strains of *Salmonella typhimurium* (TA100 and TA98). More than 300 structural descriptors are calculated that encode the topological, geometrical, electronic, and polar surface area features of the compounds. In addition, we report the development and use of a new class of descriptors we call hydrophobic surface area (HSA) descriptors. The new descriptors should help to generate more accurate toxicity models due to the role that hydrophobicity has been shown to play for toxicity prediction. To establish diversity, a subsetting approach is employed to generate multiple training and prediction sets ensuring that consistent results are obtained regardless of training set membership. The resultant predictions are subjected to a 'majority rules' voting scheme to form a model ensemble. Linear discriminant analysis produces the best results for the TA100 strain where the model ensemble correctly classifies ~77%of the prediction set compounds. On the other hand, the probabilistic neural network generates the best results for the TA98 strain where a prediction set accuracy of ~80%is obtained by the ensemble.

192.
DEVELOPMENT OF AN IN SILICO PREDICTIVE PROTOCOL FOR HERG LIABILITY. ***Hongwu Wang**[1], Vincent Madison[1], Xue-Song Zhang[2], and Steve Sorota[2]. (1) Department of Structural Chemistry, Schering-Plough Research Institute, 2015 Galloping Hill Road, Kenilworth, NJ 07033, Fax: 908-740-4640, hongwu.wang@spcorp.com, (2) Department of CNS-CV Research, Schering-Plough Research Institute*

Inhibition of the human Ether-a-go-go Related Gene (hERG) ion channel is associated with prolongation of the QT interval of the surface electrocardiogram, reflecting delayed repolarization of the heart. Compounds exhibiting this action may predispose patients to ventricular arrhythmias and sudden death. Because many structurally diverse compounds have been found to inhibit the hERG channel, limiting the hERG liability has become a major hurdle for many drug discovery programs. We developed a computational protocol for the prediction of hERG inhibition using screening data from a rubidium efflux assay on 2695 Schering compounds from 20 drug discovery projects. The protocol consists of two independent models: a categorical model developed using a Bayesian method and a similarity search method that takes advantage of the growing experimental database. Each model by itself can correctly predict the hERG activity for 70%-80%of the potent and weak inhibitors in a test set. The combination of these two models can make very reliable predictions for a large portion of the compounds. Issues regarding the quality of the screening data and structural features critical for hERG inhibition will also be discussed. This protocol can be employed as a virtual screening tool in drug discovery to reduce hERG liability.

193.
USING TARGETED MEASUREMENTS TO IMPROVE THE ACCURACY OF PREDICTIONS OF MOLECULAR PHYSICAL PROPERTIES. ***Robert S. DeWitte**, Advanced Chemistry Development, 90 Adelaide W, Toronto, ON M5H 3V9, Canada, Fax: 518 276-4045, rob@acdlabs.com, and Eduard Kolovanov, Advanced Chemistry Development, Inc*

Even with the state of the art prediction technology available today for LogP, pKa and LogD, there are compound classes (specifically proprietary chemical classes) that are under-represented in the algorithmic "training space". This talk focuses on a combined system for determining physical properties that uses prediction when the algorithm has a high confidence of accuracy, and uses measurement when this confidence is low, and then employs these measurements to expand the scope of chemical classes for which it can confidently predict physical properties. By employing this hybrid approach, thermodynamic quality can be achieved with high accuracy and very high throughput. Specific aspects to be addressed include: how to know when you need to measure; Overcoming the quality/throughput trade-off; continually improving the accuracy of predictions; and minimizing total cost of measurements.

194.
THE FAILURE OF IN VITRO ADME PROPERTIES TO CORRECTLY DETERMINE IN VIVO OUTCOMES. ***Daniel A. Norris**, Troy Bremer, Kevin Holme, Glen Leesman, and Manish Sud, LION bioscience Inc, 9880 Campus Point Drive, San Diego, CA 92121, Fax: 858-410-6501, daniel.norris@lionbioscience.com*

In vitro ADME properties have long been used as surrogates for in vivo pharmacokinetic outcomes to compare drugs and drug candidates. Some properties, such as Caco-2 permeability and metabolic turnover are widely used in high throughput assays to select hits, leads, and candidates early in the drug discovery process. The value of these properties to provide accurate information for drug selection decisions has been investigated. Clinical pharmacokinetic data, in vitro ADME assay data and chemical structure data were assembled for > 150 compounds. The ability of each in vitro assay (used individually, jointly, or in simple correlation models) to predict in vitro outcomes was determined. In each case, the in vitro ADME properties were unable to provide accurate information regarding the pharmacokinetic performance of the compounds. The failure of these assays to determine pharmacokinetic outcomes should be considered when making drug discovery decisions based on this type of data.

195.
CHALLENGES FOR IN SILICO MODELING OF ADME DATA. ***Terry R Stouch**, Computer-Assisted Drug Design, Bristol-Myers Squibb, MS H23-07, PO Box 4000, Princeton, NJ 08543-4000, Fax: 609-252-6030, terry.stouch@bms.com*

The approximations inherent in much ADME data presents several challenges for in silico modeling. The properties, themselves, are often not rigorously defined and are often multicomponent with difficult underlying biology. Endpoints are not always determined precisely and are often qualitative, making quantitation difficult. Demands on these models can be extreme and go beyond good QSAR practices commonly employed for less challenging, but still demanding, endpoints. In particular, "general" models that cover large amounts of chemical space are desirable. Yet, the lack of standardization of assays means that data can not be quantitatively compared between laboratories, and often can not be compared at all, making it difficult to assemble sufficient data to develop such models. These and other problems will be detailed and their effect on the resulting modeling effort will be discussed.

196.
MOLECULAR MODELING OF THE THERMODYNAMIC AND TRANSPORT PROPERTIES OF INDUSTRIALLY-RELEVANT FLUIDS: METHODS, RESULTS AND INSIGHTS. ***Edward J. Maginn**, Department of Chemical and Biomolecular Engineering, University of Notre Dame, 182 Fitzpatrick Hall, Notre Dame, IN 46556, Fax: 574-631-8366, ed@nd.edu*

This talk highlights recent work from our group on the use of molecular-based simulation methods for computing thermodynamic and transport properties of a

range of industrially relevant fluids, including lubricants, ionic liquids, aqueous solutions of small molecules and refrigerants. Techniques used include molecular dynamics (MD), Monte Carlo (MC), and quantitative structure-property relationship (QSPR) modeling. We discuss developments and extensions to standard MD and MC methods that make the calculations tractable. We stress the benefits and limitations of each method, with particular emphasis placed on accuracy, speed and predictive capabilities.

197.
MOLECULAR AND MESOSCOPIC SIMULATIONS OF PHASE EQUILIBRIA. ***Athanassios Z. Panagiotopoulos***, *Department of Chemical Engineering, Princeton University, Engineering Quad, Princeton, NJ 08544, Fax: 609-258-0211, azp@princeton.edu*

Molecular-based methods for determining phase equilibria will first be reviewed briefly. Earlier methods applicable to fluids have been expanded recently to solids. However, several major issues remain unresolved and limit practical applications of these methods. The first barrier is the lack of appropriately validated force field models for many systems of interest. The second major issue is that for the majority of industrially relevant systems, time and length scales of interest exceed by far accessible ranges for atomistically detailed calculations. Current research in the author's group in these two areas will be summarized.

198.
MODELING CHEMICAL REACTIVITY IN FLUIDS. ***Bruce Garrett***, *Chemical Sciences Department, Pacific Northwest National Laboratory, PO Box 999, Mail Stop K1-83, Richland, WA 99352, Fax: 509-375-4381, bruce.garrett@pnl.gov*

While numerous advances have been made in computational methods that allow accurate predictions of gas-phase reaction rate constants, the development of methods to accurately calculate rate constants for reactions in condensed-phase fluids remains a challenge. First, electronic structure methods sufficient to predict accurate interaction energies for gas-phase reactions are typically not affordable for extended systems such as reaction in liquids. Second, accurate dynamical treatments of chemical reactions is a particular challenge if quantum mechanical effects are important, such as for systems in which hydrogen atoms are involved in the reaction. We will review a systematically improvable approach that combines variational transition state theory, which provides a framework for including important liquid-phase effects on reaction rates, with a hierarchy of computational methods for reaction energetics.

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199.
TOWARD TRANSFERABLE, EXTENSIBLE, ACCURATE AND MODULARIZED FORCE FIELDS. ***Huai Sun***, *School of Chemistry and Chemical Engineering, Shanghai Jiao Tong University, 800 Dong Chuan Road, Shanghai 200240, China, huaisun@yahoo.com*

In this presentation, we will analyze the shortcomings of atom typing in force field methods. We will explain how these problems could impair the transferability and extensibility of a general force field, which in turn is the main obstacle hindering the broader usage of force field technology, particularly in industrial applications. In order to solve these problems, we propose the usage of molecular fragments to identify force field interaction terms and computer database technology to manage the fragments and their parameters. This new framework, coupled with automatic parameterization tools, promises to make truly transferable, extensible, accurate and modularized force fields possible. We will demonstrate this methodology with a few examples.

200.
ENERGY LANDSCAPES AND SIGNAL TRANSDUCTION PROCESSES. ***Peter G. Wolynes***, *and Garegin A. Papoian, Department of Chemistry and Biochemistry, University of California, San Diego, 9500 Gilman Drive, mc 0371, San Diego, CA 92093-0371, Fax: 858-822-4560, pwolynes@ucsd.edu*

Signal transduction involves a cascade of binding, conformational and chemical modification events. Protein binding specificity can itself be understood using an energy landscape theory for the cellular milieu as a source of potential traps. Proteins have evolved in the context of a heterogeneous intracellular environment and the requirement of specificity shapes the interactions actually seen at protein-protein interfaces. Equilibrium statistical mechanics does not provide the whole picture of signal transduction, however. Many pathways are kinetically controlled. We explore a kinetic generalization of energy landscape theory applicable for multistep signaling pathways, emphasizing the effects of cross-talk between pathways and stochastic effects on amplification.

