

Receptor-Ligand Docking Simulation for Membrane Proteins

○Takatsugu Hirokawa (Computational Biology Research Center, AIST)

Protein structure-based molecular design using the computational techniques of protein structure prediction, ligand docking and virtual screening is an integral part of drug discovery for limiting the application of structure-based approach to target proteins such as G-protein coupled receptors (GPCRs). GPCRs play an important role in living organisms, and are of major interest to the pharmaceutical industry. However, structural data of ligand binding forms for GPCRs from experiments to elucidate structural templates for docking simulations are lacking due to the difficulties associated with crystallization and crystallography. Therefore, structural prediction of GPCRs in the ligand-bound state using a computational methods has been introduced, but the prediction of ligand conformation onto target GPCRs is still constructed manually by human experts. We developed a molecular modeling technique for the prediction of ligand-receptor binding using comparative ligand-binding analysis (CoLBA) that not only considers interaction energy, but also similarity of interaction profiles among ligands. The advantage of CoLBA is that it can facilitate intuitive and flexible screening based on docking results when protein structures with low resolution (or theoretical models) are targeted. We applied CoLBA to ligand binding prediction in several GPCRs. The predicted ligand binding models were evaluated by site-directed mutagenesis experiments in collaborative research and the enrichment rate of activated ligands was compared with the random compounds in virtual screening simulations. We propose that CoLBA can be applied to large scale modeling of ligand-receptor complexes and virtual screening for GPCRs.