A practical procedure to calculate intermolecular interactions including statistical information between a protein and a large ligand

Hiroyuki Sato1
shryk@jp.fujitsu.com

Kentaro Takai2
takai.kentaro@jp.fujitsu.com

Hajime Sugiyama2
sugiyama.hajime@jp.fujitsu.com

Yoshiaki Tanida1
tanida.yoshiaki@jp.fujitsu.com

Azuma Matsuura1
matsuura.azuma@jp.fujitsu.com

Shunji Matsumoto2
shun@jp.fujitsu.com

Hiroaki Suga3
hsuga@chem.s.u-tokyo.ac.jp

1 Design Engineering Lab., Hardware Technologies Laboratories, Fujitsu Laboratories Ltd., 10-1 Morinosato-Wakamiya, Atsugi 243-0197, Japan
2 Bio IT Development, Business Planning & Promotion Div., Healthcare & Educational Systems Unit, Fujitsu Ltd., 1-9-3 Nakase, Mihama, Chiba 261-8588, Japan
3 Department of Chemistry and Biotechnology, School of Engineering, The University of Tokyo, 7-3-1 Hongo, Bunkyo, Tokyo 113-0033, Japan

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We investigated the method to compute intermolecular interactions around the binding site in the system composed of the histone deacetylase SIRT2[1], a nonstandard cyclic peptide (S2iL5[2]) and solvent, especially in view of the influence of water molecules.

First, we performed 1 µs molecular dynamics (MD) simulation in the system and obtained an equilibrium time region corresponding to local fluctuations of SIRT2 from the MD trajectory. In this region, we selected the water molecules whose RMSF values were as small as those of SIRT2. These water molecules were considered to be less fluctuated and thus stable. In order to include the statistical information in one typical structure, we averaged the structures of the complex with the stable water molecules in the region and then optimized the obtained structure by the molecular mechanics method. Next, we investigated the conformation of the binding sites and calculated the intermolecular interaction energy by the fragment molecular orbital (FMO[3]) method. We found that the optimized structure reproduced the binding site that had been frequently caused in the trajectory although the structure without the stable water molecules did not. We also found that the interaction energy between SIRT2 and each residue of S2iL5 with the stable water molecules were different from that without the stable water molecules by about 20 kcal/mol in the maximum. This indicates that it is important for the intermolecular interaction by the quantum mechanical method to determine the structure of the system including the stable water molecules.

A series of techniques presented here is considered to be a practical procedure to include statistical information in the intermolecular interactions by quantum mechanical method, relating the quantum mechanical method and the classical MD simulation.