

# Molecular Dynamics Simulations of Disease-Related Biomolecules

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## Education

1998 B.S. Keio University  
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## Professional Employment

2002 Postdoctoral Fellow, The University of Tokyo  
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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

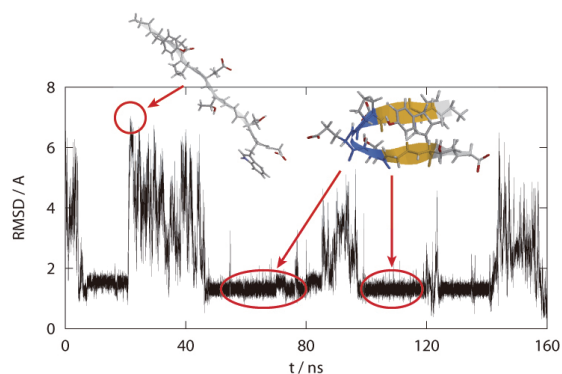
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## Keywords

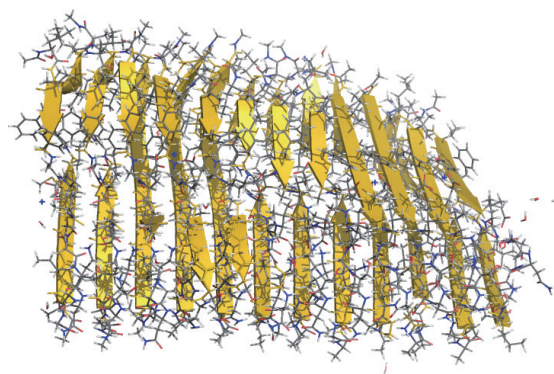
Molecular Dynamics Simulation, Protein, Amyloid

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 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.



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

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- $\beta$  ( $A\beta$ ) peptides. To overcome these diseases, it is essential to understand the aggregate genesis and disruption of  $A\beta$  peptides. We perform such MD simulations of oligomers and amyloid fibrils.



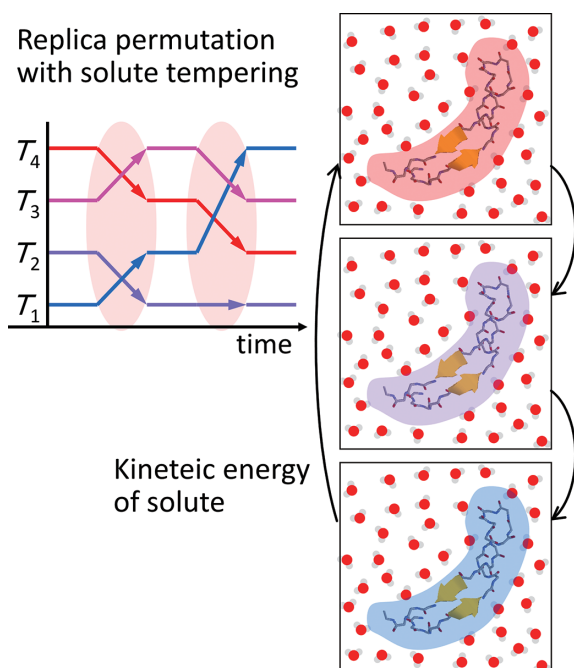
**Figure 2.** Snapshot of an  $A\beta$  amyloid fibril.

## 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- $\beta$ (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. Replica Permutation with Solute Tempering for Molecular Dynamics Simulation and Its Application to the Dimerization of Amyloid- $\beta$ Fragments

We proposed the replica permutation with solute tempering (RPST)<sup>1)</sup> by combining the replica-permutation method (RPM) and the replica exchange with solute tempering (REST), as in Figure 3. Temperature permutations are performed among more than two replicas in RPM, whereas temperature exchanges are performed between two replicas in the replica-exchange method (REM). The temperature transition in RPM occurs more efficiently than in REM. In REST, only the temperatures of the solute region, the solute temperatures, are exchanged to reduce the number of replicas compared to REM. Therefore, RPST is expected to be an improved method taking advantage of these methods. For comparison, we applied RPST, REST, RPM, and REM to two amyloid- $\beta$ (16–22) peptides in explicit water. We calculated the transition ratio and number of tunneling events in the temperature space, and the number of dimerization events of amyloid- $\beta$ (16–22) peptides. The results indicate that in RPST, the number of replicas necessary for frequent random walks in the temperature and conformational spaces is reduced compared to the other three methods. Additionally, we focused on the dimerization process of amyloid- $\beta$ (16–22) peptides. The RPST simulation with a relatively small number of replicas shows that the two amyloid- $\beta$ (16–22) peptides form the intermolecular antiparallel  $\beta$ -bridges due to the hydrophilic side-chain contact between Lys and Glu and hydrophobic side-chain contact between Leu, Val, and Phe, which stabilizes the dimer of the peptides.



**Figure 3.** Schematic illustration of replica permutation with solute tempering. Temperatures in the solute region are permuted among more than two replicas.

## 2. Implementations of Replica-Permutation and Replica Sub-Permutation Methods into LAMMPS

The replica-permutation method (RPM) and the replica sub-permutation method (RSPM) have been proposed as improved alternatives to the replica-exchange method (REM). We implemented the RPM and RSPM in the canonical and isothermal-isobaric ensembles into an open-source classical molecular dynamics package, LAMMPS.<sup>2)</sup> We applied the RPM and RSPM to a polyethylene chain in a vacuum and an alanine dipeptide in explicit water to test the implemented codes. We demonstrated that the RPM and RSPM by our codes achieved higher transition ratios of temperatures and faster convergence of physical quantities than the REM. We also validated that the RPM and RSPM generate statistical ensembles correctly.

## 3. Dimerization of $\alpha$ -Synuclein Fragments Studied by Isothermal-Isobaric Replica-Permutation Molecular Dynamics Simulation

Aggregates and fibrils of intrinsically disordered  $\alpha$ -synuclein are associated with Parkinson's disease. Within a non-amyloid  $\beta$  component (NAC) spanning from 61st to 95th residues of  $\alpha$ -synuclein, an 11-residue segment called NACore is an essential region for both fibril formation and cytotoxicity. Although NACore peptides alone are known to form aggregates and amyloid fibrils, the mechanisms of the aggregation and fibrillation remain unknown. We investigated the dimerization process of NACore peptides as the initial stage of the aggregation and fibrillation process by isothermal-isobaric replica-permutation molecular dynamics simulation.<sup>3)</sup> The simulation succeeded in sampling a variety of dimer structures. An analysis of secondary structure revealed that most of NACore dimer forms intermolecular  $\beta$ -bridges. In particular, more antiparallel  $\beta$ -bridges were observed than parallel  $\beta$ -bridges. We also found that intramolecular secondary structures such as  $\alpha$ -helix and antiparallel  $\beta$ -bridge are stabilized in the pre-dimer state. However, we identified that the intermolecular  $\beta$ -bridges tend to form directly with no specific structure because the NACore peptides have a low propensity to form the intramolecular secondary structures.

### References

- 1) D. Fukuhara, S. G. Itoh and H. Okumura, *J. Chem. Phys.* **156**, 084109 (12 pages) (2022).
- 2) M. Yamauchi, G. La Penna, S. G. Itoh and H. Okumura, *Comput. Phys. Commun.* **276**, 108362 (12 pages) (2022).
- 3) M. Yamauchi and H. Okumura, *J. Chem. Inf. Model.* **61**, 1307–1321 (2021).