Interactive computer animation of macromolecules

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Conformational properties of complex macromolecules are studied using a number of simulation techniques including energy minimization and molecular dynamics. Analysis of conformational parameters and their evaluation in the course of the simulation process is a crucial part of the study but proves to be an extremely tedious and time-consuming task. Software tools which incorporate computer graphics, animation and numerical operations in an interactive database environment, should make the process much more efficient. A system for performing interactive animation of molecular motion using the BRUGEL graphics package is described. By 'interactive' is meant not only control over animation speed but also the possibility of freezing the animation stream at will and analysing individual conformations with the same tools available for analysis of complex molecular models. This is implemented for two distinct animation cases: for non-affine transformations by streaming coordinate data from disc storage and for rigid-body movement by streaming orthogonal transformation matrices.

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Several simulation techniques are used today to study conformational changes in proteins. Molecular dynamics are used to study atomic movements on the sub-nanosecond timescale which usually involve small atomic displacements. Larger movements which involve concerted displacements of many atoms or those requiring the crossing of energy barriers have to be investigated by other techniques. These involve the use of energy minimization or molecular dynamics constrained along a predetermined reaction pathway[1,2], with minimization techniques predominantly used for large systems.

In both types of simulation, analysis of conformational parameters and their evaluation in the course of the simulation process are a tedious task. With the advent of faster and more versatile information processing tools, both in hard- and software, the use of a relational database may become the most efficient solution to the problem of analysing simulation data. Software incorporating computer graphics and animation in an interactive database environment should be more efficient still.

Here we show how interactive animation of molecular motion is accomplished using the BRUGEL graphics package and present some of its crucial features. After a brief introduction to BRUGEL, an enhanced version of PROGRAPH[3], we describe interactive animation for two distinct cases: non-affine transformations, via streaming of coordinate data from disc storage, and rigid-body movements, using a succession of previously generated transformation matrices.

In non-affine transformations, the transformed object is not a homogeneous linear function of the original object. In affine transformations it is. Rigid-body movements are a special case of affine transformations in which the shape of the transformed object is strictly conserved.

BRUGEL GRAPHICS PACKAGE

BRUGEL (for Biological Research Utilities, Graphics and Editing Language) has been designed for the visualisation and manipulation of biological macromolecules. It has now been implemented on the Picture System 2 and MultiPicture Systems from Evans and Sutherland, on PDP 11/34 minicomputers under the RSX11M operating system.

BRUGEL is made up of four cooperating tasks: GRAPH, EDIM, FIT and ANIMO, communicating via a system-wide, memory resident common block, as illustrated in Figure 1. Since RSX11M does not provide a Resource Lock mechanism, and to minimize usage of kernel resources, system calls are used only to start all cooperatives and to broadcast a so-called 'significant event' whenever a task has released the common block, while Common Interlock itself is controlled through flags in the common block, following an algorithm by Peterson[4].

The GRAPH task handles all interactive graphics manipulations, including overall rotation and translation, online geometric computations controlled by atom choice, rigid-body movement of parts of the displayed model along and about user-specified axes as well as about atomic bonds and the invoking, via the choice of items on a user menu, of the three other cooperatives.

EDIM handles input of molecular structure data from disc file and editing operations for display purposes. The complete coordinate datasets contain atomic coordinates, topological information, identifiers and labels for atoms, in BGF (Brussels Graphic Format). Datasets are implemented as direct access binary disc files which are scanned to produce the user-

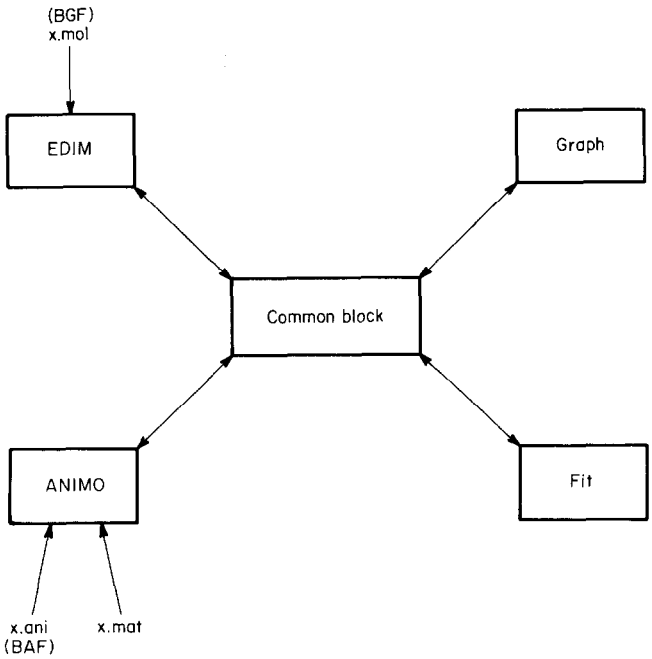

Figure 1. Schematic representation of BRUGEL. EDIM, GRAPH, ANIMO and FIT are the four cooperating tasks which communicate via the common block. The essential datasets are x.mol, the molecular dataset (in BGF); x.ani, the animation dataset for non-affine transformations (in BAF) and the dataset containing the orthogonal transformation matrices, x.mat

