Bayesian Estimation of Free Energies From Equilibrium Simulations

Michael Habeck*

Max-Planck-Institute for Developmental Biology, Spemannstrasse 35, 72076 Tübingen, Germany
Max-Planck-Institute for Intelligent Systems, Spemannstrasse 38, 72076 Tübingen, Germany

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Free energy calculations are an important tool in statistical physics and biomolecular simulation. This Letter outlines a Bayesian method to estimate free energies from equilibrium Monte Carlo simulations. A Gibbs sampler is developed that allows efficient sampling of free energies and the density of states. The Gibbs sampling output can be used to estimate expected free energy differences and their uncertainties. The probabilistic formulation offers a unifying framework for existing methods such as the weighted histogram analysis method and the multistate Bennett acceptance ratio; both are shown to be approximate versions of the full probabilistic treatment.

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Evaluation of normalization constants is a ubiquitous task in statistical physics and Bayesian inference. Partition functions characterize the equilibrium state. The marginal likelihood, a probabilistic analog of the partition function, is the key quantity in Bayesian model comparison. A common strategy to solve high-dimensional normalization integrals is to use Monte Carlo sampling, typically in an extended ensemble. One straightforward approach to obtain ratios of partition functions from tempered Monte Carlo simulations is thermodynamic integration [1]. Multiple histogram reweighting is a versatile alternative pioneered by Ferrenberg and Swendsen [2]. The original method has been extended to the weighted histogram analysis method (WHAM) in the context of biomolecular simulation [3,4]. WHAM estimates the density of states from equilibrium simulations at multiple temperatures and derives the free energies as secondary quantities. More recently, Shirts and Chodera [5] extended Bennett's acceptance ratio [6] to the case when multiple simulations are available and combined. The resulting multistate Bennett acceptance ratio (MBAR) estimates free energy differences directly and provides uncertainty estimates.

Although WHAM and MBAR involve similar iterations, their exact relation and statistical foundations remain somewhat obscure. Moreover, the uncertainty estimates calculated by MBAR only hold asymptotically in the large sample limit. WHAM iterations were shown to converge to maximum likelihood [7] or maximum *a posteriori* (MAP) estimates [8]. Shirts and Chodera derive the MBAR iterations from extended bridge sampling estimators [5]. However, it is also possible to obtain the MBAR iterations by means of a nonparametric maximum likelihood method [9]. This suggests that MBAR and WHAM are two sides of the same coin: MBAR focusses on the free energies, whereas WHAM estimates the density of states as an intermediate quantity from which free energy estimates are derived.

Here we outline a direct and efficient method to compute estimates of free energies and their uncertainties with the use of Bayesian statistics [10] and Gibbs sampling [11]. We will first extend the Bayesian formulation of WHAM [8] and show that both MBAR and WHAM can be interpreted as MAP estimates. A Gibbs sampler is developed, which has the same computational complexity as the MBAR and WHAM iterations. The Gibbs sampler allows us to estimate not only the posterior mean of free energy or of some other state variable but also their posterior variances. The approach also holds for continuous systems and can be treated as the nonparametric limit of the finite case.

Let us first outline the method for finite, discrete systems for which multiple histogram reweigthing has been developed originally [2]. We start by following the approach pursued in Ref. [8] and first estimate the density of states using Bayesian inference. The system has K energy levels $E_1, \ldots, E_K$. Our task is to infer the density of states g_k from equilibrium samples drawn from a series of L ensembles $q_l(E)$. The statistical ensemble could involve the Boltzmann factor $q_l(E) = \exp\{-\beta_l E\}$, but our approach works also for non-Boltzmann sampling schemes. We summarize the simulation by two $K \times L$ matrices. Matrix $q_{kl} \equiv q_l(E_k)$ stores the weights of energy levels E_k in all of the L ensembles. Matrix n_{kl} counts how often the kth energy level has been visited in the lth ensemble. Therefore, $H_k = \sum_l n_{kl}$ is the energy histogram and $N_l = \sum_k n_{kl}$ counts the number of samples drawn from the lth ensemble. The posterior probability of the density of states arising from simulation data D summarized by the matrices q_{kl} and n_{kl} is [8]

