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Extraction of the Energetics of Selected Types of Motion from Molecular Dynamics Trajectories by Filtering

Pnina Dauber-Osguthorpe and David J. Osguthorpe*
Molecular Graphics Unit, University of Bath, Claverton Down, Bath BA2 7AY, U.K.
Received March 15, 1990; Revised Manuscript Received May 11, 1990

ABSTRACT: A novel method for analyzing molecular dynamics trajectories has been developed which enables the study of selected motions and the corresponding energetics. In particular, it is possible to filter out the high-frequency motions and focus on the structural and energetic features of low-frequency collective motions. The trajectories of the properties of interest are Fourier transformed to the frequency domain, a filtering function is applied, and then an inverse transformation back to the time domain yields the filtered trajectory. The method is demonstrated for harmonic fluctuations and conformational transitions of acetamide and *N*-acetylalanine *N*-methylamide, as models for peptides and proteins.

In recent years the theoretical and experimental study of the dynamics of molecules has expanded dramatically. In particular, attention has been drawn to the flexibility and motion of biomolecules such as proteins and nucleic acid polymers and the role of the dynamic features in their biological function (Karplus & McCammon, 1981; McCammon & Harvey, 1987). Phenomena such as domain closure on ligand binding to enzymes (Remington et al., 1982), DNA unwinding when bound to drugs (Neidle & Waring, 1983), allosteric effects (Fletterick & Madsen, 1977), etc. all involve the collective motion of large regions of the molecules. Atomic and molecular mobility are of importance in other fields as well, for example, the diffusion of adsorbed molecules in zeolites, ion migration in superionic materials (Richards, 1989), the dynamic properties of bulk liquids and gases (Allen & Tildesley, 1987), and more. Thus, the investigation of such motion is of great interest.

In order to understand the dynamic behavior of molecular systems, it is important to be able to characterize the various motions in terms of changes in structure and energy. The theoretical investigation of conformational motion has involved three approaches to date. First, there is adiabatic (or flexible geometry) mapping in which steps along a conformation change path are taken (e.g., incrementing torsion angles or

