# Molecular Dynamics Simulations of Disease-Related Biomolecules

**Department of Theoretical and Computational Molecular Science**
**Division of Computational Molecular Science**

**OKUMURA, Hisashi**
Associate Professor
[hokumura@ims.ac.jp]

**Education**
1998 B.S. Keio University
2002 Ph.D. Keio University

**Professional Employment**
2002 Postdoctoral Fellow, The University of Tokyo
2002 Research Associate, Institute for Molecular Science
2004 Research Associate, The Graduate University for Advanced Studies
2006 Research Lecturer, Nagoya University
2008 Research Assistant, Rutgers University
2009 Assistant Research Professor, Rutgers University
2009 Associate Professor, Institute for Molecular Science
Associate Professor, The Graduate University for Advanced Studies
2018 Associate Professor, Exploratory Research Center on Life and Living Systems (ExCELLS)

**Award**
2014 Academic Award of the Molecular Simulation Society of Japan

**Member**
Assistant Professor
ITOH, Satoru G.
Post-Doctoral Fellow
TANIMOTO, Shoichi
Graduate Student
FUKUHARA, Daiki
OTAWA, Masaki
SUZUKI, Hinako*
Secretary
KAWAGUCHI, Ritsuko

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

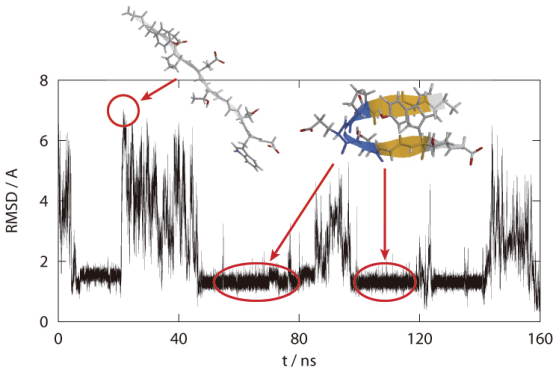


**Figure 1.** Time series of protein folding simulation.

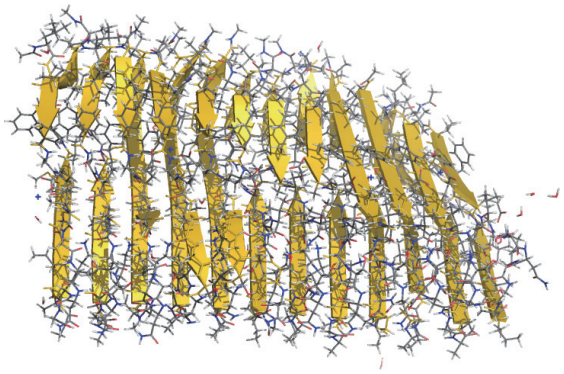

**Figure 2.** Snapshot of an Aβ amyloid fibril.

## 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, "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).
- H. Okumura, S. G. Itoh, K. Nakamura and T. Kawasaki, "Role of Water Molecules in the Laser-Induced Disruption of Amyloid Fibrils Observed by Nonequilibrium Molecular Dynamics Simulations," *J. Phys. Chem. B* **125**, 4964–4976 (2021).
- S. Tanimoto, S. G. Itoh and H. Okumura, ""Bucket Brigade" Using Lysine Residues in RNA-Dependent RNA Polymerase of SARS-CoV-2," *Biophys. J.* **120**, 3615–3627 (2021).

## 1. Key Residue for Aggregation of Amyloid-β Peptides

Aβ mainly has two isoforms, Aβ40 and Aβ42. Although the difference between Aβ40 and Aβ42 is only two additional C-terminal residues, Aβ42 aggregates much faster than Aβ40. It is not known what role the C-terminal two residues play in accelerating aggregation. Since Aβ42 is more toxic, its oligomerization process needs to be clarified. Moreover, clarifying the differences between the oligomerization processes of Aβ40 and Aβ42 is essential to elucidate the key factors of oligomerization. To investigate the dimerization process, which is the early process of the oligomerization, Hamiltonian replica-permutation molecular dynamics simulations were performed for Aβ40 and Aβ42.[1] We identified the key residue, Arg5, for the Aβ42 dimerization, as shown in Figure 3. The two additional residues in Aβ42 allow the C-terminus to form a contact with Arg5, and this contact stabilizes β-hairpin. This β-hairpin promotes dimer formation with formation of intermolecular β-bridges. To approve this theoretical prediction, experiments on Aβ aggregations were also conducted. We confirmed that the aggregation of Aβ42 is remarkably suppressed by a mutation of Arg5. Moreover, mutation of Arg5 also suppresses the Aβ40 aggregation. It was found by analyzing the simulations that Arg5 is important for Aβ40 to form the intermolecular contacts. Thus, it was clarified that the role of Arg5 in the oligomerization process is changed by the two additional C-terminal residues.

