MD-SAXS: Hybrid method of molecular dynamics simulations and small-angle x-ray scattering experiments

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Molecular dynamics (MD) is crucially important for protein functions. MD simulation is a powerful computational tool for investigating molecular dynamics of proteins in atom detail. However, due to the time-scale limitation of MD simulation, conformational samplings in MD simulation are occasionally insufficient. Thus, to validate simulation structures, the comparison of the simulation structures with experimental results is useful.

Small-angle x-ray scattering (SAXS) experiments is a powerful method to measure protein structures in solution. Although the resolution of SAXS is limited to low because of the orientational and conformational averaging, the information of protein conformations in solution can be obtained. Therefore, the comparison of simulation results with SAXS data serves to obtain the protein solution structures consistent with experiments.

We have developed a hybrid method of MD simulations and SAXS (MD-SAXS) [1–3]. The first example of MD-SAXS applications was EcoO109I, a type II restriction endonuclease [1]. The enzyme was revealed to be substantially flexible, and the intrinsic flexibility was found to be closely related to the structural changes upon DNA binding.

Ion effects on SAXS data were investigated using MD-SAXS [2]. At a series of ion concentrations from 0 to 1 M, the MD-SAXS analysis for lysozyme was performed. The SAXS excess intensities were strongly dependent on ion concentrations. Based on the MD-SAXS, we developed a fast method to handle ion effects.

MD-SAXS was also applied to the drug target protein [4]. Vitamin D receptor (VDR) is a member of the nuclear receptor family, and functions as the control of the expression of genes through Vitamin D binding. The VDR ligand binding domain (LBD) is expected to undergo conformational changes upon agonist or antagonist binding. However, the crystal structures of VDR-LBD share a similar structure even with bound agonist or antagonist. The crystal structure of VDR-LBD in the ligand-free state has not been determined. The SAXS experiments suggest that both the ligand-free and antagonist-bound structures in solution are different from the crystal structure. Thus, the MD-SAXS analysis was performed to elucidate the solution structures of VDR-LBD in both the states. In the ligand-free and antagonist-bound state, the obtained solution structures were in good agreement with their SAXS data. Their structural features were consistent with the function of VDR.

Sampling capability of all-atom MD simulations is occasionally insufficient for very flexible and large molecules. To overcome the limitation, we developed a hybrid method of a coarse-grained MD simulations and SAXS (CG-MD-SAXS) [5]. Even in the coarse-grained models (e.g., Cα only), SAXS data were accurately reproduced from the structure models. CG-MD-SAXS was applied to the three types of nucleosomes (canonical, CENP-A, and H2A.B nucleosomes), and revealed the substantial difference in the dynamics of DNA around histones.

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