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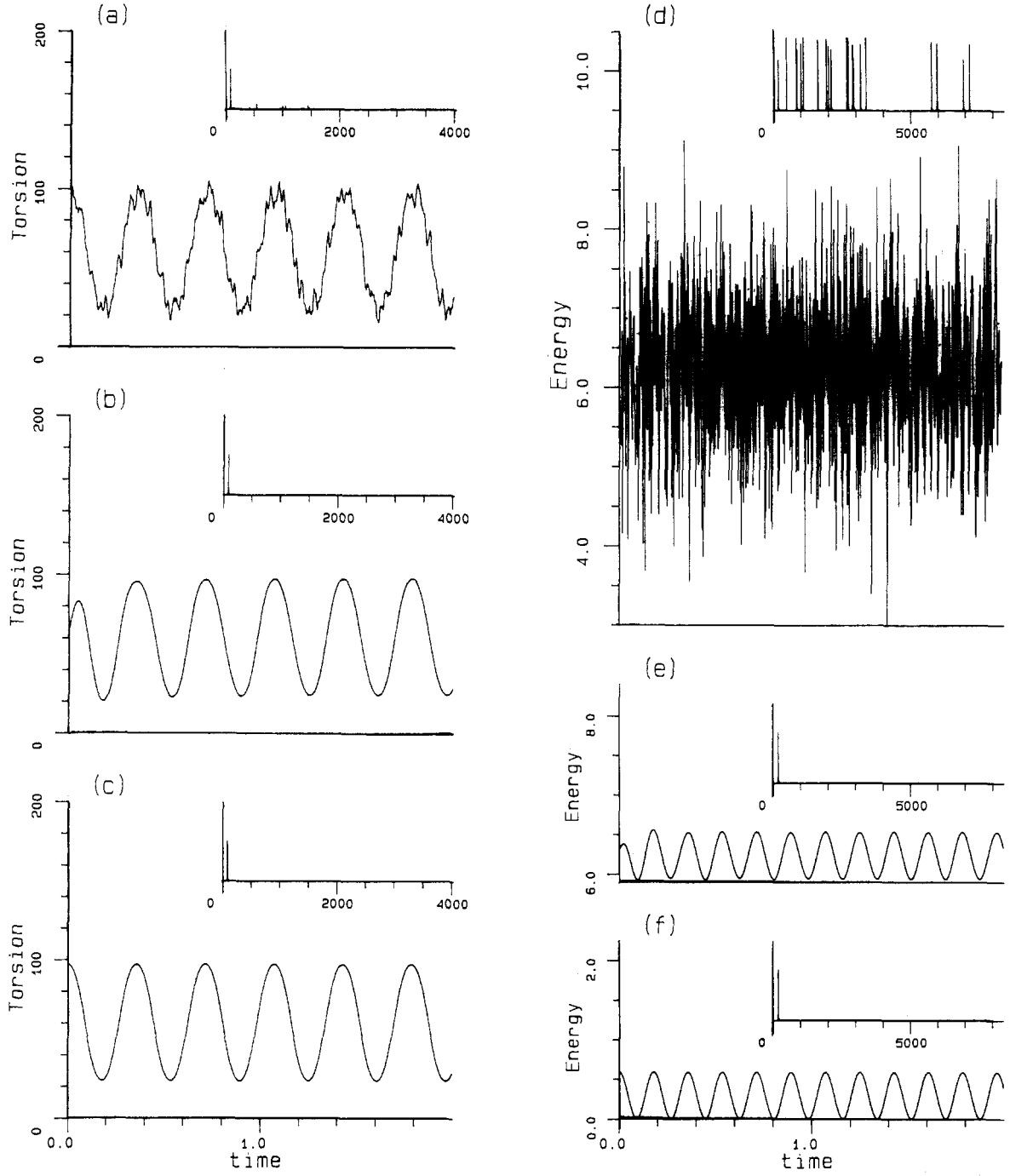

FIGURE 1: Oscillation in methyl torsion (τ) and potential energy (V), in normal mode trajectories of acetamide. A 32-ps trajectory that is a superposition of all normal modes was generated (sampling frequency 2 fs). A section of the trajectory of τ and V is given in (a) and (d), and the corresponding frequency distributions are depicted in the upper right-hand corners. These indicate that the lowest frequency of oscillation in τ is $\approx$95 cm^{-1}, the lowest normal mode. The lowest frequency for V is double that, $\approx$190 cm^{-1}. Low-pass filters with V_{max} = 170 cm^{-1} and ν_{max} = 290 cm^{-1} were applied to the Cartesian coordinates and the potential energy, respectively. A section of the resultant trajectory of τ and V is given in (b) and (e). The corresponding trajectories of τ and V in a trajectory of a single mode (ν = 95 cm^{-1}) are given in (c) and (f). These trajectories are nearly identical with the filtered trajectories in (b) and (e). Time is in picoseconds, frequencies are in cm^{-1}, angles are in degrees, and energies are in kcal/mol.

rotations around a hinge bend axis) and the energy of the system is minimized with respect to all other degrees of freedom. This method requires prior knowledge of the parameters defining the conformational change or a complete mapping of conformational space. The second method is normal mode analysis (Wilson et al., 1955), which results in a "pictorial" description of all modes of motion at the vicinity of a local minimum, as well as the associated thermodynamic properties. It has been widely applied to small molecules as an aid in interpreting vibrational spectra and has been extended to larger systems such as peptides (Dauber et al., 1981) and proteins (Nishikawa & Go, 1987). The third method is molecular dynamics, which involves solving Newton's equations of motion numerically to produce trajectories of the atomic positions, velocities, and energies. It explicitly takes into account anharmonicity and the full flexibility of the molecules (including conformational transitons). Although the laws governing molecular dynamics are simple, the combined effect of the many forces exerted on each atom can result in complex trajectories resembling "random noise".

