COVER STORY

FROM THE ACS MEETING

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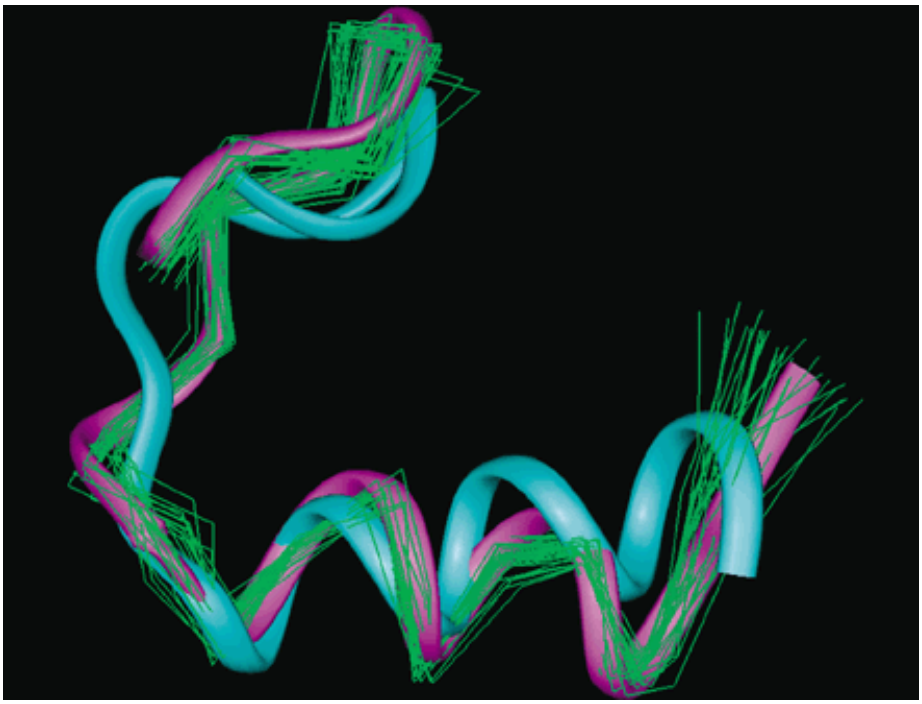
COMPUTERS & CHEMISTRY

Symposium speakers showcase new developments in computational chemistry



SUPERPOSITION Zinc finger mimic BB1 native structure (magenta and green) and simulated folded structure (blue). COURTESY OF R. LUO

ELIZABETH K. WILSON, C&EN WEST COAST NEWS BUREAU

Computational chemistry has infiltrated just about every subdiscipline of chemistry. Once-theory-shy experimentalists now routinely include calculations in their experimental papers. With this increase in popularity, the American Chemical Society's Computers in Chemistry Division is naturally eager to draw in more members.

To that end, the division is instituting speaking and poster contests, held at ACS meetings, to spread the word on everything from new strategies in

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protein folding to nuclear magnetic resonance (NMR) calculations to molecular dynamics. The national meeting in Chicago in August marked the division's second annual Emerging Technologies symposium, sponsored by Schrödinger, and the third CCG Excellence Awards poster contest, sponsored by Chemical Computing Group.

"The whole idea is to make sure people understand there are emerging technologies throughout the use of computers in chemistry," says the division's chair, David Spellmeyer, chief scientific officer and vice president of drug discovery at Signature BioScience in Hayward, Calif.

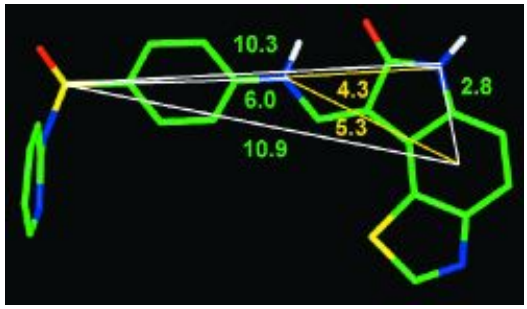
The strategy appears to be working. The division now has 2,600 members, up 13% from last year, compared with the average 8% membership increase for other ACS divisions, Spellmeyer says.

