8 December 2000

ELSEVIER

Chemical Physics Letters 331 (2000) 446–454

CHEMICAL PHYSICS LETTERS

www.elsevier.nl/locate/cplett

Analyzing biased Monte Carlo and molecular dynamics simulations

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Received 26 June 2000; in final form 5 October 2000

Abstract

Using the maximum likelihood method, a formalism is derived to analyze a series of biased Monte Carlo or molecular dynamics simulations. The formalism is applied to different examples, in particular the estimation of thermodynamic properties of molecular systems such as potentials of mean force and free energy differences. The formalism is shown to be a generalization of existing methods that are known to be efficient. For the derivation, it is assumed that the values of the distribution function of subsequent states that are analyzed are uncorrelated. © 2000 Elsevier Science B.V. All rights reserved.

1. Introduction

Models of complex systems, such as atomic models of proteins, are often studied with simulations since analytical expressions to calculate directly the properties of the systems cannot be obtained. Simulations produce sets of states from which the properties of the system have to be estimated. Unbiased molecular dynamics or Monte Carlo simulations produce states from which estimates are obtained as simple averages. In many cases, there exist, however, states that are of interest, but which are rarely sampled in unbiased simulations [1,2]. Examples are estimates of free energy differences between two systems, or studies of systems that exist in different states separated by barriers. In such cases, suitable biases can be used to increase sampling of the relevant states and transitions. Once the biased simulations are finished, the effect of the bias on the simulations has to be reverted to calculate the properties of the unbiased system. In the case of a single biased simulation, the results of the biased simulation have to be re-weighted with the ratio of the unbiased distribution function divided by the biased distribution function (Eq. (3)) [1,2]. However, in many cases, it is necessary to carry out a series of simulations with different biases. Examples are the determination of potentials of mean force of an internal degree of freedom of a molecular system [3–8], the estimation of differences in the solvation free energies or in the binding free energies of different molecules [9,10], or the calculation of rate constants of chemical reactions [11,12]. For the analysis of such a series of simulations, a formalism is needed to combine the data obtained with the different biases. In the present work, the maximum likelihood method [13,14] is used to derive an equation (Eqs. (19a) and 19b) to analyze a series

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0009-2614/00/$ - see front matter
PII: S0009-2614(00)01215-X

of simulations with different biases and to estimate the properties of the system. It is shown that when used to calculate the potential of mean force of an internal degree of freedom of a molecular system, Eqs. (19a) and (19b) correspond to the weighted histogram analysis method (WHAM) equations [6,8,15]. Of a set of formalisms to calculate potentials of mean force, the WHAM equations were found to be the most reliable [4,5]. Similar, when Eqs. (19a) and (19b) are used to calculate free energy differences, it corresponds to the composite reference state formalism found to be the most reliable out of a set of formalisms that were compared [9]. Thus, Eqs. (19a) and (19b) derived in the present work are a generalization of the most efficient formalisms to combine data from simulations with different biases. In contrast to earlier derivations, the present formalism gives an optimal estimate of the distribution function $\rho^\circ(x)$ (e.g., Eq. (1)) rather than of a free energy difference or of a low dimensional potential of mean force. This is an advantage since it is straightforward to use the estimate of $\rho^\circ(x)$ to calculate estimates of any observable of interest (Eq. (2); see also Section 4).

To focus ideas and to introduce the notation, established ways to analyze simulations are presented in the rest of this section [1,2]. Consider a system with states x, and with the probability of finding the system in state x given by the distribution function $\rho^\circ(x)$. If the configurations of a classical many-body system in contact with a heat bath at temperature T° are studied, the canonical distribution function

$$\rho_{\mathrm{c}}^\circ(x) = \mathrm{e}^{-V^\circ(x)/k_{\mathrm{B}}T^\circ}/Z^\circ, \tag{1}$$

is the appropriate distribution function. In Eq. (1), $V^\circ(x)$ is the potential energy function of the system, k_{B} Boltzmann's constant, and Z° is the configurational integral that normalizes the distribution function. The ensemble average $\langle A\rangle$ of an observable is obtained by averaging the value $A(x)$ of the observable over all states x, e.g., for a system with a continuum of states