201.
MODELING OF PROTEIN-PROTEIN COMPLEXES IN STRUCTURAL GENOMICS. ***Ilya A. Vakser***, *and Andrei Tovchigrechko, Bioinformatics Lab, Department of Applied Math & Statistics, SUNY Stony Brook, Stony Brook, NY 11794, Fax: 631-632-8490, vakser@ams.stonybrook.edu*

An important problem in structural genomics is recreating the network of connections between proteins in a genome. The major aspects of this problem are: (1) the number of protein-protein interactions is very large (significantly larger than the number of individual proteins), and (2) most protein structures will be models of limited accuracy. Thus, the structure-based methods for building this network have to be (a) fast, and (b) insensitive to the inaccuracies of modeled structures. The docking program GRAMM has been shown to adequately address these issues. The procedure predicts the structure of protein complexes at variable resolutions, depending on the accuracy of the structural components. Systematic studies showed a high degree of tolerance to the structural inaccuracies of protein models. The methodology is being applied to modeling of protein-protein interactions in entire genomes.

202.
EFFECTIVE POTENTIALS FOR PROTEIN-LIGAND BINDING AND FOLDING WITH THERMODYNAMIC CONSTRAINTS. ***Ronald M. Levy***, *Emillio Gallicchio, Anthony Felts, and Linda Zhang, Department of Chemistry and Chemical Biology and BioMaPS Institute, Rutgers University, Piscataway, NJ 08855, ronlevy@lutece.rutgers.edu*

The development of effective potential models for biomolecular simulations has proceeded along two paths: (1) "physics based" implicit solvent effective potentials, and (2) "knowledge based" scoring functions. I will describe our development of the AGB/NP implicit solvent model for biomolecular simulations which combines features of "physics based" and "knowledge based" models. The AGB/NP solvation model consists of an analytical generalized Born term for the solvent electrostatic reaction field combined with a novel estimator for the nonpolar hydration term. I will describe how the performance, and transferability of the model among different kinds of protein structural problems (protein-ligand binding prediction, protein structure prediction) are greatly enhanced by enforcing "physics based" thermodynamic constraints on the parameter optimization. The iterative construction of free energy surfaces of polypeptides with alpha helix and beta sheet propensities which may be used for further parameter optimization will also be discussed.

203.
DOCKING STUDIES OF PROTEIN-LIGAND INTERACTIONS IN KINASES USING MULTIPLE PROTEIN CONFORMATIONS AND INDUCED FIT MODELING. ***Richard A. Friesner***, *Department of Chemistry, Columbia University, 3000 Broadway, MC 3110, New York, NY 10027, Fax: 212-854-7454, rich@chem.columbia.edu*

We have developed new methods for high throughput protein-ligand docking and scoring which are implemented in the Glide program. These methods will be briefly discussed and their performance surveyed across a wide range of receptors. The major focus will be on application of the methods to docking ligands into two kinases, p38 map kinase and CDK2. We will show how docking into multiple conformations of the receptor substantially improves rankings of active compounds (as compared to a database of random ligands) and binding mode prediction. Preliminary results for docking into homology models, and employing protein structure refinement to capture induced fit effects, using our new Prime protein modeling environment, will also be presented.

204.
MODELING THE INTERACTIONS BETWEEN PROTEIN KINASES AND THEIR INHIBITORS. ***Chung F Wong**, Howard Hughes Medical Institute and Department of Pharmacology, University of California, San Diego, 9500 Gilman Drive, MC0365, La Jolla, CA 92093-0365, c4wong@ucsd.edu, Peter Sims, Department of Chemistry and Biochemistry, University of California, San Diego, Jeremy Kua, Department of Chemistry, University of San Diego, Yingkai Zhang, Department of Chemistry & Biochemistry, Howard Hughes Medical Institute, and J. Andrew McCammon, Howard Hughes Medical Institute, Department of Chemistry and Biochemistry, University of California, San Diego*

Protein kinases are important players in cell signalling and are popular targets for drug design. We have been using a combination of quantitative methods for aiding the design of protein kinase inhibitors. These methods include sensitivity analysis, molecular dynamics, Brownian dynamics, and molecular docking. Selectivity is taken into account by building full or hybrid homology models and by constructing an approximate picture of the binding pocket of a large number of protein kinases. This talk will report some of our experiences on applying these methods to study several protein kinases. The methods are more successful when the experimental structure of at least one protein-ligand complex provides a starting point for the modeling. However, it is more challenging when only the crystal structure of the apo protein is known or when no experimental structure for the intended targets is available. I will discuss some of our efforts on tackling these problems.

205.
COMBINATION OF DE NOVO METHODS OF DRUG DESIGN, VIRTUAL FOCUSED COMBINATORIAL LIBRARIES, AND IN SILICO SCREENING AS A HIGHLY EFFICIENT TOOL FOR LEAD GENERATION. ***Pavel A. Petukhov**[1], Eugene A. Volpe[2], Yuzhi Yin[2], Robert I. Glazer[2], and Alan P. Kozikowski[1]. (1) Drug Discovery Program, Department of Neurology, Georgetown University Medical Center, 3970 Reservoir Road, NW, New Research Building, Rm EP15, Washington, DC 20057, Fax: 202-687-0738, pap4@georgetown.edu, (2) Departments of Oncology and Pharmacology, Georgetown University Medical Center*

Efficient, fast drug discovery using in silico methods is one of the challenges in modern computational chemistry/molecular modeling. We have developed and successfully applied a novel methodology of in silico drug discovery based on a combination of in silico methods including de novo/rational design, virtual focused combinatorial libraries, lead-like and drug-like filtering, docking, and scoring. This methodology has proven to be effective and has led to the discovery of new peroxisome proliferators-activated receptor (PPAR) inhibitors with at least 5 %hit rate. The details of the approach and its application for the design of these and other inhibitors will be presented.

206.
WITHDRAWN.

207.
3D ATOM-BASED ALIGNMENT WITH HYPERMOLECULES. ***Nicola J. Richmond**[1], Peter Willett[1], and Robert D. Clark[2]. (1) Department of Information Studies, University of Sheffield, Sheffield, England, United Kingdom, Fax: +44 114 278 0300, (2) Research, Tripos, Inc*

We describe a novel algorithm for rapidly generating an atom-based alignment of a dataset of 3D molecules. The method builds a 3D hypermolecule from the dataset - a 3D structure into which every data member can be embedded – to which each molecule can then be aligned. The main component of the algorithm, which is based on a computer vision technique for matching 2D shapes, lies in finding corresponding atoms between two molecules. Pairs of atoms, one from each molecule, are tentatively matched using an algorithm for solving the linear assignment problem, the objective being to find an alignment that superimposes atoms having similar local geometries and properties. Several heuristics are then applied to eliminate geometrically inappropriate atom equivalences. Examples of the hypermolecules obtained and their corresponding molecular alignments will be presented for a range of datasets to demonstrate the efficiency and the effectiveness of the method.

208.
INVESTIGATIONS IN SHAPE CLUSTERING FOR LEAD HOPPING. ***Norah E. MacCuish**, and John D. MacCuish, Mesa Analytics & Computing, LLC, 212 Corona St., Santa Fe, NM 87501, Fax: 509-472-8131, norah.maccuish@mesaac.com*

Searching for novel chemical leads for pharmaceutical targets using computational methods is commonplace in the pharmaceutical industry. We demonstrate a new approach to finding chemical leads which employs shape and sub-shape similarity as a means of clustering shape similar, but structurally diverse chemical structures. This facilitates the ability to 'hop' from active leads in a chemical series to active novel leads, both containing shape similar features. Shape similarity clustering will also be demonstrated as a useful alignment tool, where shape overlays of structurally diverse leads can be a start to a pharmacophore model.

209.
DIPEPTIDE QSAR USING TOPOLOGICAL REPRESENTATION OF STRUCTURE. ***Lowell H. Hall II**[1], L. Mark Hall[1], Lemont B Kier[2], and Borislav Spasov[3]. (1) Department of Chemistry, Eastern Nazarene College, 23 East Elm Avenue, Quincy, MA 02170, Fax: 617-745-3905, hall@enc.edu, (2) Department of Medicinal Chemistry, Virginia Commonwealth University, (3) Chemistry, Eastern Nazarene College*

QSAR models were developed for dipeptides in two data sets. In both cases molecular structure is represented by the electrotopological state and molecular connectivity chi indices. In the first study 58 dipeptides were analyzed for the inhibition (pIC50) of angeotensin converting enzyme (ACE). In the second study the relative bitter taste of dipeptides was modeled. Cross-validation in the leave-group-out form is used to validate the models. The models include E-State descriptors for specific atoms in the peptide backbone, E-State descriptors for residue features, in addition to molecular connectivity chi descriptor representation of skeletal variation. The possibility of creating an amino acid residue library of topological descriptors will be discussed.

210.
DEVELOPMENT AND APPLICATIONS OF A HANSCH SUBSTITUENT CONSTANT PREDICTOR. ***Ting-Lan Chiu**, and Sung-Sau So, Discovery Chemistry, Hoffmann-La Roche, Inc, 340 Kingsland Street, Nutley, NJ 07110, ting-lan.chiu@roche.com*

In an attempt to develop predictive models for Hansch substituent constants for novel compounds, neural network QSPR (Quantitative Structure-Property Relationship) studies were conducted to correlate Hansch substituent constants with two different molecular descriptor sets for hundreds of chemically diverse functional groups. The Hansch substituent constants under study were π, MR, F and R, describing the hydrophobic, steric, and electronic (field and resonance) characteristics of the substituents, respectively. For π and MR, E-state descriptors were used for correlation, while for F and R, the molecular descriptor set based upon the approach of Kvasnicka, Sklenak, and Pospichal was adopted. Both QSPR models demonstrated good predictivity in the test set. We demonstrate the applications of our Hansch substituent constant predictor in the QSAR

studies of E. coli dihydrofolate reductase (DHFR) inhibitors 2,4-diamino-5-(substituted-benzyl) pyrimidines as well as HIV-1 reverse transcriptase (RT) inhibitors 1-[(2-hydroxyethoxy)methyl]-6-(phenylthio) thymine (HEPT) derivatives. Both data sets contain substituents of which the Hansch substituent constants (π, MR, F and R) could not be found in constant tables. We show that our predictor allowed us to obtain predicted π, MR, F and R values for all substituents in both data sets thus enabling the generation of easily interpretable QSAR models of comparable or better predictivity than previous QSAR models. As can be expected, the predictor is going to play an important role in assisting various functional groups in drug research and development in pharmaceutical industry.

