Development of New Molecular Dynamics Algorithms for Biomolecular Systems

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Biomolecules such as proteins and peptides have complicated free-energy landscape with many local minima. The conventional canonical-ensemble molecular dynamics (MD) simulations tend to get trapped in a few of the local-minimum states. To overcome these difficulties, we have proposed new generalized-ensemble algorithms, such as replica-permutation method. We apply these methods to proteins and peptides and try to predict the native structures of proteins as in Figure 1.

We are also interested in amyloid fibrils, which are insoluble aggregates of misfolded fibrous proteins and associated with more than 20 human neurodegenerative diseases (Figure 2). For example, Alzheimer's disease is related to amyloid-β (Aβ) peptides. To overcome these diseases, it is essential to understand amyloid genesis and disruption. We perform such MD simulations of amyloid fibrils.

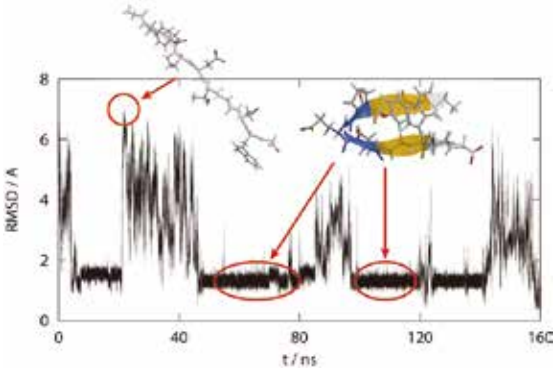

Figure 1. Time series of protein folding simulation.

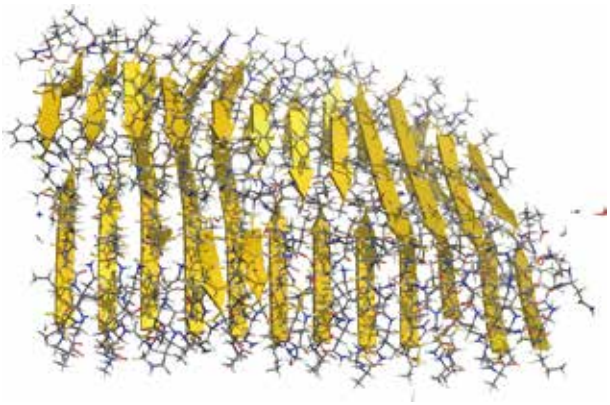

Figure 2. Snapshot of amyloid fibril.

Selected Publications

- H. Okumura and S. G. Itoh, "Amyloid Fibril Disruption by Ultrasonic Cavitation: Nonequilibrium Molecular Dynamics Simulations," *J. Am. Chem. Soc.* **136**, 10549–10552 (2014).
- S. G. Itoh and H. Okumura, "Replica-Permutation Method with the Suwa-Todo Algorithm beyond the Replica-Exchange Method," *J. Chem. Theory Comput.* **9**, 570–581 (2013).
- Y. Mori and H. Okumura, "Pressure-Induced Helical Structure of a Peptide Studied by Simulated Tempering Molecular Dynamics Simulations," *J. Phys. Chem. Lett.* **4**, 2079–2083 (2013).
- H. Okumura, "Temperature and Pressure Denaturation of Chignolin: Folding and Unfolding Simulation by Multibaric-Multithermal Molecular Dynamics Method," *Proteins* **80**, 2397–2416 (2012).

1. Dimerization Process of Amyloid-β(29-42) by the Hamiltonian Replica-Permutation Molecular Dynamics Simulations

In order to investigate the dimerization process and conformations of amyloid-β peptides, we applied the Hamiltonian replica-permutation method, which is a better alternative to the Hamiltonian replica-exchange method, to two amyloid-β(29-42) molecules in explicit water solvent.[1] At the first step of the dimerization process, two amyloid-β(29-42) molecules came close to each other and had intermolecular sidechain contacts. When two molecules had the intermolecular sidechain contacts, the amyloid-β(29-42) tended to have intramolecular secondary structures, especially β-hairpin structures as in Figure 3. The two molecules had intermolecular β-bridge structures by coming much closer at the second step of the dimerization process. Formation of these intermolecular β-bridge structures were induced by the β-hairpin structures. The intermolecular β-sheet structures elongated at the final step. Structures of the amyloid-β(29-42) in the monomer and dimer states are also shown with the free-energy landscapes, which were obtained by performing efficient sampling in the conformational space in our simulations.

