The BRUGEL Package: Toward Computer-Aided Design of Macromolecules

P. Delhaise, M. Bardiaux, M. De Maeyer, M. Prevost,* D. Van Belle, J. Donneux, I. Lasters, E. Van Custem,* P. Alard and S.J. Wodak*
Plant Genetic Systems
and *Unité de Conformation de Macromolécules Biologiques, Université Libre de Bruxelles CP160, P2, Avenue P. Héger 1050–Bruxelles, Belgium

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

Paul A. Bash, Martin J. Field and Martin Karplus
Department of Chemistry, Harvard University, Cambridge, MA 02138, USA

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

David Bacon and Wayne F. Anderson
MRC Group on Protein Structure and Function, Department of Biochemistry, University of Alberta, Alberta, Canada

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

tile is limited. Then a simple hidden-surface algorithm can be used on the limited data.

For example, if a van der Waals surface picture is being prepared, there might be, say, 50 atoms impinging on a given tile in projection on the screen. The specifications of the atoms are initially sorted by closeness to the viewer, and the new algorithm can then perform a very fast hidden-surface elimination for any given pixel within the tile. The algorithm starts with the atom closest to the viewer and works its way down the list until it gets to an atom that cannot possibly have a surface point closer to the viewer at the given pixel position than the closest atom yet chosen. In the language of computer graphics, this algorithm is said to use a priority list combined with z-buffering.

Once the hidden surfaces have been eliminated, and it is known which parts of the molecule are in shadow, the shading computation is straightforward and in the present case is based entirely on Chapter 16 of Foley & van Dam,[1] with specular reflections approximated using the Phong model.

This work was supported by the Medical Research Council of Canada through the MRC Group on Protein Structure and Function.

1 Foley, J. D., and van Dam, A. *Fundamentals of Interactive Computer Graphics*. Addison-Wesley, Reading, MA, 1982

Protein Surface Analysis: Qualitative Approach Using B-spline Functions and Quantitative Comparison

Nathalie Colloc'h and Jean-Paul Mornon
Laboratoire de Minéralogie-Cristallographie, CNRS, UA09 Université Paris VI et Paris VII, Tour 16, 4 place Jussieu, 75230 Paris Cedex 05, France

A new way to describe protein surfaces is suggested, bringing out the interesting potentially functional features to facilitate their analysis and comparison. The classical representation of molecular surfaces (often calculated with the algorithm of M.L. Connolly[1,2] is very efficient for detailed surface examination but is unsuitable for an overall view, the few significant features being buried in many small amplitude bumps. In order to improve this representation of protein surfaces, we use B-spline functions,[3] smoothing the surface iteratively from atomic details to overall shape.

The program SURSPLIN uses, as starting data, the solvent-accessible surface of M.L. Connolly and is interfaced with the general-purpose molecular modeling software MANOSK.[4,5] It could be added easily to other software.

Up to now, SURSPLIN has been employed to study and compare more than 50 macromolecules, mainly proteins. In addition to the well-recognized active sites, a small number of conical pits, about 7Å in diameter and depth, are often encountered among interesting and repetitive topological features observed on protein surfaces.

The above comparison also shows that the rugosity of protein surfaces is variable. Several proteins, such as Azurin, are particularly smooth; others, such as Ferredoxin, possess very complex and uneven surfaces.

Currently, the splined surface is displayed by three-dimensional (3D) grids with a 50% reduction of memory occupancy, in comparison with the corresponding solvent-accessible surface displayed as dots. Large macromolecule complexes, such as the icosahedral face of a virus, can therefore be handled. Using fine grids, the splined surfaces are also valuable in displaying features of small molecules.

To complement the SURSPLIN program, we have developed a program (SURSCOP) for the analysis and comparison of quantitative aspects of surfaces. SIRSCOP allows a count of the distribution in size of topological features at the surface of molecules, which is especially useful for proteins. Typical examples of results obtained with SURSPLIN and SURSCOP programs will be presented.

The programs SURSPLIN and SIRSCOP are available upon request to the authors.

1 Connolly, M. L. Solvent-accessible surfaces of proteins and nucleic acids. *Science* 1983, **221**, 709–713
2 Connolly, M. L. *Quantum Chem. Prog. Exchange Bull* 1981, **1**, 75
3 Dube, P. Preliminary specification of splines curves. *IEEE Trans. on Comput.* 1979, **C–28**, 4
4 Vaney, M. C., Surcouf, E., Cherfils, J., Morize, I., and Mornon, J. P. MANOSK, a new graphics program designed for macromolecular modeling. *J. Mol. Graph.* 1985, **3**, 123–124
5 Cherfils, J., Vaney, M. C., Morize, I., Surcouf, E., Colloc'h, N., and Mornon, J.P., MANOSK: a general-purpose graphics program for analysis of molecular and macromolecular structure and functions. *J. Mol. Graph.* 1988, **6**, 155–160

The Quantitative Measurement of Molecular Shape and of Binding Interfaces Using Molecular Shape Descriptors

Robert Bywater
Molecular Biophysics Department, Pharmacia AB, S–75182 Uppsala, Sweden

Within the field of molecular graphics, much effort has been devoted to displaying the molecular skeleton of complex biomolecules, providing an elegant demonstration of the way in which these molecules are constructed. There is, however, a need for displaying surfaces, especially if one is interested in carrying out docking or drug design studies. Here, too, some elegant methods exist; foremost among these is the method due to Connolly,[1,2] but these methods are of use primarily for display purposes and do not give any quantitative measure of shape or of differences in shape.

The molecules of interest in biological processes are characterized *inter alia* by well-defined but apparently