211.
COMPARISON OF VIRTUAL SCREENING PROGRAMS. ***Maxwell D. Cummings***, *Renee L. DesJarlais, Alan C. Gibbs, Venkatraman Mohan, and Edward P. Jaeger, Computational Chemistry, 3-Dimensional Pharmaceuticals, 665 Stockton Drive, Suite 104, Exton, PA 19341, Fax: 610-458-8258, max.cummings@3dp.com*

We have compared the performance of several commercially available docking programs in the context of virtual screening. Five different protein targets were used, each with several known ligands. For many of the known ligands, crystal structures of the relevant protein-ligand complexes were available. Our simulated screening deck, which was used in all the virtual screening tests, comprised 1000 molecules from a cleansed version of the MDDR and the forty-nine known ligands. We attempted to run experiments that were as similar as possible with each docking program. Detailed analysis of the results, including consensus analysis of results obtained with different programs, will be presented.

212.
OPTIMIZING THE STATISTICAL SIGNIFICANCE OF IN VITRO AND IN SILICO ASSAYS. ***Robert S. DeWitte***, *Advanced Chemistry Development, 90 Adelaide W, Toronto, ON M5H 3V9, Canada, Fax: 518 276-4045, rob@acdlabs.com*

Today, in silico screens are being run as proxies to in vitro screens, which are in turn proxies for in vivo screens. How can we be sure that each such proxy assay is providing real information in a cost-beneficial manner? This talk develops a set of impact metrics that quantify the significance of a proxy assay in terms of enrichment in the future odds of success, and cost savings due to avoided work. Interestingly, these metrics show that most assays are developed using artificial sampling of active vs inactive compounds, and therefore provide less information than originally thought: this problem is particularly acute in the area of in silico drug discovery. Implications for HTS, Virtual Screening, in vitro ADME are also discussed and a method for correcting this mistake during assay development is presented.

213.
AD-HOC SEARCHING AND EXPLORING OF INTEGRATED DATABASES AND DATA SOURCES. ***Lewis Jardine***, *Anatoli Krassavine, Andrew Payne, and Steven Porter, Intellidos Limited, 173 Curie Avenue, Harwell Internation Business Centre, Didcot, Oxon, OX11 0QG, United Kingdom, lewis.jardine@intellidos.com*

Data integration is widely recognized as a key step towards enhancing the efficiency of drug discovery. Solutions now exist that can integrate diverse data sources. Unfortunately, this is just the first step, scientists need to be able to search this integrated data. As yet, there are few tools for performing ad-hoc searches on complex cross-domain databases, e.g. chemical, pharmacological and genetic.

There are two problems – scientists don't write SQL and the internal IT staff find that the understanding of core database schemas tends to be spread across the enterprise.

This paper presents a flexible discovery environment that links together electronic dossiers with a powerful graphical cross-domain query tool enabling scientists to build queries in the language of science and not IT.

Additionally, we explore collaborative solutions to data integration and show how small groups such as academics can participate in and benefit from the provision of data exploration technology.

214.
EXTENSIBLE COMPUTATIONAL CHEMISTRY ENVIRONMENT: A TOOLKIT FOR THEORETICAL CHEMISTRY. ***Bruce J. Palmer***[1], *Gary D. Black*[1], *Karen L. Schuchardt*[1], *and Erich R. Vorpagel*[2]. *(1) Computational Sciences and Mathematics Division, Pacific Northwest National Laboratory, Box 999, Richland, WA 99352, bruce.palmer@pnl.gov, (2) MSCF Visualization and User Services, Pacific Northwest National Laboratory*

The Extensible Computational Chemistry Environment (Ecce) is a suite of programs seamlessly integrated together to allow researchers to set up, execute, analyze, store, and manage theoretical chemistry calculations starting from a single point of entry. The environment consists of three major components: the workstation actually running the Ecce graphical user interface applications, compute servers that execute the computational chemistry codes, and a web technology based data server or servers that act as a persistent repository for user calculation setup and results data. Ecce differs from a standard user interface in several ways: 1) it is a suite of programs instead of a single monolithic code 2) the environment is extensible and 3) the primary workflow functions of executing computational chemistry codes and storing the results can be delegated to different hardware resources. Major capabilities of the current version of Ecce are reviewed and future enhancements will be discussed.

215.
PREDICTING PHASE EQUILIBRIA USING TRANSFERABLE FORCE FIELDS. ***J. Ilja Siepmann***[1], *Bin Chen*[2], *Collin D. Wick*[3], *John M. Stubbs*[3], *Ling Zhang*[3], *Li Sun*[3], *and Xin S. Zhao*[3]. *(1) Departments of Chemistry, Chemical Engineering and Materials Science, University of Minnesota, 207 Pleasant St. SE, Minneapolis, MN 55455, Fax: 612-626-7541, siepmann@chem.umn.edu, (2) Department of Chemistry, University of Pennsylvania, (3) Department of Chemistry, University of Minnesota*

Configurational-bias Monte Carlo simulations in the Gibbs ensemble and the transferable potentials for phase equilibria (TraPPE) force field are used to investigate multicomponent phase equilibria for systems and processes of technological importance: (i) retention in chromatography, (ii) gas-expanded liquids, (iii) polymorphism for organic solids, and (iv) binary vapor-liquid nucleation.

216.
MOLECULAR MODELING OF NANO-POROUS MATERIALS AND CONFINED FLUIDS. ***Keith E. Gubbins***[1], *Roland J.-M. Pellenq*[2], *Jorge Pikunic*[1], *and Flor R. Siperstein*[3]. *(1) Department of Chemical Engineering, North Carolina State University, Raleigh, NC 27695, Fax: 919-513-2262, keg@ncsu.edu, (2) CNRS-UPR 7251, (3) Department of Chemical Engineering, Universitat Rovira i Virgili*

Molecular simulation methods can be used to construct realistic molecular models of nano-porous materials using either mimetic simulation or reconstruction methods. In the first approach a simulation protocol is developed that mimics the experimental synthesis of the material. In reconstruction methods, a molecular model is built that matches experimental structural data for the material. In principle, mimetic simulation is preferable, since it yields unique structures, but can only be used when the synthesis is sufficiently well understood. Several examples of applications of these methods will be presented, including their use to model porous glasses, templated mesoporous materials, and activated carbons. Such materials are used industrially in purification and separation of fluid mixtures, and as catalyst supports. The resulting model materials can be used to characterize experimental materials by matching the model to the real material. They can also be used to investigate the physical properties and chemical reactivity of fluids confined within the materials. Several examples will be given.

217.
CALCULATION OF EXCESS THERMODYNAMIC PROPERTIES USING FORCE FIELD-BASED METHODS. ***David Rigby***, *Accelrys, Inc, 9685 Scranton Road, San Diego, CA 92121-3752, Fax: 858-799-5100, david@accelrys.com*

In recent work in our laboratory, it has been demonstrated that a carefully parameterized force field can be used to calculate densities which often agree with experiment to within about one percent over extended ranges of temperature and pressure. While this represents a considerable improvement over the

situation which prevailed just a few years ago, there remains the significant challenge of determining the level of accuracy to be expected when force field based methods are applied to predict some of the fluid properties of greatest interest, as represented by the thermodynamic *excess* properties.

After reviewing the results of density and cohesive energy predictions for pure liquids obtained in recent work using the COMPASS force field, we discuss the requirements for precise calculation of excess mixture volumes and enthalpies, and will examine the accuracy achievable in nonpolar aromatic/aliphatic hydrocarbon systems and in other more polar systems for which extensive experimental data are available.

218.
MOLECULAR SIMULATIONS OF MEMBRANE BASED SEPARATION PROCESSES. ***Sohail Murad**, Wei Jia, and Mukund Krishnamurthy, Department of Chemical Engineering, University of Illinois at Chicago, 810 S Clinton Street, Chicago, IL 60607, murad@uic.edu*

Molecular simulations using a method developed by us to study fluids confined by membranes has been used to study a variety of separation processes. These include exchange of cations in zeolite membranes, separation of air and N2-CO2 mixtures using zeolite membranes such as chabazite and faujasite, as well as the effect of electric fields in membrane based separation processes (electro-osmosis). This method has previously been used to study osmosis and reverse osmosis in a range of systems. We have studied ion exchange between aqueous LiCl solutions and NaA membranes. Both sub-critical and supercritical solutions have been investigated. Our results clearly show ion exchange taking place in such systems. The effect of the usual driving forces in ion exchange has been investigated. These include the concentration of the aqueous solution, the density (pressure) and the temperature. In addition we have simulated the separation of gas mixtures using zeolite membranes. Our results compare well with available experimental data.

We have also investigated the role of external alternating electric fields in accelerating these separation processes. Our results show that these rates can be significantly increased with electric fields. In our previous studies we have found that the solvent flux across a membrane in a reverse osmosis separation can also be similarly increased. We plan to investigate a range of solutions and zeolites in our studies.