$$\langle A\rangle = \int \rho^\circ(x)A(x)\,\mathrm{d}x. \tag{2}$$

Monte Carlo methods and molecular dynamics simulations sample states according to a sampling distribution function $\rho_j(x)$. The formalism to analyze the results of a single simulation is established [2]. From the obtained set of states $\{x_{j,t}\}$ with $j=1$ and $t=1,\ldots,N_j$, where N_j is the number of states produced in the simulation, the distribution function $\rho^\circ(x)$ is estimated according to

$$\tilde{\rho}^\circ(x) = \frac{\sum_{t=1}^{N_j}\delta(x_{j,t}-x)/c_j(x_{j,t})}{\sum_{t=1}^{N_j}1/c_j(x_{j,t})}. \tag{3}$$

The function $c_j(x)$ in Eq. (3) is, up to a normalization constant f_j, equal to the ratio of the sampling distribution function $\rho_j(x)$ divided by the distribution function $\rho^\circ(x)$ of the system studied, i.e., the bias function $c_j(x)$ is defined by the relation

$$\rho_j(x) = f_j c_j(x)\rho^\circ(x) \tag{4}$$

with the normalization constant defined by

$$f_j = \left(\int c_j(x)\rho^\circ(x)\,\mathrm{d}x\right)^{-1}. \tag{5}$$

Inserting Eq. (3) into Eq. (2) gives

$$\tilde{A} = \frac{\sum_{t=1}^{N_j}A(x_{j,t})/c_j(x_{j,t})}{\sum_{t=1}^{N_j}1/c_j(x_{j,t})} \tag{6}$$

for the estimate of the ensemble average $\langle A\rangle$. If the configurations of a classical many-body system in the canonical ensemble are studied (Eq. (1)) and a canonical sampling distribution function

$$\rho_{\mathrm{c}j}(x) = \mathrm{e}^{-V_j(x)/k_{\mathrm{B}}T_j}/Z_j \tag{7}$$

analogous to Eq. (1) is used in the simulation, the bias function $c_{\mathrm{c}j}(x)$ can be set equal to

$$c_{\mathrm{c}j}(x) = \mathrm{e}^{-V_j(x)/k_{\mathrm{B}}T_j + V^\circ(x)/k_{\mathrm{B}}T^\circ}. \tag{8}$$

In what follows, more general equations are derived that can be used to analyze the results of a set of simulations carried out with different sampling distribution functions.

2. Theory

An estimate $\tilde{\rho}^\circ(x)$ of the distribution $\rho^\circ(x)$ is determined from a set of states $\{x_{j,t}\}$ generated in

a series of simulations j. In each of the simulations, states are sampled according to the distribution functions $\rho_j(x)$, i.e., $\rho_j(x)$ is used to calculate the forces in molecular dynamics simulations [8], or to decide whether to accept or to reject states in Monte Carlo simulations [16]. The relation between $\rho_j(x)$ and $\rho^\circ(x)$ is given by the bias function $c_j(x)$ (Eq. (4)) and the normalization constant f_j. The bias function $c_j(x)$ needs to be known to analyze the simulations; an example is given by Eq. (8). An estimate $\tilde{f}_j$ of the normalization constant is calculated together with the estimate $\tilde{\rho}^\circ(x)$ of the distribution function. Once the estimate $\tilde{\rho}^\circ(x)$ of the distribution $\rho^\circ(x)$ is known other properties of the system that are functions of $\rho^\circ(x)$ (e.g., Eq. (2)) can be calculated.

To determine $\tilde{\rho}^\circ(x)$ from the set of states $\{x_{j,t}\}$, the maximum likelihood method [13,14] is used. With the maximum likelihood method an estimate $\tilde{\rho}^\circ(x)$ of the distribution function $\rho^\circ(x)$ is determined that maximizes the conditional probability $p(\{x_{j,t}\}|\rho^\circ(x))$ of the observed set of states given the distribution function $\rho^\circ(x)$. It is assumed (see Section 5) that the conditional probability $p(\{x_{j,t}\}|\rho^\circ(x))$, which is equal to the distribution of the sets of states that would be obtained if the series of simulations is repeated many times, is given by

$$p(\{x_{j,t}\}|\rho^\circ(x)) = g(\{x_{j,t}\}) \prod_j \prod_t^{N_j} \rho_j(x_{j,t}). \tag{9}$$

