highly irregular surfaces, but where certain surfaces features endow the molecule with the property of specifically recognizing and binding to other molecules. In the case of globular proteins, these recognition phenomena include the binding of specific ligands that may alter the properties of the protein or of the ligand itself, and the association of the protein with other proteins, with sugars, nucleic acids, or lipids. In order to understand these phenomena fully, a complete audit of the various energetic contributions to the interaction is required, but it cannot have escaped the notice of anyone studying these processes that the shape of the complementary binding regions of two molecules participating in the binding is an important feature. The natural explanation for this is that the shape of a region on the surface implies a specific spatial distribution of the atoms, electrons, etc., which are responsible for the energetic contributions to the interaction, be it charge, van der Waals interactions, polarizabililty, and so on.

A new type of shape descriptor has been developed for use in the study of biomolecules, which is a three-dimensional (3D) version of a Fourier shape descriptor technique already developed for pattern recognition of 2D objects, such as machine parts and radar images of aircraft. The 3D version, which employs spherical harmonics, has been used to describe the surfaces of globular proteins[3] and the contact interfaces of protein-protein and enzyme-substrate complexes.[4] The coefficients obtained in the expansion in spherical harmonics represent the shape descriptors themselves, and their magnitude allows one to make a quantitative estimate of shape similarity between two shapes or between contingent surfaces on interacting molecules.

In the early stages of this work, only van der Waals surfaces have been considered, but the method is easily adaptable to the case of charge or other kinds of interaction.

Fourier methods lend themselves naturally to a consideration of spectral analysis. The methods employed here enable one to construct "shape spectra" of molecules. From such spectra for two molecules known to bind to each other, it is possible to extract the common features that correspond to their congruent surface binding regions. In this way it is even feasible to contrive routines for "automatic docking" of two molecules in cases where it is not known how they associate with one another.

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Molecular Graphics Software on a Raster Device

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Most recent developments in molecular graphics software attempt to drive raster device hardware. High-resolution and fast three-dimensional (3D) local transformations have been achieved in new graphics processors. At the Microbiology Lab, University of Liège, a Megatek 9300 is linked to a VAX 11/780 through an Ethernet interface.

On the same bus are connected several local processors with specific functionalities, such as real-time manipulations of 3D wire-frame and shaded objects and z–buffering with hidden-surface removal.

Through the Local Task Language, graphic objects refer to host entities that can be organized into a hierarchical database by FORTRAN-callable subroutines (APPRENTICE). Moreover, the communication protocol allows a full dialog between the application program running on the host and the graphic processor.

To begin with, two well-known programs have been adapted to the 9300:

- PAKGGRAF, from the Department of Biological Sciences of Columbia University, has extensive facilities for handling protein data sets, including connectivity changes, rigid motion of the whole molecule, or "jiggles," energy calculation and minimization. We have improved this last feature and written the visualization tools using interactive devices.
- FRODO, first written by Alwyn Jones (Wallenberg Laboratory, University of Uppsala, Sweden), is used worldwide by protein crystallographers as well as in molecular modeling applications. The graphic part of the E&S MPS (B.L. Bush, MSD and Co.) was converted into MEGATEK software, giving rise to an efficient real-time version.

At last, we have developed software for calculating and representing 3D electrostatic potential maps at the quantum chemistry level.

These graphic developments are the first step of a wider project that has to be seen as a more general program in the molecular interaction study.

Extracting Conformational Information from Molecular Dynamics Trajectories Using Digital Signal Processing Techniques

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New techniques will be presented that allow conformational information from molecular dynamics trajectories to be analyzed and displayed on interactive computer graphics systems.

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