COMBINING 3D-RISM CALCULATION WITH HYDROPATHIC CHARACTER FOR WATER SELECTION: APPLICATION IN DOCKING WITH FLEXIBLE EXPLICIT WATER

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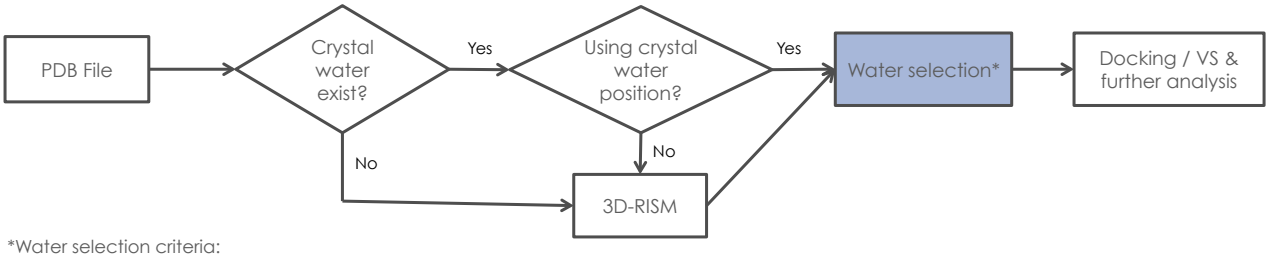
Introduction

Including explicit water molecules is deemed important in the process of docking and virtual screening. Several attempts have been made to identify important water molecules in crystal structures in the past decade.[1-3] However, the intrinsic drawbacks of crystallography suggested that such methods inevitably lack of comprehensiveness. Therefore, we applied the well-established 3D reference interaction site model (3D-RISM[4,5]) method to map the water positions, followed by a relatively efficient water selection process about the binding site. Both the distance to ligand and receptor, and the hydropathic character[6] are taken into account for evaluating water molecules. We will include this water selection process for docking or virtual screening in our later simulations once it is been validated for both protein-ligand and protein-protein interactions.

Workflow



*Water selection criteria:

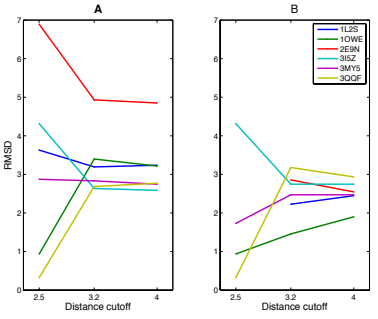
1. Distacne cutoff to ligand and protein (2.5, 3.2, and 4.0 Å).
2. Hydropathic character cutoff at -3.66 of residues closest to the selected water molecule from criteria 1.

Crystal structures chosen (PDB ID in parentheses): AmpC beta-lactamase (1L2S), Urokinase (1OWE), CHK1 (2E9N), ERK2 (3I5Z), CDK2-CyclinA (3MY5), and CDK2 (3QQF).

RMSD to Water Molecules in the Crystal Structures

A: RMSD to water molecules in crystal structure when only distance cutoff was used as the selection criterion

B: RMSD to water molecules in crystal structure when distance and hydropathic character cut-offs were both used as the selection criteria

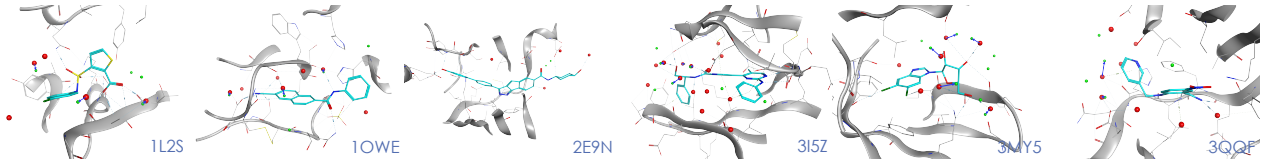


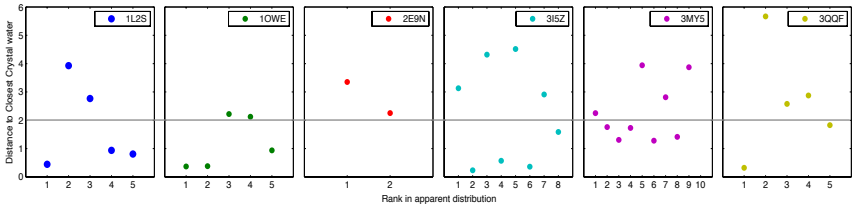
Number of Selected Water Molecule

Water molecules from crystal structures and 3D-RISM calculations were calculated using the same water selection criteria: distance and hydropathoc character cut-offs.
Results show that the 3D-RISM calculation plus the selection criteria applied in this work can pick out the crystal structure relatively accurately.

* Further analysis on the water positions selected from 3D-RISM calculation using a 2 Å cut-off

PDB ID	Distance cutoff (Å)	No. of water selected from crystal structure	No. of water selected from 3D-RISM	Close to crystal structure (within 2 Å) *
1L2S	2.5	0	0	0
	3.2	2	5	3
	4.0	3	6	3
1OWE	2.5	0	1	1
	3.2	3	5	3
	4.0	3	6	3
2E9N	2.5	0	0	0
	3.2	0	2	0
	4.0	1	4	1
3I5Z	2.5	0	1	0
	3.2	4	8	4
	4.0	5	8	4
3MY5	2.5	2	1	1
	3.2	5	8	5
	4.0	5	9	5
3QQF	2.5	0	1	1
	3.2	3	5	2
	4.0	3	8	3





Discussions and Future Works

The preliminary results show that the methods of choice can reproduced water positions that resolved from crystal structure with good accuracy. While including hydropathic character evaluation, the water selection process improved with lowered RMSD to water positions in crystal structures. To further improve the accuracy, we consider that water molecules that are close to the protein backbone are also potential bridging candidates for ligand binding. Therefore additional criteria for water selection will be included in the future. Moreover, the water selection process will also be validated with protein-protein interactions in later works. We expect such workflow can provide sturdiness for reproducing important crystal water molecules, meanwhile, introducing certain flexibility about those water molecules that crystallography fails to resolve.

Reference

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