brief communication

Molecular dynamics simulation by atomic mass weighting

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ABSTRACT A molecular dynamics-based simulation method in which atomic masses are weighted is described. Results from this method showed that the capability for conformation search in molecular dynamics simulation of a short peptide (FMRF-amide) is significantly increased by mass weighting.

INTRODUCTION

Energy minimization and molecular dynamics simulation techniques have been useful tools in structure and function studies of proteins and nucleic acids in which these biological macromolecules are represented by empirical potential energy function of the molecular mechanics type (1, 2). The high dimensionality of biomolecular systems, however, results in the so-called "multiple minimum" problem (3) and generally limits the simulation methods to studying more localized motions. For example, molecular dynamics simulations showed that the potential of mean force for atoms in proteins is highly anisotropic (4) and anharmonic (5, 6). Although atomic position fluctuations have been found to be collective (7–9), it is usually necessary to devise alternative methods for studying large scale structural changes (10–12). For short polypeptide chains, sampling of molecular conformation may also be limited (13, 14). In this communication, we show that for the tetrapeptide Phe-Met-Arg-Phe-amide (FMRF-amide), which may function as a neuromodulator of acetylcholine release in molluscs (15), weighting atomic masses in the system increases the effective momentum of rotational motion in barrier crossing and therefore increases the conformational search in molecular dynamics simulations.

For each residue in FMRF-amide, the starting internal coordinates, i.e., bond lengths, bond angles, and dihedral angles, are chosen to have the values for the amino acid residue type averaged from globular proteins (Mao, unpublished data). The conformation of the tetrapeptide is then energy minimized by Adopted Basis Newton-RRphson procedure followed by Verlet molecular dynamics integration (16), with a dielectric constant of 80 in place of explicit solvent molecules. The molecular dynamics was run for a total of 100 ps; in the first 5 ps the system was assigned successively higher temperatures to reach a nominal system temperature T_s, and this "heating period" is followed by an "equilibriation period" during which the temperature is repetitively assigned at T_s. In the remaining 80 ps, the system then runs in a free molecular dynamics without intervention (see Fig. 1 for details of simulation protocols). The trajectories in Fig. 1 for ϕ_3 and ϕ_4, the dihedral angle C^{i-1}-N^i-C^i_α-C^i of residue i for Arg_3 ($i = 3$) and for Phe_4 ($i = 4$), respectively, show that at 300 K these two backbone dihedrals remain in the same potential well. As reported previously in MD simulations

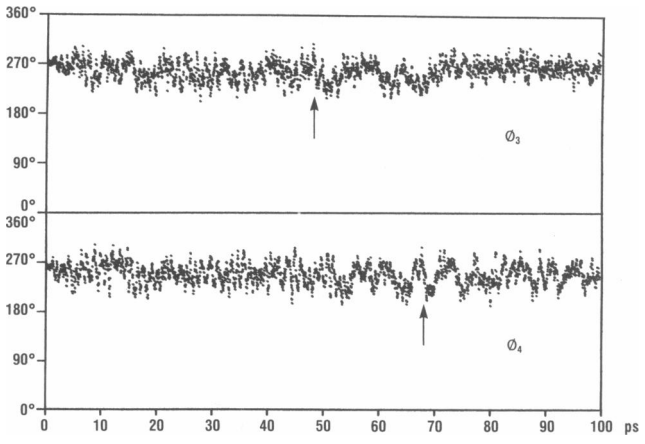

FIGURE 1 Trajectories for dihedral angles ϕ_3 and ϕ_4 of FMRF-amide in a normal molecular dynamics simulation at 300 K. The Verlet algorithm was used for time integration, with an integration time step of 0.001 ps. The simulation was run with a constant dielectric constant of 80; lists of atom pairs in nonbonded and hydrogen-bond interactions are generated at 20-step intervals, with a cutoff distance of 8.0 Å for nonbonded interactions and a cutoff distance of 4.5 Å for hydrogen-bond interactions. The temperature increment is 30 K in the heating period. For heating and equilibriation, a Gaussian distribution at the given temperature was assigned to atomic velocities, at intervals of 0.5 ps.

