The role of water in mediating biomolecular binding: from water locations to their impact on binding affinity

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Water plays an intimate role in protein-ligand binding, not only through solvation/desolvation effects, but more subtly through the formation of direct interactions between the protein and ligand in the binding site. The targeting of bound water molecules for displacement as part of ligand optimization is a long invoked paradigm based around the release of configurational entropy, but there are many examples where displacing water leads to a loss in ligand binding affinity. Quantitatively accurate approaches to address this problem are arguable inadequate – water displacement and ligand interactions are intimately related and difficult to disentangle both experimentally and, hitherto, computationally.

We have a long-standing interest in developing and using Grand Canonical Monte Carlo (GCMC) simulation approaches to explore water binding in protein-ligand systems. Through GCMC we are able to locate water molecules with good accuracy when compared against crystal structures. More significantly, the simulations clearly demonstrate the important role of water cooperativity; the mutual stabilization of water molecules means that individual water molecules cannot always be considered in isolation, but rather as part of a network.

GCMC allows water binding sites and network binding free energies to be simultaneously calculated. In addition, by combining GCMC with alchemical perturbations of the ligand, networks of bound water molecules are able to adapt and maintain equilibrium with bulk water as the perturbation proceeds. Furthermore, the ability to extract active-site hydration free energies allows the deconvolution of protein-ligand binding free energies into separate protein- and water-mediated components, thereby providing rich, additional detail to the structure-activity relationship (SAR).

In this presentation, our underlying methodology GCMC methodology will be described, together with examples of its application to water placement, binding free energy calculations, and protein-ligand affinity prediction.