



Brock University

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## Looking forward

In mid-January 2006, I initiated consultations with faculty members on the Strategic Research Plan (SRP) for Brock University. Over the next couple of weeks I will be meeting with a variety of groups on campus including the Graduate Council, Humanities Research Institute and the Chairs and Directors of the Faculty of Mathematics and Science.

The SRP will form the foundation for strategic investments in research, scholarship and creativity over the next five to ten years by identifying broadly based thematic thrusts. These thematic areas reflect existing research strengths at Brock University and identify areas into which faculty research and scholarship will expand.

The intent of the consultation is to lay out the external and internal environments in which research, scholarship and creativity exist and to create a vision to respond to those environments in ways that will that value all forms and methodologies of research, scholarship and creativity. Although it is impossible to create a plan that highlights the research interests of every individual, the intent is to include all forms of inquiry and expression.

The SRP will identify priorities. The SRP will also identify gaps that exist in the institutional infrastructure – gaps that need to be bridged in order for Brock to provide an optimal environment where research, scholarship and creativity can flourish.

In the next two weeks you will be receiving a report on the first phase of consultations with faculty members. We will also be creating an on-line feedback mechanism through which you can provide me with advice on the direction and content of the SRP.



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## Ambidexterity Is Not Always a Boon: Leading Chemist Works on Synthesis of Handed Molecules

Dr. Costa Metallinos joined Brock's Department of Chemistry as an assistant professor in 2003. Since then, his synthetic chemistry group has grown to the stately size of eight students plus himself, and he has opened his career here with the study of *N*-heterocyclic carbenes. Carbenes are interesting because of their developing role in the synthesis of chiral compounds.

Chirality, a characteristic of many molecules, plays a crucial role in their chemical and biological activity. Chiral molecules share identical chemical formulae, but are mirror images of one another. As an analogy to help us understand chirality, Metallinos uses

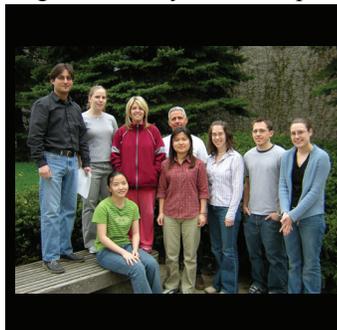
our own two hands. If for each hand you think of your palm as one kind of atom, your thumb as an another, and the four fingers as a third, then each of your two hands would have the same 'chemical formula' – something like  $\text{PALM}_1\text{THUMB}_1\text{FINGER}_4$ . Yet their actual three-dimensional structures are not quite the same, for if you lay your two hands on top of one another so that the palms face in the same direction, the corresponding fingers and thumbs don't overlap. Like chiral molecules, our hands are mirror images of each other. Actually, the hand metaphor is so natural that chiral molecules are often referred to explicitly as right- and left-handed.

"A really important aspect of modern synthetic chemistry is to be able to make molecules exclusively in left- or right-handed forms," explains Metallinos.

"That became important to pharmaceutical companies when thalidomide was available on the market in the late 1950's and early 1960's."

Thalidomide became last century's most infamous drug design (or misdesign) tragedy, and it is a poignant example of the difference that chirality can make in how a chemical interacts with the human body.

Until then, "people didn't appreciate the implications of chirality," says Metallinos. "Thalidomide was prescribed to pregnant women to alleviate



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morning sickness, but it caused major birth defects. Thalidomide came with both right- and left-handed forms of the active molecule. Although one of the forms was good at alleviating morning sickness, the other one was a teratogen that led to birth defects."

Drug companies now go to great lengths to create drugs that are purely left- or right-handed. Metallinos is working on novel reagents to facilitate the preparation of such products. *N*-Heterocyclic carbenes in particular are a new class of chiral molecule that may catalyze reactions to create products which inherit their chirality.

Different carbenes make possible different reactions to produce different products, and so the more types of carbenes that Metallinos' group can create, the greater the variety of molecules that may eventually be synthesized using them. And as it happens, the more product molecules the next researcher in line has

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to try out as candidates for a new drug, the greater chance they have of finding one that fits the bill. Hence, Metallinos is endeavouring to produce as wide an array of structurally new carbenes as possible in order to best open future possibilities.