The fact that we could predict the experimental results from the simulation results means that the differences seen in the formation of dimers make a difference in the formation of much larger aggregates, such as amyloid fibrils observed in experiments. Thus, it is essential to elucidate the process of small oligomer formation to fully understand the Aβ aggregation.

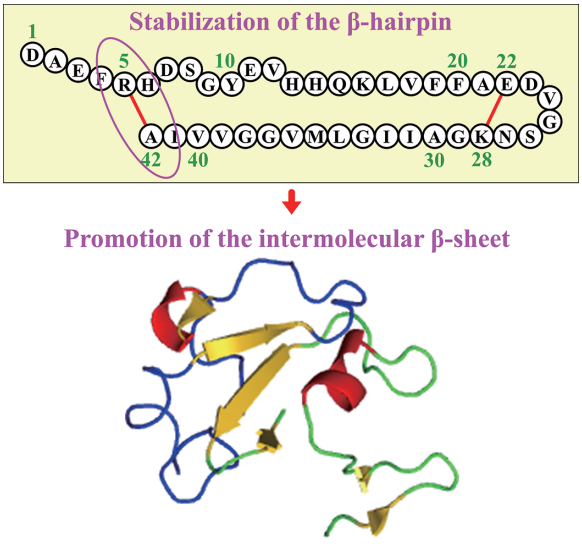


**Figure 3.** The key residue for the aggregation of amyloid-β peptides is Arg5, which stabilizes the β-hairpin structure and promotes the intermolecular β-sheet.

## 2. Ingenuity in Performing Replica Permutation: How to Order the State Labels for Improving Sampling Efficiency

Replica-exchange method (REM) is one of the generalized ensemble algorithms and is widely used for systems with many local minima, such as biomolecules. In this method, copies of the systems, call replicas, are prepared. The temperatures are excahnged between two replicas, as shown in Figure 4. As an advanced alternative to REM, the replica-permutation method (RPM) has been developed. In this method, all combinations of replicas and parameters are considered for parameter permutation, and a list of all the combinations is prepared. We reported that the temperature transition probability depends on how the list is created, especially in replica permutation with solute tempering (RPST).[2] We found that the transition probabilities decrease at large replica indices when the combinations are sequentially assigned to the state labels as in the originally proposed list. To solve this problem, we propose to modify the list by randomly assigning the combinations to the state labels. We performed molecular dynamics simulations of amyloid-β(16–22) peptides using RPST with the "randomly assigned" list (RPST-RA) and RPST with the "sequentially assigned" list (RPST-SA). The results show the decreases in the transition probabilities in RPST-SA are eliminated, and the sampling efficiency is improved in RPST-RA.

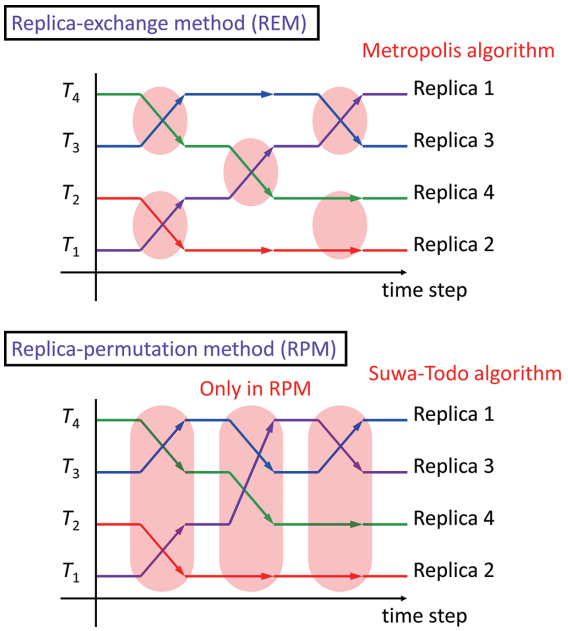


**Figure 4.** Schematic illustration of replica-exchange method (REM) and replica permutation method (RPM).

### References

1) S. G. Itoh, M. Yagi-Utsumi, K. Kato and H. Okumura, *ACS Chem. Neurosci.* **13**, 3139–3151 (2022).
2) D. Fukuhara, M. Yamauchi, S. G. Itoh and H. Okumura, *J. Comput. Chem.* **44**, 534–545 (2023).

* carrying out graduate research on Cooperative Education Program of IMS with Shinshu University