219.
TRANSFERABLE FORCE FIELDS FOR THERMOPHYSICAL PROPERTY SIMULATION. ***James F. Ely**, and Haizhong Zhang, Chemical Engineering Department, Colorado School of Mines, 1500 Illinois St., Golden, CO 80401-1887, jely@mines.edu*

During the past 10-12 years there have been a substantial number of "transferable" force fields reported for the molecular simulation of various configurational and intramolecular properties. Generally these force fields have worked well if they are applied for the family of materials and thermophysical property for which they were optimized. Problems arise, however, when force fields optimized for one property are used to simulate other properties of the same family. A simple example is when a phase equilibiria optimized force field for alkanes is used to simulate transport properties of those same alkanes. Typically, the transport simulations result in values which are 30-40%different as compared to experimental results.

Clearly, this lack of transferability of force field parameters is problematic in the industrial application of simulation methodology. Ideally, one could use a single force field for the simulation of any property of interest, but this is not currently the case. In this study, results are presented from our efforts to develop force fields that are transferable between family members and different thermophysical properties.

220.
MECHANISTIC INSIGHTS INTO RECEPTOR-MEDIATED CELL SIGNALING FROM COMPUTATIONAL AND EXPERIMENTAL PROBING OF STRUCTURE-FUNCTION RELATIONS. ***Harel Weinstein**, Department of Physiology and Biophysics, Weill College of Medicine of CORNELL University, 1300 York Ave., New York, NY 10021, Fax: 212-325-7344, harel.weinstein@mssm.edu*

G protein coupled receptors (GPCRs) are among the most widely studied membrane proteins, because they are responsible for recognizing and transducing signals in a large variety of signaling pathways. Elucidation of their function at a fundamental molecular level requires a detailed understanding of structure-based mechanisms of action. The discovery of mechanisms by which ligands activate these receptors is of great interest to biological research in general, and to drug design in particular. The presentation will illustrate results from interdisciplinary collaborations involving computational modeling and simulation, and various experimental approaches, in the study of signal transduction by GPCRs and their oligomeric complexes. Results reveal the role of specific elements of receptor structure in the stabilization of constructs that modulate receptor activity, and in ligand-induced transduction of the activation signal. The studies will be shown to: 1) identify structural motifs that act as functional microdomains for activation that are common to classes of GPCRs; and 2) provide insights into receptor specific oligomerization.

221.
SIGNAL TRANSDUCTION BY JNK. ***Roger J. Davis**, Program in Molecular Medicine, Howard Hughes Medical Institute and UMASS Medical School, 373 Plantation Street, Worcester, MA 01605, Fax: 508-856-3210, Roger.Davis@Umassmed.edu*

The JNK group of stress-activated MAP kinases consists of ten protein kinases that phosphorylate the NH2-terminal activation domain of c-Jun on Ser-63 and Ser-73 causing increased transcriptional activity. JNK protein kinase activity is increased in response to treatment of cells with pro-inflammatory cytokines or exposure to environmental stress. Activated JNK is phosphorylated on Thr and Tyr within the tripeptide motif Thr-Pro-Tyr located in kinase sub-domain VIII. Mutational analysis demonstrates that JNK activation requires the phosphorylation of both Thr and Tyr within this motif. This phosphorylation is mediated by dual specificity protein kinases, including MKK4 and MKK7.

The function of the JNK signaling pathway has been studied using a combination of biochemical and genetic approaches. Genetic analysis of JNK signaling in Drosophila demonstrates that JNK is required for early embryonic morphogenesis. Similarly, disruption of the JNK signaling pathway in mice using homologous recombination demonstrates that JNK is required for embryonic viability. In contrast, mice with genetically engineered selective defects in JNK signaling are viable, but exhibit changes in stress-induced gene expression and apoptosis. These studies provide insight into the role of the JNK stress-activated MAP kinase pathway in the cellular response to environmental stress and illustrate the potential for the use of JNK as a therapeutic target for inhibition by small molecules in the treatment of many diseases, including cancer and inflammation.

222.
ACTIVATION OF SR PROTEINS BY PHOSPHORYLATION. ***Joseph Adams**, Department of Pharmacology, University of California San Diego, La Jolla, CA 92093-0657, Fax: 858-822-3361, joeadams@chem.ucsd.edu*

Both the assembly and selection of splice sites in the spliceosome relies on the participation of protein factors known as SR proteins. These splicing factors, named for their large arginine-serine dipeptide repeats, are activated through phosphorylation by a class of enzymes known as SR protein kinases [SRPKs]. The SRPKs are highly unique members of the protein kinase family and are distinguished by a large domain insert (approx. 250 a.a.) that bifurcates the canonical kinase domain. Although the domain insert lies near the domain linker region, it does not influence nucleotide binding. We showed that the yeast SRPK, Sky1p, phosphorylates the SR protein, Npl3, at a single site using a typical protein kinase pathway in which slow product release controls substrate turnover. This simple process is juxtaposed by more complex systems where multiple serines are modified. For example, the human splicing factor, ASF/SF2, is phosphorylated at 9 serines by SRPK1. Using a start-trap experiment, we showed that SRPK1 phosphorylates these serines without dissociating from ASF/SF2. Thus, SRPK1 is a fully processive protein kinase that 'locks' the splicing factor in place and pulls the stretch of serines into the active site. This novel mode of splicing factor activation offers significant catalytic advantage over a distributive mechanism where phospho-intermediates are released after each round of catalysis.

223.
CHEMICAL GENETIC AND PROTEOMIC APPROACHES TO THE STUDY OF PROTEIN TYROSINE PHOSPHATASES. ***Zhong-Yin Zhang**, Molecular Pharmacology, Albert Einstein College of Medicine, 1300 Morris Park Avenue, Bronx, NY 10461, Fax: 718-430-8922, zyzhang@aecom.yu.edu*

Protein tyrosine phosphatases (PTPs) form a large family of enzymes that serve as key regulatory components in signal transduction pathways. Defective or inappropriate regulation of PTP activity leads to aberrant tyrosine phosphorylation, which contributes to the development of many human diseases including cancers and diabetes. Analysis of the nearly completed human genome reveals 112 predicted human PTPs. Although members of the PTP family have conserved catalytic domains and share a common mechanism of action (hydrolysis of phosphotyrosine), the cellular processes in which they are involved can be both highly specialized and fundamentally important. Thus, attributing a general role to a PTP gene product based on structural homologies is relatively easy. However, determination of the exact physiological function of a PTP requires a tedious and protracted effort. Our research effort is focused on developing and applying novel technologies and reagents in interaction proteomics and chemical genetics to study the physiological functions of all PTPs. Specifically, we have developed high affinity PTP substrate-trapping mutants that can be used in combination with mass spectrometry for rapid isolation, identification, and characterization of physiological PTP substrates. We have also developed potent and selective PTP inhibitors and mechanism-based common PTP modifiers using combinatory chemistry and high-throughput screening of small molecule libraries. Identification and characterization of cellular PTP substrates will help elucidate the function of individual PTPs as well as assignment of a PTP to a specific signaling pathway. Highly potent and selective PTP inhibitors mechanism-based common PTP modifiers will serve as powerful tools to delineate the physiological roles of these enzymes in vivo.

224.
CHEMICAL APPROACHES TO SORTING OUT PROTEIN PHOSPHORYLATION. ***Philip A. Cole**, Department of Pharmacology and Molecular Sciences, Johns Hopkins University, 725 N. Wolfe St., Baltimore, MD 21205, Fax: 410-614-7717, pcole@jhmi.edu*

Reversible protein phosphorylation represents a major mechanism for cell signal transduction. We will summarize a few recent technologies developed and applied in our lab to understand the function of protein kinases in various contexts. In particular, we will discuss the design and application of bisubstrate analogs as protein kinase inhibitors, the chemical rescue of mutant tyrosine kinases, and the use of expressed protein ligation in protein phosphorylation analysis.

225.
CHEMICAL GENETIC APPROACHES TO STUDY SIGNAL TRANSDUCTION. ***Kavita Shah**, Fabien Vincent, Silas Cook, and Sungjoon Kim, Genomics Institute of the Novartis Research Foundation, San Diego, CA 92121, kshah@gnf.org*

Deregulated kinase activity has been implicated in a number of diseases, prompting the emergence of kinases as a major source of novel drug targets. In particular, hyperphosphorylation of diverse proteins is a hallmark of several neurodegenerative illnesses. Using a chemical genetic approach, we conducted a proteome-wide search for the substrates of a kinase implicated in Alzheimer's disease (AD). A combination of specific polypeptide labeling, 2D electrophoresis and mass spectrometry enabled us to identify more than 25 protein substrates. Their classification in different functional categories not only agrees with the know functions of this kinase but also suggests an alternative role in AD. Additionally, we are applying this chemical genetic strategy to the study of G proteins, another class of signal transduction enzymes. The high degree of conservation of the nucleotide binding site in this family potentially allows the design of a specific inhibitor/mutant protein pair that can be readily translated to other family members. In this presentation, we discuss the structure-based design of specific inhibitors of G proteins using H-Ras as a model system.

226.
"ANTIFREEZE" PROTEINS AT THE ICE/WATER INTERFACE. ***Pranav Dalal**[1], Jared E. Knickelbein[2], A.D.J. Haymet[3], and Jeffry D. Madura[1]. (1) Department of Chemistry and Biochemistry, Center for Computational Sciences, Duquesne University, 600 Forbes Avenue, Pittsburgh, PA 15226, Fax: 412-396-5683, dalal@duq.edu, (2) Department of Chemistry and Biochemistry, Duquesne University, (3) Department of Chemistry and Institute for Molecular Design, University of Houston*

Three properties of the winter flounder Type I antifreeze protein: the surface area of the protein, a measure of the interaction of the protein with neighboring water molecules, and the side-chain angles of the Thr residues are calculated from molecular dynamics simulations of the water/protein/ice system. These three properties discriminate among the orientation of the protein within the broad ice/water interface and show that the Thr-Ala-Asx orientation based upon absolute zero temperature ice/vacuum models is incorrect and that the Thr-Ala-Ala orientation is favored. These results are consistent with the experimentally determined Thr-Ala-Ala orientation. We have undertaken potential mean force (pmf) simulations to determine the free energy of interaction of the Thr-Ala-Ala and Thr-Ala-Asx orientations with the ice/water interfacial region. The results and analysis of the pmf simulations will also be presented.