Recently, we have developed a method that is aimed at deciphering and interpreting the complex trajectories of

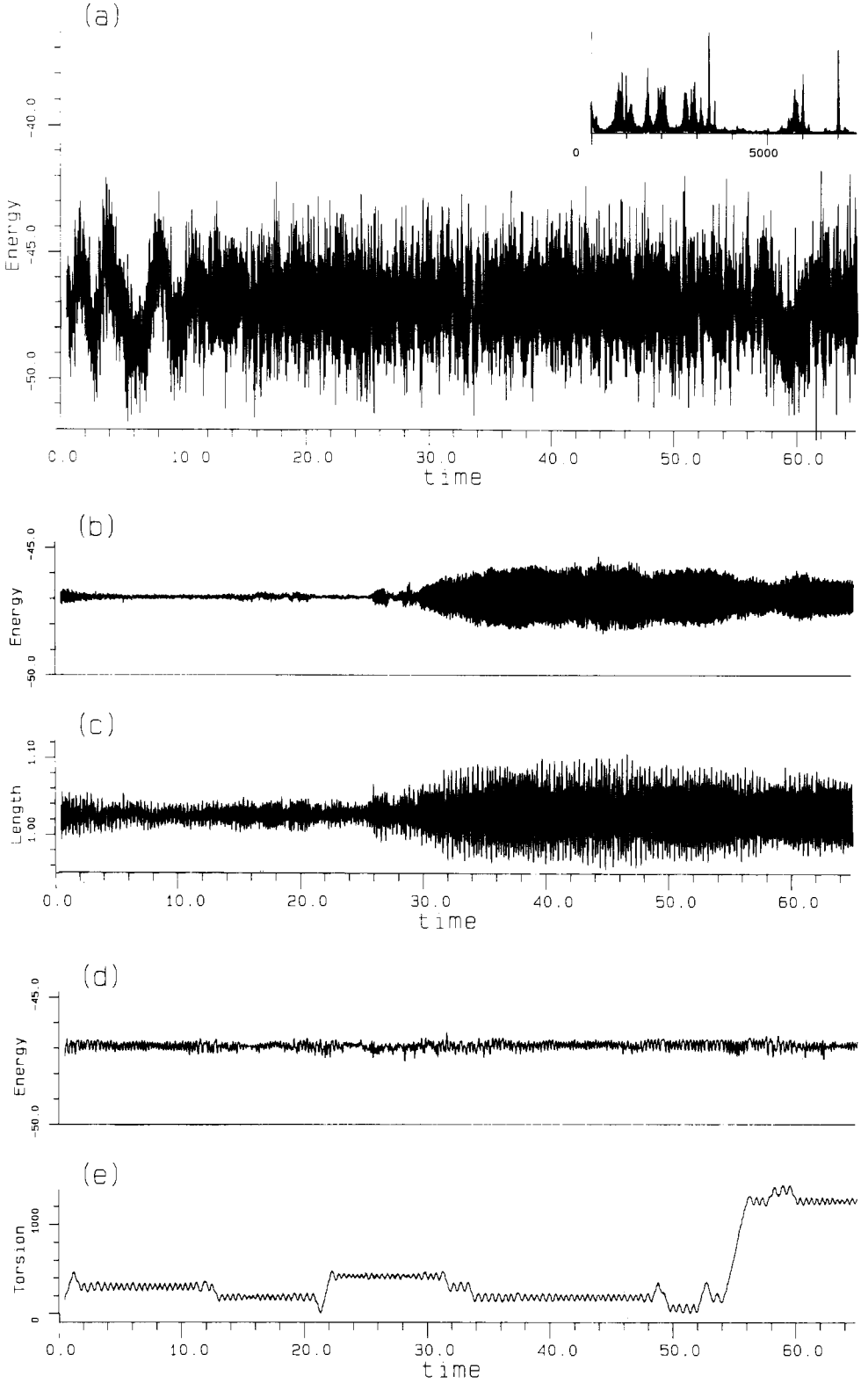

FIGURE 2: Filtering a molecular dynamics trajectory of acetamide. A 64-ps molecular dynamics trajectory of acetamide was generated (sampling frequency of 2 fs). (a) Fluctuations in potential energy during the molecular dynamics. The corresponding frequency distribution is given in the upper right-hand corner. (b) A high-pass filter (6400–7600 cm^{-1}) of the energy. (c) Fluctuations in N–H bond after application of a high-pass filter (3400–3800 cm^{-1}). (d) A low-pass filter (0–290 cm^{-1}) of the energy. (e) Fluctuations in C–C torsion after application of a lowpass filter (0–170 cm^{-1}). A correlation between the high-frequency oscillations in NH bond length and the high-frequency oscillations in energy are demonstrated by (b) and (c). Large fluctuations in the dihedral angle are not reflected in large fluctuations in energy as demonstrated by (d) and (e). Time is in picoseconds, frequencies are in cm^{-1}, angles are in degrees, bond lengths are in angstroms, and energies are in kcal/mol.

structural and energetic properties resulting from a molecular dynamics simulation. The method involves filtering out some of the motions and retaining selected motions. We have studied in detail the application of the filtering technique for characterizing and extracting different modes of motion of acetamide and *N*-acetylalanine *N*-methylamide, as model compounds for peptides and proteins (Dauber-Osguthorpe & Osguthorpe, 1990), and for revealing low-frequency collective motions in proteins (Sessions et al., 1989). Here we focus on the elucidation of the energetics associated with intramolecular