The Emerging Technologies contest, with its $1,000 award, is also designed to help encourage speakers to talk explicitly about their methodology, says the symposium's organizer, Donald B. Boyd, research chemistry professor at Indiana University-Purdue University. He hopes the contest, with its emphasis on substantive explanation, will help offset a trend of secrecy, where speakers gloss over their methods to protect potential commercial ventures.

The panel of computational chemists that judged this year's Emerging Technologies speakers included Spellmeyer; Curtis M. Breneman, professor at Rensselaer Polytechnic Institute; Wendy D. Cornell of Novartis; George R. Famini at the U.S. Army Edgewood Research Development & Engineering Center, Aberdeen, Md.; John McKelvey at McKelvey Computational Chemistry; and Peter S. Shenkin, vice president of software development at Schrödinger.

Together, the six competing presentations, which are summarized here, illustrated the breadth and depth of computational chemistry.

VIRTUAL CLUSTERS. A huge, frequently untapped scientific resource lies on the desktops of people who work in offices, from chief executive officers to administrative assistants: their computers.



FAST SCREEN Pharmacophoric points in oxindole B, found by SCAMPI on a virtual cluster. COURTESY OF C. KEEFER

Scientists like Christopher E. Keefer and his colleagues at GlaxoSmithKline in Research Triangle Park, N. C., frequently need lots of computing power to do lengthy and expensive chemical computations. But with limited funds for mammoth supercomputers or clusters, their research would ordinarily be curtailed.

A new strategy, however, is gaining popularity: A computer server harnesses the formidable collective computing power of hundreds of networked

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Donald B. Boyd

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desktop computers that for the most part lie idle. While someone's out to lunch or in a meeting, his or her computer can join the "collective" to help crunch huge databases or solve complex equations.

For example, Keefer's group has developed a new method to search compound databases for pharmacophores--spatial arrangements of atoms or functional groups that could confer biological activity. Such search programs are computationally intensive and generally don't work with big data sets, Keefer says. To realize the power of their new algorithm, they've set up their own version of this so-called distributed computing. With it, the program can analyze large numbers of compounds in days, rather than months.

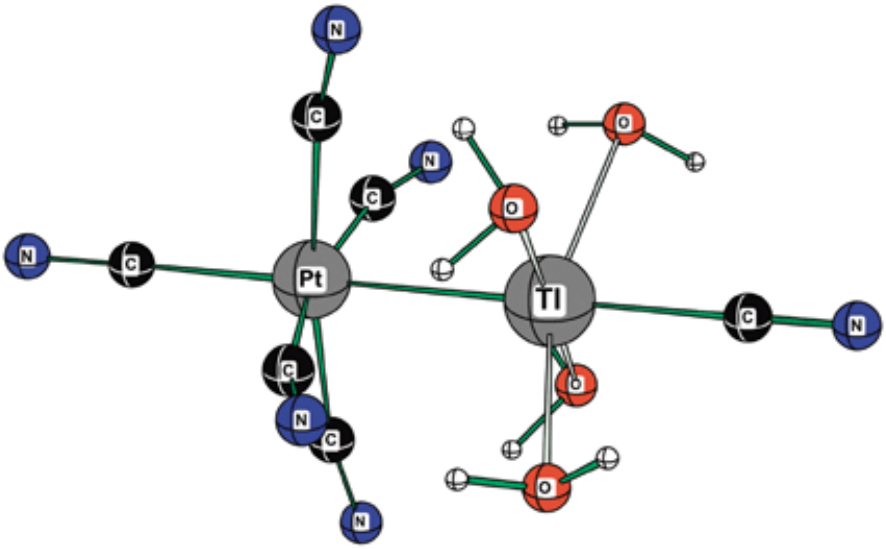
Keefer, who won the Emerging Technologies contest, describes the program, called SCAMPI (for Statistical Classification of Activities of Molecules for Pharmacophore Identification), which he wrote with colleagues Eric C. Bigham and S. Stanley Young. Their pharmacophore search method includes a technique known as recursive partitioning, which pares down an unwieldy list by comparing pharmacophores in two groups of compounds and throwing out the group with less active pharmacophores. The program then does more comparisons within the group of compounds it kept, repeating the process until it settles on a likely candidate.