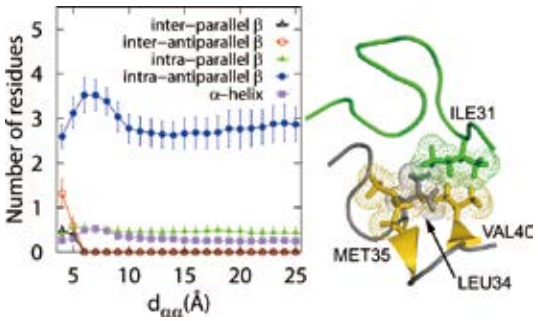

Figure 3. Ensemble-averages of the numbers of residues that have secondary structures at the corresponding intermolecular distance $d_{\alpha\alpha}$ (left) and a snapshot of a representative conformation at $d_{\alpha\alpha}$ = 8 Å (right).

2. Molecular Dynamics of the Structural Changes of Helical Peptides Induced by Pressure

An AK16 peptide and a C-peptide analog are experimentally known to form more helical structures under high pressure conditions than those at atmospheric pressure, even though most proteins usually unfold at high pressure as in Figure 4. To understand the pressure-induced structural changes of the two peptides, molecular dynamics simulations with the simulated tempering method for the isobaric-isothermal ensemble were performed in a wide pressure range from 0.1 MPa to 1.4 GPa.[2] We found that the fraction of the folded state decreases once and then increases with increasing pressure for both peptides. The partial molar volume change of both peptides from the folded state to the unfolded state increases monotonically from a negative value to a positive value as pressure increases. By calculating the radius of gyration and interatomic distances of the AK16 peptide and the C-peptide analog, we found that these peptides are compressed under high-pressure conditions, which causes the folded state to be more stable at high pressure. Furthermore, we found that the salt bridge of the C-peptide analog is broken under high pressure.

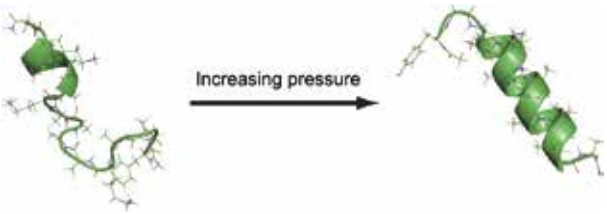

Figure 4. Coil structure of an AK16 peptide (left) and the helically folded structure of this peptide (right).

3. Comparison of Replica-Permutation Molecular Dynamics Simulations with and without Detailed Balance Condition

In the replica-permutation method (RPM), temperatures are not only exchanged between two replicas but also permutated among more than two replicas using the Suwa–Todo algorithm, which minimizes the rejection ratio in Monte Carlo trials. We verify the sampling efficiency of RPM that adopts Suwa–Todo algorithms with and without a detailed balance condition (DBC).[3] To compare these techniques, molecular dynamics simulations of RPM with and without the DBC and the replica-exchange method (REM) were carried out for a chignolin molecule in explicit water. Although no difference in the numbers of folding and unfolding events was observed, the numbers of tunneling events of the two RPM simulations were larger than that of REM. This indicates that the minimization of the rejection ratio by the Suwa–Todo algorithm in RPM realizes efficient sampling. Furthermore, the sampling efficiency was slightly higher in the RPM without the DBC than in that with the DBC. The reason for this difference is also discussed.

References

1) S. G. Itoh and H. Okumura, *J. Phys. Chem. B* **118**, 11428–11436 (2014).
2) Y. Mori and H. Okumura, *Proteins* **82**, 2970–2981 (2014).
3) H. Nishizawa and H. Okumura, *J. Phys. Soc. Jpn.* **85**, 074801 (6 pages) (2015).

Award

OKUMURA, Hisashi; Academic Award of the Molecular Simulation Society of Japan (2014).

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