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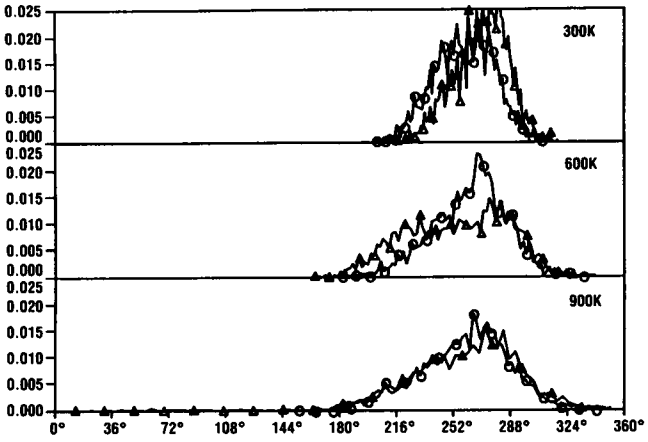

FIGURE 2 Histograms of the dihedral angle values of ϕ_3 (*triangles*) and ϕ_4 (*circles*) during MD simulations at T_s = 300 K, 600 K, and 900 K. The actual temperatures for the three curves are 275, 550, and 980 K, respectively, with root-mean-square (RMS) temperature fluctuations of 20, 40, and 80 K. RMS fluctuations of the total energy are 0.1, 0.2, and 0.1%, respectively, whereas the ratios of RMS fluctuation of total energy to RMS fluctuation of kinetic energy are 3.0, 4.1, and 2.5%, respectively. Each curve has 90 bins within its maximum and minimum X-values and is normalized to a total area of 1.

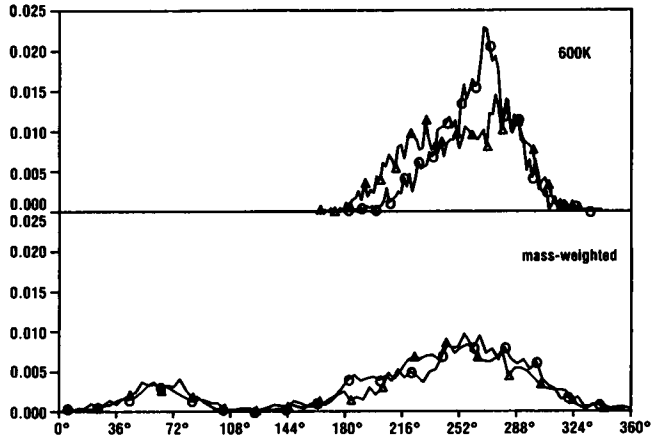

FIGURE 3 Histograms of dihedral angles ϕ_3 (*triangles*) and ϕ_4 (*circles*) in 600 K and mass-weighted MD simulations. In the mass-weighted simulation, the weighting factor ω for atomic masses (i.e., $m_i' = \omega \cdot m_i$) is 10.0, and $T_s' = \omega \cdot 600$ K = 6,000 K. Thus the root-mean-squared velocities of the two simulations are the same according to the equipartition relationship, $kT_s/2 = (\Sigma m_i \cdot V_i^2/2)/(3 \cdot N\text{-}6)$, where N is the number of atoms in the molecular dynamics system and k is the Boltzmann constant.

