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Calculation of free-energy differences and potentials of mean force by a multi-energy gap method

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A method is proposed to significantly accelerate the convergence of free-energy calculations. It introduces a bias factor in Monte Carlo simulations or, equivalently, a bias force in molecular dynamics simulations. The bias factor targets the energy gap, i.e., the difference in energy function between two states, and is therefore specifically designed for calculating free-energy differences. The goal is to make the probability density of the energy gap as uniform as possible, thus allowing for its accurate determination. An iterative procedure, based on simulations at higher temperatures, is devised to obtain the bias factor. The same method naturally extends to the calculation of potentials of mean force. The generalized coordinate, for which the potential of mean force is to be calculated, now plays the role of the energy gap. Applications to model systems confirm the expected increase in accuracy of calculated free-energy differences and potentials of mean force.
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I. INTRODUCTION

Free energy is a fundamental molecular property that plays an essential role in characterizing chemical and biological systems.[1] It is also a property that is inherently difficult to calculate. The seminal ideas of thermodynamic integration, free-energy perturbation, and umbrella sampling developed by Kirkwood,[2] Zwanzig,[3] and Torrie and Valleau[4] have now been widely implemented in computer simulations. Many more recent free-energy methods have been proposed.[5–10] Given the formidable task of getting convergent results, it is important that diverse methods are explored. The diversity provides the opportunity to choose methods most suited for particular problems, and allows for a combination of several methods to be used on a single problem, such that the challenge faced by each individual method is reduced. It is in this spirit that we report here a method for significantly accelerating the convergence of free-energy calculations.

The free-energy difference ΔG between two states, 0 and 1, is given by

$$\exp(-\beta\Delta G) = \frac{\int \exp[-\beta V_1(\mathbf{x})]d\mathbf{x}}{\int \exp[-\beta V_0(\mathbf{x})]d\mathbf{x}} \tag{1a}$$

$$= \frac{\int \exp[-\beta\Delta V(\mathbf{x})]\exp[-\beta V_0(\mathbf{x})]d\mathbf{x}}{\int \exp[-\beta V_0(\mathbf{x})]d\mathbf{x}} \tag{1b}$$

$$= \langle \exp[-\beta\Delta V(\mathbf{x})]\rangle_0, \tag{1c}$$

where $\beta=(k_BT)^{-1}$, $V_0(\mathbf{x})$ and $V_1(\mathbf{x})$ are the potential energy functions in the two states, $\Delta V(\mathbf{x})=V_1(\mathbf{x})-V_0(\mathbf{x})$ is the energy gap function, $d\mathbf{x}$ denotes the volume element in configurational space, and $\langle\cdots\rangle_0$ signifies an average with the Boltzmann distribution $\exp[-\beta V_0(\mathbf{x})]$. The probability density of the energy gap in state 0 is

$$\rho_0(\Delta V) = \langle \delta[\Delta V(\mathbf{x}) - \Delta V]\rangle_0, \tag{2}$$

where ΔV without an argument denotes a specific value taken by the energy gap function. ΔG can then be expressed as

$$\exp(-\beta\Delta G) = \int d\Delta V \rho_0(\Delta V)\exp(-\beta\Delta V). \tag{3}$$

The difficulty in obtaining accurate values for ΔG can be appreciated through Eq. (3).[11] It stems from the disparate dependences of the probability density $\rho_0(\Delta V)$ and the Boltzmann factor $\exp(-\beta\Delta V)$. $\rho_0(\Delta V)$ is generally peaked at a value at which $\exp(-\beta\Delta V)$ contributes a negligible weight. Conversely, at low values of ΔV where $\exp(-\beta\Delta V)$ is significant, $\rho_0(\Delta V)$ is exceedingly small and hence challenging to determine accurately in computer simulations. The larger the magnitude of the energy gap, the more difficult it is to determine ΔG.

For future reference, let us briefly summarize the basic ideas of free-energy perturbation and thermodynamic integration. If the energy gap function is decomposed into many "small" pieces,

$$\Delta V(\mathbf{x}) = \sum_{l=1}^{L} \delta V_l(\mathbf{x}), \tag{4}$$

then

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$$\exp(-\beta\Delta G) = \frac{\int \exp\{-\beta[V_0(\mathbf{x}) + \delta V_1(\mathbf{x})]\}d\mathbf{x}}{\int \exp[-\beta V_0(\mathbf{x})]d\mathbf{x}} \times \frac{\int \exp\{ -\beta[V_0(\mathbf{x}) + \delta V_1(\mathbf{x})] + \delta V_2(\mathbf{x})]\}d\mathbf{x}}{\int \exp\{-\beta[V_0(\mathbf{x}) + \delta V_1(\mathbf{x})]\}d\mathbf{x}} \times \cdots \times \frac{\int \exp\{-\beta[V_0(\mathbf{x}) + \Sigma_{l=1}^{L}\delta V_l(\mathbf{x})]\}d\mathbf{x}}{\int \exp\{-\beta[V_0(\mathbf{x}) + \Sigma_{l=1}^{L-1}\delta V_l(\mathbf{x})]\}d\mathbf{x}} = \prod_{l=0}^{L-1} \langle \exp[-\beta\delta V_{l+1}(\mathbf{x})]\rangle_\lambda, \tag{5}$$

where $\lambda \equiv l/L$ and $\langle\cdots\rangle_\lambda$ signifies an average over the Boltzmann distribution with the energy function $V_\lambda(\mathbf{x}) \equiv V_0(\mathbf{x}) + \Delta V_\lambda(\mathbf{x}) \equiv V_0(\mathbf{x}) + \Sigma_{l=1}^{\lambda L}\delta V_1(\mathbf{x})$. Note that $\Delta V_1(\mathbf{x}) = \Delta V(\mathbf{x})$. Each of the factors in Eq. (5) is similar to that in Eq. (1c), but an individual piece of the energy gap, $\delta V_{l+1}(\mathbf{x})$, is smaller than the full energy gap and hence the averaging can be more accurately determined. If λ is taken to be continuous, this free-energy perturbation technique turns into the thermodynamic integration technique. The final result can be most conveniently obtained with the help of a free-energy function $\Delta G(\lambda)$ defined by

$$\exp[-\beta\Delta G(\lambda)] = \langle \exp[-\beta\Delta V_\lambda(\mathbf{x})]\rangle_0. \tag{6}$$

