EMERSON CENTER Newsletter

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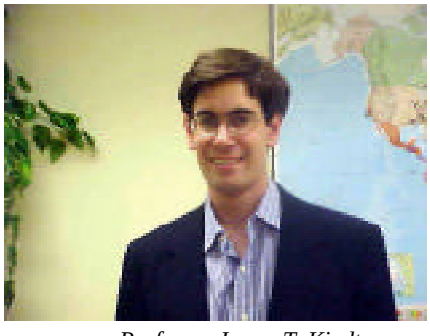
Inside This Issue . . .

COMPUTATIONAL CHEMIST JAMES KINDT JOINS EMERSON CENTER

The Emerson Center welcomes Dr. James Kindt, who has recently joined the Department of Chemistry as an Assistant Professor and a new subscriber to the Emerson Center. His office and laboratory are located in the Emerson Center on the 5th floor of the Cherry Logan Emerson Hall. Prof. Kindt's specialty is computational chemistry, in particular, modeling of biomolecular systems. He says that his primary research goal will be to explore, by computer simulation and theory, how lipid composition and molecular structure contribute to the organization and structure of lipid bilayers. He will be using Emerson Center's computational and graphic facilities extensively for his research. He recently received a prestigious New Faculty Award from the Camille and Henry Dreyfus Foundation. Prof. Kindt received his PhD from Yale University and was a postdoctoral fellow at UCLA before joining Emory. Please refer to page 3 of this newsletter for one of Prof. Kindt's research proposals using the Emerson Center facilities.



Professor James T. Kindt

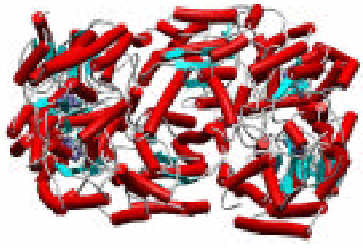
In the News

◆ ***Emerson Center Fee Change***

With approval from the Emerson Center Executive Committee, the Emerson Center subscriber fee is increased by 5% effective September 2001. The new fee will be $1312.50 for one unit and $5250 for one share. This is the first fee increase since the center's subscriber program started in 1992. This increase is necessary to meet the needs for increased costs in hardware and software maintenance and in the increasing personnel expenses. For details regarding the Emerson Center fee schedule and related subscriber benefits, please refer to the Emerson Center webpage at http://www.emerson.emory.edu/Cover/EC_Fee.html.

New Biomolecular Modeling & Visualization Facility at EC

In response to popular demand from the biomolecular modeling community at Emory and with grant support from the National Science Foundation, the Emerson Center recently established its new Biomolecular Modeling and Visualization Facility. This facility consists of one SGI Origin3200 as a compute server and two SGI Octane2 graphics workstations (with 2 processors each) for visualization and computing. The new facility supports a variety of biomolecular modeling software, including MacroModel, Sybyl, Cerius2, Amber and Tinker, some of which are available only on the SGI platform. The superb graphics engines will provide image processing and opportunities for many other applications. Technical details of the facility are reported on page 4 of this newsletter. This facility supplements the capability of the High Performance Computing Facility at Emerson Center, which was acquired in December 2000 and consists of an IBM SP supercomputer complex with 58 Winterhawk II CPUs. Anyone interested in trying out our new Biomolecular Modeling and Visualization Facility as well as the High Performance Computing Facility is encouraged to contact the Emerson Center.



NEWS FROM THE ECEC MEETING

The Emerson Center Executive Committee (ECEC) met on Thursday, Sept. 13, 2001, to discuss issues related to the new school year. On the agenda were administrative issues including membership, income & expenses, and the EC newsletter. A detailed technical report was presented by the center's scientific staff about the new SGI computer and related software purchase. Plans for 2001-2002 were discussed including budget issues, the Visiting Fellows Program, technical staff salaries and additional hardware upgrade of the center's equipment. A 5% increase to the subscriber fee was approved by the committee. Please refer to "*In the News*" section on this page for details about the increase.