"You can use computer modeling nowadays to give you at least a first approximation of what you need, but even with that level of sophistication, there's still really no substitute for actual experimentation," says Metallinos. Experimental chemistry proper dates back to the seventeenth century with the

discovery of oxygen, and has roots anchored much earlier. Today, hands-on chemistry remains the mainstay of the field, and there is no shortage of pressing problems waiting to occupy this leading chemist over the coming thirty years.

Dr. Metallinos is funded by NSERC and Research Corporation.

~ Giles Holland

## Theoretical Chemist Pursues Quantum Monte Carlo Models of Proteins

Traditionally, new drugs have come more by discovery than by design. Like bobbing for apples, good luck and personal intuition were more important tools of the trade than good planning or theory. Towards the end of the twentieth century, though, all this began to change with our nascent ability to actually understand and plan what we want to achieve on a biochemical level. A game of chance gave way to an art, which is at last giving way to a science.

Still, for the applied science of pharmaceutical design, many more discoveries lie ahead.

Dr. Stuart Rothstein in the Departments of Chemistry and Physics works at the theoretical foundations of this burgeoning field.

Rothstein explores the physics of molecules using computer simulations. Proteins, which are among the basic building blocks of life, are enormous compounds with highly complex structures comprised of many loops and strands, all of which are constantly in motion. Many drugs act by binding to proteins in the human body, so Rothstein is interested in modelling the dynamics of proteins and how they interact with other molecules.

Rothstein explains, "One can relate the mobility of the structure to the biological functioning of the protein. Right now, the codes that are used to model the response of a protein to another molecule are rather crude. They only look at what's happen-

ing in the neighbourhood of the smaller molecule, and only on a time scale of a few nanoseconds. We want to design more sophisticated algorithms to get a more realistic view of what's happening globally to the protein when it's interacting."

Unfortunately, current models employ only classical Newtonian considerations, ignoring the insights of contempo-

rary quantum physics. The models only show researchers part of the picture. Rothstein hopes to change that. "Quantum mechanical effects are probably quite impor-

tant," says Rothstein. "What I would like to do is quantum molecular dynamics where these effects are taken into account, and see how that approach changes one's predictions."

A computer methodology essential for doing just this is called Quantum Monte Carlo. Rothstein is one of two resident experts in this technique in Canadian chemistry departments.

"Quantum Monte Carlo is arguably the gold standard of theoretical chemistry," says Rothstein. "It gives the most accurate estimates with theory that you can get."

Unfortunately, the time needed to compute a molecule using Quantum Monte Carlo increases exponentially with the number of electrons in the molecule — double a molecule's size and you need eight times as much time to model it, presuming you can't find a computer that is

eight times faster.

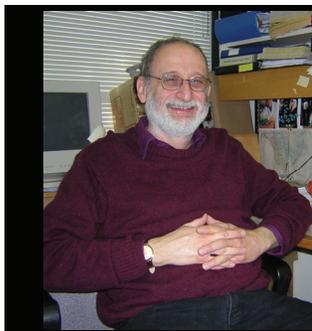
Rothstein explains, "It's currently just not feasible to throw Quantum Monte Carlo at a protein. Let me put this in perspective: A standard Quantum Monte Carlo calculation routinely takes weeks on a very, very fast computer for a molecule of, say, fifty atoms. And that's as opposed to thousands of atoms in a protein."

Rothstein hopes to solve this tug-of-war between accuracy and feasibility, possibly by melding Quantum Monte Carlo with older Newtonian techniques. It's an endeavour that he describes as "risky" and, at the present time, even "science fiction. But," says Rothstein with a smile, "that's what keeps me off the streets at night."

Theoretical physicists and chemists such as Stuart Rothstein have chosen to work behind the scenes in science. Short of rare individuals who happen to be in the right place at the right time, their science rarely attracts much public attention. However, like proteins in the human body, the theoretical bricks that Dr. Rothstein, his students, and faculty collaborators lay are the basic building blocks from which higher science is constructed, and upon which it ultimately rests. The tools that they are pursuing could be crucial for finding a cure for whatever ails you.

Dr. Rothstein is funded by NSERC, Research Corporation, and the Japanese Science and Technology Corporation. In addition to facilities at Brock, he makes use of SHARCNET, WestGrid and Niagara College computers.

~ Giles Holland



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