In Eq. (9), the index j distinguishes different simulations, the index t distinguishes the different states obtained in each of the simulations, N_j is the number of states generated in simulation j, and the product is over all states of all simulations. Eq. (9) expresses the probability of a set of states $\{x_{j,t}\}$ as the product of the probabilities $\rho_j(x_{j,t})$ of the individual states times a factor $g(\{x_{j,t}\})$ that accounts for the correlation between subsequent states. The factor $g(\{x_{j,t}\})$ depends on the details of the simulation method used, e.g., on the set of moves used in a Monte Carlo simulation. In the derivation that follows, it is assumed that the factor $g(\{x_{j,t}\})$ does not depend on the distribution function $\rho_j(x)$ (see Section 5). This condition is sufficient for the factor $g(\{x_{j,t}\})$ to drop out later in the derivation.

The estimate $\tilde{\rho}^\circ(x)$ is determined that maximizes the likelihood function

$$\begin{aligned} L(\rho^\circ(x)) &= \ln(p(\{x_{j,t}\}|\rho^\circ(x))) \\ &= \ln g(\{x_{j,t}\}) + \sum_j \sum_t^{N_j} \ln \rho_j(x_{j,t}) \\ &= \ln g(\{x_{j,t}\}) + \sum_j \sum_t^{N_j} \ln f_j c_j(x_{j,t}) \rho^\circ(x_{j,t}). \end{aligned} \tag{10}$$

The second equality in Eq. (10) was obtained by inserting Eq. (9), and the last equality in Eq. (10) was obtained by inserting the relation between the distribution function $\rho^\circ(x)$ and the sampling distribution functions $\rho_j(x)$ (Eq. (4)). The functions $\rho^\circ(x)$ and the $\rho_j(x)$ are probability distributions that are positive or zero for all x and that are normalized to one, i.e.,

$$\int \rho^\circ(x)\,\mathrm{d}x = 1 \tag{11}$$

and

$$\int f_j c_j(x) \rho^\circ(x)\,\mathrm{d}x = 1. \tag{12}$$

For states $x \notin \{x_{j,t}\}$ that are not sampled, the optimal estimate $\tilde{\rho}^\circ(x)$ is equal to zero. This can be shown by comparing the value of the likelihood function for the estimate $\tilde{\rho}^a(x)$ assumed to be different from zero for some $x \notin \{x_{j,t}\}$ and for the estimate

$$\tilde{\rho}^b(x) = \frac{\tilde{\rho}^a(x)\delta_{x\in\{x_{i,t}\}}}{\sum_i \sum_{t=1}^{N_i} \tilde{\rho}^a(x_{i,t})} \tag{13}$$

obtained from $\tilde{\rho}^a(x)$ by setting the estimate equal to zero for all states $x \notin \{x_{j,t}\}$ and renormalizing the resulting probability distribution to one. In Eq. (13), $\delta_{x\in\{x_{i,t}\}}$ denotes the function that is equal to one if $x \in \{x_{i,t}\}$ and equal to zero, otherwise. The estimates of the scaling factors $\tilde{f}_j^a$ and $\tilde{f}_j^b$ associated with the estimates $\tilde{\rho}^a(x)$ and $\tilde{\rho}^b(x)$ are found from Eq. (12) to be equal to

$$\tilde{f}_j^a = \frac{1}{\int c_j(x)\tilde{\rho}^a(x)\,\mathrm{d}x} \tag{14a}$$

and

$$\tilde{f}_j^b = \frac{\sum_i \sum_{t=1}^{N_i} \tilde{\rho}^a(x_{i,t})}{\int \mathrm{d}x\, c_j(x)\tilde{\rho}^a(x)\delta_{x\in\{x_{i,t}\}}}, \tag{14b}$$

respectively. Inserting the two estimates $\tilde{\rho}^a(x)$ and $\tilde{\rho}^b(x)$ and the associated scaling factors into the likelihood function (Eq. (10)) gives

$$L(\tilde{\rho}^a(x)) = \ln g(\{x_{j,t}\}) + \sum_j \sum_t^{N_j} \ln \frac{c_j(x_{j,t})\tilde{\rho}^a(x_{j,t})}{\int \mathrm{d}x\, c_j(x)\tilde{\rho}^a(x)} \tag{15a}$$