Note that $\Delta G(1)$ is the desired free-energy difference ΔG. Taking the derivative of $\Delta G(\lambda)$ with respect to λ, one obtains

$$\frac{\partial\Delta G(\lambda)}{\partial\lambda} - \frac{\langle \exp[-\beta\Delta V_\lambda(\mathbf{x})]\partial\Delta V_\lambda(\mathbf{x})/\partial\lambda\rangle_0}{\langle \exp[-\beta\Delta V_\lambda(\mathbf{x})]\rangle_0} = \langle \partial\Delta V_\lambda(\mathbf{x})/\partial\lambda\rangle_\lambda. \tag{7}$$

Integration then leads to the familiar result

$$\Delta G = \int_0^1 d\lambda \langle \partial\Delta V_\lambda(\mathbf{x})/\partial\lambda\rangle_\lambda. \tag{8}$$

In practice the integration has to be approximated as the sum of a finite number of terms. Therefore the same configurations, sampled from the Boltzmann distribution $\exp[-\beta V_\lambda(\mathbf{x})]$, can be used to implement both the free-energy perturbation and thermodynamic integration techniques. A common choice of the intermediate gap function is

$$\Delta V_\lambda(\mathbf{x}) = \lambda\Delta V(\mathbf{x}). \tag{9}$$

In that case Eq. (8) can be written, in terms of the probability density of the energy gap $\rho_\lambda(\Delta V)$ in the intermediate state, as

$$\Delta G = \int_0^1 d\lambda \int d\Delta V \rho_\lambda(\Delta V)\Delta V. \tag{10}$$

Two types of approaches to free-energy calculations have been a focus of recent methodological developments. One has its roots in Jarzynski's identity[5]

$$\exp(-\beta\Delta G) = \langle \exp(-\beta W)\rangle_0, \tag{11}$$

where

$$W = \int_0^{t_s} dt \frac{\partial\Delta V_\lambda}{\partial\lambda}\frac{d\lambda}{dt} \tag{12}$$

is the work done on the system over a path which brings the energy function from $V_0(\mathbf{x})$ from $V_1(\mathbf{x})$ over the time period from 0 to t_s. The average in Eq. (11) is over an ensemble of paths started from a Boltzmann distribution in state 0. A particular area of development is to make the implementation of Eq. (11) practical.[6,9]

The second type of approaches introduces biases to "flatten" the energy landscape,[8,10] borrowing ideas from sampling methods exploiting generalized (i.e., non-Boltzmann distribution) ensembles. In the well-known multicanonical ensemble,[12,13] the desired bias factor is inversely proportional to the density of states, so the resulting probability density of energy is uniform. A recent variant of the multicanonical approach is multioverlap,[14] which introduces a bias factor that is determined by the overlap of the current configuration with a reference configuration. In analogy to the multicanonical method, the desired bias factor is inversely proportional to the probability density of the overlap.

The method proposed here follows the long tradition of exploiting generalized ensembles. Unlike previous developments, the bias is on the energy gap $\Delta V(\mathbf{x})$ instead of the energy function $V_0(\mathbf{x})$. The method is specifically designed for calculating free-energy differences. To highlight the focus on energy gap, the method is given the name multi-energy gap (MEGA). When some (to be specified) MEGA bias factor, $w_{\mathrm{MEGA}}[\Delta V(\mathbf{x})]$, is introduced, the overall statistical weight becomes $w_{\mathrm{MEGA}}[\Delta V(\mathbf{x})]\exp[-\beta V_0(\mathbf{x})] \equiv W(\mathbf{x})$. The resulting probability density of the energy gap is [cf. Eq. (2)]

$$\rho_{\mathrm{MEGA}}(\Delta V) = \frac{\int \delta[\Delta V(\mathbf{x}) - \Delta V]W(\mathbf{x})d\mathbf{x}}{\int W(\mathbf{x})d\mathbf{x}} \tag{13a}$$

$$= \frac{\langle \delta[\Delta V(\mathbf{x}) - \Delta V]w_{\mathrm{MEGA}}(\Delta V)\rangle_0}{\langle w_{\mathrm{MEGA}}[\Delta V(\mathbf{x})]\rangle_0} \tag{13b}$$

$$= \frac{\rho_0(\Delta V)w_{\mathrm{MEGA}}(\Delta V)}{\langle w_{\mathrm{MEGA}}[\Delta V(\mathbf{x})]\rangle_0}. \tag{13c}$$

The *ideal* MEGA bias factor is inversely proportional to the probability density of the energy gap, $\rho_0(\Delta V)$, in the canonical ensemble, which would lead to a uniform distribution for $\rho_{\mathrm{MEGA}}(\Delta V)$. The uniform distribution allows $\rho_{\mathrm{MEGA}}(\Delta V)$ to be determined accurately in the region where contributions to ΔG are important [but, as noted above, where $\rho_0(\Delta V)$ is too small to be determined accurately]. Once $\rho_{\mathrm{MEGA}}(\Delta V)$ is obtained, one can recover $\rho_0(\Delta V)$ via

$$\rho_0(\Delta V) = \frac{\rho_{\mathrm{MEGA}}(\Delta V)\langle w_{\mathrm{MEGA}}[\Delta V(\mathbf{x})]\rangle_0}{w_{\mathrm{MEGA}}(\Delta V)}, \tag{14}$$

which is obtained simply rearranging Eq. (13c). ΔG can then be calculated according to Eq. (3). Note that Eqs. (13) and (14) are valid for an arbitrary bias factor $w(\Delta V)$. The goal of MEGA is to find a bias factor such that $\rho_{\mathrm{MEGA}}(\Delta V)$ is as uniform as possible.

