

Poster Presentation

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Accurate water site determination in macromolecular refinement using 3D-RSIM

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Structure Based Drug Discovery (SBDD) is employed by virtually all pharmaceutical R&D organizations, and understanding the protein:ligand complex structure along with explicit solvent effects is necessary to obtain meaningful results from docking, thermodynamic calculations, and active site exploration. Phenix/DivCon is able to accurately elucidate the protein:ligand complex structure through in situ treatment of the structure using quantum mechanics; however, at standard SBDD resolutions, the crystallographic data unambiguously reveals only a small fraction of water molecules in protein crystals - even within the first hydrogen shell of the protein molecule. Further, the implicit solvent correction in conventional methods does not take into account non-linear effects of hydrogen bonding and dispersion interactions introduced by the nearest hydration shells. To address this deficiency, we have used the 3D Reference Interaction Site Model (3D-RISM) method as implemented in MOE to filter crystallographic map data and create a more complete first solvation shell of the biomolecular complex. The combination, implemented within the Phenix/DivCon refinement workflow, allows us to capture weaker difference density peaks and thus "rescue" water sites that are normally undetectable using conventional crystallographic protocols. This workflow has been applied to "standard" resolution structures, and the results have been compared to corresponding higher-resolution structures. We have observed consistent improvements in R-factors and in water site determination. For example, the lysozyme structure PDBid:2EPE (2.5 Å) has 48 crystallographic waters while PDBid:193L (1.33 Å) has 142 waters. When considering overlapping sites, 2EPE captures 30% of the waters found in 193L. When our method is applied to 2EPE however, it is able to find almost 60% of the waters observed in the higher-resolution, and it is able to predict sites that may have been missed at the higher resolution.

Keywords: 3D-RISM, Solvent structure, X-ray refinement