and

$$L(\tilde{\rho}^b(x)) = \ln g(\{x_{j,t}\}) + \sum_j \sum_t^{N_j} \ln \frac{c_j(x_{j,t})\tilde{\rho}^a(x_{j,t})}{\int \mathrm{d}x\, c_j(x)\tilde{\rho}^a(x)\delta_{x\in\{x_{i,t}\}}}, \tag{15b}$$

respectively. The expressions (Eqs. (15a) and (15b)) for the likelihood of the two estimates $\tilde{\rho}^a(x)$ and $\tilde{\rho}^b(x)$ are the same with the exception of the value of the integral, which is smaller in Eq. (15b) since for all values x the integrand in Eq. (15b) is equal to or smaller than the integrand in Eq. (15a). Thus, for every $\tilde{\rho}^a(x)$ that is different from zero for some $x \notin \{x_{j,t}\}$, an improved estimate $\tilde{\rho}^b(x)$ with a higher likelihood can be constructed that is zero for all $x \notin \{x_{j,t}\}$. It follows that the optimal estimate $\tilde{\rho}^\circ(x)$ is equal to zero for all states $x \notin \{x_{j,t}\}$ that were not sampled and that the optimal estimate can be written as

$$\tilde{\rho}^\circ(x) = \sum_i \sum_{t=1}^{N_i} \delta(x_{i,t} - x)\tilde{\rho}^\circ_{i,t}, \tag{16}$$

where the $\tilde{\rho}^\circ_{i,t}$ are parameters that have to be determined.

The parameters $\tilde{\rho}^\circ_{i,t}$ that maximize the likelihood function are determined by setting the partial derivatives of the likelihood function with respect to the parameters $\tilde{\rho}^\circ_{i,t}$ equal to zero. To take into account the normalization conditions (Eqs. (11) and (12)) Lagrange multipliers α_j and β are used. This gives the expression

$$\ln g(\{x_{j,t}\}) + \sum_j \sum_t^{N_j} \ln f_j c_j(x_{j,t})\rho^\circ(x_{j,t}) + \sum_j \alpha_j \left(1 - \int f_j c_j(x)\rho^\circ(x)\,\mathrm{d}x\right) + \beta\left(1 - \int \rho^\circ(x)\,\mathrm{d}x\right) \tag{17}$$

whose derivatives with respect to $\rho^\circ_{i,t}$, f_j, α_j, and β have to be set equal to zero to determine the estimates $\tilde{\rho}^\circ_{i,t}$ and $\tilde{f}_j$. Using Eq. (16) to substitute $\tilde{\rho}^\circ(x)$ in Eq. (17), and carrying out the differentiations gives:

$$\forall j: \sum_i \sum_{t=1}^{N_i} \tilde{f}_j c_j(x_{i,t})\tilde{\rho}^\circ_{i,t} = 1, \tag{18a}$$

$$\sum_i \sum_{t=1}^{N_i} \tilde{\rho}^\circ_{i,t} = 1, \tag{18b}$$

$$\forall i,t: 1/\tilde{\rho}^\circ_{i,t} - \sum_j \alpha_j \tilde{f}_j c_j(x_{i,t}) - \beta = 0, \tag{18c}$$

$$\forall j: \sum_{t=1}^{N_j} 1/\tilde{f}_j - \alpha_j \sum_i \sum_{t=1}^{N_i} c_j(x_{i,t})\tilde{\rho}^\circ_{i,t} = 0. \tag{18d}$$

Multiplying Eq. (18d) by $\tilde{f}_j$, substituting the sum over all states with Eq. (18a), and solving the resulting expression for the Lagrange multipliers α_j affords $\alpha_j = N_j$. Multiplying Eq. (18c) by $\tilde{\rho}^\circ_{i,t}$, summing up over all states $x_{i,t}$, and substituting the resulting sums using Eqs. (18a) and (18b), β is found to be equal to zero. Substituting the Lagrange multiplier α_j and β in Eq. (18c) and solving for $\tilde{\rho}^\circ_{i,t}$ gives

$$\tilde{\rho}^\circ_{i,t} = \left(\sum_j N_j \tilde{f}_j c_j(x_{i,t})\right)^{-1}. \tag{19a}$$

