Grand Canonical Simulations for In Silico Prediction of Fragment Binding Sites, Modes, and Affinities

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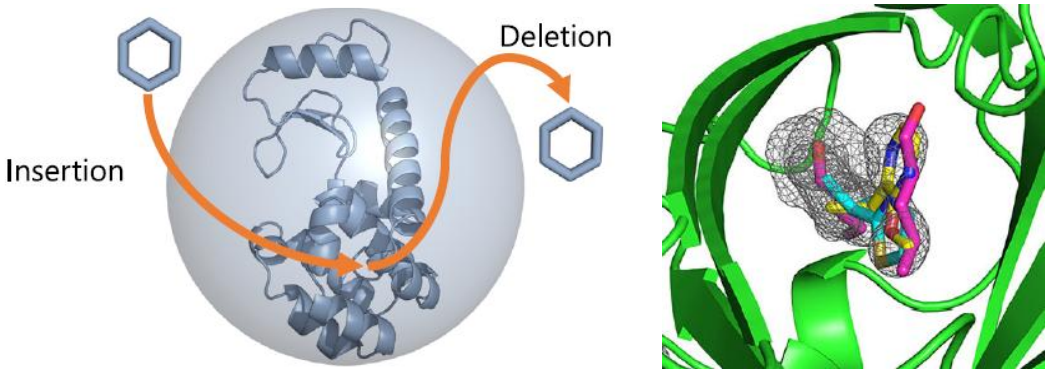
Fragment based drug discovery (FBDD) is widely used in the pharmaceutical industry as a route to generating lead compounds. Through knowledge of their binding sites, fragment hits may be combined into single molecules with good potency and physical properties. Computational FBDD supports experiment by providing a route to library design, virtual screening, binding site identification and binding affinity prediction.

In this talk, the development and application of grand canonical non-equilibrium Monte Carlo (GCNCMC) in this domain will be discussed. [1] By combining non-equilibrium move proposals, with grand canonical Monte Carlo acceptance tests, we are able to insert and delete small molecules into the binding sites of host-guest and protein systems, much more efficiently than conventional molecular dynamics. Through these simulations we are able to identify potential ligand binding sites by augmenting the sampling in mixed-solvent molecular dynamics. Fragment binding poses, including situations where multiple binding poses have been reported, are also readily identified. Finally, by varying the chemical potential of the simulations, absolute ligand binding free energies may be calculated, without the need for restraints or corrections to address multiple binding poses. Binding sites, poses, and affinities may all be calculated through a single series of simulations run at different chemical potentials. [2] Finally, cases where methodological improvements are needed will be discussed.



[1] O.J. Melling, M.L. Samways, Y. Ge, D.L. Mobley, J.W. Essex, *J. Chem. Theory Comput.*, **2023**, *19*, 1050-1062.
[2] W.G. Poole, M.L. Samways. D. Branduardi, R.D. Taylor, M.L. Verdonk, J.W. Essex, *Nat. Commun.*, **2025**, *16*, 6198.