The remainder of this paper is organized as follows. In Sec. II we present an iterative procedure for obtaining the

MEGA bias factor $w_{\mathrm{MEGA}}(\Delta V)$ through Monte Carlo (MC) simulations. For illustration, in Sec. III this procedure is implemented on two model systems to calculate the free-energy differences. In Sec. IV the MEGA method is extended to calculating potentials of mean force. While the method can be naturally implemented by MC simulations, given the popularity of molecular dynamics (MD) simulations, it is desirable to develop a MD version of MEGA. This version is presented in Sec. V. Finally, we give some concluding remarks in Sec. VI.

II. MEGA FOR FREE-ENERGY DIFFERENCE

Berg *et al.*[14] devised an iterative procedure for obtaining the multioverlap bias factor. This procedure is adapted here to find the MEGA bias factor. The key observation is that the probability density of the energy gap is temperature dependent, and is more easily determined at high temperatures (i.e., small values of β). From here on the dependence on β will be explicitly denoted. Suppose that the MEGA bias factor, $w_{\mathrm{MEGA}}(\Delta V;\beta')$, at an inverse temperature $\beta'<\beta$ is obtained from a simulation at that temperature. If this bias factor is introduced to a simulation at the desired inverse temperature β, then the resulting MEGA probability density is [see Eq. (13c)]

$$\rho_{\mathrm{MEGA}}(\Delta V;\beta;\beta') = \frac{\rho_0(\Delta V;\beta) w_{\mathrm{MEGA}}(\Delta V;\beta')}{\langle w_{\mathrm{MEGA}}[\Delta V(\mathbf{x});\beta']\rangle_0}. \tag{15}$$

From this the MEGA bias factor can be found as

$$w_{\mathrm{MEGA}}(\Delta V;\beta) \propto \frac{1}{\rho_0(\Delta V;\beta)} \propto \frac{w_{\mathrm{MEGA}}(\Delta V;\beta')}{\rho_{\mathrm{MEGA}}(\Delta V;\beta;\beta')}. \tag{16}$$

The above description can be expanded to include intermediate values of the inverse temperature, resulting in an iterative procedure. The procedure starts with a Metropolis simulation at a small value β_0, from which $\rho_0(\Delta V;\beta_0)$ is obtained. A bias factor $w_{\mathrm{MEGA}}(\Delta V;\beta_0)\propto 1/\rho_0(\Delta V;\beta_0)$ is then introduced to a new simulation at a larger value β_1. The MEGA probability density of the energy gap, $\rho_{\mathrm{MEGA}}(\Delta V;\beta_1;\beta_0)$, is obtained from the simulation at β_1 by histogram, and the result is used to find the new bias factor, $w_{\mathrm{MEGA}}(\Delta V;\beta_1)$, according to Eq. (16). The new bias factor is fed to yet another simulation at a still larger value β_2, and the process is repeated until the desired value β is reached. We note that operationally this iterative procedure is very similar to a sampling procedure, proposed by Berg,[15,16] in which the Boltzmann distribution obtained at a higher temperature is used for proposing new positions in a Metropolis[17] MC simulation.

It is straightforward to implement in MC simulations the iterative procedure for obtaining the MEGA bias factor. At $\beta=\beta_i$, if a move from $\mathbf{x}_0$ to $\mathbf{x}$ is proposed from a distribution $\Lambda_i(\mathbf{x}_0\rightarrow\mathbf{x})$, then the acceptance probability is[17]

$$\min\left\{1, \frac{\Lambda_i(\mathbf{x}\rightarrow\mathbf{x}_0) w_{\mathrm{MEGA}}[\Delta V(\mathbf{x});\beta_{i-1}]\exp[-\beta_i V_0(\mathbf{x})]}{\Lambda_i(\mathbf{x}_0\rightarrow\mathbf{x}) w_{\mathrm{MEGA}}[\Delta V(\mathbf{x}_0);\beta_{i-1}]\exp[-\beta_i V_0(\mathbf{x}_0)]}\right\}. \tag{17}$$

We see that it is very convenient to adapt Berg's recipe[15,16] for the distribution $\Lambda_i(\mathbf{x}_0\rightarrow\mathbf{x})$. In the original method, $\Lambda_i(\mathbf{x}_0\rightarrow\mathbf{x})$ is obtained as a histogram of $\mathbf{x}$ in a Metropolis simulation in the preceding temperature; by design $\Lambda_i(\mathbf{x}_0\rightarrow\mathbf{x})$ mimics the Boltzmann distribution $\exp[-\beta_{i-1}V_0(\mathbf{x})]$ and is independent of $\mathbf{x}_0$. In our simulations, a histogram in $\mathbf{x}$ would mimic the distribution $w_{\mathrm{MEGA}}[\Delta V(\mathbf{x});\beta_{i-2}]\times\exp[-\beta_{i-1}V_0(\mathbf{x})]$; hence the distribution for proposing a new position $\mathbf{x}$ would be

$$\Lambda_i(\mathbf{x}_0\rightarrow\mathbf{x}) \propto w_{\mathrm{MEGA}}[\Delta V(\mathbf{x});\beta_{i-2}]\exp[-\beta_{i-1}V_0(\mathbf{x})]. \tag{18}$$

The presentation of the MEGA method has so far been directed to the full energy gap function $\Delta V(\mathbf{x})$. It applies just as well to each of its small pieces, i.e., $\delta V_{l+1}(\mathbf{x})$, appearing in Eq. (5). Such an application will incorporate MEGA into the free-energy perturbation technique. This application produces the probability density of the energy gap $\rho_\lambda(\Delta V)$ in an intermediate state, which in turn will allow for the calculation of the free-energy difference via thermodynamic integration according to Eq. (10).