specified displayed object. Editing may be performed according to residue type, residue number or distance criterion (show all atoms within a given distance of a specified atom), or any combination of the above, together with control of the level of detail (C-alpha only, main chain only, all heavy atoms or all atoms). A fair amount of information about the selected subset, such as atomic coordinates or amino-acid sequence, may be examined via the terminal, and the original dataset can be accessed to replace incorrect entries.

FIT handles superposition of two user specified displayed items. Coordinate superposition is performed using McLachlan's EZEFIT[5]. Residual displacements values and transformation matrices are listed at the terminal, while the superimposed models are displayed and can be manipulated with all the tools made available in GRAPH.

INTERACTIVE ANIMATION IN BRUGEL

The power of animation as a pedagogical tool has been demonstrated by films on molecular motion such as those made by Feldman and Levitt[6] and Karplus *et al*[7], but has not yet been fully exploited as a research tool. The viewer has no control at all over what is being displayed and is therefore ill-equipped to analyse the animated images at any level other than visual. There have been reports of systems providing the user with some control in setting up the animation[8–10].

The system we describe here goes further in that it not only provides control over the animation, but also allows one to freeze and analyse interactively any frame with all of the methods available for analysing static molecular models. This is performed by ANIMO, the fourth cooperative in the BRUGEL package. ANIMO handles animation of non-affine coordinate transformations as well as rigid-body movements described by orthogonal matrices.

Interactive animation of non-affine transformations

Coordinate data represent molecular conformations generated by computer simulations such as molecular dynamics or conformational energy minimization, usually carried out in batch mode on mainframe or minicomputers. These are arranged on a direct access, binary disc file of 512 bytes per record in BAF (Brussels Animation Format). The first record holds information such as the total number of frames and the number of atoms per frame. The start of a new frame is marked by a record containing an identifier for the position of the frame in the animation sequence.

The user initializes BRUGEL by starting GRAPH which in turn initializes its three cooperatives. EDIM is then activated to read in a molecular dataset in BGF, corresponding to the molecule the user wishes to animate. Such a dataset always exists since it is also a mandatory input to the existing simulation programs. It is needed because it contains topological and labelling information that is not duplicated in the BAF file. If the user wishes to focus on specific parts of the molecule, EDIM can be requested at this point (as well as later, during or between animation sequences) to display only the portions of interest.

The animation session is initialized when the ANIMATION menu option is first selected. ANIMO is activated and prompts the user for the identification of the BAF dataset. Again using tablet control, the user may then start streaming in the coordinate sets corresponding to successive frames. In order to achieve a high streaming rate and thus a smooth visual effect, the display object is not rebuilt for every frame. Rather, ANIMO uses a list of pointers built by GRAPH after every EDIM activity, to patch new coordinates in their correct places in the PS2 memory, avoiding all kernel and driver overheads.

Because of memory limitations of the PS2–PDP system, the current version allows interactive study of only one coordinate set at a time. The user may however specify, at any time during or between animation sequences, any frame as fixed and permanent and use it as a visual reference while others stream by, as illustrated in Figure 2. BRUGEL treats the fixed frame as a static background object and the animated picture as a foreground object dynamically modified under user control. This control extends to the rate and direction (forward/backward) of streaming and, more important still, to the possibility of halting the stream to change view angles, scale factor, type of labelling, or evaluate geometric properties, of the current conformation, such as bond angles, dihedral angles and interatomic distances. An interrupted stream may, of course, be resumed at any time. The interactive capabilities are now being expanded to include computations on both the fixed and animated objects, of energy contributions, or of other properties to be evaluated and displayed while streaming.

Interactive animation of rigid-body movements

Some conformational changes involve correlated movements of a large number of atoms, of entire protein domains or subunits relative to one another. In such cases rigid-body displacements are coupled with changes in tertiary structure and it is therefore important to have all the necessary tools for analysing both components.

Animation of rigid-body movements is one of these tools. We will now describe how this is done interactively in BRUGEL, and illustrate its application to the study of the allosteric transition in hemoglobin.

