III. Description of MMPBSA Theory

In this method, the binding free energy is decomposed into the relative free energy of the solvated receptor(protein)-ligand complex and the separated, solvated ligand and receptor:

$$\Delta G_{\text{binding,solvated}} = \Delta G_{\text{complex,solvated}} - \Delta G_{\text{receptor,solvated}} - \Delta G_{\text{ligand,solvated}} \ . \quad (1)$$

Each free energy change in eq. 1 is comprised of the sum of several terms:

$$\Delta G_{\text{solvated}} = \Delta E_{\text{MM}} + \Delta G_{\text{pol}} + \Delta G_{\text{nonpol}} + \Delta G_{\text{dispersion}} - T\Delta S \ , \quad (2)$$

which are i) the molecular mechanics energy, ii) the polar solvation free energy estimated from the Poisson-Boltzmann(PB)[1] or Generalized Born (GB)[2] models, iii) the nonpolar solvation energy obtained as a function of the solvent accessible surface area, iv) a cavity dispersion term, and v) an estimate of the solute entropy. Typically[3], the solute entropy term is neglected, as its inclusion is more sensitive to incomplete sampling errors than other terms. The molecular mechanics energy (ΔE_{MM}) is further decomposed into an electrostatic (elst) component and a van der Waals (vdW) contribution. Within MMPBSA, rigid binding is assumed and configurational effects are averaged over several hundred snapshots (see Computational Details in main text) and therefore any differences in internal, bonded terms between the complex, receptor, and ligand are zero. The total binding free energy may be grouped into a solvent contribution:

$$\Delta G_{\text{solv}} = \Delta G_{\text{disper}} + \Delta G_{\text{pol}} + \Delta G_{\text{nonpol}} \ , \quad (3)$$

and a gas phase contribution:

$$\Delta G_{\text{gas}} = \Delta G_{\text{elst}} + \Delta G_{\text{vdW}} \ . \quad (4)$$

Gas phase binding energies are likely to be strongly favorable, while the solvation contribution is likely to be repulsive, as it includes the energetic cost of desolvating the ligand.

References

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