Rosenbluth-sampled nonequilibrium work method for calculation of free energies in molecular simulation

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We present methods that introduce concepts from Rosenbluth sampling [M. N. Rosenbluth and A. W. Rosenbluth, J. Chem. Phys. **23**, 356 (1955)] into the Jarzynski nonequilibrium work (NEW) free-energy calculation technique [C. Jarzynski, Phys. Rev. Lett. **78**, 2690 (1997)]. The proposed hybrid modifies the way steps are taken in the NEW process. With it, each step is selected from a range of alternatives, with bias given to steps that contribute the least work. The definition of the work average is modified to account for the bias. We introduce two variants of this method, λ-bias sampling and configuration-bias sampling, respectively; a combined λ- and configuration-bias method is also considered. By reducing the likelihood that large nonequilibrated work values enter the ensemble average, the Rosenbluth sampling aids in remedying problems of inaccuracy of the calculation. We demonstrate the performance of the proposed methods through a model system of *N* independent harmonic oscillators. This model captures the difficulties involved in calculating free energies in real systems while retaining many tractable features that are helpful to the study. We examine four variants of this model that differ qualitatively in the nature of their phase-space overlap. Results indicate that the λ-bias sampling method is most useful for systems with entropic sampling barriers, while the configuration-bias methods are best for systems with energetic sampling barriers. The Rosenbluth-sampling schemes yield much more accurate results than the unbiased nonequilibrium work method. Typically the accuracy can be improved by about an order of magnitude for a given amount of sampling; this improvement translates into two or more orders of magnitude less sampling required to obtain a given level of accuracy, owing to the generally slow convergence of the NEW calculation when the inaccuracy is large. © *2005 American Institute of Physics*. [DOI: 10.1063/1.1906209]

I. INTRODUCTION

Calculation of free-energy differences via nonequilibrium processes can be accomplished using the nonequilibrium work (NEW) relation due to Jarzynski.[1,2] Part of the power of this idea lies in the flexibility available in the definition of the nonequilibrium process. It can be a totally nonequilibrated process, whereby the system instantaneously changes from its initial state to the final state (from which the free-energy perturbation[3] identity is recovered); it can be a semiequilibrated process with a moderate rate of progress; or it can be a nearly equilibrated process, such that the system evolves at slow speed. The independence of the NEW method on the rate of the nonequilibrium process facilitates its implementation in experiments, and several demonstrations of this use have been described.[4]

A significant limitation of the NEW method is its tendency to yield results that are inaccurate, even when implemented in a way that is technically correct. The problem is exacerbated as the rate of the nonequilibrium process is increased, or in other words, as the process becomes more irreversible. This is easily understood mathematically, as at faster speed the system is more subject to larger work values which contribute little to the average because the work is Boltzmann weighted; rare contributions from small-work values are required to get accurate results, and in many situations these contributions might be never encountered. Previous studies[5–8] examined the inaccuracy for Gaussian and non-Gaussian distributed work values. For asymmetric work distributions, the inaccuracy depends greatly on the direction in which the nonequilibrium process is conducted. With one direction (which we label *insertion*) the result can be much more accurate than the other direction (*deletion*). The reason has been explained in previous work,[8,9] and relates to the way the important regions of phase space overlap for the systems of interest. Combining results from two directions is important to make the method effective in the general case, as suggested by Bennett,[10] Crooks[11] and others.[12] Such methods still take as input the results of single-direction NEW calculations, which is the focus of the present work.

A recent approach to improve the performance of NEW calculations is based on the notion of sampling of paths.[13,14] The idea is to write the Jarzynski formula in terms of path integrals, which thereby prescribes sampling of trajectories as well as configurations as part of the NEW averaging process. This step opens the door to importance sampling applied to the generation of paths, and can exploit path-sampling methods established previously in the context of other problems.[14,15] Importance sampling is conducted such

that the accumulated work along the preferred paths contribute significantly to the ensemble average. The studies show improved performance when using the path sampling of the nonequilibrium trajectories. In the present work we introduce a method that also involves sampling of trajectories as well as configurations for the NEW averaging process, and in this regard it may be considered in the path-sampling context. However, the biasing approach we use relates to both the path and configuration sampling, and is more naturally expressed in terms of the Rosenbluth-sampling ideas that inspired it.

The aim of the present work is to introduce a bias to the NEW calculation so that it gives better sampling of the important small-work contributions to the NEW average. We begin in the following section by reviewing the original NEW method as formulated by Jarzynski. In Sec. III we describe how ideas from Rosenbluth sampling[16] can be applied to the NEW calculation. We consider three general bias schemes, namely, λ-*bias sampling*, *configuration-bias sampling*, and *hybrid* λ- *and configuration-bias sampling* schemes. Each one has several variations, and we give a full explanation of these variations in Sec. III. Briefly, λ-bias sampling slows down the process (by decreasing the rate) if the system encounters large-work values. Configuration-bias sampling helps to avoid configurations that are unfavorable for the subsequent work process. *Hybrid-bias sampling* unites the advantages of both sampling schemes. In Sec. IV we introduce our test system (*N* independent harmonic oscillators), we present and discuss the results in Sec. V, and we conclude in Sec. VI.

II. NONEQUILIBRIUM WORK METHOD (NEW)

The nonequilibrium work relation was proposed by Jarzynski.[1,2] It relates a state quantity, the *free energy*, to a path quantity, the *work*, by the equation

$$\exp(-\beta\Delta F) = \overline{\exp(-\beta W)}, \tag{1}$$

where $\Delta F = F_B - F_A$ is the Helmholtz free-energy difference between two systems *A* and *B*, $\beta = 1/kT$ is the reciprocal temperature in energy units, and *W* is the work performed on the system through a path from *A* into *B*. The overbar indicates the average over measurements of *W* taken over paths initiated from an equilibrium distribution of *A*. This is a remarkable result, as it says the equilibrium quantity ΔF can be extracted by averaging the nonequilibrium quantity *W*. This nonequilibrium work value depends on details of the initial configuration when the work process starts, the rate of traversal of the path, as well as the definition of the path itself. Yet when averaged as in Eq. (1), this path-dependent quantity yields a path-independent average.

We define the path via a parameter λ, which takes values between 0 and 1. When $\lambda = 0$, it represents system *A*, and $\lambda = 1$ for system *B*. For a Monte Carlo (MC) evolution transitioning from system *A* to system *B*, λ successively takes a set of discrete values $\{\lambda_0 = 0, \lambda_1, \lambda_2, \ldots, \lambda_n = 1\}$ (the selection of the range [0,1] is merely a convention which does not affect the generality of the method). Monte Carlo or molecular dynamics methods are used to generate configurations $\mathbf{z}$, and at regular intervals during this process λ is switched from its current value λ_{i-1} to a new value λ_i, and the work accompanying this change is recorded. Jarzynski presented an elegant derivation of Eq. (1) for this case.[2] It begins by writing an expression for the ensemble-averaged work

$$\overline{\exp(-\beta W)} = \int dz_0 \frac{e^{-\beta H_{\lambda_0}(z_0)}}{Q_0} \prod_{i=1}^{n} \times \int dz_i P_{\lambda_i}(\mathbf{z}_{i-1}|\mathbf{z}_i) e^{-\beta W_{\mathbf{z}_{i-1}}(\lambda_{i-1}\to\lambda_i)}, \tag{2}$$

where Q_0 is the canonical partition function of system *A*, and H_λ is the Hamiltonian of the system when $\lambda = \lambda_i$; in particular $H_{\lambda=0} \equiv H_0 = H_A$, the Hamiltonian of system *A*, and $H_{\lambda=1} \equiv H_1 = H_B$, the Hamiltonian of system *B*. The total work is the sum of the work performed with each increment of λ,

$$W = \sum_{i=1}^{n} W_{\mathbf{z}_{i-1}}(\lambda_{i-1} \to \lambda_i) = \sum_{i=1}^{n} [H_{\lambda_i}(\mathbf{z}_{i-1}) - H_{\lambda_{i-1}}(\mathbf{z}_{i-1})], \tag{3}$$

which defines $W_{\mathbf{z}_{i-1}}(\lambda_{i-1} \to \lambda_i)$. In Eq. (2), $P_{\lambda_i}(\mathbf{z}_{i-1}|\mathbf{z}_i)$ is the Markov transition probability for evolving to configuration $\mathbf{z}_i$ from configuration $\mathbf{z}_{i-1}$ while the value of λ is λ_i. The ratio $e^{-\beta H_{\lambda_0}(\mathbf{z}_0)}/Q_0$ is the probability that configuration $\mathbf{z}_0$ is the current configuration at the start of the process. Stipulating that detailed balance is satisfied for the evolution of configurations, such that

$$P_{\lambda_i}(\mathbf{z}_{i-1}|\mathbf{z}_i) e^{-\beta H_{\lambda_i}(\mathbf{z}_{i-1})} = P_{\lambda_i}(\mathbf{z}_i|\mathbf{z}_{i-1}) e^{-\beta H_{\lambda_i}(\mathbf{z}_i)}, \tag{4}$$

Eq. (2) can be reduced through successive application of Eq. (4), leaving

$$\overline{\exp(-\beta W)} = \int d\mathbf{z} \frac{e^{-\beta H_1(\mathbf{z})}}{Q_0}, \tag{5}$$

which is a restatement of Eq. (1), but in terms of the partition functions of the *A* and *B* systems.