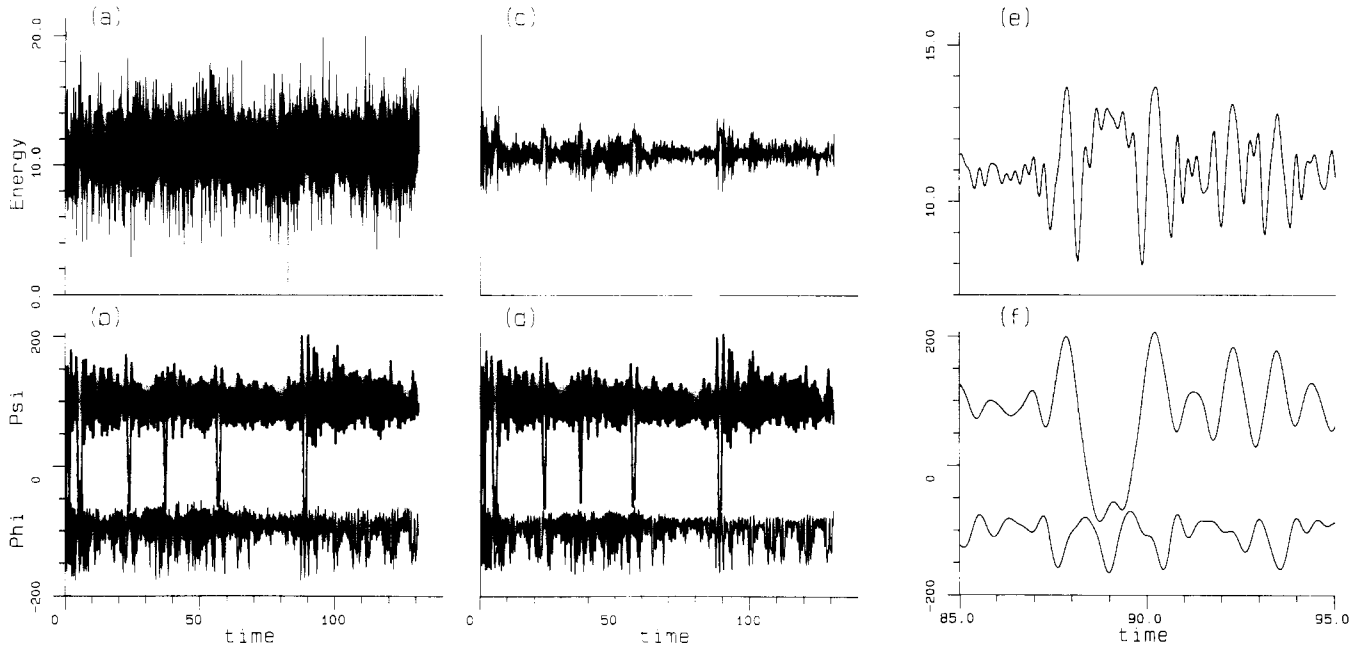

FIGURE 3: Filtering a molecular dynamics trajectory of *N*-acetylalanine *N*-methylamide. The original trajectories of the potential energy, V, and the torsions ϕ and ψ are given in (a) and (b), respectively. The only indication for conformational transitions is in the torsions. A low-pass filter of 0–70 cm^{-1} was applied to the Cartesian coordinates, and a corresponding filter of 0–140 cm^{-1} was applied to the potential energy. The resultant filtered trajectories are given in (c) and (d). (b) and (d) are very similar since most of the torsional motion is of low frequency. Trajectory c reveals the changes in potential energy accompanying the change in torsion angles during the conformational transitions, which were hidden by high-frequency oscillations in the original trajectories. Expanded sections of the filtered energy and torsions are given in (e) and (f). Time is in picoseconds, angles are in degrees, and energies are in kcal/mol.

motion and particularly conformational motion.

In order to evaluate the ability of the new method to extract selective modes of motion and the corresponding energies, we applied it first to a trajectory with known characteristic motions and energetics, namely, a "normal mode trajectory". This was followed up by applying the method to "real" molecular dynamics trajectories, which included fluctuations around one conformation as well as conformational transitions.

Experimental Procedures

All calculations presented here are based on an empirical force field in which the potential energy of the system is defined as an analytical function of internal coordinates and interatomic distances. The parameters for this function were refined to reproduce experimental data of a set of model compounds including functional groups occurring in amino acids. (Dauber-Osguthorpe et al., 1988a). The first step of the calculations was to minimize the molecules with a quasi-Newton method (Fletcher, 1980).