Solving Eq. (18a) for $\tilde{f}_j$ gives

$$\tilde{f}_j = \left(\sum_i \sum_{t=1}^{N_i} c_j(x_{i,t})\tilde{\rho}^\circ_{i,t}\right)^{-1}. \tag{19b}$$

Eqs. (19a) and (19b) define $\tilde{\rho}^\circ_{i,t}$ and $\tilde{f}_j$ up to a constant factor. The value of the constant factor is determined by the normalization condition (Eq. (18b)). Once $\tilde{\rho}^\circ_{i,t}$ is known, $\tilde{\rho}^\circ(x)$ can be calculated with Eq. (16).

One way to solve the system of equations (Eqs. (16), (18b), (19a) and (19b)) is to determine first a solution, $\tilde{\rho}_{i,t}^{\text{self}}$ and $\tilde{f}_j^{\text{self}}$, of Eqs. (19a) and (19b); this can be done by applying the equations

$$\tilde{f}_j^{\text{self}} = \left(\sum_i \sum_{t=1}^{N_i} c_j(x_{i,t}) \tilde{\rho}_{i,t}^{\text{self}} \right)^{-1}, \tag{20a}$$

$$\tilde{\rho}_{i,t}^{\text{self}} = \left(\sum_j N_j \tilde{f}_j^{\text{self}} c_j(x_{i,t}) \right)^{-1} \tag{20b}$$

iteratively until a self-consistent solution is found. Subsequently, the normalization condition (Eq. (18b)) can be imposed by setting

$$\tilde{\rho}_{i,t}^{\circ} = \tilde{\rho}_{i,t}^{\text{self}} \Big/ \sum_j \sum_t^{N_j} \tilde{\rho}_{j,t}^{\text{self}}. \tag{20c}$$

The only property of the system that affects the simulations is its distribution function $\rho^{\circ}(x)$. Thus, once the estimate $\tilde{\rho}^{\circ}(x)$ is known, all information has been extracted that can be obtained from the simulations. Observables can subsequently be calculated from the estimate $\tilde{\rho}^{\circ}(x)$. An estimate of the ensemble average $\langle A \rangle$ of an observable is obtained by substituting Eq. (16) into Eq. (2); this gives

$$\tilde{A} = \sum_i \sum_{t=1}^{N_i} A(x_{i,t}) \tilde{\rho}_{i,t}^{\circ}. \tag{21}$$

Souaille and Roux [17] have derived a variant of Eqs. (19a) and (19b) as a generalization of the WHAM equations. In Ref. [17], the equation is used to estimate free energy differences and energy differences of simple, but realistic molecular systems. In this Letter, the relation between Eqs. (19a) and (19b) and established methods to analyze biased simulations is further analyzed.

3. Special cases

3.1. Single biased simulation

To estimate properties of a system from a single biased simulation, a solution of Eqs. (20a) and (20b) is obtained by setting $\tilde{f}_1^{\text{self}} = 1$ and $\tilde{\rho}_{1,t}^{\text{self}} = 1/c_1(x_{1,t})$. Substituting this solution into Eq. (20c) and using the result in Eq. (21) to estimate the ensemble average of an observable, Eq. (6) is obtained. Thus, if only a single simulation is analyzed the present formalism is identical with the well-established re-weighting method [2] to determine estimates from a single biased simulation.

3.2. Using a histogram to analyze a set of biased simulations

To solve Eqs. (16), (18b), (19a) and (19b), the values of the bias functions $c_j(x)$ need to be known for all states $\{x_{i,t}\}$ and for all simulations j. If the sampling distribution functions are known prior to starting the first simulation, the values of the bias functions $c_j(x)$ can be calculated at the same time as the simulations are carried out. Otherwise, e.g., if the sampling distribution function for simulation j is constructed based on the results from the preceding simulations $1, 2, \ldots, j-1$, the entire set of states $\{x_{j,t}\}$ needs to be stored and the biases $c_j(x_{i,t})$ for $j > i$ have to be calculated in a post-processing step. In any case, to solve Eqs. (16), (18b), (19a) and (19b) directly, a large amount of data has to be stored.

