Structure-based Drug Design

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If the structure of a biological target is known, one can use structure-based drug design to identify candidate drugs that have high binding affinity and selectivity. We apply a free energy perturbation simulation method, free energy perturbation/replica exchange with solute tempering, to two modifications of protein–ligand complexes that lead to significant conformational changes, the first in the protein and the second in the ligand. The approach is shown to facilitate sampling in these challenging cases where high free energy barriers separate the initial and final conformations and leads to superior convergence of the free energy as demonstrated both by consistency of the results (independence from the starting conformation) and agreement with experimental binding affinity data. The second case, consisting of two neutral thrombin ligands that are taken from a recent medicinal chemistry program for this interesting pharmaceutical tar- get, is of particular significance in that it demonstrates that good results can be obtained for large, complex ligands, as opposed to relatively simple model systems. To achieve quantitative agreement with experiment in the thrombin case, a next generation force field, Optimized Potentials for Liquid Simulations 2.0, is required, which provides superior charges and torsional parameters as compared to earlier alternatives.[1]

[1] L. Wang, B. J. Berne, R. A. Friesner, On achieving high accuracy and reliability in the calculation of relative protein–ligand binding affinities. *Proc. Nat. Acad. Sci.* USA 2012, 109, 1937.