III. ILLUSTRATION OF FREE-ENERGY CALCULATION BY MEGA

We now illustrate the use of the MEGA method for calculating free-energy differences in model systems. The first system is one dimensional. The two states have harmonic potentials, with

$$V_0(x) = x^2/2, \tag{19a}$$

$$V_1(x) = a(x-x_0)^2/2, \quad a>1. \tag{19b}$$

The energy gap function is thus

$$\begin{aligned}\Delta V(x) &= a(x-x_0)^2/2 - x^2/2 \\ &= (a-1)[x-ax_0/(a-1)]^2/2 + \Delta V_m,\end{aligned} \tag{19c}$$

where $\Delta V_m=-ax_0{}^2 2(a-1)$ is the minimum value of $\Delta V(x)$. The free-energy difference is given by

$$\exp(-\beta\Delta G) = \frac{\int \exp[-\beta a(x-x_0)^2/2]dx}{\int \exp(-\beta x^2/2)dx} = a^{-1/2}. \tag{20}$$

Note that the Boltzmann distribution $\exp[-\beta V_0(x)]$ is a Gaussian function. For later reference, the probability density of the energy gap is

$$\rho_0(\Delta V) = \int \delta\{(a-1)[x - ax_0/(a-1)]^2/2 - (\Delta V - \Delta V_m)\}\exp(-\beta x^2/2)dx/(2\pi/\beta)^{1/2}$$
$$= \frac{\exp\{-\beta[(v - ax_0)/(a-1)]^2/2\} + \exp\{-\beta[(v + ax_0)/(a-1)]^2/2\}}{(2\pi/\beta)^{1/2}v}, \tag{21}$$

where $v=[2(a-1)(\Delta V-\Delta V_m)]^{1/2}$.

Though the result in Eq. (20) is temperature independent, for specificity the MC simulations implementing MEGA are for $\beta=1$. Details of the simulations are as follows. The initial β value is $\beta_0=0.01$, and four intermediate β values are used: 0.1, 0.2, 0.4, and 0.8.[18] The probability density of the energy gap is obtained from a histogram with a bin size of 1; a total of 600 bins starting at ΔV_m are used. In the Metropolis simulation at $\beta_0=0.01$, the Gaussian Boltzmann distribution is generated by the Box–Muller method.[19] At each of the larger β values, the probability density for proposing moves is taken as the Boltzmann distribution at the preceding β value [Eq. (18) without the bias factor]. The number of simulated configurations at the desired inverse temperature, $\beta=1$, is 10 times that at each of the smaller β values. Therefore the total number of simulated configurations in the iterative procedure is 1.5 times that for the production run at $\beta=1$, or an overhead of 50%. To benchmark the accelerating effect of MEGA on the convergence of calculated free-energy difference, a Metropolis simulation at $\beta=1$ is also carried out.

Table I shows the simulation results for five sets of a and x_0 values. Each reported value and the associated error for $\exp(-\beta\Delta G)$ are obtained as the average and the standard deviation over 10 repetitions, each with the reported total number of simulated configurations (under N_{conf}). It can be seen that, to reach comparable accuracy in calculated value for $\exp(-\beta\Delta G)$, the Metropolis simulation requires at least 3 to 12 times as many configurations as the MEGA simulation.

Figure 1 illustrates why calculating the free-energy difference by a Metropolis simulation is difficult and how a MEGA simulation reduces the calculation error, with results for $a=2$ and $x_0=5$. As Fig. 1(a) shows, the exponential function $\exp[-\beta(\Delta V-\Delta V_m)]$ decreases rapidly from 1 at $\Delta V=\Delta V_m$ to 5×10^{-12} at $\Delta V=\Delta V_m+26$. The integration for obtaining $\exp(-\beta\Delta G)$ [according to Eq. (3), with $\rho_0(\Delta V)$ given by Eq. (21)] is complete around this value of ΔV. Thus it is essential to determine $\rho_0(\Delta V)$ accurately below this value. However, as can be seen from Fig. 1(b), at this value $\rho_0(\Delta V)$ is only 3.4% of its maximum (at $\Delta V=\Delta V_m+49$). In a Metropolis simulation with 15×10^6 configurations, values of ΔV below ΔV_m+12 are never sampled. On the other hand, in a MEGA simulation with the same number of configurations, the lowest ΔV value sampled decreases to ΔV_m+8, at which $\rho_0(\Delta V)$ is smaller than its maximum value by over seven orders of magnitude. Within the sampled ranges of the energy gap, the exact result for $\rho_0(\Delta V)$ [given by Eq. (21)] is well reproduced by both simulations [Fig. 1(b)]. The widened range of the MEGA simulation therefore accounts for the higher accuracy in calculated free-energy difference.

The implementation of the MEGA in higher-dimensional systems does not introduce additional difficulty. We further illustrate the method on a two-dimensional system first studied by Ytreberg and Zuckerman,[9] with the energy functions

$$V_0(x,y) = (x+2)^2/2 + y^2, \tag{22a}$$

$$V_1(x,y) = 0.1\{[(x-1)^2 - y^2] + 10(x^2-5)^2 + (x+y)^4 + (x-y)^4\}. \tag{22b}$$

State 0 has a single energy minimum at $(-2,0)$, but state 1 has two minima, one around $(-2,0)$ and the other around (2, 0). The exact free-energy difference, as obtained according to Eq. (1a) by numerical integration, is $\Delta G=6.55k_BT$. It is found that an initial β value at $\beta_0=0.5$, without additional intermediate β values, leads to efficient MEGA simulations at $\beta=1$. These simulations are essentially the same as those for the one-dimensional system described earlier. Minor differences include binning the probability density of the energy gap at a bin size of 0.5 (again with a total of 600 bins) and a lower bound of −20. The distribution for proposing new positions in simulations at both $\beta_0=0.5$ and $\beta=1$ is taken as the Boltzmann distribution in state 0, which is Gaussian for both x and y.