There are two limiting cases for this process: infinitely fast switching from *A* to *B* ($n = 1$) and infinitely slowly switching ($n \to \infty$). The former is the well-known free-energy perturbation method[3] $\exp(-\beta\Delta F) = \langle \exp(-\beta W) \rangle_A$. It is fast and convenient because there is no time needed for equilibration, however it suffers severely from inaccuracy if there is lack of overlap of the important configurations between the two systems. The other extreme corresponds to the reversible work process $\Delta F = W_{\text{rev}}$. It is accurate but at some point becomes inefficient as *n* becomes very large. Improvements to the NEW method would enable it to provide more accurate results for small *n*.

If not used at or close to the limit of a reversible process, NEW methods must be applied in what we have termed the insertion direction.[9] This means that the configurations important to the target or destination system (*B*) must be a wholly contained subset of the configurations important to the reference or initiation system (*A*), and this relation must be satisfied for each successive pair of points $(\lambda_{i-1}, \lambda_i)$ along

the path. If this is not the case, the numerical calculation will omit contributions from very large-work values that have a correspondingly small probability of being sampled. The resulting average will be inaccurate for any achievable amount of work sampling. Properly conducted insertion calculations are also prone to inaccuracy, but to a much smaller extent. The nature of the inaccuracy in insertion calculations is such that most contributions to the average are practically zero, with a few (perhaps very few) less commonly encountered contributions of moderate size. Inadequate sampling of these moderate contributions produces the inaccuracy. Our aim in the present work is to provide a method that can improve the efficiency of insertion-type NEW calculations.

III. ROSENBLUTH-SAMPLED NEW

Rosenbluth-sampling methods originated in applications to lattice models of polymers, where they have been used as a means to generate configurations of large-molecule systems.[16] The idea of the Rosenbluth method is to sample an unusual event (e.g., randomized insertion of a long chain molecule into a dense phase without overlap) by breaking it up into many smaller events (e.g., insertion of a segment at the end of a partial chain), repeating each of the smaller events many times, and assembling the larger event from the more favorable samples of the smaller ones.

In the present context the larger event is the traversal of the path $A \to B$, and the smaller events are the increments in λ. To get a moderate value of the work for this traversal, it is necessary that every work increment [cf. Eq. (3)] be of moderate size. If a large contribution to the work is encountered at any step, it is very unlikely that a correspondingly large-and-negative contribution will be subsequently encountered to offset it. By applying Rosenbluth sampling to each increment, we can improve the likelihood that a moderate work value will result at the end of the traversal. To this end we can apply either or both of the two kinds of bias sampling schemes, λ-bias sampling and configuration-bias sampling.

A. λ-bias sampling

The standard MC NEW method uses a prespecified set of λ values, typically chosen to be equally spaced along the path from *A* to *B*. An increment of work is contributed with every step in λ. The configuration present before λ is incremented is at least partially equilibrated to the current value λ_{i-1}, inasmuch as some configurations were generated for it under the influence of $H_{\lambda_{i-1}}$. However, the configuration may or may not be suited to the next λ in the schedule, and the work increment $H_{\lambda_i} - H_{\lambda_{i-1}}$ may therefore be very large. Regardless, the prespecified step in λ is taken at the prefixed point in the process, with the possible result of a large-work value for this step, which will promote inaccuracy in the calculation. The aim of introducing Rosenbluth sampling is to permit λ to select a value that is not inappropriate to the current configuration. We choose λ from a set of values weighted by the Hamiltonian, and because the Hamiltonian depends on λ in a simple way, we can select λ from a continuum. The selection might be taken from its full spectrum, [0, 1], but this choice is likely to be counterproductive in that it permits λ to regress. Instead we require that λ ratchet upwards toward unity, and we select $\lambda_i \in [\lambda_{i-1}, a_i]$, where a_i is a prespecified set of constants, such that

$$0 < a_1 \leqslant a_2 \cdots \leqslant a_{n-1} = 1, \tag{6}$$

which admits the possibility that $a_i = 1$ for all *i*. We weight the selection of λ according to the current configuration, choosing λ with probability density

$$P_{\mathbf{z}_{i-1}}(\lambda_i) = \frac{1}{R_i(\mathbf{z}_{i-1};\lambda_{i-1})} p_i(\lambda_i) e^{-\beta\alpha H_{\lambda_i}(\mathbf{z}_{i-1})}, \tag{7}$$

where $R_i(\mathbf{z}_{i-1};\lambda_{i-1})$ is the Rosenbluth weight, which ensures a normalized probability:

$$R_i(\mathbf{z}_{i-1};\lambda_{i-1}) = \int_{\lambda_{i-1}}^{a_i} p_i(\lambda) e^{-\beta\alpha H_\lambda(\mathbf{z}_{i-1})} d\lambda. \tag{8}$$

Here we have included two parameters that can be used to adjust the procedure. First, we attenuate the influence of the Hamiltonian on the weight using a predefined constant α. Second, we include an additional weighting function $p_i(\lambda)$; we leave open the possibility that these weights might be defined differently for each step (and thus depend on *i*), but we do require that they be prespecified and not depend on the configuration $\mathbf{z}$. We note also that we have not as yet specified the dependence of the Hamiltonian on λ (other than it correspond to the *A* and *B* systems for $\lambda = 0$ and 1, respectively). Finally, at the very last step in λ we want to ensure that we end up at the *B* system, so we do not select this value at random, but instead require $\lambda_n = 1$.

Of course we must modify the definition of the work so that repeated traversals yield an average that relates to the free energy. The appropriate "work" to contribute at each step is

$$\beta W_{\mathbf{z}_{i-1}}(\lambda_{i-1} \to \lambda_i) = \begin{cases} \beta(1-\alpha)H_{\lambda_i}(\mathbf{z}_{i-1}) - \beta H_{\lambda_{i-1}}(\mathbf{z}_{i-1}) - \ln[R_i(\mathbf{z}_{i-1};\lambda_{i-1})/I_i(\lambda_{i-1})] & 1 \leqslant i < n \\ \beta H_{\lambda_n}(\mathbf{z}_{n-1}) - \beta H_{\lambda_{n-1}}(\mathbf{z}_{n-1}) & i = n \end{cases}, \tag{9}$$

where we introduce $I_i(\lambda_{i-1}) = \int_{\lambda_{i-1}}^{a_i} d\lambda p_i(\lambda)$ to account for the ideal-gas normalization for switching λ from λ_{i-1} to λ_i (note that R_i/I_i is unity for an ideal gas, $H \equiv 0$). One could instead take $I_i \equiv 1$ and treat the ideal-gas normalization by multiplying the work average by a constant, but we have found that this approach does not work as well as using the I_i shown here.

