Development of New Molecular Dynamics Algorithms for Biomolecular Systems

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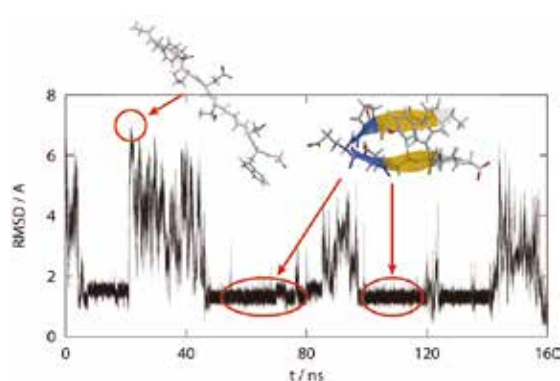   Associate Professor, The Graduate University for Advanced Studies
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Biomolecules such as proteins and peptides have complicated free-energy landscape with many local minima. The conventional canonical-ensemble molecular dynamics (MD) simulations tend 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.
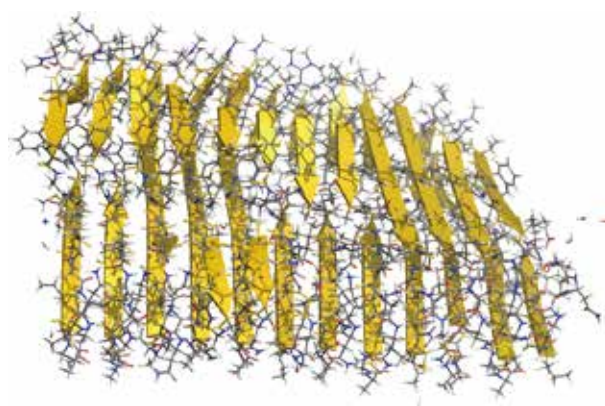
Figure 2. Snapshot of amyloid fibril.

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. Oligomer Formation of Amyloid-β(29-42) from Its Monomers Using the Hamiltonian Replica-Permutation Molecular Dynamics Simulation

Oligomers of amyloid-β peptides (Aβ) are formed during the early stage of the amyloidogenesis process and exhibit neurotoxicity. The oligomer formation process of Aβ and even that of Aβ fragments are still poorly understood, though understanding of these processes is essential for remedying Alzheimer's disease. In order to better understand the oligomerization process of the C-terminal Aβ fragment Aβ(29-42) at the atomic level, we performed the Hamiltonian replica-permutation molecular dynamics simulation with Aβ(29-42) molecules using the explicit water solvent model.[1] We observed that oligomers increased in size through the sequential addition of monomers to the oligomer, rather than through the assembly of small oligomers. Moreover, solvent effects played an important role in this oligomerization process.
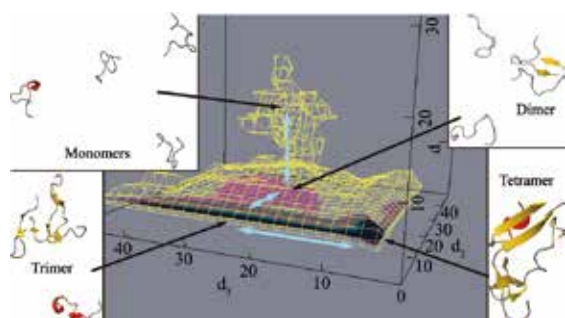

Figure 3. Free-energy surface and typical conformations of four Aβ(29-42) molecules.

2. Simulated Tempering Based on Global Balance or Detailed Balance Conditions: Suwa-Todo, Heat Bath, and Metropolis Algorithms

Simulated tempering (ST) is a useful method to enhance sampling of molecular simulations. When ST is used, the Metropolis algorithm, which satisfies the detailed balance condition, is usually applied to calculate the transition probability. Recently, an alternative method that satisfies the global balance condition instead of the detailed balance condition has been proposed by Suwa and Todo. In this study, ST method with the Suwa–Todo algorithm is proposed.[2] Molecular dynamics simulations with ST are performed with three algorithms (the Metropolis, heat bath, and Suwa–Todo algorithms) to calculate the transition probability. Among the three algorithms, the Suwa–Todo algorithm yields the highest acceptance ratio and the shortest autocorrelation time. These suggest

that sampling by a ST simulation with the Suwa–Todo algorithm is most efficient. In addition, because the acceptance ratio of the Suwa–Todo algorithm is higher than that of the Metropolis algorithm, the number of temperature states can be reduced by 25% for the Suwa–Todo algorithm when compared with the Metropolis algorithm.
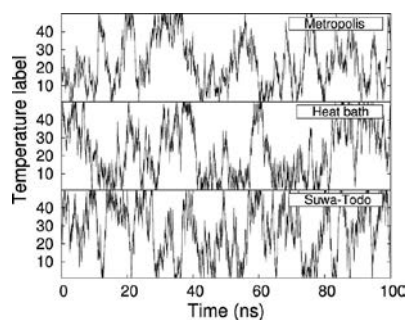
Figure 4. Time series of the temperature label in the simulations with the Metropolis, heat bath, and Suwa–Todo algorithms

3. Conformation Study of ε-Cyclodextrin: Replica-Exchange Molecular Dynamics Simulations

There is growing interest in large-ring cyclodextrins (LR-CDs) which are known to be good host molecules for larger ligands. The isolation of a defined size LR-CD is an essential prerequisite for studying their structural properties. Unfortunately the purification procedure of these substances turned out to be very laborious. Finally the problem could be circumvented by a theoretical consideration: The replica exchange molecular dynamics (REMD) simulation offers an ideal approach for studying the conformational change of ε-cyclodextrin (CD10), a smaller representative of LR-CDs. Three carbohydrate force fields and three solvent models were tested.[3] The conformational behavior of CD10 was analyzed in terms of the flip (turn) of the glucose subunits within the macrocyclic ring. In addition a ranking of conformations with various numbers of turns was performed. Our findings might be also helpful in the temperature controlled synthesis of LR-CDs as well as other experimental conditions, in particular for the host–guest reaction.

References
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3) W. Khuntawee, T. Rungrotmongkol, P. Wolschann, P Pongsawasdi, N. Kungwan, H. Okumura and S. Hannongbua, *Carbohydr. Polym.* **141**, 99–105 (2016).

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