RS-Mtdock: Movabletype Ligand Docking Method Using X- Ray/Cryo-EM Experimental Density and Integrated QM/MM Realspace Refinement for Drug Design

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X-ray crystallography and cryogenic electron microscopy (cryo-EM) are the primary experimental techniques used to determine the three-dimensional (3D) structure of protein:ligand and protein:protein complexes, and these methods play a central role in Structure Based Drug Design (SBDD). To overcome typical weaknesses of the conventional X-ray refinement due to using stereochemical-restraints we incorporated advanced QM or QM/MM functionals into the crystal structure refinement [1, 2]. Later we also demonstrated the critical role of the QM/MM refinement for the affinity predictions in SBDD [3]. During the model building stage of X-ray and Cryo-EM refinement, a significant challenge in ligand model placement is determination of the correct ligand orientation especially when the experimental density is weak or incomplete. We have addressed this ligand placement and refinement problem with the use of our MovableType fast free energy based docking algorithm (MT_{Dock}) [4] coupled with a built-in realspace (RS) refinement engine in which geometry energy and gradients - derived using a QM, MM or mixed QM/MM Hamiltonian - are combined with electron density values/gradients derived from X-ray data / Cryo-EM maps [1, 2]. In this work, we will present this integrated RS-MT_{Dock} protocol which involves automated electron density blob selection followed by MT-driven ligand placement and RS refinement. Each refined pose is then scored using MT_{Score} to determine which pose is correct. For the maximum performance, these steps have been fully integrated within QuantumBio's Discovery Suite to provide user-friendly, fully automated and fast software to directly use in any SBDD protocol. We have validated the RS-MT_{Dock} protocol using 480 protein:ligand structures taken from the Iridium and PDBBind sets. We demonstrated top scored ligand poses have RMSD to the published structures below 0.3 Å and/or exhibit better fit versus the electron density in over 90% cases.

{1} Borbulevych, O. Y., Plumley, J. A., Martin, R. I., Merz K. M. & Westerhoff, L. M. (2014). Acta Cryst., D70, 1233.
{2} Borbulevych, O. Y., Martin, R. I. & Westerhoff, L. M. (2018). Acta Cryst., D74, 1063.
[3] Borbulevych, O. Y., Martin, R. I. & Westerhoff, L. M. (2021). J. Comput. Aided Mol. Des., 35, 433.
[4] Zheng, Z., Borbulevych, O. Y., Liu, H., Deng, J., Martin, R. I. & Westerhoff, L. M. (2020). J. Chem. Inf. Model., 60, 5437.