227.
NOVEL VARIABLE TRANSFORMATION APPROACH FOR ENHANCING CONFORMATIONAL SAMPLING IN COMPLEX SYSTEMS. ***Peter Minary**[1], **Glenn Martyna**[2], and **Mark E. Tuckerman**[1]. (1) Department of Chemistry, New York University, 100 Washington Square East, New York, NY 10003, Fax: 212-260-7905, pm432@nyu.edu, mark.tuckerman@nyu.edu, (2) Physical Science Division, IBM Research, TJ Watson Research Center, PO Box 218, Yorktown Heights, NY 10598, Fax: 914-945-4506, martyna@us.ibm.com*

Determining conformational equilibria of complex systems, such as biomolecules, characterized by rough energy landscapes, is one of the current computational grand challenge problems. In such systems, ordinary molecular dynamics and Monte Carlo simulations suffer from severe ergodicity problems. The development of new methods aimed at overcoming these issues could potentially significantly impact important problems such as protein folding. In this work a new approach for sampling the conformational space of complex systems will be presented. The new method builds on the variable transformation or REPSWA (Reference Potential Spatial Wrapping Algorithm) approach previously introduced by us, in which a change of variables in the canonical partition function is made that effects a shrinking of barrier regions and an expansion of attractive basins in the phase space. In order to treat realistic systems with intermolecular interactions, a novel dynamic transformation scheme is introduced which senses the barriers that arise as neighboring atoms approach one another. Thus, trapped states arising from strong non-bonded and solute-solvent interactions are largely avoided. The performance of these novel developments are tested on long alkane chains and united residue B-barrel model proteins. Comparision is made to other sampling methods such as parallel tempering.

228.
EFFICIENT GENERATION AND CHARACTERIZATION OF LOW-ENERGY FOLDED STATES OF A MODEL PROTEIN: AUTOMATED HISTOGRAM FILTERING. *Stefan A. Larrass, Laurel M. Pegram, Heather L. Gordon, and **Stuart M. Rothstein**, Department of Chemistry, Brock University, 500 Glenridge Avenue, St. Catharines, ON L2S 3A1, Canada, Fax: 905-682-9020, sl98ag@badger.ac.brocku.ca, srothste@abacus.ac.brocku.ca*

Highly-frustrated protein energy landscapes present two severe challenges for computational chemists. First, a large number of local minima are present, making it difficult, if not impossible in principle, to locate them all, a task necessary to reliably compute physical properties by statistical mechanics. Second, it is difficult to characterize the structures which occupy the various low-energy regions of the potential energy surface as one has only an incomplete sample of these. We address these problems using automated histogram filtering (AHF) in combination with well-known distance geometry software. AHF is a new technology for clustering high-dimensional data and will be the focus of our paper. Our application is to a previously unstudied, highly-frustrated 69-mer off-lattice model protein, consisting of a chain of beads which are either hydrophobic, hydrophilic, or neutral in nature.

229.

DENSITY OF STATES SIMULATION OF PROTEINS IN A CONTINUUM. ***Nitin Rathore**, Department of Chemical Engineering, University of Wisconsin-Madison, 1415 Engineering Drive, 1037 Engineering Hall, Madison, WI 53706, Fax: 608-262-5434, rathore@cae.wisc.edu, and Juan J de Pablo, Department of Chemical Engineering, University of Wisconsin - Madison*

Canonical simulations of folding processes in model proteins are challenging due to the rough potential energy landscape of these systems. In this work an algorithm that calculates density of states by performing a random walk in energy space has been proposed and implemented to study protein folding in a continuum using a united atom representation and the CHARMM19 force field. We will show that unlike the earlier formulation that showed slow convergence for continuum simulations, this methodology is designed to achieve better sampling and faster convergence. We will also present a variant of this method that computes the density of states from the instantaneous temperature of the system. An intrinsic temperature is computed as a function of potential energy based on the just the configurational information of the protein and the density of states is then computed by integrating the reciprocal temperature with respect to the potential energy. A comparison between the two methods in terms of their efficiency, speed and accuracy will be made. The method is further extended to study protein folding using an explicit solvent treatment.

230.

PROTEINS UNDER STRESS: MOLECULAR SIMULATION STUDIES OF PRESSURE DENATURATION OF PROTEINS. *Shekhar Garde[1], Angel E. Garcia[2], and **Tuhin Ghosh**[1]. (1) Department of Chemical Engineering, Rensselaer Polytechnic Institute, 110 Eighth Street, Troy, NY 12180, Fax: 518-276-4030, gardes@rpi.edu, ghosht@rpi.edu, (2) Theoretical Biology and Biophysics Group, Los Alamos National Laboratory*

Pressure effects on proteins have received increased attention in the recent past as a result of their fundamental and applied relevance to various biophysical phenomena in solution. Pressure denatured protein structures are relatively compact and are thought to provide a picture of intermediate states along thermal or denaturant induced unfolding pathways. Understanding pressure stability of proteins is thought to be relevant to barophilic adaptation processes. High pressures have also been used a mild means for separating protein complexes.

Recent experimental and theoretical studies have shown that, unlike heat denaturation, the molecular mechanism of pressure denaturation involves penetration of protein interior by bulk water molecules followed by gradual swelling and unfolding of protein structure. Molecular simulations of this process require novel methods since the unfolding occurs over the timescales of minutes to hours, which are well beyond the reach of conventional simulations. We have used a combination of molecular dynamics and Monte-Carlo simulation techniques where water molecules are inserted into protein interior at periodic intervals. Results on protein structure, volumes of folding and unfolding for protein Staphyloccocal Nuclease obtained from our simulations are consistent with recent experimental studies. These and complementary results on pressure effects on hydrophobic interactions will be presented.

231.

TWO-PHASE THERMODYNAMIC METHOD FOR ACCURATE FREE ENERGIES FOR LIQUIDS DIRECTLY FROM MOLECULAR DYNAMICS SIMULATIONS. ***Shiang-Tai Lin**, Chemistry and Chemical Engineering, California Institute of Technology, Materials and Process Simulation Center, MC 193-74, Pasadena, CA 91125, Fax: 626-395-8150, stlin@wag.caltech.edu, M. Blanco, Materials and process Simulation Center, California Institute of Technology, and William A. Goddard III, Materials and Process Simulation Center, California Insitute of Technology*

We propose a general approach for determining the entropy and free energy of complex systems as a function of temperature and pressure. In this method the Fourier transform of the velocity autocorrelation function obtained from a short (20,000 steps) molecular dynamics trajectory is used to obtain the vibrational density of states (DoS), which in turn is used to calculate the thermodynamic properties. In the simplest approach one could apply quantum statistics assuming each mode to be a harmonic oscillator. This leads to accurate results for solids but results in significant errors for liquids because (1) The DoS at zero frequency is not zero, resulting in a singular contribution to the entropy and (2) There is significant anharmonicity in low frequency modes.

We resolve these problems for liquids by using the two-phase thermodynamic model (2PT) consisting of: · a solid phase for which the DoS goes to zero smoothly at zero frequency, as in a Debye solid · a gas phase (highly anharmonic), described as a gas of hard spheres. This decomposition allows for the separation of the overall DoS into gas-like and solid-like components. Through the proper statistical weighting functions for each component we obtain accurate thermodynamic properties.

We validated the 2PT method for pure Lennard-Jones systems over a range of reduced temperatures (0.9 to 1.8) and reduced densities (0.05 to 1.10). These conditions cover the gas, liquid, crystal, metastable, and unstable states in the phase diagram. Our results compare quite well with accurate Monte Carlo calculations of the phase diagram for classical Lennard-Jones particles throughout the entire phase diagram (including metastable and unstable regions), demonstrating that the Two-Phase Thermodynamics (2PT) approach provides an efficient means for extracting thermodynamic properties of liquids, gases, and solids).

We will report the application of the 2PT method to other problems such as the equation of state for bucky balls and the phase diagram of metallic alloys.

232.

ACCURATE CALCULATIONS OF ABSOLUTE PKA VALUES FOR SUBSTITUTED PHENOLS IN WATER WITH A POLARIZABLE FORCE FIELD. ***George A. Kaminski**, Department of Chemistry, Central Michigan University, Mount Pleasant, MI 48859, Fax: 989-774-3883, kamin1ga@cmich.edu*

Absolute values of acidity constants in water have been computed for a series of substituted phenols. Explicit solvation model was utilized, and statistical perturbation theory with Monte Carlo and molecular dynamics was employed to obtain free energy changes in the condensed phase. Comparison of results produced with a polarizable (pff) and a fixed-charges force fields demonstrates that, while the latter leads to pKa errors of several units, the former allows an accuracy level of ca. 0.8 . It should be emphasized that the pff was not fitted specifically to reproduce acidity constants, and the accuracy of the calculations stems purely from its ability to correctly reproduce responses to changes in the electrostatic environment.

233.

MODELING METAL AFFINITIE AS A FUNCTION OF INTERMOLECULAR FORCES. ***Marvin Charton**, Chemistry, Pratt Institute, Brooklyn, NY 11205, Fax: 718-722-7706, mcharton@pratt.edu*

Metal ion affinities (MA) of organic compounds XY where X is a variable substituent and Y is constant have been reported in the literature for Li and Na ions. We have modeled their variation with structure on the assumption that only ion-dipole, ion-induced dipole, and steric effects ar involved. For X=alkyl only polarizability, the number of alkyl groups, and steric effects need be considered. Excellent results were obtained when steric effects were accounted for by the sum of the number of branches at the first and second C atoms of the alkyl group and polarizability by the sum of the number of C atoms in the alkyl groups. Y studied included O, S, OH, SH, and Cl. When Y is alkyl and X varies The correlation equation used the bond moment of the X-C bond and A polarizability parameter based on group molar refractivies. The results indicate that this model does account for the structural dependence of metal affinities.