$$p(g|D, \alpha) \propto \prod_{k=1}^{K} g_k^{H_k+\alpha/K-1} / \prod_{l=1}^{L} Z_l^{N_l} \qquad (1)$$

where $Z_l = \sum_k g_k q_{kl}$ is the partition function of the lth ensemble and a homogenous Dirichlet prior with concentration parameter $\alpha \geq 0$ was assumed as in Ref. [8] (α can

be interpreted as a pseudocount). The partition function is a function of the density of states and can therefore not be neglected. At first sight, the posterior probability Eq. (1) does not appear amenable to further analytical treatment because it is not of a standard form. However, we can circumvent this problem by making use of the integral representation $x^{-n} = \frac{1}{(n-1)!}\int_0^\infty t^{n-1}e^{-tx}dt$, which is valid for any positive x. Using this identity, we can interpret the posterior probability Eq. (1) as the marginal distribution of the augmented posterior probability

$$p(g, t|D, \alpha) \propto \left(\prod_k g_k^{H_k+(\alpha/K)-1}\right)\left(\prod_l t_l^{N_l-1}\right)\prod_{k,l} e^{-g_k t_l q_{kl}} \quad (2)$$

where $t_1, \ldots, t_L$ are the auxiliary variables introduced to represent the normalization constant of each of the L ensembles. We have $p(g|D, \alpha) = \int p(g, t|D, \alpha)dt$. Instead of integrating out t analytically, we use Gibbs sampling [11] to draw g and t iteratively from their conditional posterior probabilities

$$p(t_l|g, D, \alpha) = G\left(N_l, \sum_k g_k q_{kl}\right) \quad (3a)$$

$$p(g_k|t, D, \alpha) = G\left(H_k + \alpha/K, \sum_l t_l q_{kl}\right) \quad (3b)$$

where $G(a, b)$ denotes the Gamma distribution with shape parameter a and scale parameter b. After each iteration, we normalize the density of states. Upon convergence, the g and t samples generated in each iteration are valid samples from the augmented distribution Eq. (2). The conditional expectations are

$$\langle t_l|g\rangle = \frac{N_l}{\sum_k g_k q_{kl}} = \frac{N_l}{Z_l} \text{ and } \langle g_k|t\rangle = \frac{H_k + \alpha/K}{\sum_l t_l q_{kl}}. \quad (4)$$

Let us ignore the prior probability of the density of states ($\alpha = 0$) for a moment. If we plug the expectations $\langle t_l|g\rangle$ into the estimate of the density of states $\langle g_k|t\rangle$, we obtain the self-consistent histogram reweighting updates [2]. If we plug the expectations $\langle g_k|t\rangle$ into the estimates $\langle t_l|g\rangle$, we obtain the MBAR iterations [5]. Therefore, both WHAM and MBAR can be viewed as iterative maximum likelihood methods similar to expectation maximization [9,12]. In WHAM, the inverse partition functions t_l are auxiliary variables introduced to estimate the density of states g_k. In MBAR, the density of states g_k is an auxiliary variable to estimate the inverse partition functions t_l, or equivalently the free energy differences.

The auxiliary variables t_l are inversely proportional to the partition function of the corresponding ensemble. Therefore $f_l = \log t_l$ is an analog of the free energy. Application of this parameter transformation results in the augmented distribution of the density of states and free energies $p(g, f|D, \alpha)$. By integrating over the density of states, we obtain the posterior probability of the free energies, given the simulation data $p(f|D, \alpha) = \int p(g, f|D, \alpha)dg$:

$$p(f|D, \alpha) \propto \prod_l e^{N_l f_l} / \prod_k \left(\sum_{l'} q_{kl'} e^{f_{l'}}\right)^{H_k+\alpha/K} \quad (5)$$

Compared to Eq. (1), it is less obvious how to derive the posterior probability of the free energies Eq. (5) from scratch. The integration over the density of states is perhaps the most informative way to obtain $p(f|D, \alpha)$. However, it is also possible to motivate Eq. (5) directly. The probability of visiting the kth energy level in the lth ensemble is $g_k q_{kl} e^{f_l}$. Bayes's theorem gives us the inverse probability that a state with energy E_k was generated from the lth ensemble:

$$p_{kl} = \frac{q_{kl}e^{f_l}}{\sum_{l'} q_{kl'} e^{f_{l'}}}, \qquad \sum_l p_{kl} = 1.$$

