Macromolecular Visualization: Some Advances and Future Challenges

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Introduction

Understanding the relationship between protein structure and function and the ability to predict a protein's role given its sequence or structure is the central problem in proteomics and the greatest challenge for structural biologists today. Visualization-assisted computational steering offers a powerful interaction environment for exploring such datasets in real time enabling superior insights into the underlying biochemical processes. Much of our research has been inspired by, and applicable to, the visualization and interaction with biological macromolecules. Multiresolution mesh hierarchies, view-dependent rendering, triangle strip generation, and variable-precision rendering have greatly helped in interactive visualization of static and dynamic molecular complexes. Our work on CPU-GPU cluster and large tiled displays is also building towards providing biochemists with a collaborative and active environment for visualization-assisted computational steering. We have also worked on specific problems in this domain including computation and visualization of molecular surfaces and electrostatics.

Molecular Surfaces

A *solvent-accessible smooth molecular surface* has been defined by Lee and Richards as the surface that an external probe sphere touches as it is rolled over the spherical atoms of that molecule. The probe sphere is typically assigned a value of 1.4$\mathring{A}$, the radius of the water molecule, although other values of the probe-sphere radius are also useful. The smooth molecular surface is useful for studying the structure and interactions of proteins, especially for testing the accessibility of a solvent in a molecule, for prediction of three-dimensional structures of biological macromolecules and assemblies, and for evaluating different docking conformations of molecules which can be used in drug design. We have devised a fast and efficient parallel algorithm for interactive computation of these surfaces through the development of the system, SURF, that rapidly computes and displays molecular surfaces and their interfaces. This has allowed the biochemists to (a) study the surface and interfaces of a molecule as its probe-radius is changed, (b) incorporate the effects of the solvent into the overall potential energy computations during the interactive modifications of a molecule on a computer, and (c) efficiently characterize the interactions during a protein-substrate docking and examine shape complementarity. SURF is being widely used by several research labs, universities, and the industry and has also been incorporated into the University of Illinois's VMD system and the IBM's Blue Gene project. Visualization of uncertainty is emerging as one of the significant challenges in the area of scientific visualization. However, the previous methods to compute the smooth solvent-accessible molecular surface assumed that each atom in a molecule has a fixed position without thermal motion or uncertainty. We have developed techniques to efficiently compute and visualize fuzzy molecular surfaces for atoms with uncertainty in their locations.

Molecular Electrostatics

Electrostatic interactions are of central importance for many biological processes. Experiments have shown that electrostatics influence various aspects of nearly all biochemical reactions, including macromolecular folding and conformational stability. Electrostatics also determines the structural and functional properties of biological samples, such as their shapes, binding energies, and association rates. The successful modeling of electrostatics has great practical importance in rational drug design and protein folding. We have developed a new method for efficiently computing and displaying the electrostatic potentials by explicitly generating and incorporating the solvent interface. This allows us to localize the discontinuities faster and more accurately. First, we analytically construct the solvent-accessible surface of the molecule and compute a distance field from the surface. We then construct nested iso-surface layers outwards and inwards from the surface using the distance field and adaptively adjust the density of the irregular grid based on the importance to the PBE solution using volume simplification. We build a 3D tetrahedral partition of the space directly from an analytically constructed interface layer and use an edge-collapse algorithm to control the density and uniformity of the grid. Our method is both faster and more accurate. We have generalized the finite difference methods using Taylor series expansion on the irregular grids. Our algorithm achieves about three times speedup in the iterative solution process of PBE, with more accurate results on an analytical solvable testing case, compared with the popular DelPhi V.4 system.

Future Challenges and Directions

In the near future some of the major challenges and directions our community should address (IMHO) are:

1. Move towards improved integration and interleaving of visualization with computation to enhable enhanced visual environments for better understanding and reasoning with macromolecules. This will include research into new data representations, algorithms, systems architectures, and user interfaces.
2. Facilitate visual comprehensibility of macromolecular complexes and their animations by incorporating principles of human perception as practiced in scientific illustration and art.
3. Establish generally agreed-upon principles that allow rapid adaptation of ideas from general graphics and visualization into molecular visualization (neighborhoods, uncertainty, gradients, continuity, etc.).
4. Evolve community-wide standards to enable distributed software development with plug-and-play software architectures.
5. Enhanced mechanisms for richer data sharing (beyond PDB) that includes molecular properties, attributes (computed or deduced), and visual annotations.