The BRUGEL Package: Toward Computer-Aided Design of Macromolecules

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Molecular modeling of large biomolecules encompasses today a number of different highly complementary aspects. These include graphic display of complex molecular models, computer simulations such as molecular dynamics and molecular mechanics, and comparison and analysis of different structures, as well as efficient access to databases. The advent of faster computers and more modular hardware architecture where networking is an important requirement, the proliferation of software standards and, most important, the increased demand and popularity of molecular modeling with molecular biologists, protein designers and drug designers, are calling for swift changes in many of the basic concepts of molecular modeling software.

Our efforts in responding to these recent developments within the BRUGEL package are described. BRUGEL is a fully integrated molecular modeling package especially suited for macromolecules. One of its most remarkable features is the manipulation of molecular objects (one-dimensional Boolean arrays that contain the value TRUE or FALSE for each atom). These objects can be created by a variety of user-defined criteria and by combination of existing objects using SET theory, and be subsequently used for all numerical or display manipulations requiring atom selection. A similar concept is also applied to tables containing numerical values (scalars, vectors). In addition, BRUGEL features programming tools for user-written functions and offers working solutions in a network environment. Its applications to the analysis of protein structure and function and to problems of protein design will be illustrated. The use of up-to-date software engineering techniques will also be discussed in view of the adaptability capacities of the product to future needs, to new algorithms and hardware solutions. Finally, we will discuss the different types of shading options we have developed on the Evans & Sutherland PS390 screen.

A Quantum Molecular Dynamic Free Energy Perturbation Method Applied to Chemical Reactions in the Condensed Phase

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A semiempirical quantum mechanical method is combined with molecular mechanics to obtain a potential function for studying chemical reactions in condensed phase systems. Molecular dynamics simulations based on this potential function are implemented to perform thermodynamic perturbation calculations. The method is utilized to calculate the free energy activation barrier for an S_N^2 reaction in solution. The results compare well with our experiments and those from other theoretical treatments. This technique is also used to study the isomerization of dihydroxyacetone phosphate (DHAP) to glyceraldehyde phosphate (GAP) catalyzed by the enzyme triose phosphate isomerase (TIM). Plausible pathways for the reaction are determined starting from the 1.9 Å resolution X-ray crystal structure for TIM complexed with the inhibitor phosphoglycolohydroxamic acid (PGH) (Davinport et al.). Energy profiles are calculated from these pathways and compared with experimental values (Knowles et al.). Calculations using a model with His-95 both singly and doubly protonated are carried out to investigate alternative mechanisms that result from the protonation state of this residue.

A 16mm film that accompanies this work shows the different aspects of quantum molecular dynamics.

A Fast Algorithm for Rendering Space-Filling Molecule Pictures

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Pictures that display the "surface" of a molecule are becoming increasingly important as X-ray crystallography and related techniques reveal larger and larger structures. This need is becoming particularly acute with the widespread current interest in drug design, where a very accurate impression of active sites is required for predicting complementary substrates.

To make a good "space-filling" molecule picture by computer, it is necessary both to determine which parts of the surface are visible from some viewpoint (hidden-surface elimination) and to shade this surface to make it look as if the model exists physically in space. Depth seems to be most strongly perceived if *shadows* are cast by the appropriate parts of the model on other parts when the model is lit by a simulated light source from somewhere behind and over a shoulder of the viewer.

Speed is a central concern, especially when a long series of images is to be computed, as in a movie. The new algorithm is designed to take special advantage of the relatively uniform spatial distribution of atoms in average molecules, and it happens that this algorithm is well suited to the shadow calculation, because the latter is nothing more than a hidden-surface elimination from the viewpoint of a light source.

The basic idea behind the new hidden-surface algorithm is to divide the "screen" up into a set of rectangular tiles, so that the data associated with each