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Prediction of Disassembly Pathway of Multimeric Protein Complex by Hybrid Monte Carlo Simulations

Ikuo KURISAKI[1] kurisaki1@bear.kobe-u.ac.jp
Shigenori TANAKA[1] tanaka2@kobe-u.ac.jp

[1] Kobe Univ., Grad. Sch. Sys. Inform., 1-1 Rokko-dai, Kobe, Hyogo, 657-8501, Japan

Keywords: Molecular Recognition, Molecular Dynamics, Mass Spectrometry, Hybrid Monte Carlo

Physicochemical characterization of multimeric biomacromolecule assembly and disassembly processes is a milestone for understanding biological phenomena at the molecular level. Mass spectroscopy (MS) and structural bioinformatics (SB) techniques have become feasible to identify subcomplexes involved in such processes [1,2]. This kind of information can be an initial and critical step toward calculations of free energy profiles of the processes, although the atomistic information that MS and SB studies give is not satisfactory for the purpose.

To combine information derived from MS and SB studies with conventional free energy calculation protocols, we designed a new reaction pathway sampling method by employing a hybrid Monte Carlo/Molecular Dynamics (hMC/MD) scheme [3]. Rare events such as associative and dissociative molecular diffusions are accelerated in each MD phase by employing Steered MD (SMD) method. A reaction coordinate of the SMD simulation is randomly selected from the candidates of subunit pairs. Meanwhile, a configuration generated by enhanced sampling is rejected with a certain probability by Metropolis algorithm in MC phase to circumvent selection of subcomplex configurations anomalously deformed by the usage of the SMD simulations.

First, we applied it to simulating the disassembly process of serum amyloid P component (SAP) pentamer, a ring-shaped homomeric protein complex. The disassembly process we simulated is consistent with that of the earlier MS and SB studies for SAP subcomplex species. Furthermore, we observed a novel dissociation event, the ring-opening reaction of SAP pentamer, where one of the five subunit interaction interfaces is broken. This ring-open form emerges in advance to the other set of subcomplexes, the trimer plus dimer and tetramer plus monomer.

Next, employing free energy calculation combined with the hMC/MD reaction pathway trajectories, we obtained experimentally testable observations on (1) reaction time of the ring-opening reaction and (2) importance of Asp42 and Lys117 for stable formation of SAP oligomer.

We would also present the latest progress of the hMC/MD scheme, modifications to efficiently predict the disassembly process of heteromeric protein complexes.

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