Distributed computing was required to use SCAMPI on big data sets. "Here at Glaxo, everyone has an NT machine on their desk," Keefer says. "The reality is those machines are much more powerful than what a person needs to do typical work." Indeed, 80 to 90% of the time, the computer is not occupied.

Other companies are developing distributed computing strategies. Typically, a server directly contacts each machine, asking if it is available. But this can be disruptive, Keefer says. A server's frequent pestering can slow down a computer that someone is actually trying to use.

Glaxo's Virtual Cluster Services (VCS) program, spearheaded by Joseph D. Simpkins and Stephane Murphy, takes a passive approach: Idle desktop machines themselves send a signal to the server every couple of minutes to let the server know they're available. If the server can use another computer, that computer joins the group.

For a test of the VCS prototype, Keefer used 500 desktop computers volunteered by colleagues at GlaxoSmithKline. The results? SCAMPI "worked great," Keefer says. The program's search for pharmacophores in a database of 13,000 compounds took a little over three days--a drastic improvement over the eight months it would have taken if they'd used a more traditional computing system.



COMPLEX COUPLING Solvent water molecules affect nuclear coupling in Pt-Tl complex.

HEAVY NMR. Theoretical chemists have gotten pretty good at computing the NMR spectra of atoms in various environments. However, most of the molecules they scrutinize consist of routine elements such as carbon, nitrogen, oxygen, or halides.

But as the elements get heavier and more exotic, the picture gets more complicated. In the environment around the nuclei of heavy atoms, relativistic effects come into play. Two types of phenomena muddy the waters: scalar effects and spin-orbit coupling. The scalar effects include the relativistic mass increase of electrons close to a heavy nucleus, where its large positive charge slings electrons around at close to the speed of light. Spin-orbit coupling is a more complex interaction between an electron's spin and orbit. Both scalar effects and spin-orbit coupling have large effects on the electronic system and so affect the NMR spectrum.

Typically, heavy nuclei are treated in NMR computations with what's known as relativistic effective core potentials--the upshot being that while chemists can calculate NMR observables of light atoms or ligands surrounding the heavy atom, they cannot easily calculate the NMR involving the heavy atom itself.

But Jochen Autschbach, a chemistry postdoc at the University of Calgary in Alberta, and colleagues have devised a way to treat the heavy nucleus explicitly, using an approximation known as ZORA (zero-order regular approximation) combined with density functional theory.

With this method, they can calculate the standard NMR observables known as spin-spin coupling constants, which result from the interaction between the spins of nuclei in a molecule.

Their calculations revealed some curiosities. For example, it's generally been believed that for spin-spin coupling, scalar terms like the relativistic mass increase were the dominant effect, Autschbach said at the meeting. However, the researchers found that in molecules such as thallium halides, the spin-

orbit coupling dominated the relativistic effects. "That was quite surprising for us," he said.

In addition, they found that, despite their care in including all the relativistic effects in their calculations, their results for some species, such as linear mercury and square planar platinum complexes, did not agree with experiments: The coupling constant of the central metal atoms with one of its ligands was always too small. They soon recognized that this discrepancy occurred only when the metal atom in the complex was not completely surrounded by ligands.

Solvent molecules, they reasoned, must be affecting the result. "We found they had a very strong influence on the spin-spin coupling constants in every case," Autschbach said. "If we included a few solvent molecules, we had very good agreement with experiments."

FAST FOLDING. The typical state of biological molecules isn't the gas phase. Usually they're surrounded by billions of solvent molecules--frequently water. The effects of the solvent on the molecule's structure and behavior aren't trivial, and so computational chemists need to consider the solvent in their calculations.