Letters from Fellows

When I arrived to Emory in July of 2001 for a one-month stay I was certainly not a newcomer, neither to this Center nor to this fellowship. However, I was gladly surprised by the quality of the new installations in the recently built Emerson Hall, and by the substantial increase in computer power. This has made the stay even more pleasant and fruitful than previous ones, and this was certainly a demanding goal. Another substantial factor contributing to the fruitful visit has been the continued hospitality from Prof. Morokuma and Dr. Musaev. Ms Jianli Zhao has also been extremely helpful in solving the small administrative problems in which foreign visitors (or at least me) have a certain ability to run into.

Dr. Feliu Maseras

The scientific work during this stay focused on an analysis of the performance of quantum mechanics/ molecular mechanics (QM/MM) methods in the reproduction of steric interactions. I had the chance to contribute to the original development of one of these methods (IMOMM) during a previous stay. This scheme has proven to be very efficient for the introduction of bulky ligands in the accurate modeling of real transition metal complexes. However, as the applications of the method keep growing, it becomes critical to obtain a better understanding of its strengths and weaknesses. The goal of this visit consisted of evaluating the performance of different theoretical treatments on the reproduction of the steric interactions, which is the main feature of the IMOMM method. Several small model systems presenting the closed shell/ closed shell interaction characteristic of steric effects have been chosen, and submitted to calculations with a large variety of computational methods, including several force fields and high level quantum chemical methods. The current results, which are still not final, suggest that MM methods reproduce better the steric interactions than some of the lower range of QM methods, including Hartree-Fock. This has the interesting consequence that, in some particular cases, a QM/ MM calculation can be more accurate than a full QM calculation on the same system.

After this brief report of my research, I want to use the last paragraph of this letter to thank the Emerson Center Visiting Fellowship program for giving me the chance to visit this great center, and to inform all the readers of this Newsletter what a great opportunity these fellowships constitute to do research.

**Dr. Maseras is Associate Professor of Chemistry at Autonoma University of Barcelona, Spain. He stayed at the Emerson Center in the summer of 2001 with a fellowship provided by the Visiting Fellows Program at the Emerson Center.*

EMERSON CENTER VISITING FELLOWSHIP

The Emerson Center offers visiting fellowships to interested scientists throughout the year. Scientists from academic institutions all over the world who want to perform intensive research in computational chemistry, physics, and other sciences for one to several months are encouraged to apply. We also accept faculty on sabbatical leave. Postdoctoral research associates are not supported through this program. Travel expenses (and stipends for long term stays) are available. Although fully independent research is not excluded, collaboration with an EC subscriber is desirable, and EC subscribers are encouraged to make recommendations. The deadline for Emerson Center Visiting Fellowship applications for summer 2002-summer 2003 is February 1, 2002. To formally apply, please submit:

- *1-2 page research proposal*
- *CV including publication list*
- *Amount of financial support needed*
- *Length of stay with an approximate start/end date*

Applications should be submitted to the Emerson Center (address on p. 4).

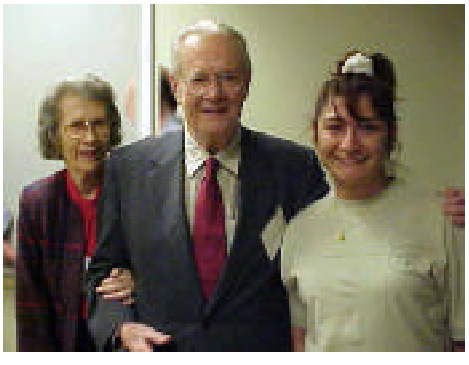
APPLICATION DEADLINE: FEBRUARY 1, 2002

My Stay at the Emerson Center as a Visiting Fellow

Dr. Ilkay Oren, Associate Professor, University of Ankara, Turkey

I would like to thank the Emerson Center for giving me the opportunity to work with Professors Dennis Liotta and James P. Snyder. I joined the Liotta-Snyder group on November 1, 2000. My stay at the Emerson Center has been incredibly pleasant and most educational in many ways. It is particularly exciting to be able to study with the excellent teaching, patience and guidance of Professor Jim Snyder.

