

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<sub>2</sub>. 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.

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### **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.

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### **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