To show that this definition is consistent with Eq. (1), we extend Jarzynski's derivation to this procedure in which the λ values are selected from a distribution. Formally, the work average for a NEW procedure that samples λ as described above is

$$\overline{\exp(-\beta W)} = \int d\mathbf{z}_0 \frac{e^{-\beta H_{\lambda_0}(\mathbf{z}_0)}}{Q_0} \prod_{i=1}^{n-1} \int_{\lambda_{i-1}}^{a_i} d\lambda_i \int d\mathbf{z}_i P_{\mathbf{z}_{i-1}}(\lambda_i) P_{\lambda_i}(\mathbf{z}_{i-1}|\mathbf{z}_i) e^{-\beta W_{\mathbf{z}_{i-1}}(\lambda_{i-1}\to\lambda_i)} \times \int d\mathbf{z}_n P_{\lambda_n}(\mathbf{z}_{n-1}|\mathbf{z}_n) e^{-\beta W_{\mathbf{z}_{n-1}}(\lambda_{n-1}\to\lambda_n)}. \tag{10}$$

Substitution of the terms defined by Eqs. (7) and (9) can be followed by a procedure similar to that leading to Eq. (5), and shows that the average on the right side of Eq. (10) is equal to the ratio of partition functions as in Eq. (5).

The development given above leaves open many choices for implementation of the method. In the following we will consider these choices and describe the various combinations we have chosen to study.

1. Dependence of Hamiltonian on λ

A popular way to define a work path is to select the intermediate Hamiltonian as a linear combination of the reference and target Hamiltonians[17]

$$H_\lambda(\mathbf{z}) = H_A(\mathbf{z}) + \lambda[H_B(\mathbf{z}) - H_A(\mathbf{z})]. \tag{11}$$

This is the definition we consider in the present work. We note that another choice has been shown to have some advantages when applied to systems that do not have good overlap of their phase spaces

$$H_\lambda(\mathbf{z}) = H_A(\mathbf{z}) + kT \ln((1-\lambda) + \lambda \exp\{+\beta[H_B(\mathbf{z}) - H_A(\mathbf{z})]\}). \tag{12}$$

This form is related to Bennett's method.[10] In previous work[12] we showed how it can be used to combine work calculations performed in both directions, $A\to B$ and $B\to A$. We have not examined this choice in the present study.

2. Parameters for λ-bias sampling

The remaining parameters to define for implementing the method are α, $\{a_i\}$ and $p_i(\lambda)$. We consider here issues regarding their selection.

Selection of α. In some situations it is very inefficient to use the full Hamiltonian in the probability density for choosing λ. The Hamiltonian is an extensive property, and when the number of particles N in the system is large the total Hamiltonian of the system can be very large. Thus using it as the weight for choosing λ will prohibit λ from ratcheting upwards sufficiently quickly. Therefore we multiply the Hamiltonian by a predefined constant α (less than 1) to reduce this effect. Among the cases we have studied (see Sec. V), we found that a reasonable selection for this parameter is $\alpha = 1/N_\lambda$, where N_λ is the number of particles involved in the difference between the A and B systems.

Selection of $\{a_i\}$. The most straightforward selection of the set of parameters a_i is to have them all equal to unity. Then with each step in λ a new value is selected over a range spanning its current value to 1. If the Hamiltonian offers no resistance to an increase in λ [meaning that $H_B(\mathbf{z}) - H_A(\mathbf{z})$ is negative, or positive and not large] then λ may jump early in the process to a value close to unity. If not for the term I_i in Eq. (9), this situation would be detrimental to the calculation, because in subsequent steps the Rosenbluth factor would be small, and the contribution to the work would not be close to zero in those steps. Interestingly, for this reason the method would yield inaccurate results for a trivial ideal-gas system if the I_i terms were instead considered only at the end of the process. This situation led us to consider different choices for a_i, and in particular we examined

$$a_i = i/(n-1), \tag{13}$$

which has them evenly spaced throughout the range from 0 to 1. This choice prevents λ from jumping too rapidly to unity, inasmuch as it is guaranteed that each time λ_i is chosen in the range $[\lambda_{i-1}, a_i]$ it cannot exceed its upper-bound value $i/(n-1)$. Given that we do include I_i in Eq. (9), the original motivation for introducing the nonunity a_i is eliminated, but we have found nevertheless that the method works better with a_i evenly distributed as in Eq. (13). In such a way, the switching process is conducted in a controlled rate. Since it requires no extra effort for implementation, it becomes our first choice for λ-bias sampling.

Selection of $\mathbf{p_i(\lambda)}$. The simplest choice for $p_i(\lambda)$ is $p_i(\lambda) \equiv 1$, meaning that no weight other than that involving $H_\lambda(\mathbf{z})$ is applied to the selection of λ. This is the choice that we use in all the results we present here. Several other choices are of interest. We considered for example $p_i(\lambda) = (1-\lambda)^{n-i-1}$, which has the property of yielding an identically correct result for the ideal gas when all $a_i = 1$ and I_i is not used as in Eq. (9). We examined this choice, but found that it provided results no better than otherwise equivalent methods, so we do not present results for it here.

Also of interest is a choice of the form

$$p_i(\lambda) = p_{i0}\delta(\lambda - \lambda_{i0}) + p_{i1}, \tag{14}$$

where δ is the Dirac delta function. This has the effect of giving a discrete weight to a specific value of λ at each step, with the amount of the weight dictated by the parameters p_{i0} and p_{i1}. Selection of $p_{i1} = 0$ for all i reduces the method to the original Jarzynski form. Another potentially useful choice would have λ_{i0} equal to the current value of λ, so that the

TABLE I. Summary of parameters used for Rosenbluth-sampling methods. Parameter $\alpha=1/N_\lambda$ for all the sampling methods (except method *d*, where it does not apply). Parameter $p_i(\lambda)=1$ for all the λ-bias and hybrid-bias sampling methods. Except where otherwise stated in the text, the number of Rosenbluth-sampled configurations $m=10$ and the number of λ steps in a traversal $n=10$ for all the methods.

Methods	Sampling schemes	$\{a_i\}$	$f\,[H_{\lambda_i}(\mathbf{z}_{i-1})]$
a	λ-bias sampling	1	
b	λ-bias sampling	$i/(n-1)$	
c	Configuration-bias sampling		$\alpha H_{\lambda_i}(\mathbf{z}_{i-1})$
d	Configuration-bias sampling		$H_{\lambda_i}(\mathbf{z}_{i-1})-H_{\lambda_{i-1}}(\mathbf{z}_{i-1})$
a-c	Hybrid-bias sampling	1	$\alpha H_{\lambda_i}(\mathbf{z}_{i-1})$
b-c	Hybrid-bias sampling	$i/(n-1)$	$\alpha H_{\lambda_i}(\mathbf{z}_{i-1})$

system always has some finite probability to not change λ at all (and incurring no work penalty), more so if the Hamiltonian difference is large at the present configuration. A drawback of allowing this is that indeed λ might never change at all, until forced to at the end.

The combinations of parameters that we have employed in this study are summarized in Table I.

B. Configuration-bias sampling

The idea of Rosenbluth sampling can also be extended into the configuration space. Unlike λ-bias sampling, one cannot generate configurations by direct sampling from a distribution. Instead we select configurations from a discrete set, as is done in the original Rosenbluth-sampling method. Rosenbluth sampling of configurations can be applied by itself, or in conjunction with Rosenbluth sampling of λ. In the former case, we keep the prefixed values of λ_i at each step. At each value of λ, we permit the system to evolve [via molecular dynamics (MD) or MC] through a range of configurations based on the Hamiltonian evaluated using the current value λ_{i-1}. We save a subset of all the configurations generated, and after some period we choose one of these configurations, biasing the choice toward that which is most adaptive to the *next* value in the schedule (λ_i). By doing this, the configuration selected is more likely to contribute to the average, and the traversal is more likely to go toward the target system's important phase space.