The mean and standard deviations of ΔG, calculated over 10 repetitions, are shown in Fig. 2 for different numbers of total configurations (N_{conf}) used in each repetition. The

TABLE I. Exact and simulation results for the free-energy difference ΔG of the one-dimensional system.

Parameters	$e^{-\beta\Delta G}$ exact	Metropolis		MEGA	
		N_{conf} (10^6)	$e^{-\beta\Delta G}$	N_{conf} (10^6)	$e^{-\beta\Delta G}$
$a=1.2$, $x_0=5$	0.913	120	0.89 ± 0.17	30	0.86 ± 0.15
$a=2$, $x_0=5$	0.707	45	0.73 ± 0.15	15	0.68 ± 0.15
$a=2$, $x_0=6$	0.707	1200	0.49 ± 0.16	300	0.61 ± 0.15
$a=8$, $x_0=5$	0.354	45	0.375 ± 0.053	15	0.366 ± 0.057
$a=8$, $x_0=6$	0.354	900	0.30 ± 0.18	75	0.35 ± 0.17

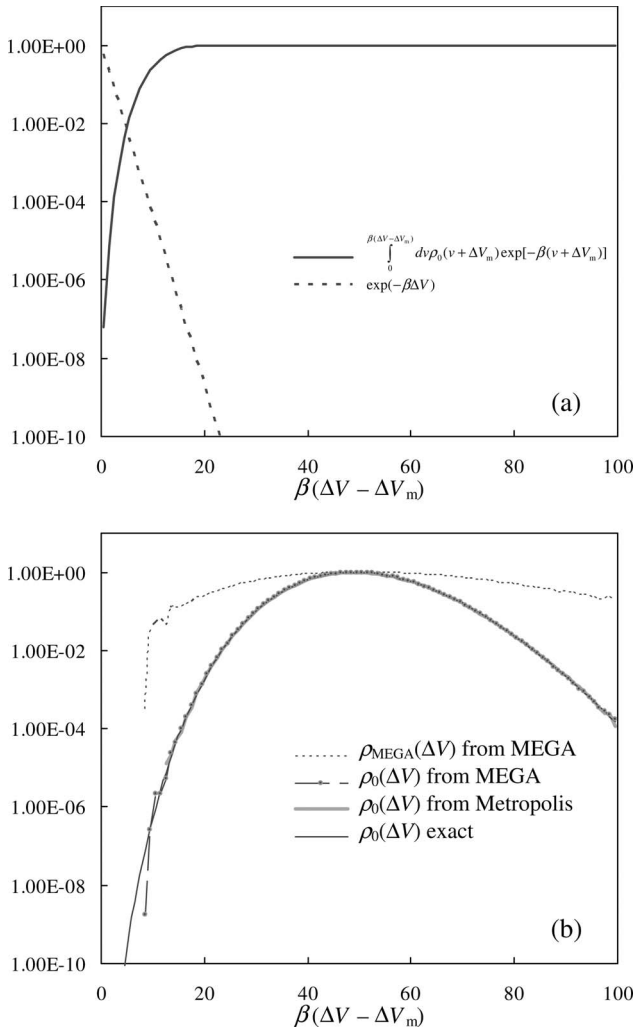

FIG. 1. Factors contributing to the free-energy difference ΔG of the one-dimensional system. (a) The exponential function $\exp(-\beta\Delta V)$ [scaled by the maximum $\exp(-\beta\Delta V_m)$] and the integration of $\rho_0(\Delta V)\exp(-\beta\Delta V)$ with a moving upper limit [integrated numerically and scaled by $\exp(-\beta\Delta G)$, with $\rho_0(\Delta V)$ given by Eq. (21)]. (b) The probability density for the energy gap in the canonical ensemble, as calculated from a MEGA simulation [via first obtaining $\rho_{MEGA}(\Delta V)$, also shown], from a Metropolis simulation, or by Eq. (21). Each curve is normalized by its maximum value.

MEGA simulations require 22×10^6 configurations to reduce the standard deviation to below 0.1. In comparison, Metropolis simulations require 4000×10^6 configurations to reach the same level of standard deviation in ΔG, suggesting that the MEGA simulations are ~100-fold more efficient. A method devised by Ytreberg and Zuckerman[9] showed a similar gain in efficiency (their calculations were done by dividing the energy gap into 10 pieces, i.e., with 10 λ values).

IV. MEGA FOR POTENTIAL OF MEAN FORCE

The potential of mean force is typically defined as a free-energy function that depends on a few remaining degrees of freedom when all other degrees of freedom have been thermodynamically averaged out. For example, if a coordinate x is of interest and all the other coordinates are collectively denoted as $\mathbf{x}'$, then the potential of mean force $U(x_v)$ at a particular value x_v of x is given by

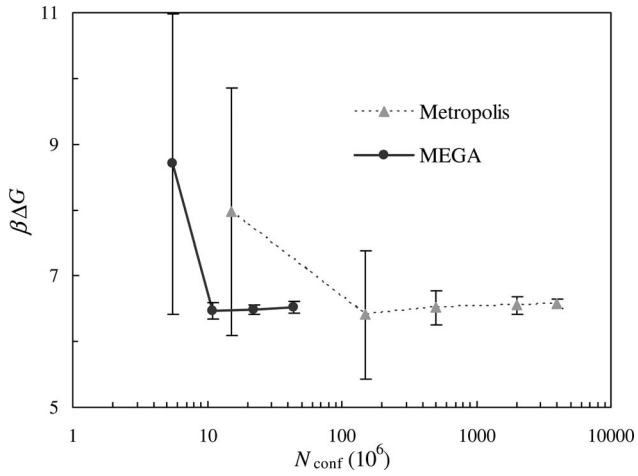

FIG. 2. Averages and standard deviations of the free-energy difference, calculated by MEGA and Metropolis simulations, for the two-dimensional system.

