# Fast binding free energy calculations

Fast and accurate prediction of the binding affinity between a small molecule and biological macromolecule is a holy grail of computational chemistry; success in this endeavor would have a large impact on drug design and chemical biology. We derive new theories that enable computational shortcuts to rigorous binding free energy calculations. We also develop and test computer software that implements the new theory.

## Implicit ligand theory

We have developed a rigorous theoretical framework that shows the connection between fast but inaccurate molecular docking methods and accurate but slow alchemical pathway techniques [1]–[3]. In principle, one can “tune a knob” that adjusts the balance between accuracy and speed required for a particular application. My research group is actively developing a computer program to estimate the binding potential of mean force (BPMF), the free energy between a flexible ligand and rigid receptor [4], [5]. We have also shown that based on implicit ligand theory, the fast Fourier transform can be used to estimate protein-ligand binding free energies [6]. We are presently able to recapitulate more expensive calculations on a simple system (T4 lysozyme) with a correlation coefficient around 0.9 [7]. In the Drug Design Data Resource (D3R) Grand Challenge 3, our workflow led to some of the submissions with the highest correlation to experimental for vascular endothelial growth factor receptor 2 [8]. Finally, we have identified a statistical metric to evaluate clustering methods used select snapshots for molecular docking or BPMF calculations.

## End point methods

We have also been developing end-point binding free energy methods, which are based on molecular simulations of bound complexes (and sometimes unbound species). We have provided a derivation of the popular Molecular Mechanics/Poisson-Boltzmann Surface Area method and showed how entropy may be estimated based on a cumulant expansion [9]. We have also evaluated the effects of harmonic restraints in end-point binding free energy calculations [10].

## Related references

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