More specifically, we generate a set of *m* configurations $\{\mathbf{z}_{i-1}\}$ by MC or MD sampling using the Hamiltonian based on λ_{i-1}. From this set we choose a configuration $\mathbf{z}_{i-1}$ according to the Hamiltonian based on λ_i, thus

$$P_{\lambda_i}(\mathbf{z}_{i-1})=\frac{1}{R_i(\lambda_i)}e^{-\beta f[H_{\lambda_i}(\mathbf{z}_{i-1})]}, \tag{15}$$

where *f* is a function of the Hamiltonian (discussed below), and we define the normalizing Rosenbluth factor

$$R_i(\lambda_i)=\sum_{j=1}^{m} e^{-\beta f[H_{\lambda_i}(\mathbf{z}_{i-1,j})]}. \tag{16}$$

Correspondingly, we modify the definition of work to account for this biased sampling,

$$\beta W_{\mathbf{z}_{i-1}}(\lambda_{i-1}\to\lambda_i)=\beta H_{\lambda_i}(\mathbf{z}_{i-1})-\beta H_{\lambda_{i-1}}(\mathbf{z}_{i-1}) - \beta f[H_{\lambda_i}(\mathbf{z}_{i-1})]-\ln[R_i(\lambda_i)/m]. \tag{17}$$

The ensemble-average formula is modified accordingly

$$\overline{\exp(-\beta W)}=\int d\mathbf{z}_0\frac{e^{-\beta H_{\lambda_0}(\mathbf{z}_0)}}{Q_0}\prod_{i=1}^{n} \times\int d\mathbf{z}_i P_{\lambda_i}(\mathbf{z}_{i-1})P_{\lambda_i}(\mathbf{z}_{i-1}|\mathbf{z}_i)e^{-\beta W_{\mathbf{z}_{i-1}}(\lambda_{i-1}\to\lambda_i)}, \tag{18}$$

which can be reduced as above to a free-energy identity for the *A* and *B* systems.

1. Parameters for configuration-bias sampling

Configuration-bias sampling has a parameter *m* and one function $f[H_{\lambda_i}(\mathbf{z}_{i-1})]$ to be specified. Now we consider the choices of these two parameters. Combinations of the parameters are shown in Table I.

Selection of *m*. The parameter *m* determines how many configurations we collect for the discrete configuration set. A large value of *m* is more likely to produce configurations that are favorable to the calculation, but of course as *m* is increased more sampling is required to generate reasonably independent configurations. One approach might involve the introduction of another biasing method to generate independent configurations (such as original Rosenbluth sampling), from which sampling may be performed for the NEW calculation.

Selection of $f[H_{\lambda_i}(\mathbf{z}_{i-1})]$. We consider two choices of the function *f*.

(1) $f[H_{\lambda_i}(\mathbf{z}_{i-1})]=\alpha H_{\lambda_i}(\mathbf{z}_{i-1})$: This is the form considered above for λ-bias sampling. Again we choose $\alpha=1/N_\lambda$. Using this form, the probability density of choosing configuration roughly has a Boltzmann distribution. So the configuration to be selected is most adaptive to $H_{\lambda i}$, which is influenced by the value of λ_i.

(2) $f[H_{\lambda_i}(\mathbf{z}_{i-1})]=H_{\lambda_i}(\mathbf{z}_{i-1})-H_{\lambda_{i-1}}(\mathbf{z}_{i-1})$: In addition to the consideration of the dependence on λ_i, we now also take account of the current Hamiltonian $H_{\lambda_{i-1}}(\mathbf{z}_{i-1})$ in this form. Since the difference in Hamiltonians is part of the average, this form simply states that the configuration to be selected will make relatively large contributions to the average. With this choice, the only term remaining in the work as given in Eq. (17) is that involving the Rosenbluth factor.

C. Hybrid λ-bias and configuration-bias sampling

The success of λ-bias sampling lies in the flexibility of choosing λ that is most adaptive to the current configuration. Its progress requires that the system has sampled configurations that have some relevance to the target (*B*) system. If not, λ does not advance and, moreover, the contribution to the work from the attempt will be large. Thus the process may encounter fairly slow traversals when there is less overlap region between the two systems' important phase space. If *n* is not sufficiently large, λ values are far from being unity

even towards the end of the traversals. The last, forced, step to $\lambda=1$ is then accompanied by a large contribution to the work. So λ-bias sampling is not suitable for systems having little or no overlap in phase space. This situation can be alleviated to some degree by configuration-bias sampling, where λ values have already been preset. However, the problem for configuration-bias sampling is it may still be vulnerable to large-work values for the first few steps.

We can combine the two bias sampling schemes to take the advantages of both and minimize their disadvantages. First, we generate several configurations and choose one that is favored by the weight of the next potential λ value. Then we choose the next λ from a continuous distribution that is adaptive to the current configuration. We use the same notations as for λ- and configuration-bias samplings, but we include a new probability density for selecting the first $n-1$ configurations

$$P'_{\lambda_{i-1}}(\mathbf{z}_{i-1}) = \frac{R_i(\mathbf{z}_{i-1};\lambda_{i-1})}{R'_i(\lambda_{i-1})}, \tag{19}$$

where $R_i(\mathbf{z}_{i-1};\lambda_{i-1})=\int_{\lambda_{i-1}}^{a_i} p_i(\lambda) e^{-\beta\alpha H_\lambda(\mathbf{z}_{i-1})} d\lambda$ is the Rosenbluth factor for λ-bias sampling and correspondingly, the new Rosenbluth factor for hybrid-bias sampling becomes

$$R'_i(\lambda_{i-1}) = \sum_{j=1}^{m} R_i(\mathbf{z}_{i-1,j};\lambda_{i-1}). \tag{20}$$

Again we modify the work to account for this biased sampling,

$$\beta W_{\mathbf{z}_{i-1}}(\lambda_{i-1}\to\lambda_i) = \begin{cases} \beta(1-\alpha)H_{\lambda_i}(\mathbf{z}_{i-1}) - \beta H_{\lambda_{i-1}}(\mathbf{z}_{i-1}) - \ln\{R'_i(\lambda_{i-1})/[mI_i(\lambda_{i-1})]\} & 1 \leqslant i < n \\ \beta H_{\lambda_n}(\mathbf{z}_{n-1}) - \beta H_{\lambda_{n-1}}(\mathbf{z}_{n-1}) - \beta f[H_{\lambda_n}(\mathbf{z}_{n-1})] - \ln[R_n(\lambda_n)/m] & i = n \end{cases}. \tag{21}$$

And finally the work average becomes

$$\overline{\exp(-\beta W)} = \int d\mathbf{z}_0 \frac{e^{-\beta H_{\lambda_0}(\mathbf{z}_0)}}{Q_0} \prod_{i=1}^{n-1} \int_{\lambda_{i-1}}^{a_i} d\lambda_i \int d\mathbf{z}_i P'_{\lambda_{i-1}}(\mathbf{z}_{i-1}) P_{\mathbf{z}_{i-1}}(\lambda_i) P_{\lambda_i}(\mathbf{z}_{i-1}|\mathbf{z}_i) e^{-\beta W_{\mathbf{z}_{i-1}}(\lambda_{i-1}\to\lambda_i)}$$
$$\times \int d\mathbf{z}_n P_{\lambda_n}(\mathbf{z}_{n-1}) P_{\lambda_n}(\mathbf{z}_{n-1}|\mathbf{z}_n) e^{-\beta W_{\mathbf{z}_{n-1}}(\lambda_{n-1}\to\lambda_n)}. \tag{22}$$

