[P21] Cucurbit[n]urils as a test-system for an advanced *in-silico* docking

Ekaterina Ratkova[1], Igor Tetko [1]

[1]*Chemoinformatics group, Institute of Structural Biology, Helmholtz Zentrum München Ingolstädter Landstraße 1, 85764 Neuherberg, Germany*

During the last decades, it was revealed that computational docking methods must routinely include treatment of *water molecules*, since they can change dramatically properties of both binding partners, protein and ligand, and regulate their affinity and selectivity [1]. In particular, the docking methods should properly consider *the desolvation penalty,* which is associated with the displacing of water molecules at a protein-ligand interface.

Development of a rigorous computational docking methodology usually requires simplified test-systems. Supramolecular host-guest inclusion complexes, where guest molecules penetrate into the container-like cavity of hosts, are widely used for this purpose [2]. Molecular recognition events in such systems are driven by the same interaction forces as in protein-ligand systems. However, the host molecules are dramatically simpler than proteins (smaller size and limited conformational flexibility), which allows higher throughput and better numerical convergence. Usually, host-guest interactions play the crucial role in strong binding affinity. However, it is not the case for cucurbit[n]urils (CBn) inclusion complexes, which in recent years have emerged as particularly appearing test cases. These rigid barrel-shaped macrocycles exhibit a wide range of affinities for varied guests in aqueous solution [3], with maximal affinities rivaling those of the tightest-binding protein-ligand systems. They display an exceptionally strong binding affinity even for uncharged guests. Recently, Biedermann and co-workers revealed that the major driving forces for this strong complexation stems from *solvent effect*, namely, the release of “high-energy” (enthalpically and/or entropically unfavorable) water molecules [4].

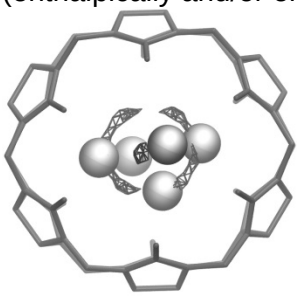

Figure 1. “High-energy” waters (grey spheres) in the CB6 cavity. Mesh iso-surface corresponds to g(r) > 5.3

In this study, we investigated cucurbit[n]urils (n = 5–8) and their complexes using RISM approximation of the integral equation theory. Water molecule distribution functions around macrocycles were obtained with NAB routine from AmberTools15 software [5]. Explicit water positions and their energetic parameters were determined from these distribution functions using SolutionMap software [6]. We showed that RISM allows a correct reproducing of quantity, location and energetic characteristics of the unfavorable water molecules inside a CBn cavity (figure1). These results will be further used for the development of a novel RISM-based docking methodology.

Particularly, “high-energy” water data can be essential to improve affinity in protein-ligand systems. In several studies it was shown that introducing of an additional group to the ligand molecule at the location of such “high-energy” hydration sites, and hence displacing the waters from these sites, makes a large favorable contribution to the binding affinity [7].

Bibliography:

[1] P. Ball, Chem. Rev. 108 (2008) 74-108
[2] Muddana et al. J. Comput.-Aided Mol. Des. 26 (2012) 475–487; Muddana et al. J. Comput.-Aided Mol. Des. 28 (2014) 305–31
[3] Lui et al. J. Am. Chem. Soc. 127 (2005) 15959-15967
[4] F. Biedermann et al, J. Am. Chem. Soc. 134 (2012) 15318-15323
[5] D.A. Case et al. (2015), AMBER 2015, University of California, San Francisco.
[6] D.J. Sindhikara, F. Hirata, J. Phys. Chem. B 117 (2013) 6718-6723
[7] R. Abel et al. J Am Chem Soc. 130 (2008) 2817-2831