What can we learn from local water happiness?

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Water molecules play an essential role in protein-ligand binding as their replacement contributes to the free energy of binding ($\Delta_{bind}G$). Different approaches have been developed that aim at predicting if a water molecule can be targeted for replacement. [1-3] Prospective, quantitative measures to identify ligand chemistry to target specific thermodynamic hydration site features are highly desirable. We therefore analyze local water thermodynamics and its influence on ligand binding with novel physics-based approaches derived from 3D reference interaction site model (RISM) integral equation theory.[1,4] The following questions are addressed: Are the ligand's physicochemical properties imprinted in the *apo* water thermodynamics? Is it possible to predict by which group a water molecule should be replaced? How does a (mis)match between water "happiness" (measured by local contributions to the hydration free energy, $\Delta_{hyd}G$) and ligand properties contribute to $\Delta_{bind}G$? How can this knowledge be used for drug design?

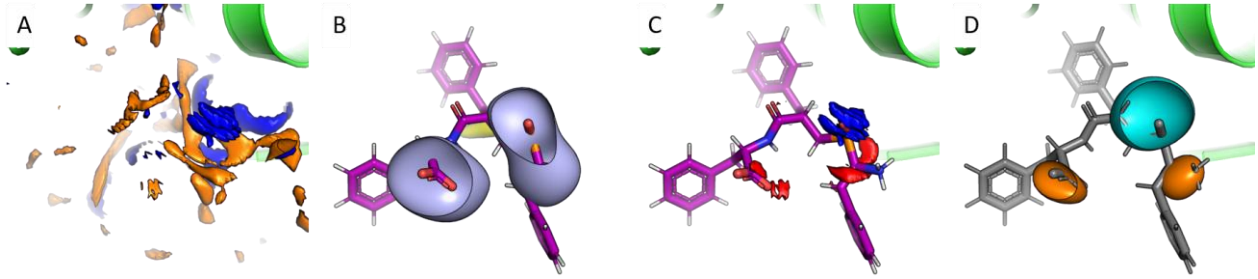

Fig. 1. Analysis for 1os0@pdb. A: "(Un)happy" (orange, blue) *apo* water regions; B: hydrophobic and hydrophilic (yellow, steel-blue) regions of the ligand; C: (mis)matching (red, blue) correlation of *apo* water and ligand properties; D: ligand regions which contribute most (un)favorably (orange, cyan) to $\Delta_{bind}G$.

3D RISM allows for the identification of localized hydration sites along with their local contribution to $\Delta_{hyd}G$. [1] Analysis of the pdbBind core set [5] shows that "unhappy" water molecules tend to be replaced by halogen atoms and aromatic carbons whereas "happy" waters are primarily replaced by polar groups. Furthermore, local contributions to *apo* ligand atom solvation and *holo* binding free energies can be estimated, which can be related to corresponding hydration site features. We can therefore quantitatively test the hypothesis that the contribution of a group to $\Delta_{bind}G$ is related to its hydrophobicity and the *apo* water "happiness", e.g. that replacement of an "unhappy" water by a hydrophobic group is favorable for binding. First results (s. Fig. 1) support this presumption.

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