In certain cases, e.g., if the biasing potentials are applied only along a single or a few degrees of freedom, the analysis can be made more efficient and less memory intensive by grouping the states into bins and generating histograms on the sampling of each of the bins in each of the simulations j. The bins have to be defined such that each state belongs to exactly one bin, and such that in all simulations j the states that are grouped together in one bin experience approximately the same bias, i.e., if two states x and y are grouped together into the same bin, $c_j(x)$ has to be approximately equal to $c_j(y)$ in all simulations j. Let $K(x)$ denote the index function that gives the index k of the bin into which the state x belongs. With this definition, the condition that each state belongs exactly into one bin can be written as

$$\sum_k \delta_{K(x),k} = 1, \tag{22}$$

where the summation is over all bins. Let further $c_{j,k}$ denote the value of the bias for states of bin k in simulation j (i.e., $c_{j,K(x)} = c_j(x)$), let

$$n_{j,k} = \sum_{t=1}^{N_j} \delta_{K(x_{j,t}),k} \tag{23}$$

denote the number of states in simulation j that belong to bin k, and

$$\tilde{p}_k^* = \sum_j \sum_{t=1}^{N_j} \delta_{K(x_{j,t}),k} \tilde{\rho}_{j,t}^\circ \tag{24}$$

the estimate of the probability that a state belongs to bin k. Using the definition of the $c_{j,k}$, Eq. (19a) can be rewritten as

$$\tilde{\rho}_{i,t} = \left(\sum_j N_j \tilde{f}_j c_{j,K(x_{i,t})} \right)^{-1}. \tag{25}$$

Inserting Eq. (25) into Eq. (24) and substituting the sum over delta function using Eq. (23) gives

$$\tilde{p}_k^* = \sum_j n_{j,k} \Big/ \sum_j N_j \tilde{f}_j c_{j,k}. \tag{26a}$$

Multiplication of each term in the double sum of Eq. (19b) with the left-hand side of Eq. (22), and using Eq. (24) to eliminate the sum over delta functions affords

$$\begin{aligned} \tilde{f}_j &= \left(\sum_i \sum_{t=1}^{N_i} \left\{ \sum_k \delta_{K(x_{i,t}),k} \right\} c_j(x_{i,t}) \tilde{\rho}_{i,t}^\circ \right)^{-1} \\ &= \left(\sum_k c_{j,k} \left\{ \sum_i \sum_{t=1}^{N_i} \delta_{K(x_{i,t}),k} \tilde{\rho}_{i,t}^\circ \right\} \right)^{-1} \\ &= \left(\sum_k c_{j,k} \tilde{p}_k^* \right)^{-1}. \end{aligned} \tag{26b}$$

Eqs. (26a) and (26b) are known as the WHAM equations [6,8,15,18]. If the number of bins is small compared to the number of states sampled in all the simulations, Eqs. (26a) and (26b) are more efficient to solve than Eqs. (20a) and (20b) since summations are over all bins rather than over all conformations. Also, the only quantities that need to be known to solve the WHAM equations are the biases $c_{j,k}$ for all bins k in all simulations j, and the total number of times each bin is visited.

A self-consistent solution, $\tilde{p}_k^{\text{self}*}$ and $\tilde{f}_j^{\text{self}}$, of the WHAM equations can be obtained by iterating Eqs. (26a) and (26b) [6,8,18]. The $\tilde{f}_j^{\text{self}}$ can then be used in Eq. (25) to calculate $\tilde{\rho}_{i,t}^{\text{self}}$, which in turn can be used to estimate other properties (Eqs. (20c) and (21)).

4. Examples of observables of molecular systems

4.1. Ensemble averages

Given the estimate $\tilde{\rho}^\circ(x)$ of the distribution function $\rho^\circ(x)$, ensemble averages are estimated with Eq. (21). If, for example, a molecule is studied, then the average distance $\langle d \rangle$ between two selected atoms of the molecule can be estimated by substituting $A(x_{i,t})$ with the distance between the two atoms measured in conformation $x_{i,t}$. Note that to calculate the dependence of the estimate $\langle d \rangle$ on some conditions, e.g., the temperature, a solution of Eqs. (16), (18b), (19a) and (19b) needs to be determined only once.

