Development of New Algorithms for Molecular Dynamics Simulation and Its Application to Biomolecular Systems

Department of Theoretical and Computational Molecular Science
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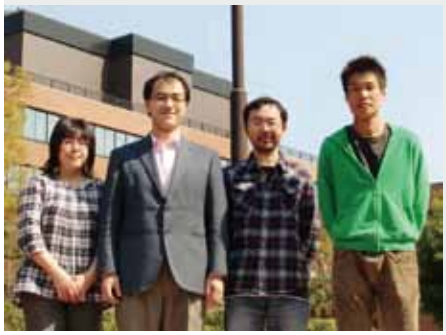

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To predict the native structures of proteins, efficient samplings in the conformational space by molecular dynamics simulations are necessary. In the conventional canonical-ensemble simulations, however, it is difficult to realize efficient samplings in proteins because the simulations tend to get trapped in a few of many local-minimum states. To overcome these difficulties, we have proposed new generalized-ensemble algorithms, such as multibaric- multithermal algorithm, partial multicanonical algorithm, and van der Waals replica exchange method. We apply these methods to proteins and peptides.

1. Temperature and Pressure Denaturation of Chignolin: Folding and Unfolding Simulation by Multibaric-Multithermal Molecular Dynamics Method

A multibaric-multithermal molecular dynamics (MD) simulation[1)] of a 10-residue protein, chignolin was performed to study its folding and unfolding thermodynamics and the denaturation mechanisms. All-atom model for the protein with Amber parm99SB force field were employed in explicit TIP3P water. This MD simulation covered wide ranges of temperature between T = 260 ~ 560 K and pressure between P = 0.1 ~ 600 MPa and sampled many conformations without getting trapped in local-minimum free-energy states. Folding events to the native β-hairpin structure occurred five times and unfolding events were observed four times. As temperature and/or pressure increases, fraction of the folded chignolin decreases. The partial molar enthalpy change ΔH and partial molar volume change ΔV upon unfolding were calculated as ΔH = 20.3 ± 4.5 kJ/mol and ΔV = –6.7 ± 2.5 cm^3/mol, respectively. These values agree well with recent experimental results.

Illustrating typical local-minimum free-energy conformations, folding and unfolding process of the chignolin was revealed, as shown in Figure 1. When it unfolds from the β-hairpin structure, only the C terminus or both C and N termini open first. It may undergo an α-helix or 3_{10}-helix structure and finally unfolds to the extended structure. Calculating radial distribution functions between chignolin backbone atoms and water oxygen atoms, hydrated water was found to decrease as temperature increases, but increase as pressure increases.

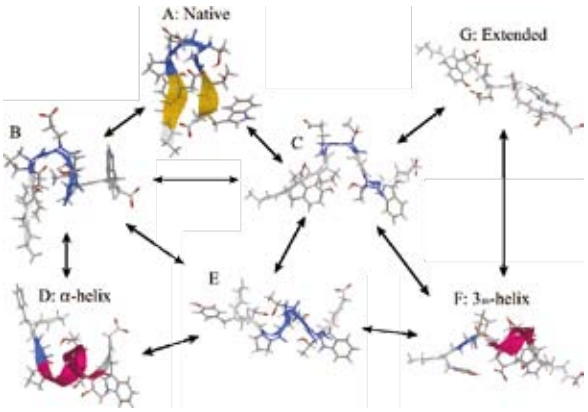

Figure 1. Typical conformations at local-minimum free-energy states and transition states obtained by the multibaric-multithermal MD simulation. The N terminus and the C terminus are on the left-hand side and on the right-hand side, respectively.

2. Length Dependence of Polyglycine Conformations in Vacuum[2)]

We performed replica-exchange molecular dynamics simulations of polyglycines in vacuum to investigate their conformational difference due to different numbers of residues. We employed the polyglycines of which the numbers of residues are 1 (PG1), 5 (PG5), 10 (PG10), and 15 (PG15). We discussed the conformations of the polyglycine molecules, which have the lowest potential energies in local minimum states. The polyglycines PG5 and PG10 often have helical structures. The helical structures of the polyglycine PG10 are β-helix structures. The PG15 have complicated tertiary structures. The tertiary structures have two β-hairpins in the N-terminal and C-terminal regions. A parallel β-sheet structure is also formed between the N-terminal side of the N-terminal β-hairpin and the C-terminal side of the C-terminal β-hairpin.

3. All-Atom Molecular Dynamics Simulations of Polyglutamine Dimers

Polyglutamine peptides form protofibrils composed by β-sheets. The aggregation of these protofibrils causes amyloidosis. It was not yet clear how polyglutamine aggregate and form β-sheets. For probing polyglutamine conformation in the β-sheets, we performed all-atom molecular dynamics simulations on pairs of the polyglutamine fragments in explicit water which consist of 10 repeated glutamine residues from parallel, anti-parallel and perpendicular initial conditions. This is the first work to simulate polyglutamine dimers in all-atom force field in explicit water. All of our simulation formed anti-parallel β-sheets and the number of β-bridges increased gradually, as shown in Figure 2. It indicates that polyglutamine dimer prefer anti-parallel β-sheet conformation than parallel conformation. This agrees well with previous researches by experiments and a coarse-grained molecular dynamics simulation. A free-energy barrier was also found at the structures with no β-bridge, which makes the transformation difficult between parallel and anti-parallel β-sheets.

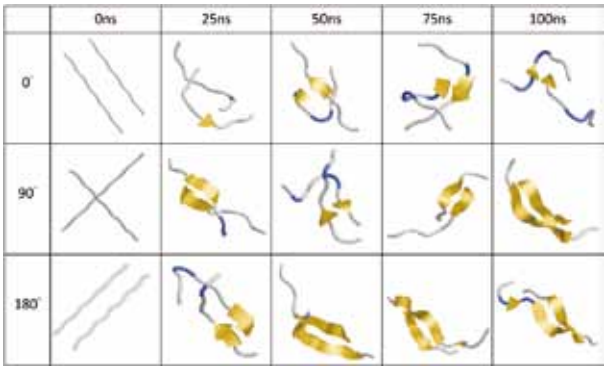

Figure 2. The snapshots at 0, 25, 50, 75, and 100 ns during the simulations. Angle 0°, 90°, and 180° stand for systems started from the parallel, perpendicular, and anti-parallel initial conditions, respectively.

References

1) H. Okumura and Y. Okamoto, *J. Phys. Chem. B* **112**, 12038–12049 (2008).
2) S. G. Itoh and H. Okumura, *J. Phys. Soc. Jpn.* **80**, 094801 (8 pages) (2011).

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