MOLECULAR DYNAMICS SIMULATIONS FOR LARGE SERIES OF PEPTIDES (COMPARATIVE STUDY)

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Summary

Dynamics and physical properties of molecules strongly depend on their potential energy landscapes. Proteins and peptides consist of several definite types natural amino acid residues and possess some specific dynamics which could be showed during folding. The following questions come about in this context: firstly – if the common features of potential energy surface exist for peptides; secondly – how the protein dynamics corresponds to the individual amino acid residues dynamics and to the dynamics of the blocks containing a few amino acids; thirdly – whether the natural amino acid residues have the original dynamic properties in contrast to similar molecules; and finally – how the surrounding solvents influence on the residues dynamics.

These questions are discussed with the help of methods based on molecular dynamics simulations. The topology of the energy level surfaces for the molecules with conformation flexibility was developed as well.

Results and Discussion

The topology of energy level surfaces for the molecules with conformational mobility was obtained with the aid of Morse theory [1]. The physical idea is similar to the inherent structure approach [2] to glass forming and supercooled liquids. But we use the multidimensional torus as the domain for the definition of the potential energy surface. In this way the representation of energy surface topology is the simplest [3-5]. We should admit that the metric of this conformation space is not Euclidian.

In terms of Morse theory, the hypersurface topology of level E of potential energy $U(q)$ is determined by the behavior of $U(q)$ in the vicinity of critical points (i.e. points where all $\frac{\partial U}{\partial q_i} = 0$). For systems with conformational degrees of freedom the matrix of second derivatives of $U$ (Hessian) at the critical point after reduction to the diagonal form will contain not only positive but also negative elements. The number of negative diagonal elements of diagonalized Hessian at the critical point is called the index of critical point. According to the lemma of Morse in the vicinity of critical point $q_0$ with index $k$ for $N$-dimensional surface $U(q)$ (reasonable from physical point of view) there are regular local coordinates $x_i = x_i(q-q_0)$ and eq.(1) is valid

$$U(q) = U(q_0) - x_1^2 - ... - x_k^2 + x_{k+1}^2 + ... + x_N^2.$$  (1)

In two-dimensional case a simple saddle point is index 1 critical point. In critical points with index 0 the local minima are situated. From eq.(1), it becomes clear that the topology of energy surface $E=U(q)$ is determined by the indexes of critical points and by the relative values of $U$.

Fig.1 shows the changes in topology of the energy level surface for the rotational isomeric model of an atomic chain. The contribution of torsion angles described by the sum of trigonometric functions $\sin(nq_i)$ is of principle here. Thus an ideal lattice assigned to a multidimensional torus arises for the surface of energy level in the space of conformations. Rather small Van der Waals
interactions in hydrocarbons do not badly distort this lattice (except the cases of Van der Waals radii overlapping). Strong Coulomb forces result in lowering of surface symmetry [6]. Some deformations of the energy level surface are also observed for peptides. However the main features of the energy level surface topology are conserved. Fig. 1 illustrates samples the topology of the potential energy (eq. 2) levels surface.

\[ U = \sin(n_1q_1) + \sin(n_2q_2) + \sin(n_3q_3). \]  

For systems with conformational mobility this topology can be represented as a multitude of hyperspheres (loci) connected by the network of tubes (handles) of different dimensions that pass through multidimensional saddle points. The number and dimension of these tubes determine the scanning rate of energy level surface by representative point.

Kinematics of conformation transitions is defined as rotational displacement of the vectors \( \exp[i\phi(t)] \), where \( \phi \) – torsion angles.

Energy landscapes topography for large series (~10^3) of small peptides in virtual (collision) and water (TIP3P soft model) media is studied by the methods based on molecular dynamics simulations (with AMBER99 force field). We consider the trajectories with good statistics only (\( T=2000 \text{K}, \) trajectory length 10ns). Routines leading to attractors aren’t used [7, 8]. Auto- (3) and crosscorrelation (4) \( \exp[i\phi(t)] \) functions, 2-D and 3-D contour maps of free energy (and the results of their cluster analysis) are applied for a classification of the peptides energy landscape topography [9].

Fig. 1. The energy level surfaces for three conformational degrees of freedom (see eq. (2)) at different values of energy \( E \) (in units of the half barrier height). Periodic boundary condition should be applied. (1) – \( n_1=2 \), the formation of a simple saddle point at \( E=-1 \) (the energy level is enough for overcoming only one barrier); (2) \( n_1=3 \), the path or tube through the simple saddle point is broadened, but the energy is still not enough for overcoming two barriers simultaneously. Darker parts denote greater values of kinetic energy. At rising of energy level the dimensions of the paths connecting local minima increase from 0 up to 3 at \( E=3 \) (it is not depicted here). At \( E=0 \) three-dimensional surface looks like Fermi surface formally. 3 – the scheme of Morse reorganization on the energy level surface. I=1 – a simple saddle point with critical index 1. I=2 – critical point with index 2 (resembles a chemical beaker with deep nose) becomes accessible if energy is enough for overcoming two barriers height simultaneously. Critical points with higher index are hardly presentable in 3D space.
\[ F(t) = \left( e^{i\omega t} e^{-i\omega(t+\tau)} \right)^2 - \left( e^{i\omega t} \right)^2 \] (3)

\[ F(t) = \left( e^{-i\omega(t) - (\omega(t+\tau))} e^{-i\omega(t) - (\omega(t+\tau))} \right) - \left( e^{-i\omega(t) - (\omega(t+\tau))} \right)^2 \] (4)

The kinematics similarity is observed in a large number of conformational degrees of freedom (see e.g. Fig. 2).

An example of autocorrelation functions cluster analysis is presented below for all natural dipeptides (Fig. 3). We should emphasize that in water medium the similarity of torsion angles kinematics in peptides becomes greater.

2-D and 3-D contour maps of free energy and possible symmetry properties of the multidimensional energy surface for natural peptides and chimeras are considered in connection with the funnel topography [10, 11]. The funnel topography and initial conditions effects on folding dynamics of some homopolymer model chains are also simulated.

**Fig. 2.** The real part of the autocorrelation functions (eq. 3) of torsion angles in dipeptides. The autocorrelation functions are chosen for: (1) – the angles \( \psi_1 \) and \( \phi_2 \) in dipeptide arg₁-his₂, \( \chi_{12} \) in glu-phe, \( \chi_{11} \) in his₁-asn₂, and (2) – the angles \( \psi_2 \) in met₁-met₂, \( \phi_1 \) in gln₁-gln₂, \( \chi_{11} \) in ser₁-ser₂, \( \psi_1 \) in tyr₁-cys₂, \( \phi_1 \) in cys₁-asn₂, \( \psi_2 \) in asp₁-his₂. The dynamic isomorphism for the torsion angles is observed.

**Fig. 3.** Cluster analysis data for the kinematics of 2400 torsion angles (abscissa axis) in 400 natural dipeptides (ACE-R1-R2-NHMe) in virtual medium. For the several groups (but not the types) of torsion angles a lot of the autocorrelation functions \( \exp[i\gamma(t)] \) are very close (see Fig. 2).
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References