Thermodynamic signatures of protein hydration sites and their correlation with ligand features

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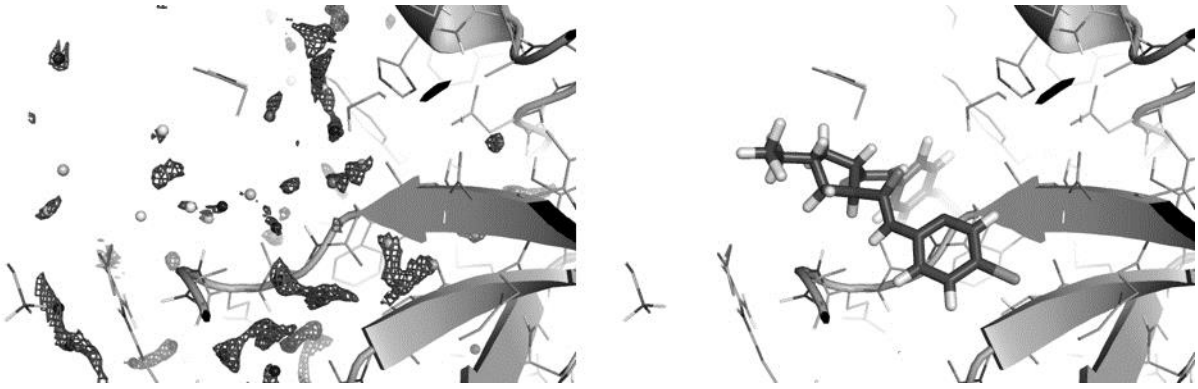
During the drug discovery process, initial hit compounds that were identified by high throughput screening are usually optimized via structure-based drug design (SBDD) [1]. In an iterative process, specific groups of the molecule are varied and the impact of these modifications on binding affinity is assessed. The introduction of new groups or modifications is typically directed by pharmacophores, compound comparison and chemical intuition which all reflect the complex interplay of protein-ligand interactions and their modulation by the solvent. To complement the SBDD toolbox with novel physics-based approaches, we here present results from our approach to predict local contributions of water molecules in binding sites to the solvation free energy [2], applied to a range of target proteins. We particularly focus on the question to what extent the thermodynamics of protein-ligand interaction is already imprinted on the hydration signatures within a binding site.

To this end, we employ the three-dimensional (3D) reference interaction site model (RISM) integral equation theory for predicting localized binding site water molecules in *apo* proteins along with their thermodynamic signatures that are relevant for rationalizing properties of the ligand groups which replace them [2]. For the proteins in the pdbBind core set [3] we analyze to what extent water molecules classified as "happy" and "unhappy" (depending on their favorable or unfavorable contribution to the hydration free energy) correlate with different types of ligand atoms displacing them in the *holo* complex. Thus, we elucidate the relevance and limitations of this methodology to aid the design or modification of a ligand to target a solvent-occupied binding site region.



Together with the 3D RISM-based binding free energy localization and local probe thermodynamics approaches recently developed in our group, this information yields an in-depth picture of the thermodynamic contributions of direct and solvent-mediated interactions in a protein ligand complex. Perspectives for using these data in the context of machine learning approaches to predict protein-ligand interactions and for design purposes are also discussed.

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[3] Y. Li, L. Han, Z. Liu, R. Wang, *J. Chem. Inf. Model*. **2014**, *54*, 1717–1736.