NEW PROGRAMS

ADAPTU: Animated dynamics analysis program at Tübingen University

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Molecular dynamics calculations are being used more and more in computational chemistry to investigate inter- and intra-molecular properties, as well as to determine structures. Visualization of a calculated trajectory is needed to allow a detailed analysis of the huge amount of data generated by such calculations. In addition to animating trajectories, ADAPTU was written to permit diagram generation in two and three dimensions for a detailed analysis, the extraction and listing of properties of a selected conformation and the visualization of the development of constraints in a restrained dynamics. The displayed trajectory, as well as the three-dimensional (3D) diagrams can be scaled, translated and rotated, and displayed in cross stereo representation. Our graphics device is a E&S PS300 system, which is connected to a host by Ethernet or by an asynchronous line.

Keywords: molecular dynamics simulation, MDS analysis, trajectory visualization, distance constraints

INTRODUCTION

The analysis of molecular dynamics (MD) calculations is difficult without graphical representation of the trajectory because of the huge amount of data generated. Examining the animated trajectory as a first step may give the researcher a new idea of what to look for in detail in analyzing the MD results. This insight, however, and the detailed analysis has to be followed by a transformation of the four-dimensional view (three spatial coordinates and time) to a two-dimensional representation for documentation. In addition to the explicit verbal description of the trajectory, diagrams are used to show the main details. These diagrams are usually of atomic or residual fluctuations, the development of H-bonds, values of dihedrals versus simulation time, correlation functions or energy functions. The evaluation of such diagrams is best done in connection with the visualized trajectory.

In the last decade a new technique of structure determination has evolved and is being used more and more in MD calculations: By taking experimental distance information from two-dimensional nuclear Overhauser effect (NOE) spectroscopy experiments, solution structures (not only of small molecules) can be determined at high resolution. The main difficulties in this approach are the correct assignment of the measured results at the molecular level and the correct use of the distance information. The latter problem requires a detailed look at the development of constraints during the MD calculation and, possibly, a new analysis of the experimental data. Therefore the visualization of the trajectory alone is useless for NOE restrained dynamics calculations; a detailed interactive retrieval of molecular features during the animation of the trajectory should be possible.

ADAPTU was written as a simple tool to make most of these demands available for conventional and restrained molecular dynamics analysis.

HARD- AND SOFTWARE

The program is written in FORTRAN 77 running on a microVAX 3500 (without VMS specific code) as host and a 4-MByte PS390/PS350 (E&S) graphics system. The host and PS390/PS350 are connected by Ethernet or by an asynchronous line. Animation is performed by first downloading all frames (conformations) to the graphic controller and then displaying them frame by frame using the E&S Graphics Supporting Routines (GSR) level-of-detail function, which is either driven by a manipulatable clocking function or connected to a function key for manual stepping. Limiting parameters are 5 000 atoms, 2 000 residues and 1 000 frames. Before downloading the trajectory, the user must specify the atoms to be displayed and how they will be colored. This makes it possible to remove "uninteresting" atoms or groups. The complexity of display of a single conformation then determines the number of loadable frames with respect to the graphics controller memory. A loaded trajectory can be removed, so that another part, or a totally different, tra-

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jectory can be loaded. The program consists of about 4 500 lines (including comments), and the executable portion takes 591 blocks (303K). Using the E&S PSX emulation software, ADAPTU also runs on the UNIX E&S workstation.

We are currently rewriting the program using PHIGS/PEX as the graphics software.

INPUT

To ensure independence from a specific molecular dynamics program and to allow the use of a non-VMS host computer to calculate the trajectory, a single file is used as input. It contains atomic coordinates, atom labels (including residue label and number), bond information, constraint definitions, time and energies. The formatted ASCII file is transformed to binary format when it is read for the first time. This binary file is then used as "external memory" for the data needed to create the different diagrams. (Storing all information in the program would enlarge greatly the executable portion.)

The MD program package used in this work is AMBER,[2] running on a CONVEX C220. Therefore, a program for generating the ADAPTU input file was written to process AMBER's output data; it can easily be enhanced to other MD programs, if the trajectory file format is available.

DISPLAY

Rotation, translation, scaling, z-clipping and change of depth cueing are available for the structure, as well as crossed stereo representation. Hydrogen bonds are searched during the loading phases, and their display can be enabled or disabled. The criterium for a H-bond determination is that the distance between proton and acceptor be less than 2.5 Å and that the nonbond angle between donor, proton and acceptor be greater than 140°.[3-5] Constraints (e.g., NOEs) are shown in different colors: magenta for those distances shorter than the lower limit, yellow within limits, and red for distances longer than the upper limit. An overlay of a maximum of 10 selectable conformations is possible either by superpositioning the frames as they are calculated or by least-squares fitting. Using the latter, all atoms, backbone or other selected atoms can be used for fitting.

DIAGRAMS

Up to nine diagrams can be displayed: one permanently displayed diagram in the upper right corner of the screen and two sets of up to four switchable diagrams in the right margin. A bar in each diagram indicates where the displayed conformation is located in the trajectory. The contents of the diagrams can be chosen to be energy terms, interatomic distances or dihedral angles (defined by atom picking) or any other time-dependent data from additional files, such as correlation functions or rms fluctuations.

