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Developments in the Theory of Protein Folding Simulations

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I would argue that, on the whole, a wrong approach is being taken to computer-aided protein engineering. The reasons for this controversial view are as follows. For many years we have been developing algorithms for treating the problem of predicting the structure and behavior of molecules. To do this we have sought, borrowed and adapted ideas from several areas of science, especially mathematics. More recently some new developments in mathematics have caused us to think in a rather different way about our algorithms, or, rather, these new developments have permitted us to overcome certain difficulties that we felt were there.

In brief, these new developments are about the behavior of simulation algorithms in general and about how to describe their behavior, possibilities, and limitations in the language of topology. In fact, a great deal of this is already inherent in control theory, but a number of recent extensions of this kind of mathematical area provide a more powerful general approach.

Except for the neglect of quantum mechanical phenomena, molecular dynamics provides us with the most complete description of the conformation and behavior of a system in terms of the phase space. The conformation and behavior of the protein, which is to say the essence of its being, is represented by a trajectory in this phase space, which is a space in three dimensions consisting of three coordinates (x,y,z) and the three momenta conjugate to them (px,py,pz) for every atom. Fundamental principles established from early this century and beyond establish the view that the main ways to envisage problems in the phase space are ways of topology (i.e., of the weaving of threads and sheets in multidimensional space). Modern developments in so-called nonlinear science, chaos theory and the like simply turn out to be in large part the sciences of solving iterative equations and interpreting their effects in terms of topology in multidimensional space. They also explicitly reveal the first glimmerings of the nature of the simulation algorithm, how to use external information from expertise and databases to direct the simulation toward a solution, and what we mean by a "solution" anyway. In short, molecular dynamics provides a route to a unification of the seemingly disparate concepts that the computer-aided protein engineer must employ.

Major advances in our programs for calculating the structures and properties of molecules have been made possible by these developments, and examples of these studies will be presented in the lecture in order to underline the fact that these theoretical advances can quickly find tangible, practical application in biomolecular computation.

An Area-Based Algorithm for Cast Shadows on Space-Filling Molecular Models

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The area-based algorithm for space-filling molecular models has been used to produce full color pictures with realistic shadows. Previous work could only "dim" atoms proportionally to the amount they were obstructed from the light source. This approximation gave soft, penumbra-like shadows, instead of the accurate, "hard-edged" "cast-shadows" that we are now able to achieve without ray tracing. The cost of the visibility calculations is independent of the raster, and the cost of the shadow calculations grows linearly with the resolution.

Space-filling molecular models are built from intersecting spheres with radii equal to the Van der Waals radii of the atoms they represent. The equilibrium distance between two nonbonded atoms under van der Waals force is represented as spheres that just touch. Shadows provide extra visual depth cues for understanding the three-dimensional structure of the molecule when it is rendered in a raster image.

One method to achieve such realism is to repeat the visibility calculations from the point of view of the light source. The visible regions are then transformed back to the final view, where they become the illuminated regions, while the rest remain in shadow. The new algorithm computes the visible portions of the atoms at floating-point precision from both the viewer reference and from the light source view. The information from these two calculations is then merged into a color image of the space-filling molecular model with cast-shadows, self-shadows and highlights.

The output of the program is kept in a flexible format that allows it to be rendered on anything from an 8-bit frame buffer to a 24-bit film recorder. This allows one to view the output on an inexpensive raster device before putting it out to film. In addition, the resolution can

be changed easily to take advantage of the output medium.

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An Educational Molecule-Building Simulation Using Interactive Computer Graphics

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A microcomputer simulation is presented that allows students to build molecules from the first 18 elements of the periodic table. Ball-and-stick representations of atoms and molecules can be manipulated to produce colored three-dimensional structures. This is accomplished by "breaking the bonds" of on-screen molecules and recombining the parts to form a new molecule. A total of 144 different molecules can be created in this way.

The Lewis structure is also shown for each atom and molecule involved. A "three-dimensional" picture of each individual atom can be viewed, showing all its nucleons and electron orbitals. Finally, the physical properties of the component elements and the completed molecules are presented pictorially (and with sound effects) to indicate color, state, melting and boiling points, acid/base properties, heat of reaction and toxicity.

Approved by the Ontario Ministry of Education as exemplary lessonware for high school chemistry classrooms, this microcomputer program with its extensive database is also being used in undergraduate instruction at the University of Toronto.

Applications of Artificial Intelligence Techniques in Conformational Analysis

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There are a number of different ways to describe a molecule's conformation. Numerically based techniques, such as energy calculation and molecular fitting, usually require the specification of the atomic coordinates and sometimes the atomic connectivity. However, this method is largely impractical for the chemist, who uses a more abstract description based upon groups of connected atoms (conformational units) about whose behavior he has some knowledge (e.g., "chair" cyclohexane). An important role of computer graphics is to provide the chemist with a means of interconverting between the numerical and the abstract descriptions.

We are developing an expert system, WIZARD–II, that aims to link these two approaches in the field of conformational analysis. The system generates high-level descriptions of a molecule by recognizing conformational units and the way in which these units are joined together. This then enables it to reason at an abstract level about the conformational possibilities available to the molecule. One application of such a system is in searching the conformational space of a molecule. If desired, the conformations it generates can then be minimized using a program such as MM2. However, in many cases, the initial conformations suggested by WIZARD lie very close to the structures obtained by energy minimization or by experimental methods such as X-ray crystallography. WIZARD can therefore be used on its own to generate structures that are good approximations to the minimum energy conformations.

This is in contrast with many of the alternative methods used to search conformational space. Such methods (e.g., torsion angle driving or random search techniques) generate an initial structure that is then driven to an energy minimum. There is frequently a significant difference between the structure initially suggested and that eventually obtained, and the minimization is therefore an integral part of such methods. Some important classes of molecules cannot yet be tackled by these techniques, as the necessary energy calculations cannot be performed (for example, because the molecular mechanics force field lacks some of the required parameters).

The conformational properties of many inorganic complexes and organometallic compounds have not been investigated for this reason, yet the ability to generate low-energy conformations for such molecules would be of use in a wide variety of fields. We are therefore investigating how the techniques employed in WIZARD can be applied to this class of molecules. We initially chose to examine transition metal coordination complexes because these show some similarities with the molecules previously investigated using WIZARD. We are now extending the system to cover a wider variety of similar molecules.

A New Approach to Rational Drug Design: Automated Structure Generation at Specified Binding Sites

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The goal of rational drug design is to construct *de novo* therapeutically useful ligands. This aim can be achieved only by a thorough understanding and description of the forces involved in molecular recognition and binding. Molecular graphics programs display regions of putative binding on protein surfaces; possible ligand binding sites can be found so that a profile of the active site can be constructed. This type of information could guide an automated structure generator; it is hoped that candidate molecules will be produced that match the hydro-