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Combining 3D-RISM with hydrophatic charateristic water evaluation: first step preparation for further PLANTS virtual screening with flexible explicit water molecules

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Docking and virtual screening with explicit water has become a hot topic within the docking community in the past decade. It was suggested that the bridging water molecules, existed between the ligand and the receptor, are important contributors to binding free energy. Multiple methods are since developed, either through direct evaluation or scoring of crystal waters, or predictions for water positions when crystal waters are in absence. Unfortunately, one limitation for such methods to become widely applicable is that the well-acknowledged force-field-based scoring functions do not allow efficient docking with flexible water molecules. Additionally, the likelihood of introducing human bias increases during the process of visual water selection. Therefore, in our work, we have combined a well-established water-predicting method, 3D-RISM[1,2], and a series of relatively simple and efficient criteria – including the consideration of hydropathic index [3] of adjacent amino acids – to select potentially important water molecules. This flow of work has allowed automatic selection of water molecules between protein-ligand or protein-protein interface. We have observed optimistic results in predicting crystal water positions within the binding pocket using several benchmark systems. Further results will be discussed during the poster session of the conference.

[1] Imai T, Oda K, Kovalenko A, Hirata F, and Kidera A: **Ligand Mapping on Protein Surfaces by the 3D_RISM Theory: Toward Computational Fragment-Based Drug Design**, *J Am Chem Soc* 2009, **131**:12430-12440

[2] Sindhikara DJ, Hirata F: **Analysis of Biomolecular Solvation Sites by 3D-RISM Theory**, *J Phys Chem B* 2013, **117**:6718-6723

[3] Kyte J, Doolittle RF: **A Simple Method for Displaying the Hydropathic Character of a Protein**, *J Mol Biol* 1982, **157**:105-132