When I came here I knew very little about computational chemistry. During my first three months, I focused on learning how to communicate with the computer network loaded with Macs and PC's, Silicon Graphics workstations and IBM mini-supercomputers. I was also introduced to several sophisticated pieces of software. For example, it was a delight to use the MacroModel force field engine, build structures, optimize their geometries and carry out conformational analyses. Following that, I became engaged in a project devoted to part of the biosynthetic pathway of the antitumor agent, Taxol. I had previously dreamed of working in this area, but was unsure whether the opportunity would ever present itself. Molecular Mechanics is insufficient to understand the pathway involving carbocationic intermediates. Therefore I had to learn how to use Quantum Chemical Methods. Ab initio and density functional theory (DFT) calculations with Gaussion-98 (at the Emerson Center) are both more appropriate and more accurate. While I was working on this project, I also started to focus on NMDA antagonists. These compounds are a potential remedy for the completely untreatable condition of stroke. During this second project I have learned how to search for pharmacophores using APOLLO. Now, I intend to apply PrGen to create a pseudoreceptor for the NMDA ligands. It will be so exciting…



Dr. Oren and Dr. & Mrs. Cherry L. Emerson at the Emerson Center Open House in April 2001

In addition, I have enjoyed very much having so many members of the Liotta-Snyder group around to talk with and share a game of badminton and volleyball. It has also been a pleasure to drink an evening coffee with Prof. Snyder and having lunch once a month with Emerson Center staff and other Fellows.

I appreciate Ben, Ami, Jim N, Pahk and Suzie for their constant willingness to help. Finally, I would like to thank the members of the Emerson center and Prof. Jim Snyder and Prof. Dennis Liotta for being so helpful in making my time so enjoyable.

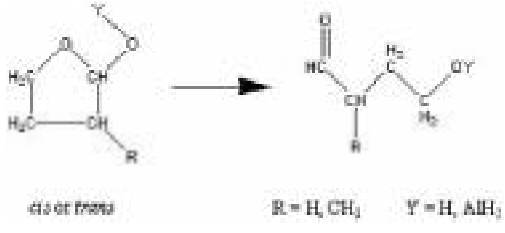
Report on Research Activities at the Emerson Center

The Emerson Center is supported, in part, by "subscribers" -- faculty members or research groups who purchase shares in order to gain access to its resources for their research projects. EC scientific staff members are also encouraged to conduct scientific research in their own areas of specialty. The following is a research report from Chemistry Department faculty member, Dr. Jonathan Rienstra-Kiracofe, along with a research proposal from the newest subscriber to the Emerson Center: Dr. James Kindt.

Use of EC facilities in Undergraduate Research

Reported by Dr. Jonathan C. Rienstra-Kiracofe
Lecturer, Department of Chemistry

During the past semester and summer, Emory undergraduate Jason Moon has been investigating the stereochemistry of substituted $C_4O_2H_6$ ring-chain tautomerism reactions [see figure]. This work is being done under the supervision of Dr. Jonathan C. Rienstra-Kiracofe, who joined Emory University as a lecturer in 2000. The isomerization reactions are closely related to the synthetic organic chemistry work performed by Emory undergraduates working with Dr. Jose Soria, who is also a Lecturer at Emory. Specifically, we have performed computations on the following reactions using the IBM SP supercomputers located at the Emerson Center:



*Our goal is to determine how the "cis" or "trans" stereochemistry of the ring isomer [2-hydroxytetrahydrofuran] is affected by the nature of the substituents (R, Y) on the chain isomer [4-hydroxybutanal]. Using the Gaussian 98 software available through the Center, we first obtained fully optimized geometries and associated vibrational frequencies for each chain and ring (cis and trans) compound. Initially, restricted Hartree-Fock theory was used, followed by computations with density functional theory (DFT). From each substituted chain compound, two transition states were located for most reactions – one leading to the cis ring tautomer and the other to the trans ring tautomer. Our preliminary results at the B3LYP/6-31G** level, indicate, regardless of substitution, that the chains are within 10 kcal mol^{-1} of the ring isomers and most corresponding transition states (whether cis or trans) lie approximately ~ 40 kcal mol^{-1} above the ring. Our work continues; we hope to refine our numbers with the CCSD and/or CCSD(T) methods and anticipate submitting our results for publication by the end of this semester (December 2001).*

The power of the Emerson computers has enabled us to perform these computations quickly and efficiently. Our largest system ($AlC_5O_2H_{11}$) requires optimized geometries and frequencies for four C_1 point-group molecules (ring, chain, and two transition states) at each level of theory employed. Such large computations, which run extremely slow on pentium-based PCs, have been made possible by the Emerson "SP2" and "SP3" supercomputer systems. Without the use of Emerson Center computers (available to us through the Emory Chemistry department) we would have been unable to perform our research.

