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Computational docking of a ligand to the target protein coping with an induced-fit

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An induced fit causes a tangled problem for computational docking of ligands to the target protein. Most of commonly used programs perform poorly on the problem, because these programs treate the protein as a rigid body. In order to make the computational docking successful, it is necessary to take protein flexibility into consideration. In this study, we have developed Brownian dynamics (BD) program to build up the protein-ligand complex taking into account the protein flexibility. As an intestinal fatty acid binding protein and a human protein tyrosine phosphatase 1B are known to exhibit significant induced-fit effects on ligand binding, we selected these proteins as model cases. Here, we applied the BD program to construct protein-ligand complexes from the structures of ligand-free proteins. First, we used a docking program, FlexX that handles ligand flexibly, to produce temporary protein-ligand complexes. Then, we carried out the BD calculations to relax and refine these complexes and compared the refined structures of the complexes with the crystal structures of them. We could show that the refined structures are very similar to the crystal structure of the complexes. The Brownian dynamics simulation seems to be very effective for refinements of protein-ligand docking models.