Note that the contribution from the density of states cancels out due to normalization. The complete probability of observing the counts n_{kl} is the multinomial distribution

$$p(n|f) \propto \prod_{k,l} p_{kl}^{n_{kl}} = \prod_{k,l}\left(\frac{q_{kl}e^{f_l}}{\sum_{l'} q_{kl'} e^{f_{l'}}}\right)^{n_{kl}}. \quad (6)$$

Using $H_k = \sum_l n_{kl}$ and $N_l = \sum_k n_{kl}$, we observe that $p(n|f)$ is proportional to Eq. (5) except for the fact that pseudocounts have not been added. By using the Gamma integral representation of x^{-n}, we could introduce the density of states as auxiliary quantity and regain the augmented posterior probability Eq. (2) of the free energies and the density of states. Also note that the negative logarithm of $p(f|D, \alpha)$ is the loss function derived in Ref. [9]. By minimizing the convex function

$$-\log p(f|D, \alpha) = -\sum_l N_l f_l + \sum_k \left(H_k + \frac{\alpha}{K}\right)\log \sum_l q_{kl} e^{f_l}$$

we obtain a direct MAP estimate of the free energies, which is achieved by cycling through the MBAR iterations.

The most general and efficient approach is to use the Gibbs sampler Eq. (3) to sample both the free energies and the density of states. This allows us to extract maximum information from the data and gain direct access to the uncertainty in the free energy and density of states or in any derived quantity such as a potential of mean force without recourse to asymptotic limits. The Gibbs sampler Eq. (3) can be initialized with a constant density of states or with the result of the maximum likelihood iterations and converges very rapidly. Each iteration requires us only to draw from the Gamma distribution for which efficient random number generators exist. Gibbs sampling therefore involves only minor computational costs in addition to the standard WHAM or MBAR calculations. The problem is well defined: the marginal probability of the free energies $p(f|D, \alpha)$ and microcanonical entropy $p(s|D, \alpha)$ [obtained

by applying the parameter transformation $s_k = \log g_k$ to $p(g|D, \alpha)$] are both log concave [9] and therefore exhibit a unique maximum.

As an illustration, let us look at the 8×8 Ising model on a two-dimensional square lattice. We used replica-exchange Monte Carlo calculations [13] to generate states at 12 inverse temperatures. Figure 1(a) shows a trace of the log-posterior probability $\log p(g, t|D, \alpha)$ [Eq. (2)] during Gibbs sampling. This is brought into relation with the convergence of WHAM and MBAR by showing the evolution of $\log p(g|D, \alpha)$ during WHAM and $\log p(f|D, \alpha)$ during MBAR. All of the three calculations were initialized with a constant density of states or free energy separately. The Gibbs sampler converges as fast as MBAR and WHAM. After convergence, the log-posterior probability scatters about the values obtained with MBAR and WHAM (only a total of 12×30 states were analyzed to emphasize the posterior variance). Figure 1(b) shows posterior samples of the microcanonical entropy obtained with the Gibbs sampler Eq. (3). The sampled entropy scatters about the true log density of states [14] and the WHAM estimate; the amount of scatter is large due to the limited data. Previous Bayesian treatments [8,15] used more complex and less efficient sampling schemes to draw samples of the density of states. Figure 1(c) shows the estimated free energy differences. The Gibbs sampling output and MBAR results both reproduce the exact free energy differences accurately. The exact curve falls well within the range covered by the Gibbs sampling output. Error bars can be obtained by calculating the standard deviation over the sampled free energy differences. MBAR derives the error bars from the Fisher information matrix [5]. Do the predicted uncertainties correlate with the absolute deviations between the estimated and exact free energy

