Large Scale Prediction of Relative Free Energies of Ligand Binding Using Multi-Site Lambda Dynamics (MSLD)

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Multi-Site Lambda Dynamics (MSLD) is an efficient relative free energy calculation approach that allows variation of the chemical structure within a system via an alchemical λ variable, which propagates dynamically throughout a molecular dynamics simulation by scaling specific interactions within the potential energy function. This technique can yield free energy predictions for different physical and biological processes such as protein folding, quaternary structure formation, protonation events and ligand binding. In the context of ligand binding, very few benchmarking studies across different pharmaceutically relevant systems have been performed using MSLD. Recently, this technique has undergone changes that enable it to be useful during lead optimization. One of the most important changes is the inclusion of biasing potentials to speed up sampling of different ligands, thus allowing MSLD to sample multiple ligands within a single simulation. On the other hand, other alchemical free energy prediction techniques only permit free energy calculations solely between two ligands at a time. To this end, our work uses MSLD to predict binding free energies across 8 different systems reported experimentally. This dataset includes proteins involved in cancer, autoimmune and neurodegenerative diseases, diabetes, and obesity. The scalability of MSLD enables the free energy calculations for multiple subsets of these ligands at once for a total of 197 ligands using a common core with CGenFF parameters and two different charging schemes: CGenFF and MATCH. The Brooks lab has previously shown that using MSLD with MATCH is accurate and fast enough to impact a drug development campaign. Our results with the CGenFF charging scheme show varying accuracies with experiment across the 8 different systems, as well as compared to other free energy prediction methodologies such as FEP/REST. These results reflect a consideration of the optimal charging scheme dependent on the type of chemical substructures of a ligand set.