$$\exp[-\beta U(x_v)] = \frac{\int \exp[-\beta V_0(x_v,\mathbf{x}')]d\mathbf{x}'}{\int \exp[-\beta V_0(\mathbf{x})]d\mathbf{x}}. \tag{23a}$$

The integration over $\mathbf{x}'$ in the numerator is equivalent to an integration over $\mathbf{x}$ with a delta function $\delta(x-x_v)$ inserted,

$$\exp[-\beta U(x_v)] = \frac{\int \delta(x-x_v)\exp[-\beta V_0(\mathbf{x})]d\mathbf{x}}{\int \exp[-\beta V_0(\mathbf{x})]d\mathbf{x}} \tag{23b}$$

$$= \langle \delta(x-x_v)\rangle_0. \tag{23c}$$

In practical implementations, one counts the number of configurations with values of x falling within a small bin around x_v. The resulting histogram is equivalent to the probability density for x. Indeed the right-hand side of Eq. (23c) is the mathematical definition of this probability density for x [cf. Eq. (2)], thus

$$\exp[-\beta U(x)] = \rho_0(x). \tag{23d}$$

More generally the variable of interest may not be a single coordinate like x but a generalized coordinate, involving many degrees of freedom. Examples include the distance of a group of atoms from two end positions in a group-transfer reaction and the "distance" from two end conformations of a protein during a conformational transition. Let this function be $u(\mathbf{x})$. A general definition for the potential of mean force U is given by

$$\exp[-\beta U(u)] = \frac{\int \delta[u(\mathbf{x})-u]\exp[-\beta V_0(\mathbf{x})]d\mathbf{x}}{\int \exp[-\beta V_0(\mathbf{x})]d\mathbf{x}} \tag{24a}$$

$$= \rho_0(u), \tag{24b}$$

where u without an argument attached denotes a particular value of $u(\mathbf{x})$.

When $U(u)$ has a high energy barrier, its values there are difficult to determine because the chance of sampling them is very small in a canonical ensemble. Umbrella sampling is designed precisely to counter this problem.[4] One introduces a bias potential, typically of the harmonic type,

$$V_{\mathrm{um}}(u) = k(u - u_\lambda)^2, \tag{25}$$

where the target value u_λ is to be shifted successively. By inserting $\exp[\beta V_{\mathrm{um}}(u(\mathbf{x}))]\exp[-\beta V_{\mathrm{um}}(u(\mathbf{x}))]=1$ into the integrals in Eq. (24a) and denoting an average with the overall weight $\exp[-\beta V_{\mathrm{um}}(u(\mathbf{x}))]\exp[-\beta V_0(\mathbf{x})] \equiv W_{\mathrm{um}}(\mathbf{x})$ as $\langle \cdots \rangle_{\mathrm{um}}$, Eq. (24a) becomes

$$\exp[-\beta U(u)] = \langle \delta[u(\mathbf{x}) - u] \rangle_{\mathrm{um}} \frac{\exp[\beta V_{\mathrm{um}}(u)]}{\langle \exp[\beta V_{\mathrm{um}}(u(\mathbf{x}))] \rangle_{\mathrm{um}}} \tag{26a}$$

$$= \rho_{\mathrm{um}}(u) \frac{\exp[\beta V_{\mathrm{um}}(u)]}{\langle \exp[\beta V_{\mathrm{um}}(u(\mathbf{x}))] \rangle_{\mathrm{um}}}, \tag{26b}$$

where $\rho_{\mathrm{um}}(u)$ is the probability density of $u(\mathbf{x})$ calculated when $\mathbf{x}$ is distributed according to $W_{\mathrm{um}}(\mathbf{x})$. A popular implementation of umbrella sampling is the weighted histogram analysis method.[20]

MEGA provides an alternative method for calculating the potential of mean force. To see that, all one needs to do is to view $u(\mathbf{x})$ as an energy gap function. Once the probability density of this "energy gap" is obtained by a MEGA simulation, scaling via a relation analogous to Eq. (14) recovers $\rho_0(u)$, which then gives the potential of mean force via Eq. (24b). In addition, by including the umbrella-sampling bias factor $\exp[-\beta V_{\mathrm{um}}(u(\mathbf{x}))]$, MEGA can also be used to generate the umbrella-sampling probability density $\rho_{\mathrm{um}}(u)$. The introduction of MEGA will likely reduce the number of target values required in umbrella-sampling simulations. Extension of MEGA to calculate potentials of mean force for multiple variables is straightforward.

To illustrate the MEGA method for calculating potentials of mean force, consider the following potential function:

$$\exp[-\beta V_0(\mathbf{x})] = \exp(-\beta \mathbf{x}^2/2) + \exp[-\beta(\mathbf{x} - \mathbf{x}_0)^2/2], \tag{27}$$

where $\mathbf{x}_0$ is on the x-axis with coordinates $(x_0, 0, 0, \ldots, 0)$. The variable of interest is x. There is no coupling between x and any other degree of freedom, so the integration over the latter coordinates is straightforward and the potential of mean force is given by

$$\exp[-\beta U(x)] = \exp(-\beta x^2/2) + \exp[-\beta(x - x_0)^2/2]. \tag{28}$$

An energy barrier with a height of $(x_0^2/8 - \ln 2)k_BT$, relative to the energy minima at $x=0$ and $x=x_0$, is located at $x = x_0/2$.