Normal mode trajectories were generated by

$$x_i = m_i^{-1/2} \sum_{k=1}^{3n-6} l_{ik} K_k \cos(\nu_k t + \epsilon_k)$$
$$V = (1/2) \sum_{k=1}^{3n-6} \nu_k^2 K_k \cos^2(\nu_k t + \epsilon_k) \quad (1)$$

where x_i are the fluctuations in Cartesian coordinates, ν_k and ϵ_k are the characteristic frequencies and phases, l_{ik} are the normal modes, and K_k define the maximum amplitudes, which are determined by the temperature of the system. V is the total potential energy. The frequencies and normal modes are obtained by diagonalizing the matrix of the mass-weighted second derivatives of the energy (eigenvalues and eigenvectors, respectively). It is important to note that for the same mode the frequency of oscillation of the potential energy is twice the frequency of the coordinates. This can easily be seen by using the trigonometric relation $\cos^2 \alpha = (1/2)(1 + \cos 2\alpha)$. In physical terms, since positive and negative fluctuations in coordinates yield an increase in energy, each cycle of the oscillation in coordinates corresponds to two cycles of the potential energy oscillation. The real molecular dynamics trajectories were generated by solving Newton's equations of motion numerically (McCammon & Harvey, 1987; Allen & Tildesley, 1987). The molecular dynamics trajectories and the normal mode vectors and frequencies were obtained with the program DISCOVER (Biosym Technologies). Trajectories were generated from the normal modes with the program NMOD (Dauber-Osguthorpe & Osguthorpe, 1987).