To treat each solvent molecule explicitly as its own entity in a calculation is prohibitively time-consuming and expensive. So chemists have treated the solvent as a continuum, a homogenous swath that's much easier to describe computationally.

But for large biochemical systems like proteins, even continuum solvent models aren't good enough. Scientists turn to the Poisson-Boltzmann equation, which does a good job of modeling the system. Unfortunately, however, it's extremely difficult to solve. This bottleneck has vexed chemists like Ray Luo, assistant professor of chemistry at the University of California, Irvine. Because performing the calculation is so slow, it's generally used only for static systems.

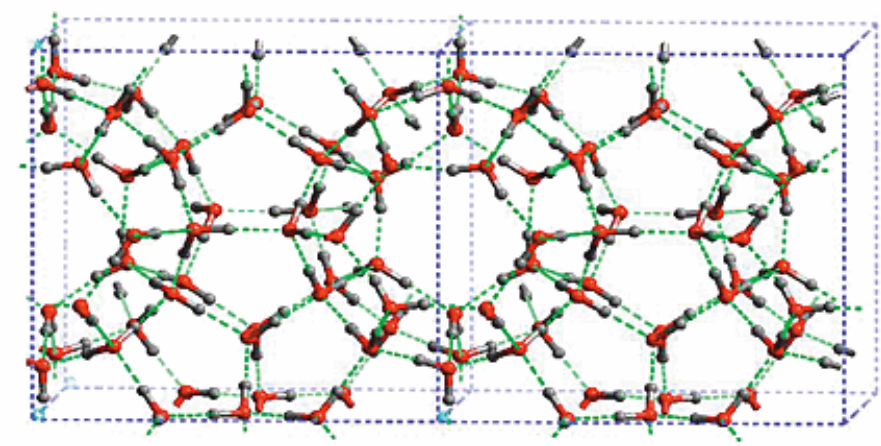
But Luo and his colleagues want to study protein folding, which requires doing molecular dynamics simulations. First as a graduate student with chemistry professor Michael Gilson at the University of Maryland, and then as a postdoc in the lab of the late Peter Kollman at UC San Francisco, Luo reworked the Poisson-Boltzmann approach, devising shortcuts and new strategies that have now made the Poisson-Boltzmann equation orders of magnitude faster to solve. And molecular dynamics simulations of protein folding using the new high-octane version of the solvent treatment are as fast as those in gas-phase simulations, Luo said at the meeting.

The group tested its method on small protein domains, first comparing their results with a previous simulation in which water molecules were treated explicitly. That simulation, of the folding of a villin headpiece (C&EN, April 24, 2000, page 39), took a month, while the new process took but a day. "It gave us confidence that this continuous solvent model approach seems to be good," Luo said.

Next, Luo modeled the folding of BB1, a zinc finger mimic which, with one a-helix and two b-strings, is the smallest stable protein domain. The protein

structure that resulted from the simulation, Luo said, is close to the real thing.

As Luo settles into his new professorship at UC Irvine, he's working to improve the method's efficiency and accuracy, he said.



CAGES Clathrate hydrate unit cell.
COURTESY OF B. TROUT

HOW CLATHRATES NUCLEATE. As scientists grapple with the knowledge that human

activity is increasing the planet's carbon dioxide levels in the atmosphere, some are studying the possibilities of releasing CO_2 directly into the ocean to buffer atmospheric CO_2.

In processes where CO_2 is injected into the ocean, curious solid materials known as clathrate hydrates, built of cages of water molecules containing CO_2, are formed. Not only do they inhibit the dispersion of CO_2, but they are also a possible CO_2 storage medium, as they may be a relatively stable solid at the temperatures and pressures of the ocean floor.

But little is understood about the mechanisms and rates by which clathrates form. Key to the process is the critical size at which a clathrate seed, or nucleus, can form, after which the self-organization of a disordered liquid into a solid proceeds rapidly. To answer these fundamental questions, Bernhardt L. Trout, assistant professor of chemical engineering at Massachusetts Institute of Technology, and his postdoc Ravi Radhakrishnan have developed a new theoretical approach that describes how the materials nucleate.