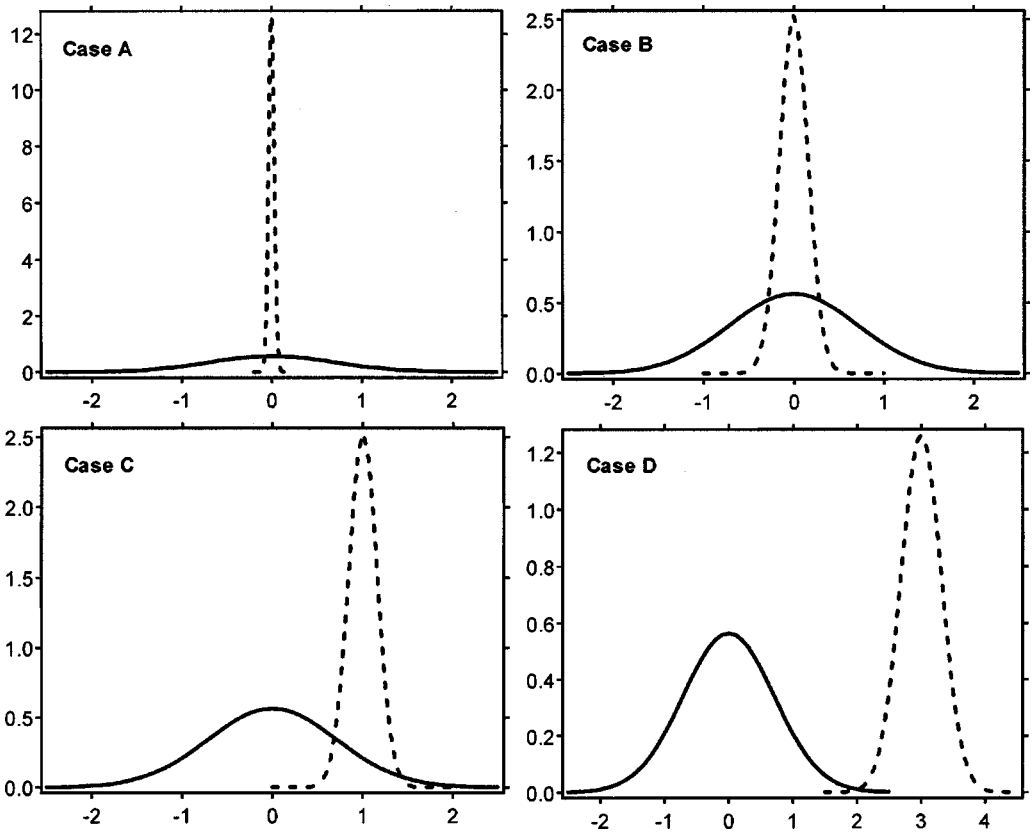

FIG. 1. One-particle phase-space distributions for cases A through D, as defined in Table II. Abscissa is the dimensionless coordinate of the particle, and distributions are normalized to unity. Solid lines are phase-space distributions for system *A* and the dashed lines are for system *B*.

Since the hybrid-bias sampling scheme mainly uses the parameters of λ-bias sampling, it also has variations of method *a* and method *b* as defined for λ-bias sampling. As described below, we find that the parameter α is important to the effectiveness of the λ-bias method. Thus we consider only the hybrids that employ the α-dependent Hamiltonian, namely, the method-*a* and method-*b* λ-bias methods with the method-*c* configuration-bias sampling. We label the two hybrid-bias sampling schemes as method $a-c$ and method $b-c$. The parameters used for these two methods are listed in Table I.

IV. TEST SYSTEM

To demonstrate and test this development, we apply the Jarzynski NEW method and Rosenbluth-sampled NEW methods to a model system of N independent harmonic oscillators. We define two systems A and B both having N particles but with different Hamiltonians,

$$H_A = \sum_{i=1}^{N} \omega_A x_i^2, \qquad H_B = \sum_{i=1}^{N} \omega_B (x_i - x_0)^2, \tag{23}$$

where x_i is a dimensionless coordinate for particle i. Four parameters describe this system: ω_A, ω_B, x_0, and N. The parameters ω_A and ω_B determine the available region in phase space that each independent particle can move. Increasing them will narrow their phase space, thus decreasing the overlap between the systems. Increasing x_0 tends to separate the two systems' important phase space, and make the pair approach the nonoverlap case. Different combinations of values of these parameters can change the degree of overlap of the two systems. By proper adjustment of the parameters, the model can capture the qualitatively different effects that complicate free-energy calculations. In particular, both entropic and energetic effects are included in a meaningful way. Energetic barriers can be introduced by displacing the B system from the A system in phase space, via the parameter x_0. Regardless of this relation, movement from A to B requires the cooperation of several degrees of freedom to progress without incurring large-work values—the requirement for this cooperation introduces an entropic barrier to the calculation, and it is increased to the extent that $x_0 \neq 0$ and, independently, $\omega_B > \omega_A$. We believe that the distinct entropic versus energetic effects included with this model give it advantages over comparably simple models, such as a double-well Landau free energy in λ. Such models are incapable of distinguishing the different phase-space overlap relations that are so important to the performance of free-energy calculation methods. Our results in the following section show that these distinctions are important determinants of the effectiveness of the proposed method.

The simplicity of the independent harmonic oscillator model permits most of its properties to remain analytically tractable. The free-energy difference is $\Delta F = \frac{1}{2} NkT \ln(\omega_B/\omega_A)$. Analytic solutions of the single-step work distributions and a detailed analysis of the performance of the free-energy perturbation applied to them can be found in Ref. 7. In terms of a nonequilibrium process, we use Eq. (11) for the definition of the Hamiltonian H_λ, so the particles remain independent over the full range of λ. For each particle the phase-space density at any λ is

$$p(x_i) = \frac{1}{\alpha\sqrt{2\pi}} e^{-[(x_i-\mu)^2/2\sigma^2]} \tag{24}$$

with mean value equal to $\mu = \lambda\omega_B x_0/[(1-\lambda)\omega_A + \lambda\omega_B]$ and variance $\sigma = \sqrt{1/\{2\beta[(1-\lambda)\omega_A + \lambda\omega_B]\}}$. This is a Gaussian distribution for all λ, which means that equilibrated configurations can be generated from scratch at each step during the nonequilibrium process. This greatly facilitates the computation while guaranteeing equilibration at each step. Nevertheless, the overall process is still nonequilibrium: discrete steps are taken in λ, and each brings the system into a nonequilibrated configuration. By generating equilibrated configurations at each λ we can control effects due to lag of the system with the advance of λ. We can consider separately the effect of this lag by not exploiting the Gaussian features of the configuration distribution, and instead generating configurations via a standard Markov Monte Carlo process.

TABLE II. Summary of parameter sets for four model-system pairs used for all the results.

Case	N	ω_B/ω_A	x_0	$\beta\Delta F$
A	10	500	0	31.07
B	10	20	0	14.98
C	10	20	1	14.98
D	10	5	3	8.05

One way of assessing the degree of overlap is by studying the systems' phase-space distributions. However this N-particle system has N degrees of freedom, and such a space cannot be visualized. But for this model the N particles are not interacting with one another, therefore we can understand the N-particle phase-space distribution by examining that of a one-particle system. Thus we use one-particle phase-space distributions for guidance in selecting systems having different degrees of phase-space overlap. We have chosen four cases to study, their parameters are given in Table II. The corresponding one-particle phase-space distributions for the four cases are plotted in Fig. 1. For case A and case B, the important phase space of system B forms a wholly contained subset of that of system A, which makes it suitable for a one-way insertion-type free-energy calculation ($A \rightarrow B$). However for case A, ω_B is large, so that the B important phase space is much narrower than that of A. When sampling system A, it is still difficult to explore B phase space, which tends to make the free-energy calculations inaccurate; this is a purely entropic barrier. For case C and case D, the degree of nonoverlap increases. There is only partial overlap between the two systems' important phase space for case C and no overlap for case D. Therefore, we