The filtering method was then applied to the normal mode or molecular dynamics trajectories to extract information about the motions which are of interest, in particular conformational ones [using the program FOCUS (Dauber-Osguthorpe et al., 1988b)]. This method is based on digital signal processing techniques, in which filtering is used to remove "noise" from an electronic signal (Oppenheim & Schafer, 1975). Here the individual trajectories of structural or energetic properties are treated in a way analogous to that of electronic signals. The technique involves three steps:

(a) Fourier transform

$$X_i(\nu) = \int_{-\infty}^{\infty} x_i(t) e^{-j\nu t}\, dt \quad (2)$$

(b) multiply by filter

$$F(\nu) = 1: \quad \nu_{min} < \nu < \nu_{max}$$
$$F(\nu) = 0: \quad \nu < \nu_{min};\ \nu > \nu_{max}$$
$$X'_i(\nu) = X_i(\nu) F(\nu)$$

(c) inverse fourier transform

$$x'_i(t) = \int_{-\infty}^{\infty} X'_i(\nu) e^{j\nu t}\, d\nu$$

where $x_i(t)$ is the trajectory of a property (e.g., Cartesian

coordinate or the energy), $X_i(\nu)$ is the Fourier transform of this property, and $F(\nu)$ is the filtering function. Since the characteristic frequencies of oscillation of the potential energy are twice the frequencies of the corresponding structural oscillation, the center of the filtering function for the energy properties has to be twice the center of the filter for structural properties.

Results and Discussion

Test Case: Normal Mode Trajectory of Acetamide. The ability of the filtering method to extract the energetics associated with specific types of motion was tested first on trajectories of normal modes. Using eq 1, we generated a trajectory of small fluctuations (coordinates and energy) around the minimum energy conformation of acetamide, which corresponds to a superposition of all normal modes. We used a low-pass filter ($\nu_{min} = 0$, eq 2) to extract the lowest frequency motion (C–C torsion) and compared the results to a trajectory of this single normal mode generated directly with eq 1. In Figure 1 we present the oscillations in torsion angle and potential energy during the simulation and the corresponding Fourier transforms (eq 2) that define the frequency distributions. It is easy to detect the low-frequency ($\approx$95 cm^{-1}) fluctuations in the methyl torsion, τ (Figure 1a). It can be seen from the frequency distribution as well that the torsion oscillation has a major low-frequency component and some very small components of higher frequency. On the other hand the fluctuations in potential energy seem like random noise (Figure 1d). The frequency distribution of the energy indicates that it has equal components for many frequencies. Applying a low-pass filter (0–170 cm^{-1}) to the Cartesian coordinates removed the low-amplitude high-frequency fluctuations in τ and resulted in a trajectory (Figure 1b) of frequency, amplitude, and phase similar to those of the trajectory including only the lowest mode (Figure 1c). The effect of the appropriate filter (0–290 cm^{-1}) on the energy trajectory is even more striking (Figure 1e)—a simple wavefunction was extracted from the noise-like original trajectory, again very similar to the one obtained from the single mode trajectory (Figure 1f). The frequency of oscillation in the two energy trajectories is $\approx$190 cm^{-1}, the amplitude is $\approx$0.6 kcal ($=kT$), and the phases are the same. The average energy in the two trajectories reflects the energy in the system—while the single mode trajectory oscillates around an average value of $(1/2)kT$, the oscillations in the filtered trajectory are around an average of $(1/2)(3n - 6)kT$ ($\approx$6.3 kcal for acetamide). A similar procedure can be applied to extract each of the characteristic modes of motion or combinations of a few modes. The amplitude of energy oscillation is $(1/2)NkT$, where N is the number of modes retained by the filtering function.

