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

vibrations occurring in a molecular system, are chosen. From molecular dynamics simulations, coordinates from equally spaced time steps along the trajectory are selected. These two approaches provide views of the changes that occur in electrostatic recognition as the system undergoes a number of concerted motions.

These computer graphics studies will be used to develop tools that provide insight into molecular recognition and interaction at a sufficiently detailed level to guide future site-directed mutagenesis experiments, which, in turn, will provide verification for these theoretical methods.

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Molecular Modeling of Silicon Compounds

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Zeolites, both naturally occurring and synthetic, have found widespread application owing to their capacity for selective absorption and catalysis.[1] In recent years considerable effort has been directed toward the elucidation of zeolite structures and the mechanisms of their catalytic processes. This has included extensive diffraction studies, together with the recent application of high-resolution magic angle spinning NMR techniques. An alternative approach is to apply computational methods. To date these have mainly been carried out on small Si, O and Al clusters using *ab initio* or semi-empirical methods, and have been restricted as to the number of atoms under consideration.

A molecular mechanics model has been developed that can handle high silica zeolites. The first stage in this development was the extension of an existing empirical scheme for partial charge calculation to include silicon-containing molecules. During the parameterization it was shown that it is necessary to include both σ and π interactions between silicon and electronegative atoms.[2] Force constants to describe the vibrations of the Si–O fragments have been calculated from an extensive theoretical study, at various levels, carried out on a number of model compounds, including disiloxane, dimethoxy-dimethylsilane and silanol; the conformation of the cyclic molecule cyclotrisiloxane has also been investigated. Our calculations show the importance of including polarization functions in order to reproduce unusual structural featues of Si-O compounds.[3] Finally, our molecular mechanics model has been tested against experimental geometries for silicon-oxygen containing molecules, and geometries and experimental energy differences for a number of alkyl silanes.[4] In each case good agreement was obtained, validating our modifications to the MM2 force filed, the application of our charges to molecular mechanics calculations and the ability of the calculated force constants to reproduce experimental features of silicon compounds.

To conclude, a discussion of applications of this model to zeolite structure will be presented. This includes optimization of substantial zeolite fragments with full relaxation.

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Spatial Density Distributions for Illustrating the Base Sequence Dependent Features of Double Helical DNA: Computer Graphic Visualization of Monte Carlo Chain Simulations

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Computer graphics is proving to be an essential tool in understanding the conformations and properties of biopolymers. The bulk of molecular applications to date have been static representations of crystallographically observed or energy minimized three-dimensional (3D) structures. A growing number of procedures, however, are being developed to study chain dynamics. Particularly popular is the animation of Newtonian molecular dynamics simulations, providing a visual description of the small-scale fluctuations of specific low-energy structures. Detailed study of large-scale molecular motions by such methods, however, is not yet computationally practical. Large-scale flexibility is generally described in terms of simplified artificial models or through computational short cuts that force the system over preselected energy barriers. Little, if any, attention has been given to visualization of the large-scale changes of macromolecular structure (involving the crossing of multiple torsional barriers) expected on the basis of local conformational flexibility.

Large-scale macromolecular motions are best deduced from direct Monte Carlo simulations. Such methods are particularly appropriate to studying polymers with properties determined by the chemical constitution of individual side groups. Specific chain conformations are generated from randomly chosen combinations of backbone structural parameters. Sequence-dependent features of structure are included in terms of the statistical