Previous attempts to understand nucleation phenomena have met with little success, Trout says. A fundamental flaw of classical nucleation theory, for example, is that bulk properties such as heats of formation, surface tension, and Gibbs' free energy of formation are used to describe tiny critical nuclei.

At the meeting, Trout, who holds MIT's Doherty Professorship in Ocean Utilization, described his group's approach, which is based in part on the order parameter method--a way of characterizing the order of a system. If a

substance is a liquid, for example, a particular order parameter will have a value of zero; if the substance is solid, the order parameter will be one. Numbers in between indicate levels of order between solid and liquid.

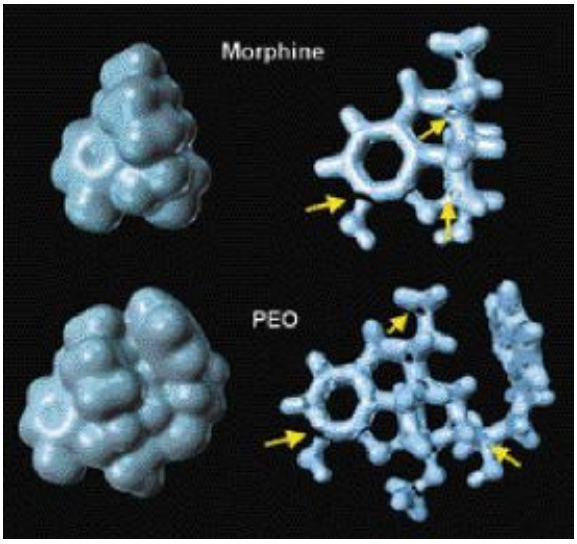
Also part of the approach are statistical Monte Carlo methods, which Trout uses to calculate the free energy of bringing a disordered mishmash of molecules into order--that is, of forming a critical nucleus. From this, he can get the critical nucleus sizes and rates of nucleation.

The clathrate of interest in CO_2 sequestration consists of cages made of water molecules with a CO_2 molecule inside, known as a clathrate hydrate. Trout's calculations show that the critical nucleus of a clathrate hydrate is 12 to 18 Å and that nucleation takes place on a timescale of roughly 0.1 second for a 2-cm droplet of CO_2. In contrast, classical theory predicts a critical nucleus of 31 Å.

The process of verifying these new predictions, Trout said, "will be a challenge for experimentalists."

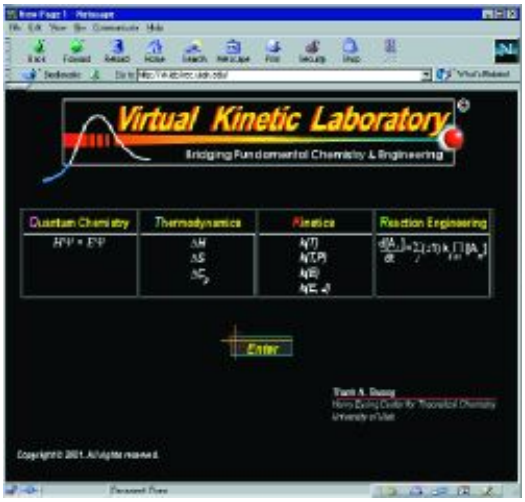
VIRTUAL KINETIC LAB. The beauty of academic computer programs is that they're available to anyone who asks for a copy. But unfortunately, distributing the programs and setting them up isn't always so easy. A scientist who may or may not be a computer expert--who, say, just wants to do a calculation to confirm his or her experimental results--might have an incompatible operating system or compiler. The result is hours or days of time spent wrestling the program into shape. And this does nothing to help get the word about a program out to the masses, either.

But a practical solution may be just a virtual step away--on the World Wide Web, says University of Utah chemistry professor Thanh N. Truong.