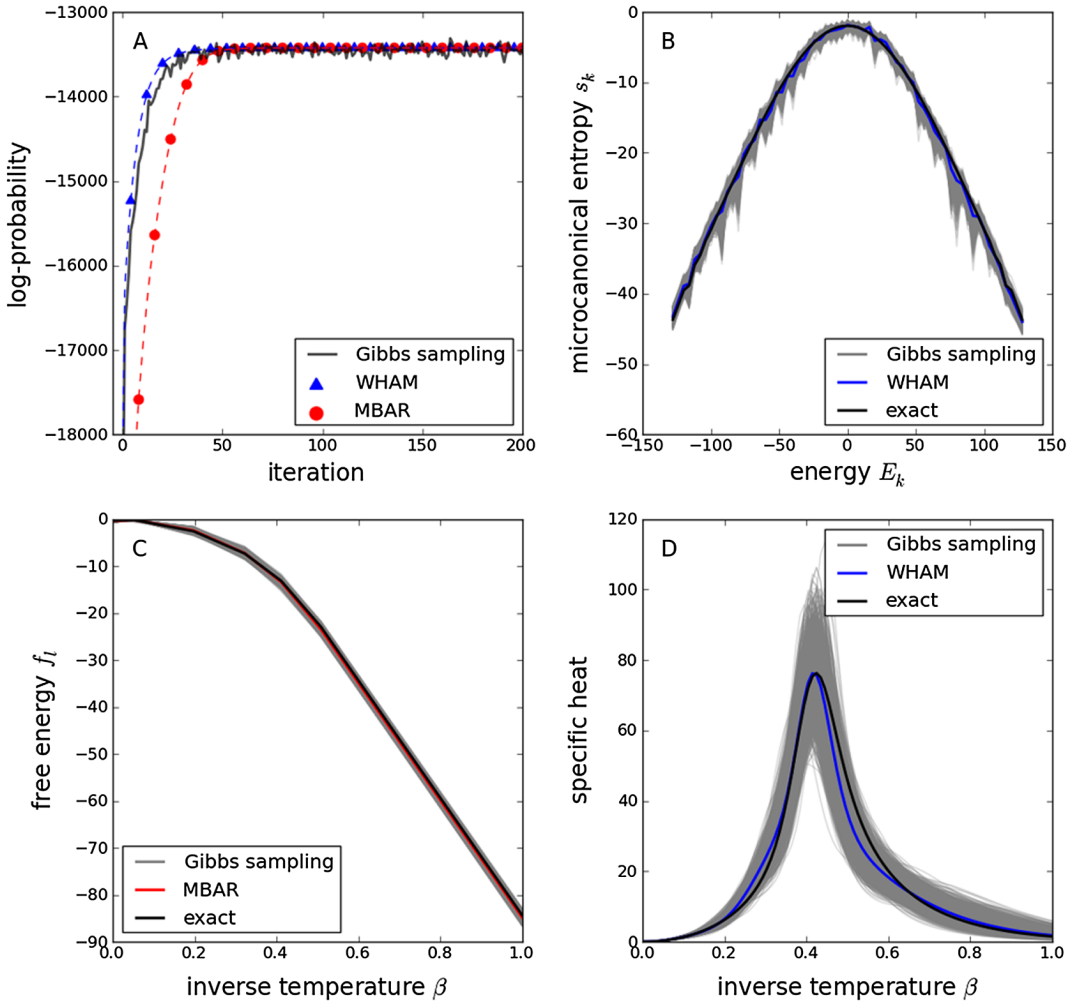

FIG. 1 (color online). Comparison of the Gibbs sampler with WHAM and MBAR for an Ising model. The exact results are shown in black, Gibbs sampling output is shown in grey, WHAM results are shown in blue, and MBAR results are shown in red. (A): Convergence of the Gibbs sampler and the MBAR and WHAM iterations. (B): Exact microcanonical entropy, Gibbs sampling output $s_k = \log g_k$ and WHAM result. (C): Exact free energies, Gibbs sampling output f_l and MBAR result. (D): Exact heat capacity, predictions based on Gibbs sampling output and WHAM result.

differences? For the Gibbs sampler, the correlation between accuracy and precision of the free energy estimates is reasonably high with a Pearson correlation coefficient of 68%. For MBAR, there is no significant correlation between accuracy and precision observable; the correlation coefficient is 2% only. This is due to the fact that MBAR tends to be overconfident about its predictions and finds too small error bars, especially for free energy differences between the ensembles at very different temperatures. We can use the Gibbs sampling output to estimate the posterior distribution of various thermodynamic properties. Figure 1(d) shows the posterior prediction of the specific heat, which matches the exact curve quite well, but clearly shows that due to the small amount of data we are limited in precision.