In addition to these two-dimensional diagrams a three-dimensional diagram can be loaded, which can be scaled, rotated, translated and shown in cross stereo. Input for this diagram may come from a file or may be computed directly; for example, in the case of NOE, distance deviation versus time and NOE number. In the case of protein or peptide dynamics mean values of the backbone angles ϕ and ψ, as well as their standard deviations, can be displayed. A three-dimensional diagram showing angle values as functions of residue and time is possible. These three-dimensional diagrams may be too complex for direct detailed analysis. By using z-clipping and strong depth-cueing, it is possible to investigate the development of a desired property with respect to the simulation time, by looking along the residue- or NOE-axis and scanning through the diagram surface by z-translation.

INTERACTIVE INFORMATION

In general, all points in the diagrams are selectable, whereby a selection displays the corresponding conformation. More informative selection can be switched on, giving simulation time and the corresponding function value. In addition, atoms and constraints may be selected, giving atom numbers and labels as well as residue labels and numbers. The selection of a constraint returns the full identification of the involved atoms, the number of the constraint and its upper and lower limits. Evaluation of the actual distance between two atoms in each conformation is possible.

OUTPUTS

From each selected conformation a list of NOE-constraints, H-bonds or peptide angles (ϕ, ψ and ω) can be written to the terminal or to a file. The user can generate a file that contains the date of a three-dimensional diagram in sequential form. Frame extraction can be performed by writing a PDB file for external use (minimization, and so forth).

EXAMPLES

Two examples will serve to demonstrate these features. The first one is a 30-ps MD simulation of the 20-residue peptide that acts as an antigenic determinant against the foot-and-mouth-disease virus (FMDV) of type O_1 *Kaufbeuren*.[6] The second example describes the nmr structure determination of the lantibiotic gallidermin.[7]

FMDV O_1 *Kaufbeuren* (141–160)

Color plate 1 shows the conformation after a 26.4-ps simulation time and diagrams (from top to bottom) of potential energy, mean values and rms fluctuations of ϕ and mean values and rms fluctuations of ψ. The ϕ angles lie within the range $-60°$ to $-90°$ with the shown fluctuation of 10–40 deg. The ψ angle of residue 21 (PRO 160) shows striking fluctuations and a different mean value than the other ψ angles. This depicts the great flexibility of the C-terminal blocking group (NMe). Smaller fluctuations of ϕ and ψ can be seen at residues 7 and 8 (GLY 146 and ASP 147). Color plate 2 displays the fluctuations: The overlay of 4 conformations after a least-squares fit of the backbone atoms (N, C_α and C) of residue 9–14 is shown. The N-terminal part (top) drifts from a linear helical conformation (frame 36 and 80) to a hinged "coil" conformation (red and yellow). This movement is caused by the change of the ψ angle of GLY 146 and the ϕ angle of ASP 147 ($\psi_7 \sim -50°$ to $\sim +80°$; $\phi_8 \sim -60°$ to $\sim -130°$), as can be seen from the diagrams.

Gallidermin

NOESY experiments on the lantibiotic gallidermin performed on a 500-MHz spectrometer revealed 123 interproton distances, from which we used a total of 88 for a restraint dynamics simulation. In addition, we set 9 torsional angle constraints, which were evaluated from *J*-coupling, as well as constraints for the formation of the thioether bridges.

The extended starting conformation in Color Plate 3 clearly shows that most NOE distances are too long (red lines). The structure includes only those hydrogens which are either polar (non-carbon bonded) or belong to a NOE constraint. The diagrams of potential and constraint energy indicate how the calculation was performed: After a 3-ps equilibration run without any constraints, distance constraints are introduced, step by step, with increasing force constants.

The three-dimensional diagram of the NOE distance deviation as a function of NOE number and simulation time (Color Plate 4) shows the NOEs taken at each calculation step. Additionally the result of a selection in the PICK-INFO environment is shown: The 12th NOE was selected at 9.327 ps simulation time where it has a deviation of −0.308 Å from the arithmetic mean of upper and lower limits of the constraint distances. The location of the corresponding conformation in the trajectory is again indicated in the two-dimensional diagrams by a red bar. By switching back to the structure display this conformation (9.327 ps) is shown. A detailed description of the structure determination of gallidermin will be published elsewhere.[7]

SUMMARY

The use of MD simulations generates a huge amount of data, which can be analyzed using ADAPTU as an interactive animation and information retrieval program. Diagrams can easily be generated that allow a more detailed description of the trajectory and that can be used for a more detailed analysis. ADAPTU is a considerable enhancement of mere movie generating programs for MDs simulation trajectories. Using analytical tools, the development of constraints can be displayed and the progress of a simulation followed. Thus, restrained simulation runs can be controlled and parameters changed by easy visualization of the development of the constraints. The program is menu driven and allows the user to select atoms within the trajectory as well as points in the two- and three-dimensional diagrams. Selected conformations can be read out to Brookhaven format files for further handling in CAMD programs. An overlay function based on least-squares fitting facilitates the interpretation of substructure movements.

Using standard FORTRAN 77 the program is portable to any operating system; the graphic system supported up to now is the PS300 line of E&S, but the PHIGS/PEX version, which is under development, will in future allow the use of other graphics systems.

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