234.

NEW FORMULATION OF NON-EQUILIBRIUM SOLVATION AND SOLVENT EFFECT OF ELECTRON TRANSFER. ***Xiang-Yuan Li**[1], Ke-Xiang Fu[2], Quan Zhu[1], and Min-Hua Shan[2]. (1) College of Chemical Engineering, Sichuan University, Chengdu 610065, China, Fax: +86-28-85407797, xyli@scu.edu.cn, (2) College of Physics, Sichuan University*

The energy change accompanying with the changes and should be expressed as . If the dielectric properties are not changed, , hence works. However, in establishing the final field of non-equilibrium, the dielectric properties are altered. By using the denotation by other authors, the two-stage approach is written as . Adopting the linear response, the work done in the 2nd stage will be

. The total work done for establishing is deduced to . This is the central expression of our work and is quite different from the traditional one. The average solvent reorganization energy for the forward and inverse ET is. We conclude that the current theory overestimates this quantity by a factor of about 2. equals to for two-sphere ET. Our formulations give satisfactory explanations for the discrepancies before.

235.
SELF-ENERGY OF REACTION FIELD AND SOLVATION SHIFT OF SPECTRA. ***Ke-Xiang Fu***[1], *Quan Zhu*[2], *Xiang-Yuan Li*[2], *and Zhen Gong*[2]. *(1) College of Physics, Sichuan University, Chengdu 610065, China, Fax: +86-28-85407797, (2) College of Chemical Engineering, Sichuan University*

Novel formulations of solvation shifts of spectra have been developed in this work. Two independent approaches have been adopted and consistent expressions for solvation shifts have been obtained. By analyzing electrostatic free energy of a solvation state, equilibrium or non-equilibrium, we have concluded that interaction energy between solute charge *r* and the reaction field equals to but the self-energy of reaction field is zero. In the case of point dipole and sphere cavity, our form of solvation free energy for non-equilibrium is quite different from those by other authors, here, and. Based on this new expression of , we have established the solvation shift of for absorption and that of for fluorescence. The total spectral shift is deduced to. Our work reveals that there exist faults in the current theories of non-equilibrium solvation.

$$\frac{1}{2}\int_V \varphi\rho \mathrm{d}V$$

$$\Delta G_2^{\mathrm{non}} = -(1/2)(R - R_{\mathrm{op}})\mu_2\ \mu_2 - (1/2)R_{\mathrm{op}}\mu_2\ \mu_2$$

$$R = (1/a^3)[2(\varepsilon - 1)/(2\varepsilon + 1)]$$

$$R_{\mathrm{op}} = (1/a^3)[2(\varepsilon_{\mathrm{op}} - 1)/(2\varepsilon_{\mathrm{op}} + 1)]$$

$$\Delta G_2^{\mathrm{non}}$$

$$\Delta h\nu_{\mathrm{ab}} = (1/2)(R\mu_1 + R_{\mathrm{op}}\mu_2)\cdot(\mu_1 - \mu_2)$$

$$\Delta h\nu_{\mathrm{em}} = (1/2)(R\mu_2 + R_{\mathrm{op}}\mu_1)\cdot(\mu_2 - \mu_1)$$

$$(1/2)(R - R_{\mathrm{op}})\cdot(\mu_1 - \mu_2)^2$$

236.
INFORMATION FLOW IN MAP KINASE PATHWAYS. ***Melanie H. Cobb***[1], *Zhu Chen*[2], *Malavika Raman*[2], *Bing-e Xu*[2], *Byung-Hoon Lee*[2], *Lisa Lenertz*[2], *Tian Zhou*[3], *Xiaoshan Min*[3], *Svetlana Earnest*[2], *Stephen Stippec*[2], *and Elizabeth J. Goldsmith Goldsmith*[3]. *(1) Department of Pharmacology, University of Texas Southwestern Medical Center, Dallas, TX 75390, mcobb@mednet.swmed.edu, (2) Department of Pharmacology, University of Texas Southwestern Medical Center, (3) Department of Biochemistry, University of Texas Southwestern Medical Center*

Considerable structural information concerning MAP kinase cascades is becoming available from crystallographic and mutational studies. We are developing an understanding of the regulatory mechanisms within protein kinases and the basis for specificity as contributed to by protein interactions through noncatalytic sites.

237.
STRUCTURAL BASIS FOR PROTEIN RECRUITMENT TO THE ACTIVATED INSULIN RECEPTOR. ***Stevan R. Hubbard***, *Skirball Institute, New York University School of Medicine, 540 First Avenue, New York, NY 10016, hubbard@saturn.med.nyu.edu*

The insulin receptor is a transmembrane $\alpha_2\beta_2$ glycoprotein, a member of the receptor tyrosine kinase family. Insulin binding to the extracellular α subunits of the receptor induces a conformational change that facilitates trans-phosphorylation of specific tyrosine residues in the cytoplasmic β subunits. Several adapter proteins are recruited to the activated (phosphorylated) insulin receptor, including APS, a positive factor in insulin-stimulated glucose uptake, and Grb10/14, a negative factor. The insulin receptor is downregulated by the tyrosine phosphatase PTP1B. Recent crystallographic and biochemical data will be presented revealing the structural basis for recruitment of these proteins to the activated insulin receptor.

238.
PHARMACOLOGICAL INHIBITORS OF CYCLIN-DEPENDENT KINASES (CDKS) AND GLYCOGEN SYNTHASE KINASE -3 (GSK-3). ***Laurent Meijer***, *Station Biologique, Centre National de la Recherche Scientifique, BP 74, Roscoff, France, Fax: 33.2.98.29.23.42, meijer@sb-roscoff.fr*

CDKs regulate the cell division cycle, apoptosis, transcription, differentiation, as well as functions in the nervous system. GSK-3, an essential element of the WNT signaling pathway, is involved in multiple physiological processes including cell cycle regulation, development, insulin action, axonal outgrowth, neurotoxicity, and Alzheimer's disease. Over 50 CDK inhibitors and 10 GSK-3 inhibitors have been identified, among which 20+ have been co-crystallized with CDK2 and one with GSK-3. They all target the ATP-binding pocket of the kinases. The actual selectivity of most compounds, and thus the underlying mechanism of their cellular effects, is poorly known. Affinity chromatography using immobilized inhibitors provides one approach to identify the actual targets of kinase inhibitors. Pharmacological inhibitors of CDKs and GSK-3 are currently being evaluated for therapeutic use against cancer, neurodegenerative disorders, cardiovascular disorders, glomerulonephritis, viral infections and parasitic protozoa. The development of these inhibitors will be presented with two examples, roscovitine and indirubins.

239.
FROM CONSENSUS SEQUENCE TO HIGH AFFINITY LIGAND: ACQUISITION OF POWERFUL INHIBITORS FOR SIGNAL TRANSDUCING PROTEINS. ***David S Lawrence***, *Department of Biochemistry, Albert Einstein College of Medicine, The Albert Einstein College of Medicine, 1300 Morris Park Ave, Bronx, NY 10461, Fax: 718-430-8565, dlawrenc@aecom.yu.edu*

A wide variety of signaling proteins recognize and bind to specific amino acid sequences contained on other signaling proteins. These sequences can be readily identified using combinatorial peptide libraries. However, peptides possessing these preferred sequences ("consensus sequence peptides") typically display only modest affinities for the consensus sequence-binding site on the intact protein. We have developed a parallel synthesis strategy that transforms consensus sequence peptides into high affinity ligands. The strategy employs a series of spatially focused libraries that challenge specific subsites on the target protein with a diverse array of functionality. Final lead compounds display between 1,000 to 10,000-fold higher affinities for their protein targets than the starting consensus sequence peptide. In addition, these final leads exhibit impressive selectivity for the targeted protein relative to closely related signaling proteins.

240.
USE OF HIGH-THROUGHPUT NANOVOLUME CRYSTALLIZATION IN STRUCTURE-BASED DRUG DESIGN. ***Jeffrey A. Stafford***, *Department of Chemistry, Syrrx, Inc, 10410 Science Center Drive, San Diego, CA 92121, jeffrey.stafford@syrrx.com*

Knowledge of the atomic structure of a targeted protein provides a considerable advantage in both the lead generation and lead optimization phases of a drug discovery program. Recent developments in high-throughput, nanovolume crystallography have greatly facilitated the solution of protein structure within gene superfamilies, such as kinases and proteases. The application of rapid and

iterative, structure-based drug design (SBDD) utilizing this enabling technology will be discussed.

241.
INSIGHTS INTO AGC-KINASE INHIBITOR BINDING FROM STUDIES WITH PKA. ***Dirk Bossemeyer***[1], *Michael Gaßel*[1], *Christine B. Breitenlechner*[2], *Satur Herrero de Vega*[1], *and Richard A. Engh*[3]. *(1) Signaling, Cell Biology and Cancer, German Cancer Research Center DKFZ, INF 210, D-69221 Heidelberg, Germany, Fax: +49 6221 423259, d.bossemeyer@dkfz.de, (2) Strukturforschung, Max-Planck-Institute für Biochemie, (3) Department of Medicinal Chemistry, Roche Diagnostics GmbH, Penzberg*

PKA is a prototype protein kinase and also a representative of the AGC-kinase subgroup which comprises important members, such as PKB/AKT, PKC, ROCK, or PDK1. Cross selectivity of small molecule protein kinase inhibitors as a consequence of the homology of these kinases is a common phenomenon. This offers the possibility to use wild type or mutated PKA as substitute for other members of the AGC-kinase group in order to elucidate inhibitor binding properties. We solved crystal structures of active PKA in complex with various inhibitors, such as the Rho-kinase inhibitors Fasudil, H-1152P or Y-27632, or PKC-selective bisindolyl maleimides to explore aspects of selectivity and binding affinity. H-1152P also occupies an additional binding site at a critical site of kinase regulation. Molecular modelling of the clinical phase III inhibitor LY333531 into the electron density of the bisindolyl maleimide molecule reveals features of its probable binding mechanism.

