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 perturbation[2] (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.

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