Insights into protein-protein and protein-ligand association from end-point free energy calculations.

Jessica Swanson, University of California, San Diego

The prediction of absolute binding affinities with end-point free energy methods will be discussed. These methods combine molecular mechanics energies from explicit solvent simulations with continuum solvation energies to measure the free energies of the end-points of a binding reaction, the bound and free states, and thus the change in free energy upon molecular association. A clear connection between statistical thermodynamics and end-point methods will be presented, highlighting several of the key methodological challenges: measuring the association free energy, arising from one molecule's loss of translational and rotational freedom from the standard state concentration; measuring the conformational free energy, due to both molecules' change in conformational freedom; and ensuring compatibility between implicit and explicit solvent models. Several methods for measuring the association free energy directly from a molecular dynamics simulation will be discussed. Results for protein-protein and protein-ligand systems suggest that the entropic cost of binding a small molecule can be substantially less than that of a large protein. Finally, a discussion of the need for additional linkage to experimental studies will be initiated.