242.
EFFICIENT CONFORMATIONAL OPTIMIZATION METHOD. ***Jianwei Che***, *Computational Discovery, Genomics Institute of the Novartis Research Foundation, 10675 John Jay Hopkins Drive, San Diego, CA 92121, jche@gnf.org, and Ebru Demet Akten, Chemistry, Scripps Research Institute*

Determining the equilibrium conformations of ligand molecules in ligand/receptor complexes is one of the most difficult challenges in molecular modeling. We introduce here an efficient optimization algorithm for fast convergence to minimum energy conformations in ligand docking. Our approach consists of representing the flexible ligand molecule with hierarchical clusters and rescaling the potential energy gradient by a factor related to the size of the cluster. Rescaling results in a more homogeneous distribution of atom movements when searching for optimal conformers. Several examples are given to demonstrate its advantages and efficiency. The limitations and a comparison with other methods are also discussed.

243.
BINDING TO AN RNA APTAMER CHANGES THE CHARGE DISTRIBUTION AND CONFORMATION OF MALACHITE GREEN. ***Thorsten Dieckmann***, *Chemistry, UC Davis, 1 Shields Ave., Davis, CA 95616, Fax: 530-752-8995, dieckman@chem.ucdavis.edu, Dat H. Nguyen, Department of Chemistry (UCD) and Biology and Biotechnology Research Program (LLNL), University of California-Davis and Lawrence Livermore National Laboratory, and William H. Fink, Department of Chemistry, University of California-Davis*

RNA plays a central role in many biological processes and is therefore an important target for drug development. In order to obtain a detailed picture of ligand structure and dynamics in RNA – small molecule complexes the Malachite Green binding aptamer was studied. The surprisingly asymmetric changes in the 13C chemical shift of the ligand methyl groups indicate that the dye undergoes changes in its conformation and charge distribution upon binding. The role of the RNA electrostatic field in this interaction was explored using ab initio calculations of the ligand structure and charge distribution. The results indicate that the uneven charge distribution in the RNA binding pocket provides a major contribution to the driving force of the ligand structural changes. The observation that not only the RNA adapts to the ligand in what is called adaptive binding, but the ligand itself also undergoes conformational changes, is crucial for the rational design of RNA ligands.

244.
ANALYSIS OF PROTEIN-SUGAR INTERACTIONS. ***Pranav Dalal***[1], *Laura L. Thomas*[1], *Nathan N. Aronson Jr.*[2], *and Jeffry D. Madura*[1]. *(1) Department of Chemistry and Biochemistry, Center for Computational Sciences, Duquesne University, 600 Forbes Avenue, Pittsburgh, PA 15226, Fax: 412-396-5683, dalal@duq.edu, (2) Department of Biochemistry and Molecular Biology, Univ. of South Alabama*

To elucidate protein-sugar interactions we compare sequence and structure of two homologous families of proteins; one having a glycoside hydrolase activity (family 18 chitinase) and another possessing only sugar binding activity for the polysaccharide chitin [poly N-Acetyl-β-D-Glucosamine $(NAG)_x$]. The proteins that have been studied are the chitinase *S. marcescens* Chitinase A (SmChiA) and three proteins from the latter family that are involved in tissue remodeling, mouse Breast Regression Protein (BRP39), human Glycoprotein (GP39) and goat Mammary Gland Protein (MGP40). In addition to our homology model of BRP39, we present results from docking studies of $(NAG)_x$ with these proteins that either hydrolyze or only bind chitin polysaccharide. The implications of our calculations as pertaining to the molecular mechanism of these two families will be discussed.

245.
COMPUTATIONAL DOCKING AND OPIOIDMIMETICS: INVESTIGATION OF δ -OPIOID AGONIST AND ANTAGONIST RECEPTOR INTERACTIONS. ***Sharon Bryant***[1], *Lawrence H. Lazarus*[2], *Severo Salvadori*[3], *Remo Guerrini*[3], *Gianfranco Balboni*[4], *and Yunden Jinsmaa*[1]. *(1) Peptide Neurochemistry, National Institute of Environmental Health Sciences (NIEHS), P.O. Box 12233; MD: C3-04, Research Triangle Park, NC 27709, Fax: 919-541-0626, bryant2@niehs.nih.gov, (2) Peptide Neurochemistry, NIEHS, (3) Department of Pharmaceutical Sciences and Biotechnology Center, Universita di Ferrara, (4) Department of Toxicology, University of Cagliary*

Opioidmimetics with disparate bioactivities containing the pharmacophores 2,6-dimethyltyrosine (Dmt) and 1,2,3,4-tetrahydroisoquinoline carboxylic acid (Tic) were used to evaluate agonist and antagonist ligand interactions via molecular modeling and docking with the δ-opioid receptor. H-Dmt-Tic-3-[(1-H-benzimidazole-2-yl)-3,4-dihydro-1H-isoquinoline-2-yl] (1), H-Dmt-Tic-NH-CH_2-1-H-benzimidazole-2-yl (Bid) (2), H-Dmt-Tic-Gly-NH-Ph (5), δ-opioid receptor agonists (pEC_{50}=7.3, 9.9, 8.5; respectively), and H-Dmt-Tic-NH-CH_2-CH_2-Bid (3), H-Dmt-Tic-Gly-NH-CH_2-Bid (4), and H-Dmt-Tic-Gly-NH-Bzl (6), δ-opioid receptor antagonists (pA_2=8.3, 9.0, 9.3, respectively) were modeled based on the X-ray crystal structure of *N,N*$(Me)_2$-Dmt-Tic-OH (δ-antagonist) and extensive conformational searching of the C-terminal modifications. Four unique low energy conformers of each ligand were selected for docking with the δ-opioid receptor. The receptor was modeled based on the x-ray structure of the G-protein coupled receptor bovine rhodopsin using molecular dynamics simulations. The conformers characterized by agonist bioactivities displayed binding in two regions of the receptor. The first mechanism involved interactions between receptor residues Arg192, His 301, His274, Tyr129 and Dmt with the Bid and Ph groups in the aromatic pocket defined by Phe222, Trp274, Tyr308, Phe218, Phe270. The second mechanism involved interactions between Dmt and Asp128, Asp95, Asn131 and Gln105 with Tic near Trp 274 and Bid or Ph in the aromatic region. In contrast, low energy conformers of the antagonist derivatives displayed interactions in only one region of the receptor; similar to the first mechanism described for the agonist analogues. Although other studies have suggested that there is not a direct interaction between Asp128 and opioid ligands, this study implies that δ-agonists containing the Dmt-Tic pharmacophore may interact with residues in the region of Asp128 to activate the δ-opioid receptor.

246.
WITHDRAWN.

247.

MOLECULAR MODELING STUDY OF PYRAZOLOPYRIMIDINONE INHIBITORS OF CYCLIN-DEPENDENT KINASES. ***Karen A. Rossi***[1]*, Jay A. Markwalder*[1]*, Steven P. Seitz*[1]*, Chong-Hwan Chang*[1]*, Sarah Cox*[1]*, M Boisclair*[2]*, Leonardo Brizuela*[3]*, Stephen L. Brenner*[1]*, and Pieter Stouten*[4]*. (1) Pharmaceutical Research Institute, Bristol-Myers Squibb Co, P.O. Box 5400, Princeton, NJ 08543, Fax: 609-818-3545, karen.rossi@bms.com, (2) Mitotix, Inc, (3) Dept. of BCMP, Harvard Medical School, (4) Molecular Modelling & Design, Pharmacia*

Cyclin-dependent kinases (CDKs) and cyclins, their activating agents, play an important role in cell cycle regulation. Naturally occurring inhibitors of the CDK family are involved in tumor suppression, prompting us to pursue CDK4/cyclin D1 (K4D1) and CDK2/cyclin E (K2E) as targets. High-throughput screening resulted in an ATP-competitive CDK inhibitor with a pyrazolopyrimidinone core. A CDK4 homology model was built based on a CDK2/cyclin A crystal structure. The inhibitor was docked into the CDK4 model, yielding a binding mode that was consistent with available SAR. The binding model was ultimately validated by a subsequent CDK2/inhibitor crystal structure. A considerable shift in selectivity of K4D1 over K2E was rationalized by the binding model, which suggested key hydrogen bonding interactions between the inhibitor and residues K22 and H95 in CDK4 (K20 and F82 in CDK2). This demonstrates that small differences between enzymes can be exploited in the design of selective inhibitors.

248.

COMPUTATIONAL APPROACHES TO UNDERSTAND SELECTIVITY BETWEEN ESTROGEN RECEPTORS ALPHA AND BETA. ***Ray J Unwalla****, Eric S Manas, Christopher P Miller, and Zb Zhang, Department of Medicinal Chemistry, Wyeth Research, 500 Arcola Road, Collegeville, PA 19426, unwallr@wyeth.com*

The Estrogen receptor (ER) mediates the activity of estrogens in the regulation of number of physiological processes which includes the development and function of the female reproductive system and maintenance of bone mineral density and cardiovascular health. Two ER subtypes (ERα and ERβ) have been characterized and their distinct tissue distribution patterns and differences in their ligand binding activity and transactivational properties suggest that they may have a separate biological role. The possibility of achieving selective ligands, which have different potencies and functional activity for the two ER subtypes has prompted interest in development of selective ER modulators. From x-ray studies, it can be seen that the overall fold of the ligand binding domains of these two receptors is strikingly similar and only two changes fall within the binding cavity (ERβ Met336 - ERαLeu384 and ERβ Ile373- ERα Met421). We have used structure based approach to understand the possible role of these two residues on receptor selectivity. A variety of computational methods such as Docking, Quantum Mechanics and GRID were used to identify functional groups most likely to increase selectivity of one isoform over another. In this presentation we will describe the optimization of ERβ selective ligands and discuss the role of the various groups in selectivity.