We can also use the Gibbs sampler Eq. (3) to analyze data for continuous systems where the energies are no longer discrete and finite. The only modification is that the energy levels E_k are replaced with the energies of all of the states that have been sampled and therefore matrix n_{kl} becomes binary. A rigid approach would be to use a Dirichlet process [16] to define the prior probability over the density of states, which is now a probability density function. We would then proceed by taking the limit of having infinitely many bins ($K \to \infty$), or equivalently of letting the bin size of the energy histogram approach zero. A more pragmatic route is to start with the multinomial model Eq. (6). The energy levels E_k are replaced by the energies $E_n = E(\theta_n)$ of the states $\theta_1, \ldots, \theta_N$, $N = \sum_l N_l$ that have been collected from the simulation of all of the L ensembles. Therefore, the product over the K energy levels in Eq. (6) is replaced by a product over the N sampled energies, and the counts n_{kl} are no longer needed; q_{kl} becomes an $N \times L$ matrix with entries $q_{nl} = q_l(E_n)$.

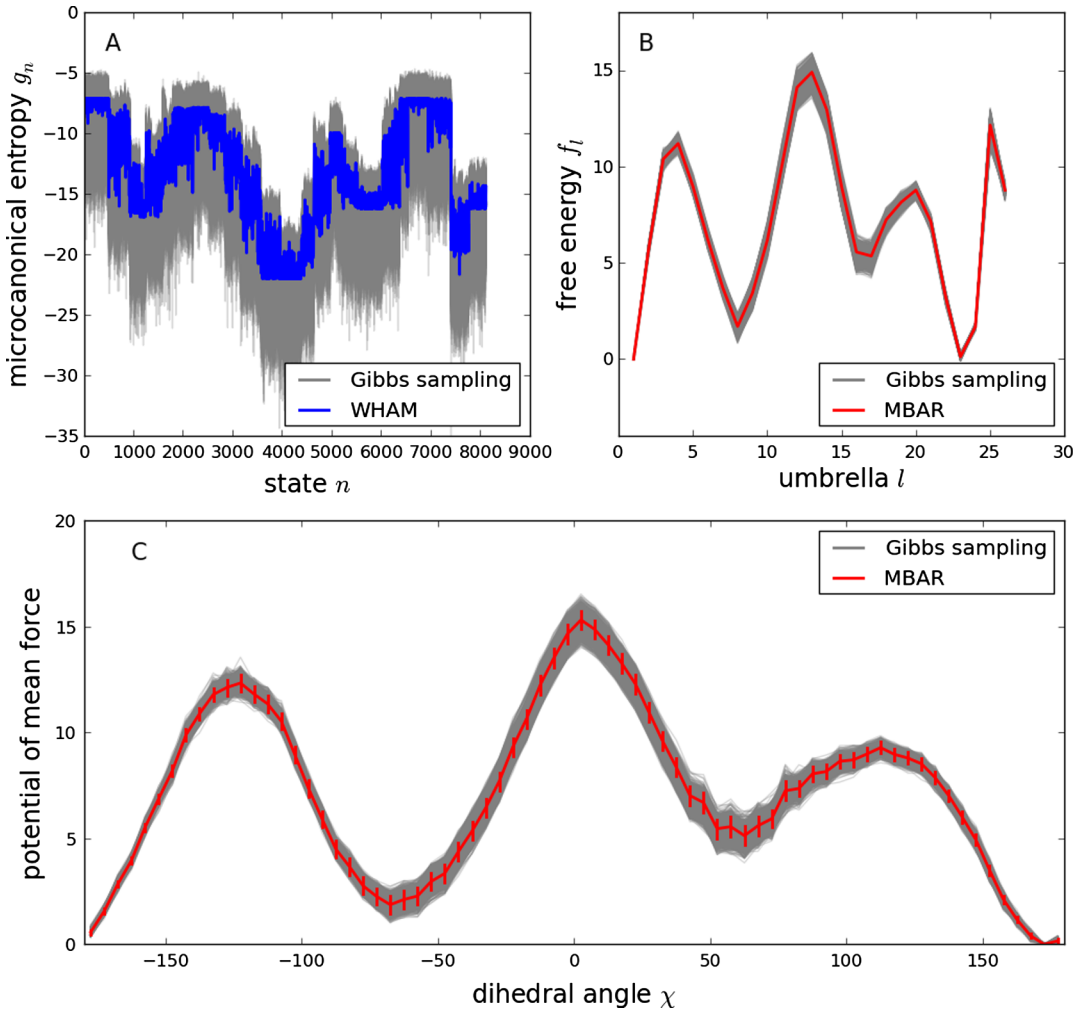

FIG. 2 (color online). Analysis of an umbrella simulation. Gibbs sampling output is shown in grey, WHAM results are shown in blue, and MBAR results are shown in red. (A): Estimates of the microcanonical entropy $s_n = \log g_n$ obtained with Gibbs sampling and nonparametric WHAM. (B): Estimates of the free energies f_l of each of the 26 umbrella ensembles using Gibbs sampling and MBAR. (C): Potential of mean force for a side chain dihedral angle χ of the Valine residue implicated in ligand binding.

Using the integral representation of x^{-1}, we then introduce the density of states g_n for each of the N sampled energies. We do not have to bin the energies and obtain a nonparametric probabilistic version of WHAM and MBAR. The Gibbs sampling iterations are

$$p(t_l|g, D) = G\Big(N_l, \sum_n g_n q_{nl}\Big), \qquad l = 1, \ldots, L \tag{7a}$$

$$p(g_n|t, D) = G\Big(1, \sum_l t_l q_{nl}\Big), \qquad n = 1, \ldots, N \tag{7b}$$

where the pseudocount has been set to zero for simplicity ($\alpha = 0$); a more rigorous treatment is also possible. As in the finite case, we normalize the density of states after each iteration. The Gibbs sampler and iterative calculation of conditional expectations both converge to estimates that are similar to those obtained with MBAR [5] or nonparametric WHAM [9].