In Fig. 3 results from a MEGA simulation and a Metropolis simulation for the potential of mean force with $x_0 = 12$ and $\beta=1$ are shown along with the exact result of Eq. (28). The details of the MEGA simulation are very similar to those reported for the one-dimensional system in Sec. III. In particular, the initial and intermediate β values are the same as before. At each β, the distribution for proposing a new x value is given by Eq. (28) with the appropriate β. The MEGA bias factor is obtained from binning x, the coordinate of interest here. The range of x from 0 to $x_0=12$ is represented by 120 bins. The MEGA simulation, with 75×10^6 configurations, reproduces the exact result well, even around the energy barrier (of $17.3k_BT$ in magnitude) at $x=x_0/2=6$. In contrast, in the Metropolis simulation at $\beta=1$ with the same number of configurations, the barrier region $5.5<x<6.5$ is poorly sampled and the barrier height cannot be determined.

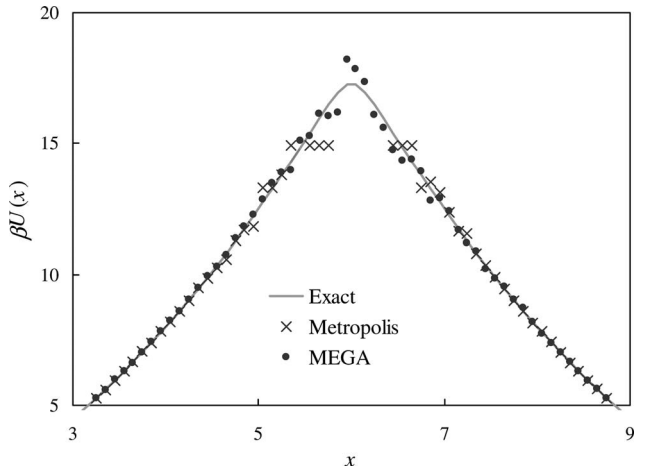

FIG. 3. Comparison of simulation and exact results for the potential of mean force in a system with potential function given by Eq. (27). The exact result (shown as solid curve) is given by Eq. (28). Results from Metropolis and MEGA simulations are given by crosses and circles, respectively.

To demonstrate the application of the MEGA method on real molecular systems, we implemented the method to calculate the potential of mean force in the torsion angle ϕ of n-butane. The potential function consists of contributions from bond stretching, angle bending, and bond rotation [Fig. 4(a)],

$$V_0(\mathbf{x}) = V_{b0}(\{b_i\}) + V_{a0}(\{\theta_i\}) + V_{t0}(\phi). \tag{29}$$

The first term is the sum of three harmonic functions, one for each of the three bonds; the second term is the sum of two harmonic functions, one for each of the two bond angles. The last term involving the torsion angle is given by[21]

$$V_{t0}(\phi) = K_1(1 + \cos\phi) + K_2(1 - \cos 2\phi) + K_3(1 + \cos 3\phi), \tag{30}$$

where the coefficients K_1, K_2, and K_3 have values of 3.044, −0.63, and 6.414 kcal/mol, respectively. This function is displayed in Fig. 4(b) as the curve labeled "exact." It has three minima, illustrating in a small way the rugged energy landscapes of complex molecules such as proteins. In the united-atom representation adopted here, n-butane has four atom centers, resulting in a total of 12 degrees of freedom. Other than the six degrees of freedom for overall translation and rotation, there are six internal degrees of freedom. These internal degrees of freedom can be specified by the three bond lengths, two bond angles, and the torsion angle. Because the potential function, given by Eq. (29), consists of additive terms in the six internal coordinates, these coordinates are effectively independent. As a result, $U(\phi)$, the potential of mean force in ϕ is identical to the energy function given by Eq. (30).

Our implementation of the MEGA method on n-butane used internal coordinates and took advantage of their inde-