Molecular Dynamics Trajectories. (A) Acetamide. Next we have applied the filtering technique to a real molecular dynamics trajectory of acetamide. In addition to fluctuations around the minimum energy structure, quite frequent rotations around the C–C bond occur during the simulation. The potential energy trajectory and the corresponding frequency distribution are given in Figure 2a. As in the normal mode trajectory the fluctuations in energy during the simulation are noise-like due to a combination of modes with different frequencies. We applied a high-pass and low-pass filter to the energy and to the coordinates. The high-pass filter corresponded to the N–H vibrations while the low-pass filter corresponded to the C–C torsional vibration. The high pass filtered energy (6400–7600 cm^{-1}) and the fluctuations in the N–H bond in the corresponding trajectory of filtered coordinates (3200–3800 cm^{-1}) are depicted in panels b and c of

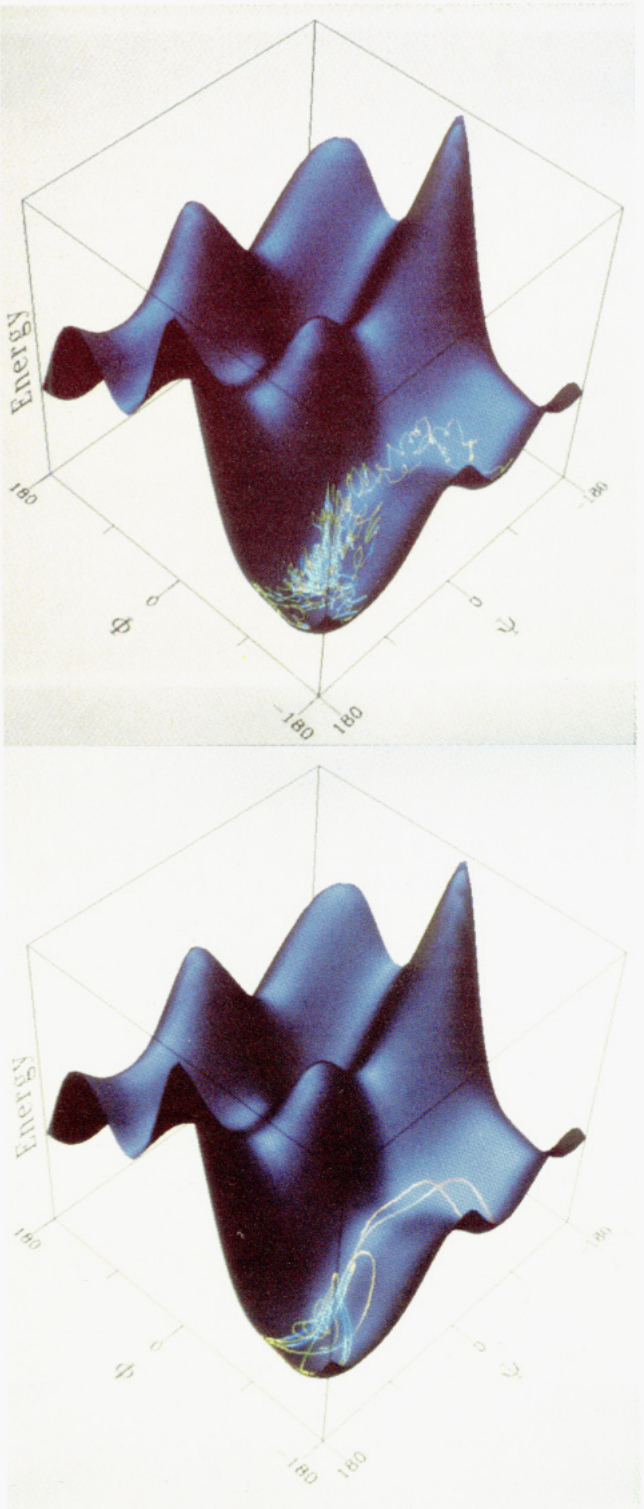

FIGURE 4: Changes in conformation and energy as obtained by flexible geometry (adiabatic) mapping and molecular dynamics of *N*-acetylalanine *N*-methylamide. The flexible geometry map was obtained by minimizing the potential energy of the molecule at grid points of ϕ and ψ. These two torsions were kept fixed at the grid point values while all other degrees of freedom were relaxed. A section of the original (top) and filtered (bottom) trajectories (85–95 ps) is superimposed on this surface. The filtered trajectory was obtained by applying a low-pass filter to the Cartesian coordinates of the original trajectory ($0 < \nu < 70$ cm^{-1}) and to the potential energy ($0 < \nu < 140$ cm^{-1}). The coloring of the trajectory was done according to the value of the energy in the molecular dynamics trajectories—blue, green, yellow, and red correspond to increasing energies. Energies are in kcal/mol, and angles are in degrees.

