Is The Functional Response of a Receptor Determined by the Thermodynamics of Ligand Binding?

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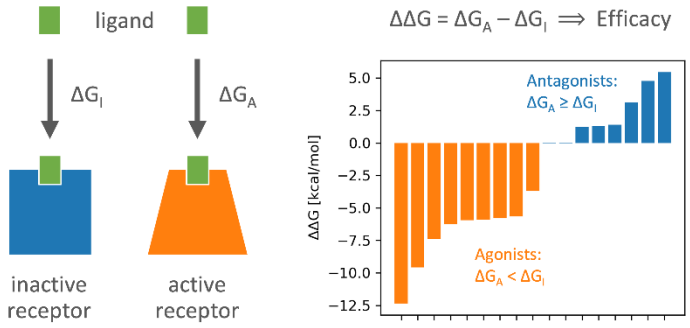
While strong binding to its target protein is crucial for a molecule's drug efficacy, it is often insufficient alone. To produce a particular functional response, drugs need to either block the proteins' functions or modulate their activities by changing the conformational equilibrium. The binding free energy of a compound to its target is routinely calculated but the time scales for protein conformational changes are prohibitively long to be efficiently modeled via physics-based simulations. Thermodynamic principles suggest that binding free energies of the ligands with different receptor conformations may infer their efficacy. However, this hypothesis has not been thoroughly validated and its practical viability has remained under-explored. We introduce a robust protocol and an exhaustive study demonstrating that binding thermodynamics provides a strong predictor for the efficacy of a ligand. Using the Absolute-Binding Free Energy Perturbation (ABFEP) method, we assess ligands bound to both active and inactive forms of eight G protein–coupled receptors (GPCRs) and a nuclear receptor, then compare the resulting values for the binding free energy. Our findings suggest the occasional need for specialized restraints to model the respective conformational ensembles accurately, and we propose an efficient approach to set them up. Remarkably, our method categorizes ligands as agonists or antagonists with unparalleled accuracy across the various investigated receptors, all of which are important drug targets. By examining receptor ensembles and ligand poses, we identify necessary conditions and limitations for real-world application. Overall, our insights have significant implications for the drug discovery process as they allow detailed predictions of a ligand's effects on its target.



M. Vögele, B.W. Zhang, J. Kaindl, L. Wang,
J. Chem. Theory Comput., **2023**, *19* (22), 8414-8422.