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.

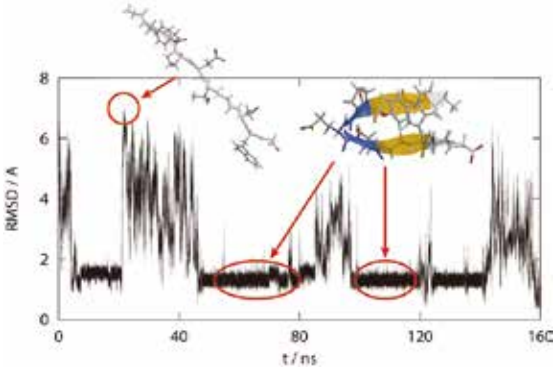

Figure 1. Time series of protein folding simulation.

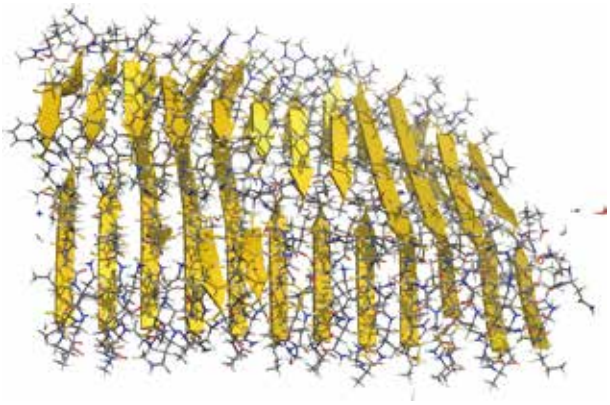

Figure 2. Snapshot of amyloid fibril.

Selected Publications

- 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).
- 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).
- 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, "Oligomer Formation of Amyloid-β(29-42) from Its Monomers Using the Hamiltonian Replica-Permutation Molecular Dynamics Simulation," *J. Phys. Chem. B* **120**, 6555–6561 (2016).

1. Development of Isothermal-Isobaric Replica-Permutation Method and Its Application to Chignolin

We developed a two-dimensional replica-permutation molecular dynamics (MD) method in the isothermal-isobaric ensemble.[1] The replica-permutation method is a better alternative to the replica-exchange method. It was originally developed in the canonical ensemble. This method employs the Suwa-Todo algorithm, instead of the Metropolis algorithm, to perform permutations of temperatures and pressures among more than two replicas so that the rejection ratio can be minimized. We showed that the isothermal-isobaric replica-permutation method performs better sampling efficiency than the isothermal-isobaric replica-exchange method. We applied this method to a β-hairpin mini protein, chignolin. In this simulation, we observed not only the folded state but also the misfolded state. We calculated the temperature and pressure dependence of the fractions of the folded, misfolded, and unfolded states. Differences in partial molar enthalpy, internal energy, entropy, partial molar volume, and heat capacity were also determined, and agreed well with experimental data. We observed a new phenomenon that misfolded chignolin becomes more stable under high-pressure conditions. We also revealed this mechanism of the stability as follows: TYR2 and TRP9 side chains cover the hydrogen bonds that form a β-hairpin structure as in Figure 3. The hydrogen bonds are protected from the water molecules that approach the protein as the pressure increases.

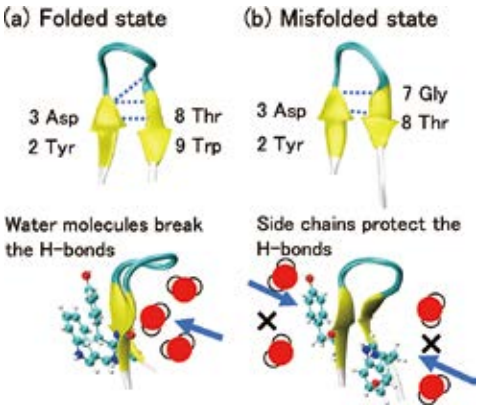

Figure 3. Schematic figure of the mechanism by which misfolded chignolin becomes stable under high-pressure conditions.

2. Classical Molecular Dynamics Simulation to Understand Role of a Zinc Ion for Aggregation of Amyloid-β Peptides

Metal ions such as those of copper and zinc are considered to accelerate initial formation of amyloid fibril of Aβ peptides. In this study, the role of a zinc ion for Aβ peptide aggregation was investigated by the classical MD simulations.[2] The MD results indicated that the negatively-charged residues gained large stabilization in the existence of a zinc ion. On the other hand, histidine and tyrosine which were reported as making a bond with a metal ion were slightly stabled. Therefore, a zinc ion is thought of as combining with histidine or tyrosine after being attracted by negatively-charged residues, because these residues exist near negatively-charged residues. These results indicate that the metal-containing system needs to be treated by quantum-mechanical techniques.

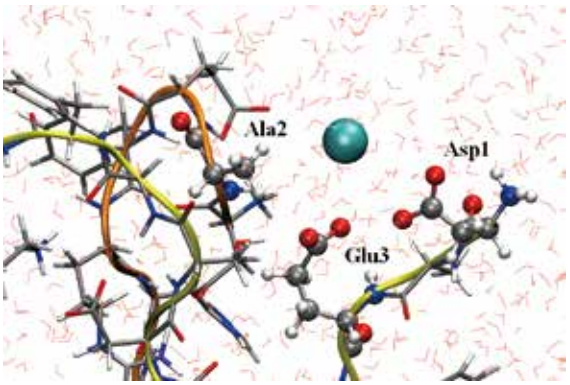

Figure 4. A snapshot around the zinc ion. Asp1 and Glu3 of one Aβ(1–16) peptide and Ala2 of the other Aβ(1–16) peptide exist near the zinc ion.

3. Antigen-Dependent Fluorescence Response of Anti-c-Myc Quenchbody Studied by Molecular Dynamics Simulations

We performed metadynamics MD simulations to reveal mechanism of antigen-dependent fluorescence response observed for site-specifically fluorescent-labeled single-chain antibody against c-Myc peptide antigen.[3] We found that V_H and V_L bind with each other only when the antigen exists and that the fluorophore labeled at the N-terminus of V_H interacts with Trp103 most stably. These results support the mechanism proposed from previous experiments: In the absence of antigen, Trp residues are partially exposed at the interface of V_H and quench the fluorophore. In the presence of antigen, the Trp residues are buried in the interface between V_H and V_L, and the quenching is eliminated.

References

1) M. Yamauchi and H. Okumura, *J. Chem. Phys.* **147**, 184107 (15 pages) (2017).
2) H. Nishizawa and H. Okumura, *J. Comput. Chem. Jpn.* **17**, 76–79 (2018).
3) Y. Mori, H. Okumura, T. Watanabe and T. Hohsaka, *Chem. Phys. Lett.* **698**, 223–226 (2018).

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