Localization of protein-ligand binding thermodynamics

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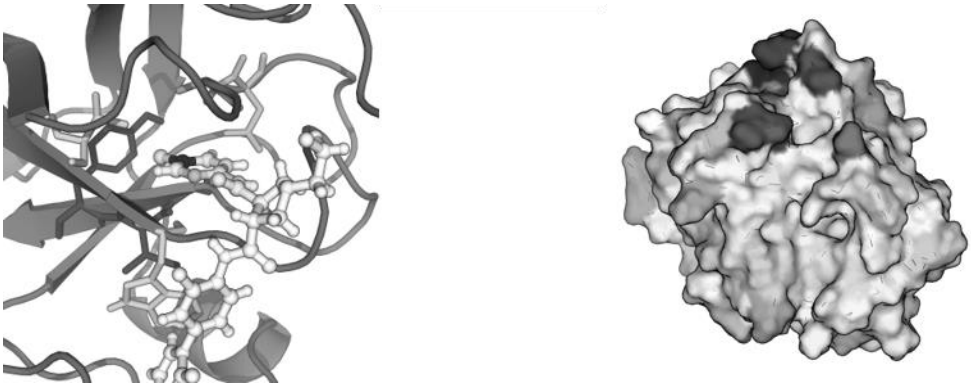
In the early stages of the drug discovery process, promising compounds, for example obtained by high throughput screening of large databases, are often optimized via structure-based drug design (SBDD) [1]. Here, specific groups of the compounds are evaluated with respect to their contribution to the formation of a protein-ligand complex, which then leads the next iteration round in the design process. This assignment is typically directed by pharmacophores, compound comparison and chemical intuition. We here complement the SBDD toolbox by presenting two novel physics-based approaches that allow for the localization of thermodynamic features in a host-guest binding system such as a protein-ligand complex which can aid the development of new drugs.

The three-dimensional (3D) reference interaction site model (RISM) integral equation theory can be formulated and applied in a way to address the problem of complex formation thermodynamics, accounting for solvation effects on an atomic level [2]. A particular advantage is the resulting definition of a free energy derivative (FED) with respect to interaction parameters developed by us. When applied to the complex formation problem, the FEDs allow for a rigorous spatially-resolved mapping of thermodynamics onto local structural features, which can be viewed and interpreted from both a ligand and a protein perspective to shed light onto crucial local interaction features.



Another complementary perspective results from applying 3D RISM for predicting highly localized binding site water molecules along with their thermodynamic features that are relevant for rationalizing properties of ligands replacing them [3]. This methodology allows for predicting interaction characteristics of a potential ligand group that targets a solvent-occupied binding site region.

Together, both approaches yield an in-depth picture of the thermodynamic contributions of direct and solvent-mediated interactions that can be employed for drug design and scoring.

[1] G. Schneider, *De Novo Molecular Design*, **2014**, Wiley-VCH, Weinheim, Germany.
[2] F. Mrugalla, S. M. Kast, *J. Phys. Condens. Matter*, **2016**, *28*, 344004.
[3] S. Güssregen, H. Matter, G. Hessler, E. Lionta, J. Heil, S. M. Kast, *J. Chem. Inf. Model.*, **2017**, *57*, 1652-1666.