4.2. Thermodynamic properties

Excess thermodynamic parameters of a classical many-body system in the canonical ensemble can be calculated from the configurational integral [2,19]:

$$Z^{\text{I}} = \int \mathrm{d}x \exp(-V^{\text{I}}(x)/k_B T^{\text{I}}) \tag{27}$$

e.g., the excess free energy is given by

$$F^{\text{I}} = -k_{\text{B}} T^{\text{I}} \ln Z^{\text{I}}. \tag{28}$$

In Eq. (27), the integration extends over the entire conformational space, and T^{I} and $V^{\text{I}}(x)$ are the temperature and the potential energy function, respectively, of the system for which the thermodynamic parameters are calculated.

Integrals $\int \mathrm{d}x O(x)$ of a property $O(x)$ over all states, e.g., the integral in Eq. (27) with $O(x) = \exp(-V^{\text{I}}(x)/k_{\text{B}} T^{\text{I}})$, can be estimated by defining the observable

$$A(x) = O(x)/\rho^\circ(x) \tag{29}$$

as can be seen by substituting Eq. (29) into Eq. (2). Substituting Eq. (29) into Eq. (21) affords

$$\tilde{A} = \sum_i \sum_{t=1}^{N_i} \frac{O(x_{i,t})}{\rho^\circ(x_{i,t})} \tilde{\rho}^\circ_{i,t}. \tag{30}$$

for the estimate of the integral $\int O(x)\,\mathrm{d}x$. Eq. (30) can be used to estimate integrals over all states independent of the distribution function $\rho^\circ(x)$ chosen as the reference in the analysis. In what follows, it is assumed that the canonical distribution function $\rho^\circ_c(x)$ (Eq. (1)) is used as the reference in the analysis to define the bias functions (Eq. (4)). Using $O(x) \equiv \exp(-V^{\mathrm{I}}(x)/k_{\mathrm{B}}T^{\mathrm{I}})$, the estimate of the configurational integral can then be written as

$$\tilde{Z}^{\mathrm{I}} = Z^\circ \sum_i \sum_{t=1}^{N_i} z_{i,t} \tag{31}$$

with

$$z_{i,t} = \tilde{\rho}^\circ_{i,t} \exp(V^\circ(x_{i,t})/k_{\mathrm{B}}T^\circ) \exp(-V^{\mathrm{I}}(x_{i,t})/k_{\mathrm{B}}T^{\mathrm{I}}). \tag{32}$$

Consider the case in which a series of simulations j is carried out with different canonical distribution functions $\rho_{cj}(x)$ (Eq. (7)) that describe systems at the temperature $T_j = T^\circ$ with different potential energy functions $V_j(x)$, and one is interested in the free energy differences between the systems simulated. The system in the canonical ensemble with potential energy function $V^\circ(x) \equiv 0$ is selected as the reference system for the analysis. The bias functions can, in this case, be defined as $c_j(x) = \exp(-V_j(x)/k_{\mathrm{B}}T^\circ)$ (Eq. (4)). For the free energy difference between systems j and j', one obtains

$$\begin{aligned}\Delta\tilde{F} &= \tilde{F}_j - \tilde{F}_{j'} = -RT^\circ \ln \frac{\tilde{Z}_j}{\tilde{Z}_{j'}} \\ &= -RT^\circ \ln \frac{\sum_i \sum_{t=1}^{N_i} \tilde{\rho}^\circ_{i,t} \exp(-V_j(x_{i,t})/k_{\mathrm{B}}T^\circ)}{\sum_i \sum_{t=1}^{N_i} \tilde{\rho}^\circ_{i,t} \exp(-V_{j'}(x_{i,t})/k_{\mathrm{B}}T^\circ)}.\end{aligned} \tag{33}$$

Realizing that the exponentials in Eq. (33) are equal to the bias functions $c_j(x_{i,t})$ and $c_{j'}(x_{i,t})$, respectively, and using Eq. (19b), Eq. (33) simplifies to

$$\Delta\tilde{F} = -RT^\circ \ln \frac{\tilde{f}_{j'}}{\tilde{f}_j}. \tag{34}$$

Eq. (34) together with Eq. (19a) corresponds to the composite reference state formalism Eqs. (14) and (15) of Ref. [9]; the correspondence between the present notation and the notation used in [9] is $\Delta\tilde{F} \leftrightarrow \Delta g_{ls} - \Delta g_{ls}$, $\tilde{f}_j \leftrightarrow \exp(\Delta g_{ks}/RT)$, $c_j(x) \leftrightarrow \exp(-V_k(r)/RT)$, $N_j \leftrightarrow n_k$, and $\tilde{\rho}_{i,t} \leftrightarrow \exp(V_s(r_{i,k})/RT)/\sum_{k=1}^{N} n_k)$.