249.

AB-INITIO MOLECULAR DYNAMICS WITH MAXIMALLY LOCALIZED WANNIER FUNCTIONS. ***Manu Sharma****, and Roberto Car, Department of Chemistry, Princeton University, Frick Laboratory, Washington Road, Princeton, NJ 08544, mmanu@Princeton.edu*

We present a novel formulation of ab-initio molecular dynamics which should be useful to simulate insulating systems. In this scheme maximally localized Wannier functions instead of delocalized Bloch states evolve on the fly during nuclear dynamics. Localized Wannier orbitals offer several advantages over orbitals that are delocalized in the entire simulation cell. In fact, at variance with the latter, they provide a picture of the electronic bonds consistent with simple chemical intuition. In addition, by taking advantage of their exponential localization it should be possible to develop ab-initio molecular dynamics schemes having a computational cost that scales linearly rather than cubically with system size. We show here that maximally localized Wannier functions can be calculated efficiently within Car-Parrinello dynamics and use water in gas and liquid phase as a test system to demonstrate our scheme and to illustrate its usefulness.

250.

AB INITIO MOLECULAR DYNAMICS STUDY OF THE AQUEOUS FORMATE ION. ***Kevin Leung****, and Susan B. Rempe, Sandia National Laboratories, MS 1415, Albuquerque, NM 87185, Fax: 505-844-1197, kleung@sandia.gov*

We perform ab initio molecular dynamics (AIMD) simulations of the aqueous formate ion. The hydration number of each formate oxygen is found to be consistent with recent experiments. The ab initio pair correlation functions and the hydration number, however, differ significantly from both classical force field results and hybrid quantum mechanics/molecular mechanics (QM/MM) predictions. Wannier function techniques are used to analyze electronic configurations along the AIMD trajectory, and the effects of varying temperature and the exchange correlation functional are also considered. Based on these AIMD results, we re-examine the hydration of simple biological species, such as the glycine zwitterion, which contain the carboxylate group and undergo tautomerization reactions in water.

251.

STRUCTURES AND DYNAMICS OF AIR-WATER INTERFACE FROM *AB INITIO* MOLECULAR DYNAMICS. ***I-Feng W. Kuo****, Chemistry and Material Science, Lawrence Livermore National Laboratory, L-370, PO BOX 808, Livermore, CA 94551-9989, Fax: 925-423-0909, kuo2@llnl.gov, Douglas J. Tobias, Department of Chemistry, University of California, and Christopher J. Mundy, Chemistry and Materials Science, Lawrence Livermore National Laboratory*

Stable air/water interface calculations were performedusing *ab initio* molecular dynamicssimulation based on the Car-Parrinello approach. The motivation behind thiswork is because the air/water interface is a recurring motif in many areas ofscientific interest, such as atmospheric chemistry, as well as being a mediumwhere many experiments are conducted in biological science. To model theair/water interface, a slab of water approximately 35A in depth was simulatedusing a 2-D periodic boundary condition on the pico-second timescale using *abinitio* molecular dynamics simulations. Fromthese simulations, we were able to determine the structure, dynamics, andelectronic properties of water near the air/water interface from firstprinciples.

252.

VIBRATIONAL SPECTRA OF 1-HEXANOL IN *N*-HEXANE VIA *AB INITIO* MOLECULAR DYNAMICS. ***John M. Stubbs****, Department of Chemistry, University of Minnesota, 207 Pleasant St. SE, Minneapolis, MN 55455, Fax: 612 626 7541, stubbs@chem.umn.edu, and J. Ilja Siepmann, Departments of Chemistry, Chemical Engineering and Materials Science, University of Minnesota*

Car-Parrinello molecular dynamics simulations were carried out for an ensemble of 1-hexanol aggregates solvated in *n*-hexane. The initial configurations for the CPMD calculations were size-selected from a distribution of aggregates obtained from a large-scale Monte Carlo simulation. The computed vibrational spectra demonstrate the extent of the contribution of “dangling hydroxyl groups” found in linear and branched aggregates to the “monomeric” peak. Furthermore, the computed spectra show that there is no simple relationship between peak shift and aggregate size.

253.

COMPARISON OF COMPUTED AND OBSERVED HEATS OF FORMATION. ***James J. P. Stewart****, Stewart Computational Chemistry, 15210 Paddington Circle, Colorado Springs, CO 80921-2512, jstewart@fujitsu.com*

Comparisons are made between experimental and calculated sets of heats of formation. Where results for specific molecules agree, it may be inferred that both calculation and experiment are accurate. The interesting cases are those where the results of calculation and experiment do not agree. A set of over 1000 gas-phase thermochemical experimental data from the NIST on-line WebBook will be compared with various semiempirical and DFT calculations.

254.

ERROR CORRECTION OF CALCULATED HEAT OF FORMATION. ***Li Hong Hu***, *Xiujun Wang, Lai Ho Wong, and Guan Hua Chen, Department of Chemistry, The University of Hong Kong, Pokfulam Road, Hong Kong, Hong Kong, lhhu@yangtze.hku.hk*

Despite of their success, the results of first-principles quantum mechanical calculations contain various errors. These errors, systematic or random, are caused by inadequate treatment of electron correlation, incompleteness of basis sets, the Born-Oppenheimer approximation, relativistic effects or approximated exchange-correlation functionals. We propose here a Neural Network based method to reduce drastically these errors. As a demonstration, the method is applied to improve the calculated heats of formation for 156 organic molecules. We find that the systematic deviations are eliminated and the remaining random numerical errors are substantially reduced. As a result the root mean square error is reduced from 25 kcal/mol to 4.7 kcal/mol.

255.

NOVEL LINEAR SCALING LOCALSCF METHOD FOR SEMIEMPIRICAL QUANTUM-CHEMICAL CALCULATION OF ULTRA-LARGE BIO-MOLECULES. *Nikolay A. Anikin[1],* ***Victor M. Anisimov[2]****, Vladislav L. Bugaenko[1], Vladimir V. Bobrikov[1], and Alexey M. Andreyev[1]. (1) Quantum Biochemistry Group, Konstantina Fedina-3 / 24, Moscow, Russia, aanikin@swf.chem.ac.ru, (2) FQS Poland, StarowisIna 13-15, Krakow, Poland, victor@fqspl.com.pl*

A novel variational linear scaling method LocalSCF has been developed for semiempirical quantum-chemical calculations of ultra-large molecular systems of biological interest. The method utilizes localized molecular orbital (LMO) approach and resolves the self-consistent field (SCF) task on a fixed atomic center expansion of weakly non-orthogonal LMOs. Developed for a popular PC platform the LocalSCF can handle 100,000+ atoms real life complex proteins. 10 steps of full geometry optimization on the 90,000+ protein (Hsluv Protease-Chaperone Complex, PDB id 1G3I) require 27 hours on a single processor Pentium-4 / 2.4GHz computer. The method allows simple control for balancing between speed and accuracy and for validation of the quality of the density matrix upon selection of a faster calculation mode. The biggest example calculated so far by the LocalSCF method is the GroEL-GroES chaperonin complex containing 119,273 atoms. The wavefunction calculation time for the fixed geometry of the protein takes less than 5 hours.

256.

SEMIEMPIRICAL STUDY OF CATIONIC POLYMERIZATION REACTIONS OF MONOMER SYSTEMS. *Andrew J. Holder[1],* ***Matthew D. Miller[1]****, J. David Eick[2], and Cecil Chappelow[3]. (1) Department of Chemistry, University of Missouri - Kansas City, UMKC, Flarsheim Hall, Rm 410h, 5110 Rockhill Road, Kansas City, MO 64110, Fax: 816-235-6543, holdera@umkc.edu, mdma95@umkc.edu, (2) School of Dentistry, Dept. of Oral Biology, University of Missouri, (3) Midwest Research Institute*

A computational study to determine reaction energetics was undertaken in support of research to identify novel dental restorative materials. Activation energies and reaction enthalpies were obtained by modeling various cationic reaction mechanisms using the AM1 semiempirical quantum mechanical method. Assuming similar steric effects for similar systems, these energies can be compared and relative reactivity inferred. The di-oxirane systems studied include 3,9-bis-(7-oxa-bicyclo[4.1.0]hept-3-ylmethyl)-1,5,7,11-tetraoxa-spiro[5.5]undecane and 3,4-epoxycyclohexylmethyl-3,4-epoxycyclohexane carboxylate. All possible combinations of the five nucleophilic sites and five nucleophilic attack sites were explored. The calculated results were compared with experimental results to verify accuracy and identify weaknesses of the methods employed.

257.

DESIGN OF A NEW FAMILIY OF MOLECULES CONTAINING PLANAR TETRACOORDINATE CARBONS. ***Alberto Vela[1]****, Gabriel Merino[1], and Miguel A. Mendez-Rojas[2]. (1) Chemistry, CINVESTAV, Av. I.P.N. 2508; A.P. 14-740, Mexico City 07000, Mexico, Fax: 525-747-7113, avela@mail.cinvestav.mx, (2) Department of Chemistry and Biology, Universidad de las Americas-Puebla*

By highly correlated ab initio methods and DFT calculations, it is shown that alkaline metals can stabilize planar tetracoordinate carbon containing molecules with the $C(C_4)$ skeleton. This family of molecules is C_5M_2, where M is an alkaline metal. The stability of these compounds is rationalized in terms of the delocalization of the p orbital perpendicular to the molecular plane, the global hardness and the electrophilicity. The analysis of several molecular scalar fields shows that the bonding between the C_5^{2-} dianion and the metals is strongly ionic. The structures reported are the first examples with a planar tetracoordinate carbon, surrounded by carbon atoms, and stabilized, only, by electronic factors.