Figure 2, respectively. The low pass filtered energy (0–290 cm^{-1}) and corresponding filtered (0–170 cm^{-1}) torsion are given in Figure 2d,e. In contrast to the filtered trajectories from the normal mode calculation (Figure 1), the amplitude of oscillation is not constant in the molecular dynamics. That is, the partitioning of energy between various modes of motion and in the various internals varies during the simulation. For example, at about 30 ps there is a dramatic increase in the N–H amplitude. With the aid of the filtering technique it is possible to reveal the corresponding increase in fluctuations in energy accompanying this motion. Although large changes in torsion occur in this simulation (Figure 2e), the low rotational barrier results in small changes in the filtered energy corresponding to this motion (Figure 2d).

(*B*) *N-Acetylalanine N-Methylamide.* We have also applied the filtering technique to a molecular dynamics trajectory of *N*-acetylalanine *N*-methylamide, which included several conformational transitions between C_7^{eq} ($\phi,\psi \approx -80,80$) and α_R ($\phi,\psi \approx -60,-60$). Figure 3 shows the trajectory of ϕ, ψ, and the potential energy in the original and filtered trajectory. Whereas the conformational transitions are clearly seen in the original torsion trajectories, the energy seems, again, like uniform noise throughout. Filtering the Cartesian coordinates revealed that the conformational motion is composed of changes in torsion as well as valence angles (Dauber-Osguthorpe & Osguthorpe, 1990). Similarly, filtering the energy revealed the energy changes accompanying the conformational fluctuations and transitions. For example, the average energy of the α_R conformation is about 2.5 kcal above the energy of the C_7^{eq} conformation with a very low $\alpha_R \rightarrow C_7^{eq}$ transition barrier (<0.5 kcal). This is similar to results from energy minimizations and flexible geometry mapping. Figure 4 shows a three-dimensional representation of the energy map of the blocked alanine, with the superimposed original and filtered trajectories colored according to the value of the energy. There is a clear correlation between the filtered energy and the flexible geometry map. The parts of the trajectory that pass through "valleys" are obviously of low energy whereas those on the top of "hills" have high energies. Note that in this section of the trajectory the highest energies (red) correspond to fluctuations in the α_R region and not to the transition point between the two regions (see also Figure 3e,f). On the other hand, in the original trajectory the high-frequency fluctuations in torsion and energy obscure the conformational components of the motion and energy. Thus it is evident that the filtering technique succeeded in extracting the energy corresponding to the conformational motion from the total energy, and the results are in agreement with flexible geometry mapping. Obviously, when many degrees of freedom are involved in the conformational motion molecular dynamics followed by filtering will be more feasible than adiabatic mapping.

Conclusions

The filtering technique can reveal the fluctuations in energy associated with characteristic types of molecular motion and is of particular importance in the study of low-frequency conformational fluctuations and transitions. Thus it is a powerful tool in the investigation of the myriad of motions in molecular dynamics trajectories and the associated energies. It provides information similar to that obtained from normal mode analysis without confining the study to small harmonic fluctuations around one local minimum or adding approximations, such as rigid geometry, to reduce the size of the computational problem. In addition, it enables the monitoring of changes in energy distribution in the various modes of motion as a function of time. It also opens up the possibility of automatic detection of conformational transitions, which is of importance in applications of molecular dynamics to searches of available conformational space.

Registry No. Acetamide, 60-35-5; *N*-acetylalanine *N*-methylamide, 19701-83-8.

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