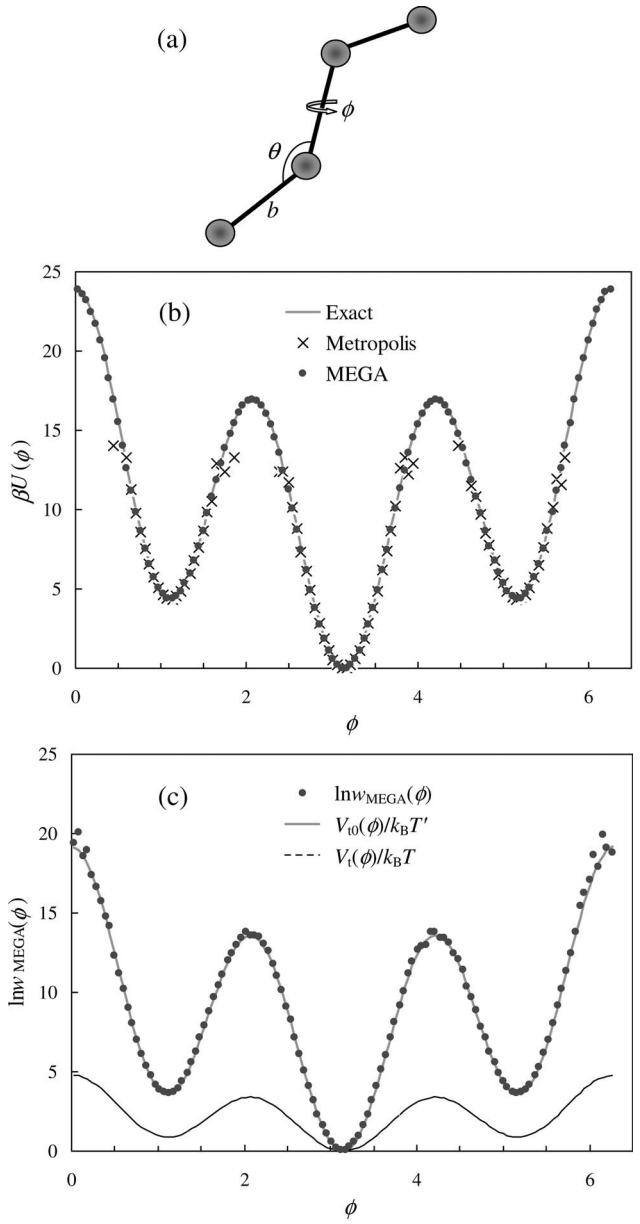

FIG. 4. Implementation of the MEGA method on *n*-butane. (a) A united-atom representation of *n*-butane. (b) Results for the potential of mean force in ϕ at $T=100$ K obtained from MEGA and Metropolis simulations, each totaling 7.5×10^6 configurations. For comparison, the exact result, given by Eq. (30), is also shown. The torsion angle ϕ is in radian. The MEGA simulation consists of 0.5×10^6 configurations each at the initial and four intermediate temperatures and 5×10^6 configurations at the final temperature. (c) Comparison of the MEGA bias factor, obtained from the simulation at the last intermediate temperature $T'=125$ K, against the expected result, $\exp[V_{t0}(\phi)/k_BT']$. The effective torsion potential, $V_t(\phi)$, upon applying the MEGA bias factor to the simulation at $T=100$ K, is also shown.

pendence. Effectively, to calculate $U(\phi)$ from simulations, we only need to be concerned with the sampling in ϕ. To demonstrate the power of the MEGA method, we obtained the potential of mean force at $T=100$ K, a temperature at which the highest energy barrier is $24k_BT$ from the global minimum at $\phi=\pi$ [see Fig. 4(b)]. The MEGA procedure started with a Metropolis run at $T_0=10\,000$ K. The inverse of the histogram of ϕ (with the full range of 0 to 2π divided into 120 bins) was taken as an initial estimate for the MEGA bias factor $w_{\mathrm{MEGA}}(\phi)$. Subsequently simulations were carried out at four intermediate temperatures of 1000, 500, 250, and 125 K,[22] and at the final temperature of 100 K. Each time the MEGA bias factor from the preceding temperature was applied and, at the end of the simulation, the bias factor was updated. For comparison, we also carried out an independent Metropolis simulation at $T=100$ K.

In Fig. 4(b) we compare the results for the potential of mean force in ϕ at $T=100$ K obtained from the MEGA and Metropolis simulations, each totaling 7.5×10^6 configurations, against the exact result of Eq. (30). The potential of mean force obtained from the MEGA simulation reproduces the exact result everywhere. In contrast, in the Metropolis simulation, the three barrier regions are not sampled, thereby precluding the determination of the barrier heights.

V. IMPLEMENTATION OF MEGA IN MD SIMULATIONS

An overall weight $W(\mathbf{x})=w_{\mathrm{MEGA}}[\Delta V(\mathbf{x})]\exp[-\beta V_0(\mathbf{x})]$ for free-energy calculations is equivalent to an effective potential energy function

$$V(\mathbf{x}) = -k_BT\ln[W(\mathbf{x})] = V_0(\mathbf{x}) - k_BT\ln\{w_{\mathrm{MEGA}}[\Delta V(\mathbf{x})]\}. \tag{31}$$

Therefore MEGA can also be implemented by MD simulations with the above potential energy. The second term gives rise to a bias force, which can be calculated as

$$\mathbf{F}_{\mathrm{MEGA}} = \frac{k_BT}{w_{\mathrm{MEGA}}[\Delta V(\mathbf{x})]}\frac{dw_{\mathrm{MEGA}}(\Delta V)}{d\Delta V}\frac{\partial\Delta V(\mathbf{x})}{\partial\mathbf{x}}. \tag{32}$$

The derivative $dw_{\mathrm{MEGA}}(\Delta V)/d\Delta V$ can be approximated either by a finite difference or by fitting $w_{\mathrm{MEGA}}(\Delta V)$ to an analytic function.

The iterative procedure for obtaining $w_{\mathrm{MEGA}}(\Delta V)$ can be implemented by MD simulations at different temperatures. It starts with a conventional MD simulation at a very high temperature T_0 (e.g., 10 000 K). The histogram of the energy gap from that simulation gives the MEGA bias factor $w_{\mathrm{MEGA}}(\Delta V;T_0)$ for the MD simulation at a lower temperature T_1. As noted already, the required derivative $dw_{\mathrm{MEGA}}(\Delta V;T_0)/d\Delta V$ can be obtained as a finite difference or from a fitted analytic function. This process is repeated at lower and lower temperatures until the desired temperature is reached. A similar procedure can be implemented for calculating potentials of mean force.

As a simple illustration, in Fig. 4(c) we display the MEGA bias factor $w_{\mathrm{MEGA}}(\phi)$ obtained after the MEGA simulation of *n*-butane at the last intermediate temperature, $T'=125$ K. The expected result for $\ln w_{\mathrm{MEGA}}(\phi)$ from the simulation at T' is $U(\phi)/k_BT'=V_{t0}(\phi)/k_BT'$. It can be seen that the simulation result for $\ln w_{\mathrm{MEGA}}(\phi)$ agrees well with $V_{t0}(\phi)/k_BT'$. Upon applying this bias factor, according to Eq. (31), the simulation at the final temperature $T=100$ K has an effective torsion potential of $V_t=V_{t0}(\phi)-k_BT[V_{t0}(\phi)/k_BT']\approx(1-T/T')V_{t0}(\phi)=0.2V_{t0}(\phi)$. With the MEGA procedure the barriers are therefore reduced to 20% of the original heights.

VI. CONCLUSIONS

We have presented a multi-energy gap method that is well suited for calculating free-energy differences and potentials of mean force. It can be used both as an alternative but also as a complement to existing techniques such as free-energy perturbation, thermodynamic integration, and umbrella sampling. Applications to model systems demonstrate that the method is able to significantly accelerate the convergence of calculated results and increase their accuracies. It is hoped that the results reported here will inspire further exploitation of the MEGA method.

ACKNOWLEDGMENTS

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