The GRAPH program described above offers the option of interactively performing orthogonal transformations in a user specified coordinate frame. These may be applied to some part of the displayed model, previously defined as the 'moving object'. Animation is performed by streaming from disc to the PS2 Matrix Arithmetic Processor, a sequence of previously computed, 4 × 4 orthogonal matrices. As was the case for non-affine transformations, the level of detail of the displayed model is determined through EDIM, streaming may be interrupted at any time, and the current conformation analysed using GRAPH. The sequence of orthogonal matrices is computed offline from a set of matrices provided by the user and expanded by linear interpolation to achieve smooth animation as well as some measure of control over the streaming rate.

This animation procedure has been applied to the analysis of the allosteric transition of hemoglobin. A previously described systematic docking procedure[11,12] has been used to analyse the quaternary structure changes in hemoglobin. In it, human hemoglobin α–β dimers are associated into tetramers after being rotated into various orientations. The stability of the tetramers thus reconstituted has been estimated from values of a simplified energy function limited to non-bonded interactions, and from the area of the surface buried in

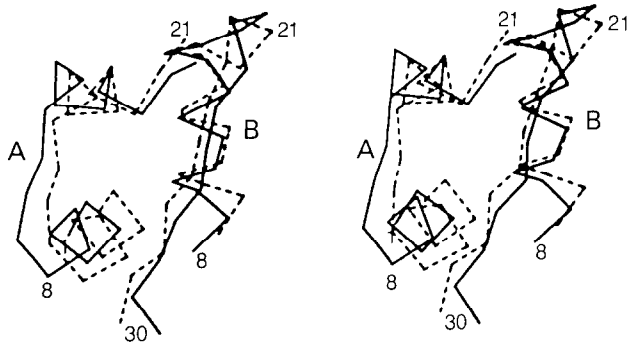

Figure 2. Animation of conformational changes in 2 Zn Insulin produced by energy minimization. The reference frame, here the starting crystal structure, is shown with full lines. The mobile frame, shown with dashed lines, represents one of the conformations sampled during the last stages of the minimization. For both frames, only Cα atoms are displayed. This particular minimization run involves 3000 energy evaluations and 150 stored intermediate conformations. The forcefield used is an older United Atom version (with polar hydrogens) which produces a 20% compaction in protein volume upon minimization in absence of solvent. This compaction is very striking in the animation

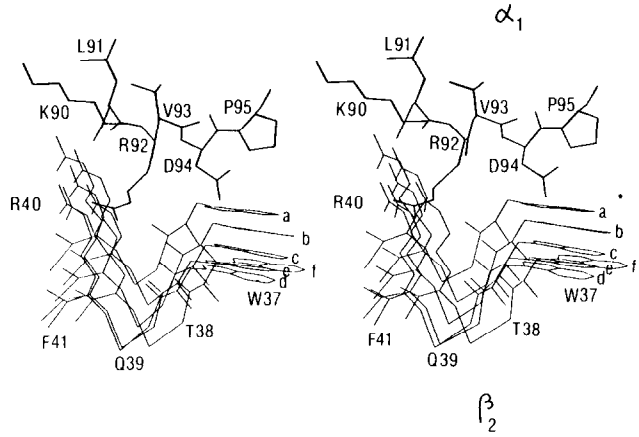

Figure 3. Animation of rigid-body movement applied to the allosteric transition in hemoglobin. Atomic positions are from the deoxy αβ dimers. Parts of $\alpha_1\beta_1$ shown in heavy lines are kept fixed. Dimer $\alpha_2\beta_2$ moves relative to dimer $\alpha_1\beta_1$ by applying orthogonal transformations computed from ref. 12. It is shown to occupy successive intermediate positions ranging all the way from the T state (Deoxy-Hb) to the R state (Co-Hb). These positions are marked a *to* f *and represent contacts between the FG corner of α_1 and the C helix of β_2. The region shown includes residues 90 to 95 of α_1 and 37 to 41 of β_2. Only the Cα atoms are shown for β38, β39 and β41*

dimer–dimer contacts, which have been taken to represent stabilizing interactions and solvent contributions.

Systematic analysis of tetramers reassembled from rigid dimers with twofold symmetry reveals that, when the dimers have the R tertiary structure, only tetramers having R-like quaternary structures are stable. On the other hand, dimers with the T tertiary structure may associate into T-like tetramers, or into a variety of quaternary structures ranging from T to near R, thus tracing a plausible reaction pathway for the allosteric transition.

A detailed analysis of the dimer–dimer atomic contacts in intermediate conformations along the proposed pathway has been carried out using the interactive animation procedure described above. A set of linearly interpolated matrices representing the pathway for the quaternary T to R transition was deduced from the docking analysis. An animated display of the transition was then made for regions of interest in the α1–α2 and α1–β2 interfaces, as illustrated in Figure 3. The corresponding animation sequences were also recorded in real time on 16 mm film.

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