

Free energy calculations in biological systems

The long and winding gilded road

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An understanding of nearly any chemical process requires, at its core, an understanding of the underlying free energy behavior.¹ For instance, in the field of rational, *de novo* drug design, such crucially important properties as protein–ligand association constants and membrane–water partition coefficients cannot be reliably and accurately predicted without the knowledge of the associated free energy changes. The ability to determine *a priori* the physical constants associated with these processes is now a part of the modeler’s toolkit — a result of relentless developments on both the software and the hardware fronts that can be traced back over the past fifty years.^{2,3}

This presentation is an opportunity for a critical look at the past successes and failures of molecular simulations targeted at the estimation of free energies, and a glimpse into their promising future. The methodological milestones paving the road of free energy calculations will be summarized, in particular free energy perturbation² (FEP), thermodynamic integration^{4,5} (TI) with constrained and unconstrained molecular dynamics,^{6,7} and the so-called “umbrella sampling” (US) method.⁸ The continuing difficulties encountered when attempting to obtain accurate estimates will be discussed with an emphasis on the usefulness of such large-scale numerical simulations in non-academic environments, like the world of the pharmaceutical industry.⁹ Applications of the free energy arsenal of methods will be illustrated through a variety of biologically relevant problems, amongst which the prediction of protein–ligand binding constants,¹⁰ the determination of membrane–water partition coefficients of small, pharmacologically active compounds — in connection with the blood–brain barrier (BBB),^{11,12} the folding of a short hydrophobic peptide,¹³ and the association of transmembrane α -helical domains,¹⁴ in line with the canonical “two-stage” model of membrane protein folding.¹⁵ Current strategies for improving the reliability of free energy calculations, while making them somewhat more affordable, and, therefore, more compatible with the constraints of an industrial environment, will be outlined.

In spite of the spectacular increase in computational resources, the development of new, efficient algorithms, and the dramatic improvements in general-purpose, empirically-based potential energy functions over the last twenty years, the accurate estimation of free energy changes in large molecular assemblies still constitutes a challenge for modern theoretical chemistry. Taking advantage of massively parallel architectures, it will be shown that cost-effective, “state-of-the-art” free energy calculations can provide a convincing answer to help rationalizing experimental observations, and, in some instances, play a predictive role in the development of new leads for a specific target.

References

- [1] Kollman, P. A., Free energy calculations: Applications to chemical and biochemical phenomena, *Chem. Rev.* **1993**, *93*, 2395–2417.
- [2] Zwanzig, R. W., High-temperature equation of state by a perturbation method. I. Nonpolar gases, *J. Chem. Phys.* **1954**, *22*, 1420–1426.
- [3] Bennett, C. H., Efficient estimation of free energy differences from Monte Carlo data, *J. Comp. Phys.* **1976**, *22*, 245–268.
- [4] Kirkwood, J. G., Statistical mechanics of fluid mixtures, *J. Chem. Phys.* **1935**, *3*, 300–313.
- [5] Straatsma, T. P.; Berendsen, H. J. C., Free energy of ionic hydration: Analysis of a thermodynamic integration technique to evaluate free energy differences by molecular dynamics simulations, *J. Chem. Phys.* **1988**, *89*, 5876–5886.
- [6] den Otter, W. K.; Briels, W. J., The calculation of free-energy differences by constrained molecular dynamics simulations, *J. Chem. Phys.* **1998**, *109*, 4139–4146.
- [7] Darve, E.; Pohorille, A., Calculating free energies using average force, *J. Chem. Phys.* **2001**, *115*, 9169–9183.
- [8] Torrie, G. M.; Valleau, J. P., Nonphysical sampling distributions in Monte Carlo free energy estimation: Umbrella sampling, *J. Comput. Phys.* **1977**, *23*, 187–199.
- [9] Chipot, C.; Pearlman, D. A., Free energy calculations. The long and winding gilded road, *Mol. Sim.* **2002**, *28*, 1–12.
- [10] Dixit, S. B.; Chipot, C., Can absolute free energies of association be estimated from molecular mechanical simulations ? The biotin-streptavidin system revisited, *J. Phys. Chem. A* **2001**, *105*, 9795–9799.
- [11] Bas, D.; Dorison-Duval, D.; Moreau, S.; Bruneau, P.; Chipot, C., Rational determination of transfer free energies of small drugs across the water-oil interface, *J. Med. Chem.* **2002**, *45*, 151–159.
- [12] Chipot, C., Rational determination of charge distributions for free energy calculations, *J. Comput. Chem.* **2003**, *24*, 409–415.

- [13] Collet, O.; Chipot, C., Non-Arrhenius behavior in the unfolding of a short, hydrophobic α -helix. Complementarity of molecular dynamics and lattice model simulations, *J. Am. Chem. Soc.* **2003**, *125*, 6573–6580.
- [14] Pohorille, A.; Wilson, M. A.; Chipot, C., Membrane peptides and their role in protobiological evolution, *Orig. Life and Evol. Biosph.* **2003**, *33*, 173–197.
- [15] Popot, J. L.; Engelman, D. M., Membrane protein folding and oligomerization: The two-stage model, *Biochemistry* **1990**, *29*, 4031–4037.