GROUP SHARING Opioid PEO and morphine share similar regions of local charge depletion and concentration. Structures on left indicate electron density; on right, reactive surfaces. COURTESY OF C. MATTA

Imagine a website that chemists can access in a heartbeat, where they can do theoretical calculations using state-of-the-art computational programs, exchange results with colleagues, teach a class, or search for kinetic data, without having to deal with their own computer systems. Truong is developing such a site, which he calls the Virtual Kinetic Laboratory. Scientists from China to Mexico have availed themselves of the virtual lab's prototype.



VIRTUAL LAB Do theoretical calculations at http://vklab.hec.utah.edu. COURTESY OF T. TRUONG

The lab includes programs, developed by Truong and others, to study, among other things, kinetics and thermodynamic properties of gas-phase reactions. For example, a scientist can upload his or her reaction data as a file simply by entering the file name, and the virtual lab will calculate the kinetic properties of the reaction.

The lab is housed on a computer server at the Henry Eyring Center at the University of Utah. It receives funding from the Department of Energy's Center for Simulations of Accidental Fires & Explosions at the University of Utah and the National Science Foundation's Information Technology Research Program. Eventually, as the number of users increases, Truong hopes national computer centers will take over as server hosts.

Truong hit on the idea of a virtual lab after scientists who wanted to use a program he'd developed kept encountering numerous headaches. "We got so many questions and problems with installing it, I said, 'This is not the way to go,' " Truong remarked. "If we want to make this method readily available to everyone, we should not make it troublesome to use."

Truong likens the lab's open-source philosophy--where computer codes are freely available and all information is shared--to that espoused by developers of the popular operating system Linux. "It's more like a community resource than a private resource," he said.

He also hopes to offset a little the trend toward keeping such information proprietary. "A lot of people come up with a tool, and close the doors," he said. "The Virtual Kinetic Lab is open so that people can take advantage of what is currently available."

OPIOID BREAKTHROUGH? Thanks to a new way of calculating chemical properties of what used to be computationally unmanageable molecules, scientists may have gained some valuable insights into structural biology and opiates.

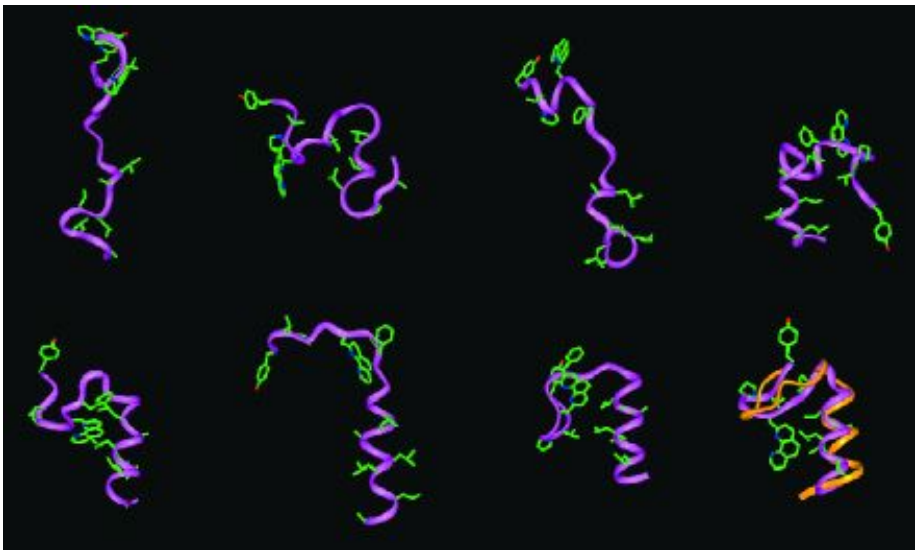
At the symposium, Chérif F. Matta, a chemistry graduate student at McMaster University, Hamilton, Ontario, explained his method of treating large, complicated molecules. The method is based on the quantum theory of Atoms in Molecules (AIM), developed by Matta's adviser, chemistry professor Richard F. W. Bader. With this theory, it's possible to extract chemical information on bonding and reactivity from the topology of the molecule's charge-density distribution.

