In the past few years, molecular dynamics simulations have become an important tool for understanding the behavior of biomolecules, particularly in the areas of drug design and protein structure modification using site-specific mutagenesis. Conformational information is of most interest in the molecular dynamics trajectories. A major drawback of molecular dynamics is that it is difficult to focus on the low-frequency conformational motions due to the superimposed high-frequency motions.

I have developed a method for "filtering" out the high-frequency motions from the trajectory using digital signal processing techniques. The atomic trajectories are treated as a "signal," and using Fourier transforms the high frequencies are filtered out, which allows the conformationally important low-frequency motions to be seen easily. A related novel development is the ability to follow the changes in the distribution of energy as a function of the frequencies of a molecule. The energy distribution can be computed using Fourier transforms of the square of the mass weighted coordinates. By applying a sliding Fourier transform across the trajectory, the change in the energy distribution as the molecule is undergoing conformational motion can be monitored.

The techniques have been tested on small molecular systems, such as N–methylacetamide and a blocked alanine residue. Normal mode dynamics trajectories, from energy minimization and normal mode analysis of these small molecular systems, in addition to molecular dynamics trajectories, were used to demonstrate the validity of the methods.

These methods have been applied to a dynamics trajectory of phospholipase A_2. This enzyme plays a key role in the inflammatory response, and control of it is likely to be of therapeutic value in the treatment of diseases such as rheumatoid arthritis and atherosclerosis. In order to elucidate the effects of dynamic properties of the enzyme and ligands on binding, a molecular dynamics simulation was performed and analyzed using these new techniques. This is used to show the importance of conformational motions around the active site that determine the shape of the site.

These techniques are intimately connected with computer graphics because one of the few methods for conveying the results, particularly for the filtering, is as an interactive trajectory on a graphics system. A 16mm movie has been made using an Evans & Sutherland PS330 color vector picture system, and this movie will be used to show the results of these techniques.

A Role for Protein Frameworks in Modeling Tertiary Structures

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Protein databases can provide key information relating to valid tertiary structures for peptide chains. Such information is an important complement to energy-based methods for determining and refining models of protein structure.

Knowledge-based methods are becoming more widely used for reviewing closely homologous proteins as determinants of the three-dimensional structures of protein cores. The ability to search and model aggregates of protein secondary structure extends such methods by offering access to wider data sets, especially where they can be focused on salient protein classes, for it is important to beware of using indiscriminate data. This concept also broadens the searching of databases for loop regions, as it enables one to incorporate integral secondary structural components into protein substructure modeling.

The central role of secondary structure identity and definition in ChemProtein provides a key platform for extending knowledge-based searching to modeling with protein frameworks — in particular, when coupled to methods for mapping sequences onto known structures and versatile means of displaying and manipulating secondary structures.

Visualization of the Electron Densities of Atoms and Molecules

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Supercomputers provide a new way for researchers to predict chemical properties of unknown molecules or to understand the mechanism of chemical reactions. The theoretical basis is given as the molecular orbital methods. With the enormous power of supercomputers, the molecular orbital methods can now be applied to more complicated systems, such as drugs and liquid crystal molecules. However, since the computed result is given as a large matrix, consisting of just numbers called molecular orbital coefficients, it becomes more difficult to interpret the chemical meanings these numbers indicate, since the molecule is getting larger. The molecular orbital coefficients are related physically to the electron density of the molecules, that is, how these electrons distribute in the molecule. Since all the chemical properties have a strong relation with the electron distribution, it is important to know their distribution from the coefficients to connect the numerical result with the real chemical phenomena.

As electrons change their distribution very smoothly in the vicinity of the atoms having no clear boundary, they are sometimes called electron clouds. Therefore, even sophisticated computer graphics may not be appropriate to illustrate the electron density in a way as they are in the molecule-like clouds. Instead, to take advantage of modern computer graphics, two new algorithms are presented to visualize the electron density obtained by the molecular orbital calculations. One is named Multiple Cross Section Method. The other is

Equi-Density Surface Method. In both methods, emphasis is placed on the illustrations of three-dimensional (3D) images of the density and the relations between the molecular skeleton and the distribution.

The procedures of the first method are as follows: (1) Planes that cut the molecule are introduced and the values of the density are calculated on the planes; (2) the planes are reconstructed in a 3D way by evaluating the refrectance coefficients and then are displayed along with the molecular skeleton; (3) the molecular skeleton is illustrated by the ball-and-stick model and is overwritten on the density figure, keeping their 3D relations; (4) outside parts of the planes, which have lower electron density, are removed to get a better perspective view of the whole system.

The procedures to draw the density by the second algorithm are: (1) The equidensity surfaces are searched, starting from the given lattice density data, and the surfaces are drawn by using nets; (2) so-called hidden-line treatments are taken to make the relative position of each surface clear; (3) the molecular skeleton drawn by the ball-and-stick model is overwritten on the figure of the nets. To see the change of the inner shell electron distribution, the nets are adapted here instead of using the ray-tracing method, since the algorithm requests less CPU time.

VIEW — Visualizations Impromptu Evaluations Workbench

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There is no single "best" way to represent molecular structure data. The best visualizations are the ones that provoke the most profound insights, and which those are depends on what is being studied and who is studying it. To find the best visualizations, the scientist needs to try many different views.

The VIEW system is a workbench for experimenting with various molecular visualizations. The system provides a set of geometric primitives and visual attributes, such as color, transparency and glossiness. The user can make impromptu assignments of parameters from the molecular data to the geometric primitives and visual attributes. The system allows an experienced user to build complex visualizations, while the novice user can build simple views easily.

A VIEW visualization is built in two steps. First, one builds a model of a molecule. A model is a three-dimensional (3D) entity that represents the molecule. Brass stick-figure or plastic CPK models are familiar examples, realized in brass or plastic. VIEW models are realized in the computer's memory only, but they have all the other attributes of real 3D models. For example, we might choose to represent the backbone atoms of an insulin molecule as spheres, colored by atom type, and the side chains of the molecule as stick figures, colored by residue hydrophobicity.

Once one has a model, it can be looked at from any direction, at any zoom, and under a variety of lighting conditions, just as with a real model. The model is built independent of the display device and can be viewed on any of several displays. Depending upon the power of the display machine, the viewing can be done interactively or dynamically.

One can save views on film or tape. One can also save all or part of the model parameters and easily make other variants. For example, we could take our insulin model and change the residue hydrophobicity coloring scheme, or decide not to color the side-chain sticks by residue hydrophobicity after all, but rather color them all white. That would not require recalculating the stick-figure structure, or any part of the backbone model. Such a simple change can be done very quickly. Changes to the underlying geometric structure, such as changing the backbone representation to a ribbon, can take the system more time to rebuild the model, but it is still a simple change for the user.

The initial VIEW prototype is implemented on a Sun 3 workstation, using X-windows for the user interface, and the database facility of the Sybyl system from Tripos Associates. Supported display devices are Adage Ikonas 3000, Evans and Sutherland PS330 and UNC Pixel-Planes.

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RSPACE — A Reciprocal-Space Modeling Tool for Planning Area-Detector Collection Strategies

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When collecting data with area detectors, crystallographers are faced with the question of how best to sweep out a volume of reciprocal space for their particular crystal. An analytical solution to maximizing coverage and minimizing X-ray exposure time is not feasible because of the large number of poorly defined variables involved — how sensitive to radiation damage a crystal is, how useful the collection of redundant data might be and how significant the loss of some low-resolution data would be. To questions of this sort, it is hard to give quantitative answers, or to imagine all the permutations. Currently strategies are planned with back-of-the-envelope calculation, mental visualizations and hard-