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-

gen-bonding, electrostatic and hydrophobic patterns found in the binding site.

HSITE is a program that finds the hydrogen-bonding sites on a receptor surface. It predicts the positions of maximum binding interaction, that is, the ligand points for the hydrogen-bonding groups in a putative ligand. It allows for free rotation within receptor residues and for steric clipping. The output from this program can be used to drive SITEFILL, which attempts to link up all the ligand points with viable, generated, chemical structure.

The process of structure generation can be divided into two sections. First, geometric templates must be generated to fill the binding site and occupy all the ligand points. Second, these templates have to be converted into feasible molecular structures by artificial intelligence methods so that the designed ligands are as complementary as possible to the site.

A planar lattice of atoms (a molecular skeleton) is placed within the receptor active site, and a fast distance-matrix algorithm is used to find the best prospective matches between the skeleton atoms and the ligand points. Each of these matches is optimally superposed on the site by a weighted, nonlinearly constrained minimization routine. The fitted skeletons are processed to remove redundant atoms and nonviable matches. These molecular templates can then be extended further to occupy any other ligand points within the site.

These programs have been used to examine the active sites of dihydrofolate reductase and trypsin. They have produced templates identical to known ligands and some novel structures. The templates can be used to constrain a molecule generator.

This new approach will allow the automated design of novel drugs where the structure of the binding site is known.

Advanced Microcomputer Rendering of Molecules

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The vast majority of molecular modeling and graphics systems have been implemented on mini or larger computers, supporting the manipulation and display of tens to hundreds of thousands of atoms. These tools have given researchers unprecedented insight into molecular structure and function. However, insight comes at a price. Single-user molecular graphics systems can easily cost $100,000. Moreover, some molecular modeling software is so complex that it can take as long as six months to learn. Such systems are not ready to be placed on every chemist's desk. Yet the need for less dedicated, less complex, and less expensive molecular modeling systems has fostered the design and development of microcomputer-based software for chemical and biochemical research.

Molecular modeling and graphics software that begins to address these needs is now available. We intend to review this software as well as present our recently developed package, MOPIC (MOlecular PICtures). In particular, results of our experiments with microcomputer implementations of algorithms for rendering shaded spheres and dot spheres will be presented. In addition, we will discuss antialiasing, shadows, and display in quantized color spaces as they relate to the representation of shaded molecular surfaces.

Vizualizing the Effects of Molecular Flexibility on Electrostatic Recognition

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We are interested in using graphics techniques to visualize the effects of molecular movement on the shape and surface of molecules and on properties of the molecule, such as electrostatic recognition. Superoxide dismutase (SOD), an enzyme that catalyzes the dismutation of the superoxide radical to hydrogen peroxide and molecular oxygen, was chosen as a model system because of the important role that electrostatic recognition plays in its action. Long-range electrostatic forces guide the superoxide substrate into the active site of SOD and contribute to the remarkably high diffusion-controlled rate at which the enzyme performs its function. The rapid action of SOD makes it possible to simulate the reaction at the theoretical level.[1,2]

The X-ray structure of SOD was used in earlier studies to depict the static behavior of the electrostatic field using a graphic representation of the electrostatic field strength and direction derived from the gradient of the Coulombic potential in shells progressively distant from the active site. This representation uncovered information about the action of SOD that was unattainable from looking at the crystal coordinates alone. The positive potential near the copper and zinc ions was found to be very high and extended outward from the active site, guiding the superoxide radical into the channel to dock with the copper. Contributions of residues distant from the active site to the electrostatic field were also found to be important.[3]

To portray the electrostatic forces in a dynamic fashion, various graphic representations coupling the molecular motions to changes in the protein electrostatics are being investigated, including different methods for driving the consensus surfaces upon which the fluctuations are visualized. Electrostatic surfaces and field vectors are calculated and color-coded by potential. Sets of coordinates describing the molecular motions are obtained through the use of normal mode analysis and molecular dynamics simulations. From normal mode analysis of SOD, coordinates that describe the low-frequency modes, which represent the more global