Electrostatics disguised as hydrophobicity: a new method to probe protein-ligand binding?

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It is accepted that electrostatics and hydrophobicity are the main determinants of biomolecular recognition and binding. We reported a few years ago about a method where an external electrostatic bias acting only on the ligand and the binding site was able to successfully lead to the bound complex state when starting from the ligand in solution.[1]
More recently, we aimed at studying the effects of varying the degree of local hydration in a bio-molecular system along a molecular dynamics simulation. We do this by adding an electrostatic repulsive potential between given regions of the studied system and nearby water molecules. We focus again on the case of protein-ligand interaction and especially on the PP1-SRC kinase case. We observe that dehydrating the ligand and the binding site with a specific and adaptive protocol may accelerate the binding process, leading to nearly native complexes. Moreover, the flexibility of this external bias allows for studying the effects of hydration and hydrophobicity on the binding process without the need to simulate different mutated systems.[2]

[1] Spitaleri A., Decherchi S., Cavalli A., and Rocchia W., “Fast dynamic docking guided by adaptive electrostatic bias: the MD-Binding approach”, J. Chem. Theory and Comp., 14 (3), pp 1727–1736, 2018
[2] Spitaleri A., Zia S.R., Di Micco P., Al-Lazikani B., Soler M.A., Rocchia W., "Tuning Local Hydration Enables a Deeper Understanding of Protein-Ligand Binding: The PP1-Src Kinase Case" J. Phys. Chem. Lett., pp. 49-58, 2021