5. Remarks

For the derivation of Eq. (16), it was assumed that the factor $g(\{x_{j,t}\})$ in Eq. (9) that accounts for the correlation between subsequent states generated in the simulations does not depend on the distribution function $\rho_j(x)$; i.e., it is assumed that $\rho_j(x_{j,t})$ and $\rho_j(x_{j,t+1})$ are uncorrelated. If the states $\{x_{j,t}\}$ are generated using molecular dynamics or Metropolis Monte Carlo simulations, subsequent states and the value of the distribution function of these states are, in general, correlated. However, if states are selected for the analysis that are separated by a long time period in the simulations, correlations disappear. If the time period between subsequent states used in the analysis is long compared to the slowest correlation time of the system, all correlations disappear and the factor $g(\{x_{j,t}\})$ will be equal to one. If the time period is comparable or shorter than the slowest correlation time of the system but long compared to the correlation time of the value of the distribution function, i.e., the correlation time of the potential energy if conformations of a classical many-body system in the canonical ensemble are studied, the values $\rho_j(x_{j,t})$ and $\rho_j(x_{j,t+1})$ of the distribution functions will be uncorrelated. Thus, in this second case, the factor $g(\{x_{j,t}\})$ that describes the correlation between subsequent states will be different from one, but will not depend on the values of the distribution function $\rho_j(x_{j,t})$, and $g(\{x_{j,t}\})$ will drop out of the derivation also in this case. However, if all the states generated in a molecular dynamics or Metropolis Monte Carlo simulation are used, the conditional probability $p(\{x_{j,t}\}|\rho^\circ(x))$

of the observed set of states given the distribution function $\rho^{\circ}(x)$, will in general be different from Eq. (9), and will depend on the particularities of the simulation method used. The estimate of $\rho^{\circ}(x)$ obtained from Eq. (9) might not be optimal in this case.

6. Conclusions

Using the maximum likelihood method, a formalism was derived to analyze a series of Monte Carlo or molecular dynamics simulations. When the formalism is used to calculate potentials of mean force or free energy differences, the formalism turns out to be equal to the WHAM equations [6,8,15,18] and to the composite reference state method [9], respectively. The latter two methods were found to be efficient compared to other existing methods to analyze a series of simulations [4,5,9]. The present formalism is thus a generalization of the most successful of the existing methods. In the derivation it was assumed that the values of the distribution function $\rho^{\circ}(x)$ of the states that are analyzed are uncorrelated.

The point of view adopted in the present derivation differs from that of earlier derivations [6,8,9,15,18,20] of methods to analyze biased simulations (see also [17]). In earlier derivations the analysis of the simulations is done such that the 'error' in the estimate of the property of interest, e.g., a free energy difference or a low dimensional potential of mean force, is minimized. Optimal estimates of other observables of interest can be obtained from such results in a second step, if they can be expressed as a function of the estimated free energy differences or the potential of mean force. An example of such an observable is the entropy difference between two systems. However, it is not a priori clear how to obtain optimal estimates for observables that are not directly related to the estimated free energy differences or potential of mean force, e.g., the average distance between pairs of atoms of a system.

The present derivation aims at determining the estimate of the distribution function $\rho^{\circ}(x)$ that agrees best with the results of the simulations. $\rho^{\circ}(x)$ is related to other observables in a unique way (Eq. (2)). With the present formalism, it is thus straightforward to obtain optimal estimates of any observable of interest.

Acknowledgements

I would like to thank Dr. M. Schaefer and Prof. M. Karplus for their helpful discussions. This work was supported by the fellowship 823A-050424 of the Swiss National Science Foundation. The laboratory is supported in part by the CNRS (ISISUPRESA 7006), by the Ministère de l'Education Nationale, by a grant from the Association pour la Recherche contre le Cancer (France), and by a grant from the National Institutes of Health (USA).

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