Development of New Simulation Algorithms and its Application to Protein Aggregates

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Education

- 1998 B.S. Keio University
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Professional Employment

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Keywords

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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.



Figure 1. Time series of protein folding simulation.

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).
- H. Okumura and S. G. Itoh, "Structural and Fluctuational Difference between Two Ends of Aβ Amyloid Fibril: MD Simulation Predicts Only One End Has Open Conformations," *Sci. Rep.* 6, 38422 (9 pages) (2016).

We are also interested in protein aggregates such as spherical substances called oligomers and acicular substances called amyloid fibrils (Figure 2). These protein aggregates cause more than 30 kinds of diseases. For example, Alzheimer's disease is thought to be caused by aggregated amyloid- β (A β) peptides. To overcome these diseases, it is essential to understand the aggregate genesis and disruption of A β peptides. We perform such MD simulations of oligomers and amyloid fibrils.

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Figure 2. Snapshot of an $A\beta$ amyloid fibril.

- 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).
- S. G. Itoh and H. Okumura, "Oligomer Formation of Amyloidβ(29-42) from Its Monomers Using the Hamiltonian Replica-Permutation Molecular Dynamics Simulation," *J. Phys. Chem. B* 120, 6555–6561 (2016).

1. Molecular Dynamics Simulations of Amyloid-β(16-22) Peptide Aggregation at Air–Water Interfaces

The formation of A β oligomers is accelerated at hydrophilic-hydrophobic interfaces, such as the cell membrane surface and air-water interface. To understand the effects of the interface on oligomerization at the atomic level, we performed MD simulations of aggregation of A β (16–22) peptides at air-water interfaces.¹⁾ First, 100 randomly distributed A β (16–22) peptides (Figure 3(a)) moved to the interface (Figure 3(b)). The high concentration of peptides then accelerated their aggregation and formation of antiparallel β -sheets. Two layers of oligomers were observed near the interface. In the first layer from the interface, the oligomer with less β -bridges exposed the hydrophobic residues to the air. The second layer consisted of oligomers with more β -bridges that protruded into water. They are more soluble in water because the hydrophobic residues are covered by N- and C-terminal hydrophilic residues that are aligned well along the oligomer edge. These results indicate that amyloid protofibril formation mainly occurs in the second layer.



Figure 3. (a) Initial conformation of 100 A β (16–22) peptides (blue) and water molecules (red) with air–water interfaces. (b) Side view of the final conformation of A β (16–22) peptides. The water molecules are not shown here. The blue frames indicate the air–water interfaces.

2. Development of Replica Sub-Permutation Method for Efficient Molecular Dynamics Simulations

We proposed an improvement of the replica-exchange and replica-permutation methods, which we call the replica subpermutation method (RSPM).²⁾ Instead of considering all permutations, this method uses a new algorithm referred to as sub-permutation to perform parameter transition, as in Figure 4. The RSPM succeeds in reducing the number of combinations between replicas and parameters without the loss of sampling efficiency. For comparison, we applied the replica sub-permutation, replica-permutation, and replica-exchange methods to a β -hairpin mini protein, chignolin, in explicit water. We calculated the transition ratio and number of tunneling events in the parameter space, the number of foldingunfolding events, the autocorrelation function, and the autocorrelation time as measures of sampling efficiency. The results indicate that among the three methods, the proposed RSPM is the most efficient in both parameter and conformational spaces.



Figure 4. This image shows sub-permutation candidates for a fourreplica system. The replica sub-permutation method succeeds in improving sampling efficiency both in parameter and conformational spaces.

References

- H. Okumura and S. G. Itoh, J. Chem. Phys. 151, 095101 (12 pages) (2020).
- M. Yamauchi and H. Okumura, J. Comput. Chem. 40, 2694–2711 (2019).