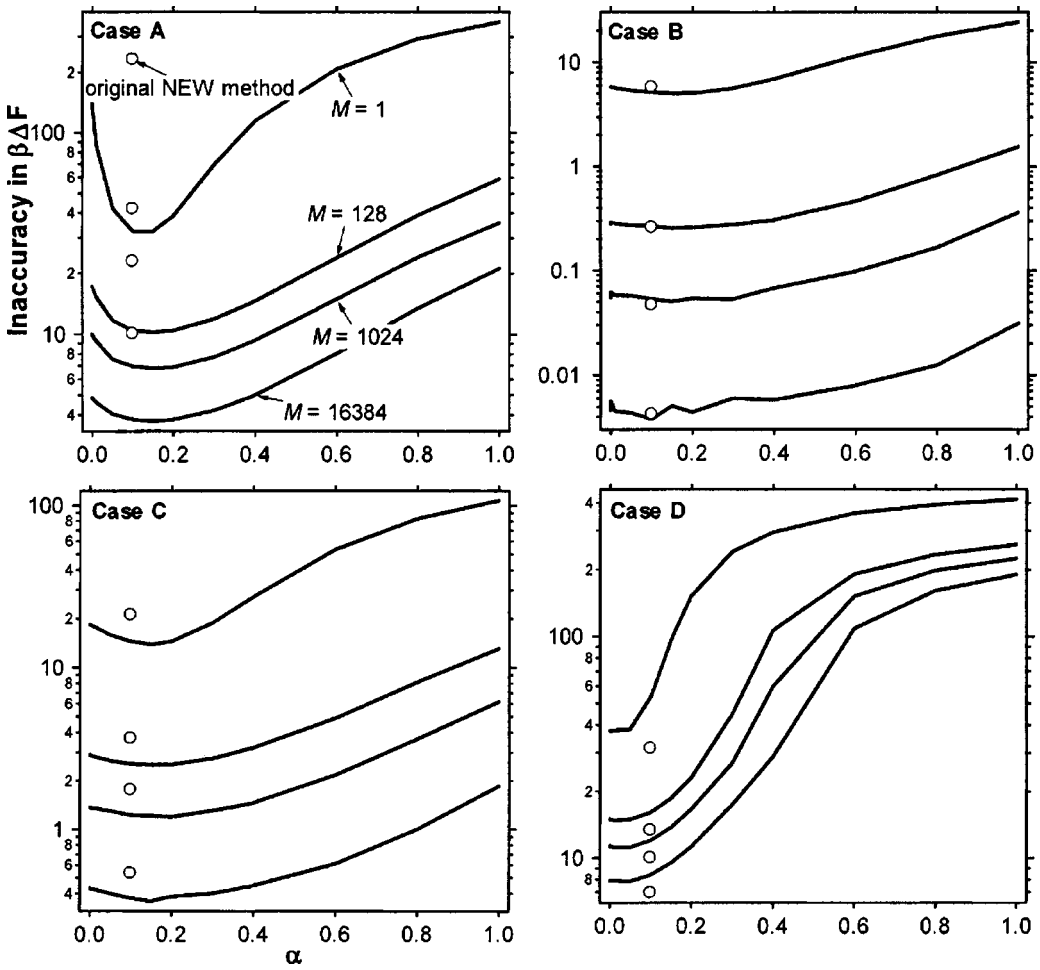

FIG. 2. Average inaccuracy of the free energy when calculated using Rosenbluth-NEW method, as a function of the parameter α for λ-bias sampling (method *b* of Table I). Four curves for each case describe results for different values of M (number of trajectories sampled for one free-energy measurement). Four circles in each plot are the corresponding results using the original NEW method for the corresponding M values. From the top to the bottom, $M=1$, 128, 1024, and 16 384. All plots use $n=10$ λ-values for each NEW trajectory from system A to system B.

anticipate the difficulties of calculating free energies increase correspondingly. We do not expect that any one-way (traversing only $A\rightarrow B$ and not considering information from $B\rightarrow A$) nonequilibrium method will produce accurate results for these cases.

V. RESULTS AND DISCUSSION

In this section, we calculate free energies and compare various Rosenbluth-sampled NEW and the original Jarzynski NEW methods for the four cases discussed above. Since for our model system there are two ways of generating configurations during a nonequilibrium process, we categorize the computations into two parts, equilibrated-move and nonequilibrated-move free-energy calculations. In the first part, we generate equilibrated configurations directly using Eq. (24). This is the very efficient and convenient way of doing the calculations, and we make comprehensive comparisons of Rosenbluth-sampling schemes with their different parameter settings in this part. In the second part, we use conventional Monte Carlo moves to generate configurations. We choose to use only the more effective Rosenbluth-sampling schemes for comparisons so as to give the general idea of their applicability for each case.

The results we report here involve two types of repetitions of the NEW calculation. First, as the NEW calculation is formulated, the standard procedure is to repeat a NEW traversal some number of times, M. Each traversal yields a work value W, and the result of the NEW calculation is the average of these work values taken as $\overline{\exp(-\beta W)}$. To characterize the inaccuracy, we performed additional "outer" repetitions, gathering independent NEW averages and evaluating the free-energy difference from $\beta\Delta F=-\ln[\overline{\exp(-\beta W)}]$. The average of ΔF over all these outer repetitions can be compared to the exact ΔF, and the difference is the average inaccuracy (systematic error) of the calculation. This inaccuracy should decrease with increasing M, but it should not be affected by the number of outer repetitions used in determining the average ΔF (these repetitions serve only to give a more precise value of the inaccuracy). We report results for the systematic error, considering different implementations of the Rosenbluth NEW method. All the results are averages of 10 000 outer repetitions.

A. Equilibrated-move free-energy calculations

In this part equilibrated configurations were directly generated [Eq. (24)] for the given λ_i value at each step. This is

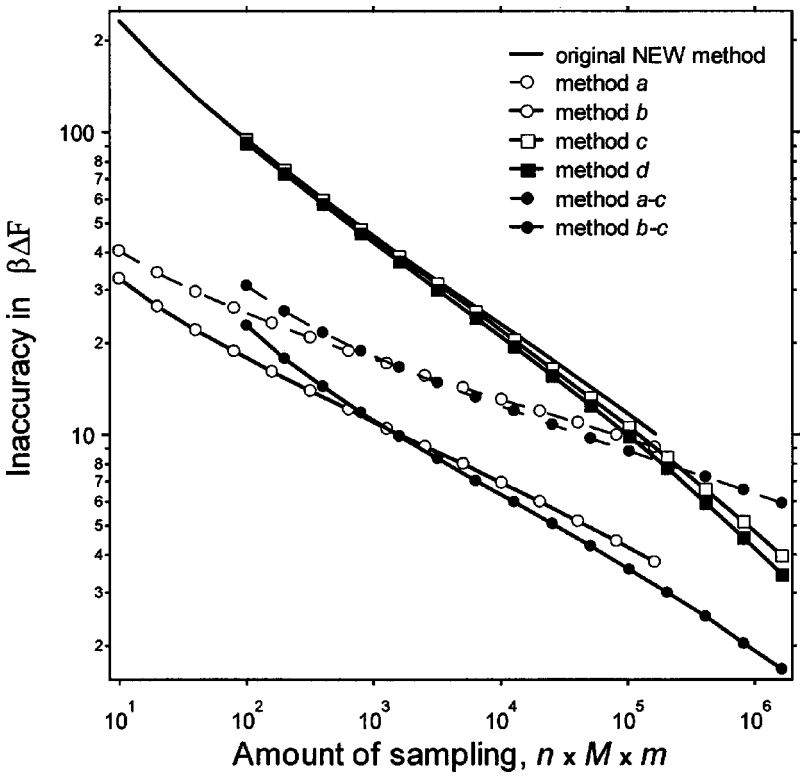

FIG. 3. Average inaccuracy of the free energy as a function of the amount of sampling for various Rosenbluth-NEW methods and the original NEW method. All curves are for case A and $n=10$. Configuration-and hybrid-bias samplings (methods *c*, *d*, *a*-*c*, and *b*-*c*) use $m=10$.

equivalent to using many MC moves at each step to equilibrate the system well before moving on to the next λ value. Therefore the only rate-determining parameter is *n*, the number of steps taken in λ. Increasing *n* allows the process to proceed more reversibly, and will yield much more accurate results. But the aim of Rosenbluth sampling is to obtain relatively accurate results with rapid traversals, thus we choose $n=10$ for most of the comparisons. We also give some comparisons using different *n* values.

First let us look at the dependence of the accuracy on the parameter α for λ-bias sampling. In Fig. 2 the inaccuracy in the free-energy difference $\beta\Delta F$ is plotted as a function of α. For all four cases, curves are presented for λ-bias sampling (method *b* in Table I) for several NEW traversal repetitions *M*, each stepping across $n=10$ values of λ. Circles represent the results obtained from the original Jarzynski NEW method, using a fixed set of *n* equally spaced λ values. We notice that there are minimum values in the curves, which correspond to an approximate α value of $1/N$. We infer that this is the optimum value for α at least for these four cases, and we use this value for all the Rosenbluth samplings that employ the parameter α. We note that λ affects the energy of all the particles ($N_\lambda=N$), and we expect that the appropriate generalization of this result is $\alpha=1/N_\lambda$, as discussed in Sec. III. In comparison to the original NEW method, the λ-bias method provides better results for the systems given in cases A and C, is about the same for case B, and is worse for case D. More detailed comparisons are given below.

Next we compare two methods (*a* and *b*) of λ-bias sampling (with $n=10$), two methods (*c* and *d*) of configuration-bias sampling (with $n=m=10$), and two methods (*a*-*c* and *b*-*c*) of hybrid-bias sampling ($n=m=10$) with the original NEW method for the case A system pair. In Fig. 3, inaccuracies are plotted against the amount of sampling ($n\times M\times m$), where *M* stands for NEW traversal count. We see methods employing λ-bias sampling are better than unbiased NEW, while configuration-bias sampling (by itself or as part of a hybrid method) does not offer much advantage. The improvement offered by λ biasing is impressive: for small sampling, the inaccuracy is nearly one order of magnitude less than the unbiased NEW method. Moreover, because of the slow falloff of the small-sample bias for systems having large values of the dissipated work,[6] this order-of-magnitude improvement in the accuracy means that the original unbiased NEW method requires more than two orders of magnitude greater sampling to achieve the same inaccuracy as the λ-biased NEW method. The discrepancy in performance decreases with additional sampling, but there remains an order-of-magnitude difference at the largest sampling amounts. Comparing the two λ-bias methods, we note that method *a* is significantly less accurate than method *b*. Method *b* introduces to the sampling of λ an upper bound that increases with each step, while method *a* permits it to sample values up to unity with each step. The reason for the improved performance of method *b* is unclear. For configuration-bias samplings ($n=m=10$), method *c* and method *d* yield almost the same results as the original NEW method for this case. From this we would conclude that configuration-bias sampling is not helpful when applied to systems with entropic sampling barriers.