Because functional groups contribute a certain amount to each molecular property in an additive way, Matta said, it's possible to judiciously split a molecule apart and do manageable calculations on the small pieces with AIM theory. One can then add the properties of the pieces together to reconstruct a whole molecule--a valuable strategy when dealing with molecules that are too big to be computed directly.

Matta described results of his calculations, which have been accepted for publication in the Journal of Physical Chemistry A, on a powerful synthetic opioid known as PEO. This molecule is the most active opioid receptor agonist known--5,000 to 10,000 times as potent as morphine--and activates the three different types of opioid receptors. But what functional group in PEO constitutes the pharmacophore is still being debated.

Matta found remarkable agreement between the properties of PEO computed using his method, and on the whole molecule. But most interestingly, he said, he found three stable conformations of PEO, which are very similar to three corresponding conformations of enkephalins--the body's natural painkillers. The natural and synthetic opiates contain groups of atoms and functional groups--such as two phenyl groups--that not only are similarly arranged spatially, but also have similar sets of atomic properties, Matta said.

The striking geometric and electronic similarity among three pairs of corresponding conformations of PEO and enkephalins suggests they might be the elusive biologically active conformations at the three known opioid receptor subtypes, Matta said. "But this suggestion needs much more work in order to be validated unequivocally," he cautioned.



FOLDING STAGES Zinc finger mimic BB1 folds (upper left to lower right); native structure superimposed on final result (yellow).

COURTESTY OF R. LUO

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STUDENT HONORS

CCG Awards Help Boost Computer Division Participation

Winners of the third round of CCG Excellence Awards were recognized at the ACS national meeting in Chicago during a ceremony at a poster session held by the Division of Computers in Chemistry. The awards were created last year to stimulate graduate student participation in the division's activities at ACS national meetings and are sponsored by Montreal-based software company Chemical Computing Group (CCG).

Awardees are selected on the basis of the quality and significance of their research and the strength of supporting materials in their application package, according to CCG Account Manager Pam Newton. The awards consist of a certificate, a one-year license of CCG's Molecular Operating Environment modeling software for the award winner's academic institution, and travel reimbursement (up to $1,150) to an ACS meeting where awardees present a poster or oral presentation on their research. An awards dinner following the poster session allows the students and their advisers to interact with other computational specialists from academia and industry.

The awardees in Chicago were as follows:

- Caterina Bissantz, department of applied bioscience, Swiss Federal Institute of Technology, Zurich, for her paper "Virtual Screening of Chemical Databases: Application of G-protein Coupled Receptors"; adviser: Gerd Folkers.
- Catherine Check, department of chemistry, Northern Illinois University, for her paper "Augmentation of the LANL2DZ Basis Set Under B3LYP and MP2 Models to Improve Calculated Results for p Block Elements"; advisers: Thomas M. Gilbert and Lee S. Sunderlin.
- Norge Cruz Hernández, department of physical chemistry, University of Seville, Spain, for his paper "DFT and Molecular Dynamic Study of ScN, TiN, and VN Materials"; adviser: Javier Fernández Sanz.
- Ohyun Kwon, department of chemistry, Auburn University, for his paper "Theoretical Studies of Main-Group Metallocenes"; adviser: Michael L. McKee.
- Nelaine Mora-Diez, department of chemistry, Dalhousie University, Halifax, Nova Scotia, for her paper "Theoretical Calculations in Atmospheric Chemistry: OH and NO_3 Hydrogen-Abstraction Reactions from Aldehydes"; adviser: Russell J. Boyd.

"We look at the awards as an opportunity for students to go to a major meeting and interact with other researchers, to see the latest in computational science, and to talk with people in industry," noted Bill Hayden, CCG vice president of sales and marketing. "And potential job contacts are always good for the students." Information on applying for the next set of awards is available on the Internet (http://membership.acs.org/C/COMP).--STEVE RITTER

JUST REWARDS **At the CCG Excellence Awards ceremony in Chicago were (from left) Newton; award winners Cruz Hernández, Check, Bissantz, Kwon, and Mora-Diez; and David Spellmeyer, 2001 chair of the Computers in Chemistry Division.**
PHOTO BY BARRY HART

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