Fast, accurate X-ray density-driven ligand docking on the free energy surface using the MovableType method coupled with Phenix/DivCon

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Abstract

X-ray crystallography is the primarily technique used to determine the three-dimensional (3D) structure of protein:ligand and protein:protein complexes, and it plays a central role in Structure Based Drug Design (SBDD). Recently, we integrated our quantum mechanics toolkit with the Phenix crystallographic package to replace the conventional stereochemical restraints with a more accurate QM/MM-based energy functional in "real time" during the refinement and we expanded this tool to include density driven solvation and tautomer/protomer/rotamer determination. While these methods are powerful, they suffer from the same limited radius of convergence as conventional methods, and their success is ultimately dependent upon the initial atom placement of the model. We have addressed this ligand placement problem with the use of a cutting edge free energy based algorithm (i.e. MovableType or MT). Unlike conventional free energy methods, the MT method - along with the directly associated MT_{Dock} tool - is an entirely novel way to assemble partition functions and, hence, free energies. Importantly, this method is based on fundamental statistical mechanics and does not rely on the use of expensive molecular dynamics, and it also does not suffer from many of the issues associated with conventional, energy-based found in typical docking and scoring methodologies.

In this study, the MT_{Dock} algorithm - coupled with the Phenix/DivCon package - was validated against the highly diverse PDBBind set. We showed that we were able to routinely place ligands with a high degree of accuracy as measured by the crystallographic Z-score of the difference density metric (ZDD).

Key Literature:

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