Jason Moon is a senior at Emory and a B.S. chemistry major. He is able to receive college credit for his research. He plans on attending medical school or possibly graduate school next year.

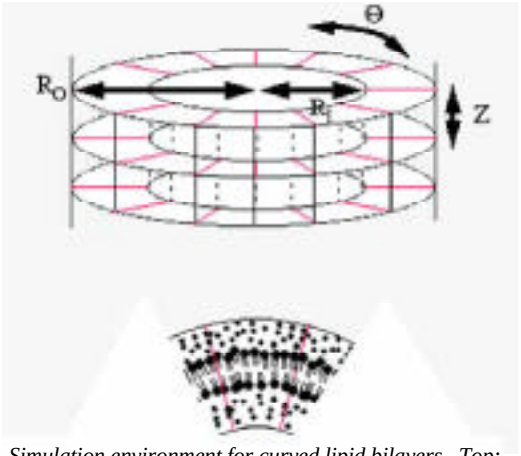
Understanding Biomembranes through Molecular Simulation

Research Proposal by Dr. James Kindt, Assistant Professor,
Department of Chemistry & Emerson Center

It is a pleasure and an honor to have joined the Emerson Center and the Chemistry Department at Emory. I am keenly looking forward to embarking on a research program, and particularly to my interactions with other Emerson Center faculty, staff, visitors, and students. The availability of computing facilities and expertise here frees me to focus on a vision for creating a research program in theoretical and computational physical chemistry with an emphasis on biological systems, a vision that I would like to outline here.

The lipid bilayer has long been a fascination of mine. This structure is formed spontaneously when lipids – molecules with a hydrophilic headgroup and two or more hydrophobic tails – self-assemble into a double layer of apposing sheets, with their hydrophobic tails facing inwards. This structural motif underlies the cellular organization of life – it is the basis for all biological membranes, those that define the boundaries of a cell and those that compartmentalize the space inside the cell. The lipid component of the membrane provides a flexible yet tough barrier for the cell, largely impervious to the indiscriminate passage of water and hydrophilic molecules. It serves as a medium for specialized "guest" macromolecules - membrane proteins and carbohydrates that regulate transport and communication across the barrier.

Computer simulation is a valuable tool in the study of bilayers, as has been proven by research in a number of groups over the past decade. The most realistic "snapshots" of bilayers available have been generated through molecular dynamics simulation, using methods and force-fields that have been carefully validated by comparison to experimental results. A typical simulation involves setting up a system consisting of a small patch of lipid bilayer – around 100 lipid molecules surrounded by several thousand water molecules – and using classical dynamics to allow the structure to evolve and exchange energy with an effective constant temperature bath. Because modeling the dynamics of these systems even over several nanoseconds of requires several weeks of processor time, I expect that our research will take full advantage of the computing power and molecular simulation software available at the Emerson Center.



Simulation environment for curved lipid bilayers. Top: packing of periodically repeating curved simulation cells, with cylindrical symmetry. Bottom: cartoon of cross-section of a curved bilayer in simulation cell.

In these simulations, our primary goal will be to address physical questions of general interest to membrane structure and energetics more

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Biomolecular Expansion of EC's Computational Resources

Jamal Musaev, Principal Scientist & Manager
Stephan Irle, Associate Scientist & System Manager
Emerson Center

We are pleased to report that our Biomolecular Modeling computers arrived in mid-May and has been heavily used since mid- June by EC subscribers who are active researchers in biomodeling. The facility consists of two SGI Octane-2 graphics workstations for visualization and computing, and one SGI Origin3200 as a pure compute server. The SGI Origin3200 (helix.chem.emory.edu) has two powerful 400MHz R12000 processors and 1GB memory, whereas the Octane-2 systems (ec-bio1.chem.emory.edu and ec-bio2.chem.emory.edu) have two 360 MHz RS12000 processors, 1.2 GB of memory, and V6 and V10 graphics equipment, respectively. The need for this latest addition to the EC hardware equipment arose from the necessity to provide a platform for biomolecular software that is only available on the SGI platform. The superb graphics engines, as well as their powerful processors running under the IRIX operating system substantially increase the diversity in compute platforms of the previous IBM RS/6000 based hardware equipment of the center and enables users to run an increased variety of applications, such as image processing and biomolecular modeling.