of other short peptides (13), the side-chain dihedrals in FMRF-amide have more freedom to undergo rotational transitions (data not shown). At higher temperatures, while transitions in other backbone dihedrals were observed (notably, those of the two terminal residues), the distribution of ϕ_3 and ϕ_4 broadened but remained essentially in the same potential well as that at 300 K (Fig. 2). Fluctuations of ~2–3 ps periodicity shown in Fig. 1 suggest, however, that the libration amplitude of the dihedral angle might be increased to the extent that it overcomes barriers in the potential of mean force for rotational motion, if the momentum of the libration can be sustained. Indeed, when atomic momenta are increased by weighting the atomic masses (and the system temperature is scaled accordingly at the same time for maintaining the same mean velocity), dihedral transitions to and from other potential wells are observed for ϕ_3 and ϕ_4; Fig. 3 shows the population of dihedral angle values outside initial potential wells. The molecular dynamics behavior of the mass-weighted system can be understood from the physics of simple harmonic oscillator, which is

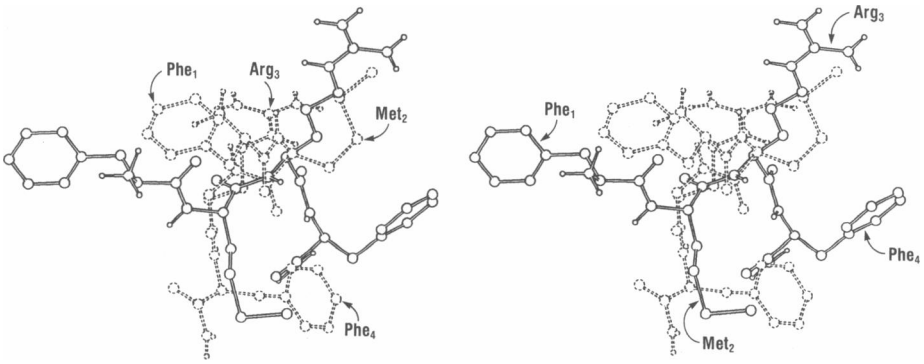

FIGURE 4 Stereoscopic view of the starting conformation (*solid lines*) and a conformation selected from the mass-scaled simulation (*dashed lines*); these two structures are taken from the simulation trajectory and displayed directly without any change in their relative orientation. The set of eight backbone dihedral angles (starting from the amino terminus) are 60.6°, 138.8°, 276.8°, 145.2°, 278.3°, 327.7°, 266.4°, 128.9° in the starting conformation, and are 228.1°, 51.9°, 45.5°, 56.0°, 33.3°, 235.3°, 51.1°, 187.2° in the selected MD structure.

applicable for the dihedral angle vibration in the limiting sense that its potential well extends not to an infinite wall but to a barrier of finite height. That is, the amplitude of a simple harmonic-like oscillation is proportional to the mass of the particle in the well for a given time-averaged squared velocity, and thus, the probability of torsional transitions is increased due to the larger amplitude of torsional vibration in the mass-weighted simulation. For comparison with the starting structure, a conformation extracted from the trajectory is shown to be drastically different (Fig. 4).

The atomic mass weighting method described above increases the conformation search capability of molecular dynamics whereas others have also employed mass scaling for different but related purposes (17, 18). In the procedure reported here, the potential energy function remains unchanged whereas the kinematics of the system is altered such that the potential energy hypersurface is surveyed more efficiently. Moreover, the integration time step need not be decreased, as it would have to be in high-temperature simulations. While transitions in other backbone dihedral angles were observed for FMRF-amide (and for short peptide molecules in other molecular dynamics simulations [19, 20]), the limited conformational sampling for ϕ_3 and ϕ_4 shown in Fig. 2 may be due to, for example, the particular starting conformation in this simulation. Results in Fig. 3 and Fig. 4 demonstrate the advantage of a mass-weighted system in increasing the conformation search in this instance. In larger molecular systems where conformation search is increasingly limited, the mass-weighted approach will be especially useful; applications of the method to such systems are in progress. Details of the procedure and data analysis, and its application to identification of stable structures of FMRF-amide will be reported.

The authors thank G. M. Maggiora and the referees for calling their attention to several different but related works now cited in the text.

Received for publication 8 March 1990 and in final form 15 June 1990.

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