appears that under most circumstances, equilibrium simulations are about the same or slightly more efficient than free energies calculated from ensembles of nonequilibrium simulations.[73,86,87] It is thus not clear that free energy calculations using Jarzynski's relationship will have much role in ligand-binding calculations in the future. There has been extensive research in this topic recently, partly because this formalism has proven useful in treating nonequilibrium experiments as well as simulations.

Bennett acceptance ratio

The free energy computed using EXP in either direction between two intermediate states converges to the same result with sufficient samples. The biases from opposite directions will cancel, which suggests that simple ways to improve EXP are to simply perform the calculation in both directions and average the results or to perform double-wide sampling. However, because of a direct relationship between the distributions of potential energy in the forward and reverse directions,[88] there is a significantly more robust and in fact provably statistically optimal way to use information in both directions. Bennett's original formulation started with a simple relationship for the free energies:

$$\Delta G_{0\to 1} = \ln kT \frac{Z_0}{Z_1} = kT \ln \frac{\langle A(\boldsymbol{x}) \exp[-\beta(H_0 - H_1)]\rangle_1}{\langle A(\boldsymbol{x}) \exp[-\beta(H_1 - H_0)]\rangle_0}, \tag{5.14}$$

which is true for any function $A(\boldsymbol{x})$. Bennett then used variational calculus to find the choice of $A(\boldsymbol{x})$ that minimizes the variance of the free energy,[89] resulting in an implicit function of ΔG that is easily solvable numerically. A separate approach demonstrates that the same formula provides the maximum likelihood estimate of the free energy given the observations of the potential energy differences between the two states.[90] Either derivation additionally gives a robust estimate for the variance of free energy. Studies have demonstrated both the theoretical and practical superiority of BAR over EXP in molecular simulations.[73,74] Significantly less overlap between the configurational space of each state is required to converge results than in the case of EXP, although some overlap must still exist.

It is difficult to directly compare TI and BAR on a theoretical basis. However, it appears that TI can be as efficient as BAR under conditions where the integrand is very smooth,[12,73] such as charging or small changes in molecular size, but BAR appears to be significantly more efficient than TI or EXP for free energies of larger molecular changes, sometimes by almost an order of magnitude.[73,74,91] If the intermediate states can be written as functions of the final states, as discussed previously, then the calculations of the potential energy in these alternate states can be very efficient, as only two computations of pairwise interactions are needed. Otherwise, the energies of changing parts of the system must be calculated for each state, which unfortunately is not necessarily implemented in most simulation codes currently.

WHAM

In most cases, alchemical free-energy computations require simulation at a number of different intermediates, and we would prefer to obtain as much thermodynamic information as possible from all of these simulations simultaneously. If one intermediate is relatively similar to a number of other intermediates, and not just the nearest neighbors, then all of this information can be used to calculate the free energy more precisely. Histogram weighting techniques were first introduced by Ferrenberg and Swendsen[92] to capture all of this information to compute free energies. A version called the weighted histogram analysis method (WHAM) was introduced in 1992 by Kumar and collaborators for alchemical simulations.[93] WHAM is provably the lowest uncertainty method to calculate the free energy for samples collected from discrete states. However, it introduces biases in continuous states (such as those obtained with atomistic simulations) because it requires discretization into bins. Other variations of WHAM based on maximum likelihood[94] and Bayesian methods[95] have also been developed. A version of WHAM-based free-energy calculation is available within the CHARMM molecular mechanics package.[96,97]

MBAR

It was noted[93,96] that one can reduce the histogrammed equations of WHAM to a simpler form by reducing the width of the histogram to zero, yielding a set of iterative equations to estimate the K free energies:

$$G_i = -\beta^{-1} \ln \sum_{k=1}^{K} \sum_{n=1}^{N_k} \frac{\exp[-\beta H_i(\boldsymbol{x}_{kn})]}{\sum\limits_{k'=1}^{K} N_{k'} \exp[\beta G_{k'} - \beta H_{k'}(\boldsymbol{x}_{kn})]}, \tag{5.15}$$

where i runs from 1 to K, the G_i are the free energies, and the H_i are the Hamiltonians of these K states. This approximation is somewhat suspect, as the derivation of WHAM involves finding the weighting factors that minimize the variance in the occupancy of the bins, which are undefined as the width goes to zero.

A recent mutitstate extension of the BAR has been derived that solves this problem. In this derivation, a series of $N \times N$ weighting functions $A_{ij}(\boldsymbol{x})$ are adjusted to minimize the free energies of all N states considered simultaneously. The lowest variance estimator can be seen to exactly be the WHAM equation in the limit of zero-width histograms [Equation (5.15)]. WHAM can therefore be seen as a histogram-based approximation to this multistate Bennett's acceptance ratio (or MBAR).[91] This MBAR derivation additionally gives the uncertainty of the calculated free energies, which is not available in WHAM.

Choice of alchemical pathways

A key point in these methods is that for almost all alchemical transformations between the initial and final