In order to make this system as user-friendly as possible, we unified our existing RS/6000 infrastructure with the new SGI equipment. NFS-mounted home directories, as well as user login ID's and passwords are the same for both systems. This gives the user the same look-and-feel on SGI systems as on the IBM's when logged in remotely, so that there is no need to remember additional accounts or remote-copy/ftp files between systems. Only slight changes in user configuration files are necessary when using the SGI-specific graphics software (located in /opt instead of libs and/or libs2) interactively.

In an effort to optimize the use of CPU cycles on the Biomolecular Modeling Facility, we implemented a queueing system (NQS) and installed a time-killer similar to the one that is running on our IBM machines. Interactive jobs are now allowed only on the Octane-2 systems, with a time limit of one full CPU hour. All other jobs have to use the queueing system, and we are pleased to report that we were able to put NQS under the control of IBM's LoadLeveler queueing system, which now controls all EC resources, including the SGI batch queues. This heterogenous queueing system we developed is unique and generic and allows us to add any type of computers (SUN, Compac etc) into the existing queuing system with minimum effort. The available queues are twodaysgi, onedaysgi, halfdaysgi, quicksgi (6 CPU hours), and fastsgi (1 CPU hour). Usage accounting is handled by LoadLeveler as in the case of our SP3 system.

Currently, the MacroModel_7.1, Sybyl_6.7, Cerius2_4.0, Amber_6.0, and Tinker software packages are available for Biomolecular modeling community at our SGI's. Our users can use those packages either in interactive or batch modes.

MacroModel is designed to minimize the energy of one structure or a series of structures, to eliminate duplicate conformations, to do conformational search and to conduct molecular dynamic simulations, including free-energy perturbation methods and mixed-mode Monte-Carlo/stochastic dynamic procedures. It includes MM2, MM3, Amber, OPLS, OPLS-AA, and MMFF94s force fields. User-friendly, front-end Maestro makes preparation of input files and analysis of the output files very easier.

Our users have 5-user (interactive) licenses to SYBYL/UNITE software. It includes Sybyl/Base, Advances Computing, Biopolymers, Dynamics, Molcad, FlexX, QSAR, UNITY and many other modules. Our users can run these modules interactively or in batch mode using Sybyl's NetBatch facility.

Amber_6.0 represents a significant change from the previous version, Amber_5.0. Briefly, the major differences include:

-A major re-write of the particle-mesh-Ewald implementation for molecular dynamics in *sander*,

- NMR refinements can be carried out with restraints derived from residual dipolar coupling measurements, or with "ambiguous" restraints whose corresponding NMR spectra are not fully assigned, or for "multiple-conformer" models generated using the LES algorithm.

- Solvent interactions can be approximated with a pairwise generalized Born model that uses continuum solvent ideas to simulate the electrostatic effects of water and of added counterions.

- The trajectory analysis program PTRAJ has been extended considerably, allowing for new analyses, including time correlation functions of interest in NMR and fluorescene anisotropy decay, and many others.

Users have unlimited access to Amber software.

Last but not least, we greatly appreciate the tremendous help and close assistance of Mr. Jim Nettles and Mr. Ben Cornett (from Prof. D. Liotta's group) during the initial setup of the Biomolecular Modeling facilities.

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than to obtain information specific to particular systems. One general property of membranes is their flexibility. Experimental studies have shown that a strongly curved bilayer is a significantly different environment than a flat bilayer, and that these changes lead to very different conformations of the lipids comprising the bilayer and at times to dramatic effects on the probability of "guest" insertion. Strongly curved bilayers are found in several cell and organelle types, and are also a feature of artificial lipid capsules ("liposomes") used in advanced drug delivery applications. We will develop new simulation methods to model curved bilayers in order to elucidate the molecular basis of these changes.

Other potential research projects include theory and simulation method development for studying mixed-lipid systems and the modeling of DNA translocation in chromatin. I would like to invite anyone interested in any of these topics to visit me in my office at E-521 Emerson Hall, call me at 712-1817, or e-mail me at jkindt@emory.edu.

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