Next we would like to examine more generally the effectiveness of configuration-bias sampling, considering all of the system-pair cases and studying the influence of parameter *m* on the performance. Figure 4 shows the comparison for configuration-bias sampling (method *d*) at different *m* values with original NEW method for the four cases ($n=10$

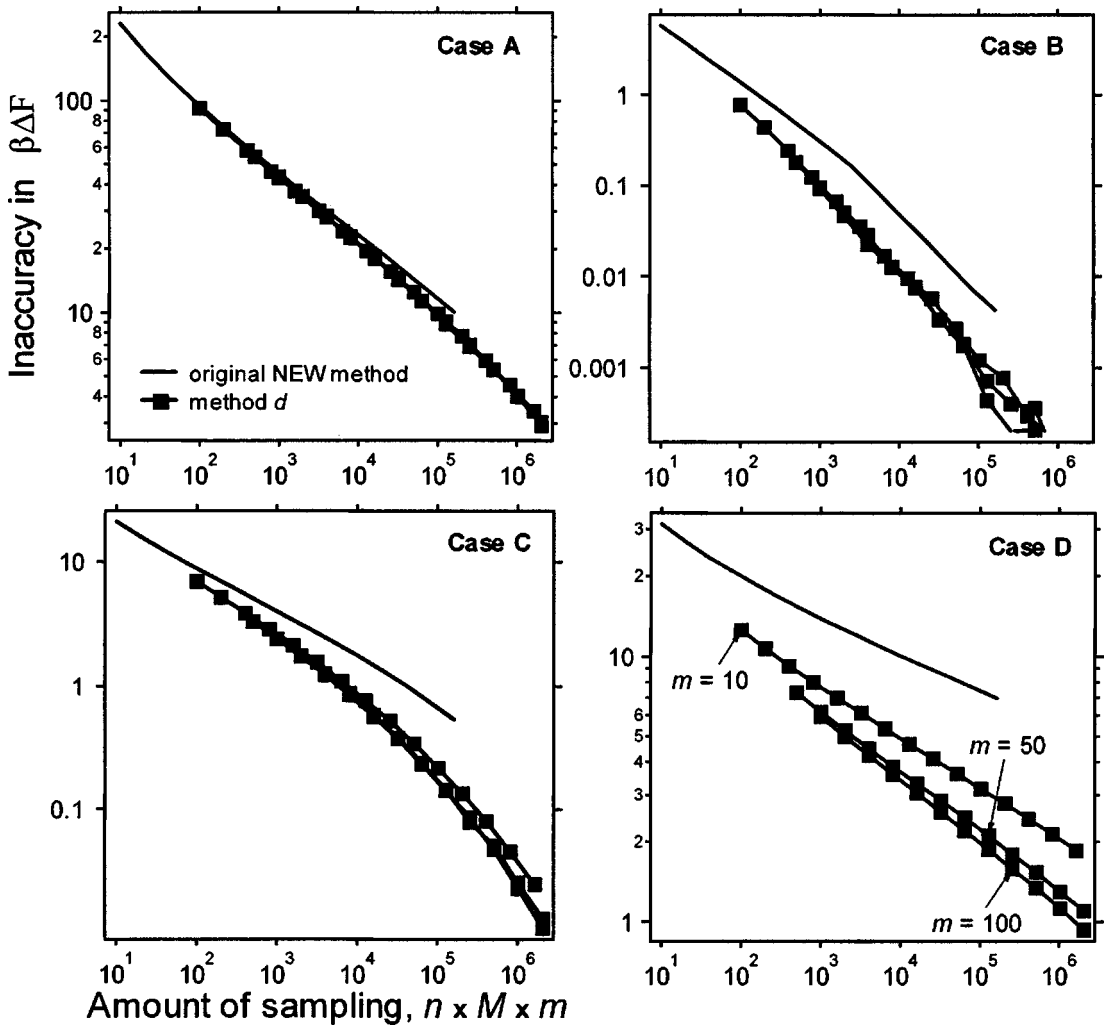

FIG. 4. Average inaccuracy of the free energy as a function of the amount of sampling for configuration-bias sampled Rosenbluth-NEW methods and the original NEW method. The curves in each plot compare results using three different values of m (10, 50, and 100), the number of configurations used for each Rosenbluth sample. In all calculations $n=10$. For the first three cases the three curves of configuration-bias samplings are nearly indistinguishable.

for all the curves). With m increased from 1 (original NEW) to 10, 50, and 100, we see results are improved only for case D, which is the pair with the nonoverlapping phase space (energetic barrier). Since the computational cost increases with increasing m, in the following results, we use $m=10$ for all the configuration-bias samplings (method *c* and method *d*) and hybrid-bias sampling (method *b*-*c*).

From the parameter studies we discussed above, we now choose λ-bias sampling (method *b*), hybrid-bias sampling (method *b*-*c*), and configuration-bias sampling (methods *c* and *d*) as the representative Rosenbluth-sampling schemes to calculate free energies and compare them with original NEW method for all the four cases. Figure 5 shows such comparisons. Case A is the case in which the target system's phase space is a tiny subset of that of the reference system. This case has practical importance; it is applied, for example, when inserting a multiatomic molecule or segment into a dense system, where it often encounters large-work values because of which the process is unlikely to create or find holes to accommodate the new atoms. As we can see in the plot, the scale of inaccuracy is large for short runs (when the amount of sampling is small). We have already discussed various Rosenbluth-sampling schemes for this case (Fig. 3), and conclude that λ-bias and hybrid-bias samplings are the best choices. Case B is a favorable case for free-energy calculations. Since it is easy for system *A* to find the target *B* phase space, all the approaches seem to be suitable for this case including the original NEW method (the scale of the inaccuracies are small even at the beginning). But we still see improvement when using pure configuration-bias Rosenbluth sampling (method *d*, but not method *c*), while λ-(method *b*) and hybrid-bias samplings (method *b*-*c*) are equal or slightly worse than the original NEW method in efficiency. Case C is similar to case B except that $x_0=1$ and the important phase spaces have only partial overlap. Rosenbluth samplings show some moderate advantages over NEW method for this case, but only those methods not involving method-*c* configuration-bias sampling. For case D, there is almost no overlap between the *A* and *B* phase spaces, and this situation makes free-energy calculations difficult. In fact, λ-bias sampling is significantly worse than the unbiased NEW method. This is because the Hamiltonian difference is large, and only small steps in λ are taken at each attempt. Thus after the $n-1$ λ steps the system is forced to jump to