To illustrate the analysis of continuous systems, we reanalyzed the umbrella simulation [17] of the protein T4 lysozyme in the presence of a ligand. The data were obtained from the examples accompanying the Python implementation of MBAR [18]. The aim of the simulation is to study the rotation of a Valine side chain implicated in ligand binding. A harmonic umbrella potential was applied to the dihedral angle χ to obtain the free energy of rotating the Valine side chain. The data comprise simulations of $L = 26$ ensembles with a different strength and center of the umbrella potential; a total of $N = 8119$ states was generated. Figure 2 shows the results of a Gibbs sampling calculation in comparison with MBAR and nonparametric WHAM. The microcanonical entropy s_n of all generated states varies strongly, but the average coincides with the estimated log density of states obtained by nonparametric WHAM. Figure 2(b) shows the estimated free energies of the different umbrella ensembles; again we see a good correspondence between the Gibbs sampling output and the MBAR results. A potential of mean force for the angle of interest can be calculated with MBAR and from the samples generated with the Gibbs sampler [see Fig. 2(c)]. As in the previous example, the error bars obtained by MBAR tend to be smaller than the posterior variances estimated with Gibbs sampling.

In summary, this Letter introduces a fully probabilistic treatment of free energy estimation from equilibrium simulations. The Bayesian approach introduces the augmented posterior probability (2), which allows us to clarify the relation between WHAM and MBAR: both methods are highly related and differ only by inverting the role of the density of states and of the free energies, which in one or the other approach becomes auxiliary variables. The Gibbs sampling schemes for finite [see Eq. (3)] and continuous systems [see Eq. (7)] have the same computational complexity and converge as quickly as WHAM and MBAR. The posterior samples can be used to estimate parameter uncertainties that are more meaningful than existing error estimates and show a good correlation with the accuracy.

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*michael.habeck@tuebingen.mpg.de

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