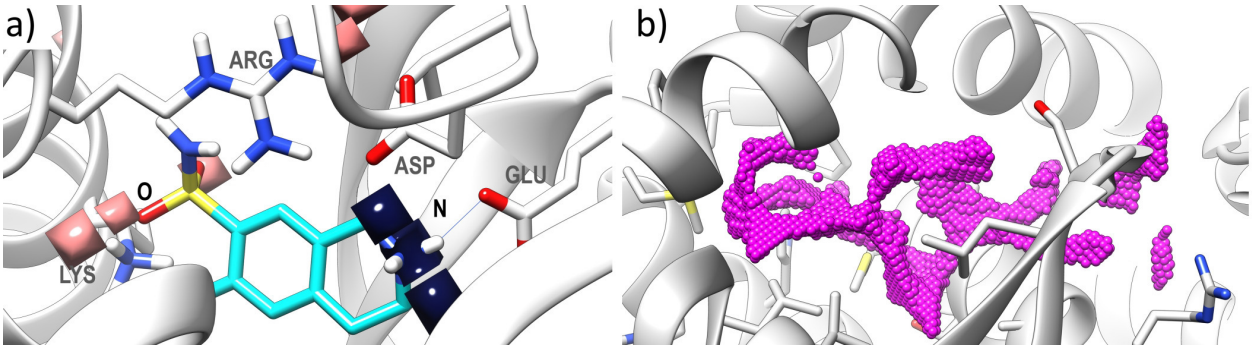
Mapping Binding Site Thermodynamics by 3D RISM Theory for Drug Design

J. B. Jasper, Y. Alber, F. Mrugalla, S. M. Kast, Oliver Koch

Faculty of Chemistry and Chemical Biology, TU Dortmund, Dortmund, Germany

The early stages of the drug discovery process require reasonably accurate and fast methods for optimising the binding affinity of protein-ligand complexes, taking into account direct and solvent-mediated interactions. Inspired by Goodford's GRID method [1] we here present a novel physics-based approach that incorporates (de-)solvation contributions to the binding thermodynamics of probe particles mimicking functional ligand groups in a protein binding site. To this end, we calculate the potential of mean force (PMF) and the distribution functions of different probes (uncharged C, charged N and O) inside the apo protein by 3D RISM (reference interaction site model) theory. [2,3]

The method allows for an intuitive and easy visualization of probe density maps inside the binding site (Fig. 1a, N and O density maps of apo protein in overlay with ligand for 1hnn@pdb) and can be exploited for various tasks in the drug development process. Applications range from pharmacophore and docking-based virtual screening up to defining design directions for medicinal chemists. In a first proof of concept study, the PMF results were embedded into the GOLD [4] docking process on a subset of the PDBbind dataset [5]. An uncharged C probe is used to calculate hydrophobic fitting points that are used for ligand placement throughout the docking process. These 3D RISM based points (Fig. 1b, for 1nav@pdb) display a more detailed representation of hydrophobicity yielding improved docking success.



[1] P. J. Goodford, *J. Med. Chem.* **1985**, 28, 849–857.
[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.
[4] G. Jones, P. Willett, R. C. Glen, A. R. Leach, R. Taylor, *J. Mol. Biol.* **1997**, 267, 727–748.
[5] Y. Li, Z. Liu, J. Li, L. Han, J. Liu, Z. Zhao, R. Wang, *J. Chem. Inf. Model.* **2014**, 54 (6), 1700–1716.