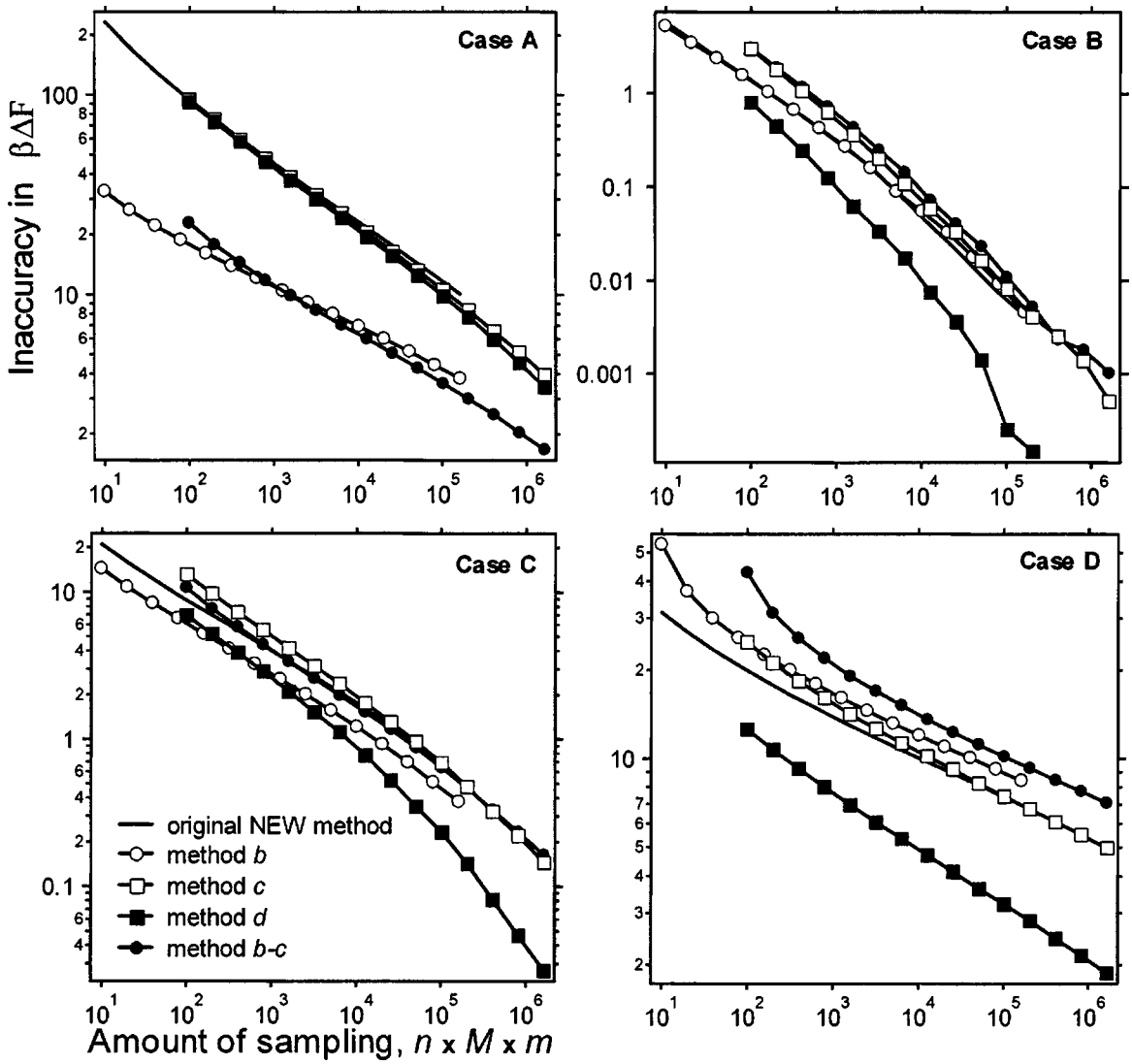

FIG. 5. Comparison of various Rosenbluth-sampled NEW methods and the original NEW method, applied for cases A–D. Average inaccuracy in the free energy is plotted as a function of amount of sampling. For all cases, $n=10$ and (where it applies) $m=10$. For case B the original NEW method and method-*b* curves are almost indistinguishable.

$\lambda=1$, incurring a single large-work contribution. Consequently, hybrid-bias sampling does not work well for this case too. However configuration-bias sampling (method *d*) still performs well, and gives inaccuracy several times smaller than original NEW method.

As a conclusion, λ-bias methods are most helpful for the cases when there is some degree of overlap, and the sampling barrier is entropic, while configuration-bias (using method *d*, not method *c*) is more useful when there is less overlap and the sampling barrier is energetic. The hybrid method might be expected to be most generally helpful if combining λ-bias with method-*d* configuration-bias samplings, but we did not pursue this because method-*d* configuration bias does not admit the parameter α which is important to the λ biasing. Combining λ bias with method-*c* configuration biasing does not seem to be especially effective.

To this point all the comparisons are made under the assumption of fast nonequilibrium processes (with $n=10$). We now consider the performance of these methods for moderate speed (or slow speed) nonequilibrium processes, and use $n=100$ steps in λ to traverse from *A* to *B*. Figure 6 shows the comparison of performance for different *n* values (solid curves for $n=10$ and dashed curves for $n=100$) for the four cases. Also in this plot, we compare two approaches, configuration-bias sampling (method *d*, using $m=10$) and the original NEW method. For all the approaches, accuracy is improved with increasing *n* and thus as the process becomes more reversible. Still, the configuration-bias samplings yield more accurate results than the original NEW method using the same number of steps in λ.

B. Nonequilibrated-move free-energy calculations

Now we turn to nonequilibrated-move calculations. Instead of generating equilibrated configurations at each step, we use standard MC trails—each attempting displacement of a randomly selected particle—between each attempt to increment λ. We apply 1000 MC trails between steps in λ. For the configuration-bias methods, we record configurations after

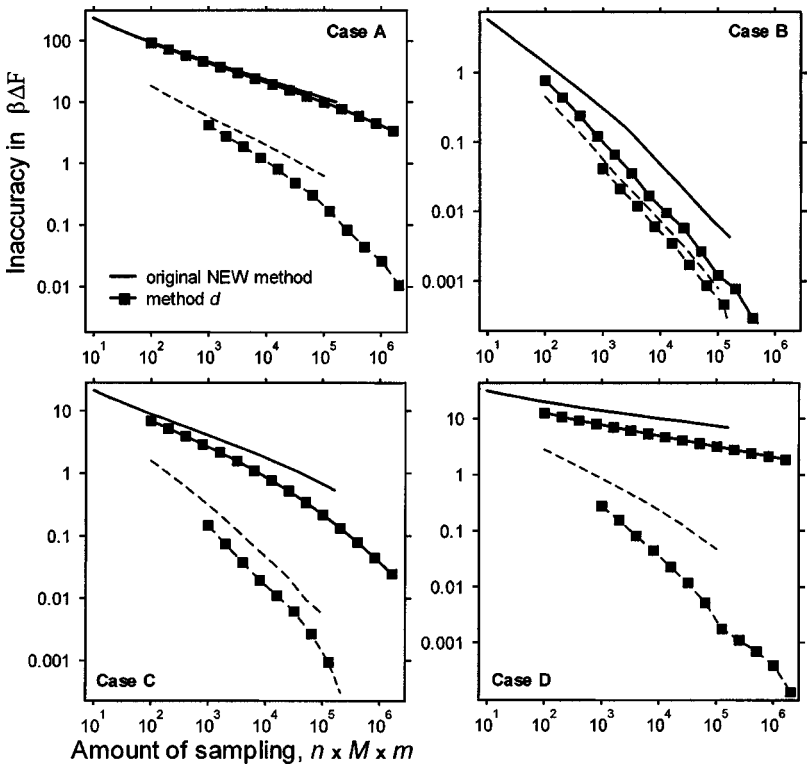

FIG. 6. Study of the effect of n (number of λ values used in a NEW traversal) for the configuration-bias (method-d) NEW (lines with square points) and the original NEW (lines with no points) methods. Average inaccuracy is plotted as a function of amount of sampling. Solid lines use $n=10$ and dashed lines use $n=100$.

every 100 MC trials, yielding ten reasonably independent configurations for use in the configuration-bias method. The configuration-bias selection is performed, followed by the λ-bias selection if working with the hybrid method. Keeping all other the parameters the same, we reproduce Fig. 5 in Fig. 7 using MC moves for the four cases. An important difference in the new results is the effectiveness of the configuration-bias sampling, which improves the accuracy in all cases, including case A. This is particularly important at sampling lengths needed to produce results of an acceptable accuracy. Whereas in Fig. 5, case A, the improvement of λ biasing is diminished relative to the unbiased NEW method for large samples, in Fig. 7 the effectiveness of the hybrid method for this case persists as the accuracy improves toward the right side of the plot. The hybrid method can for this case provide results comparable in accuracy to unbiased NEW while using several orders of magnitude less sampling.

VI. CONCLUSIONS

In conclusion, we have derived a variety of Rosenbluth-sampled nonequilibrium work methods for calculation of free-energy differences, and shown their applicability for model systems with widely different degrees of phase-space overlap. For a given amount of sampling, the biased NEW methods yield results that are up to one order of magnitude more accurate than unbiased methods. This translates into a huge savings in computation, because it can require several orders of magnitude more sampling of the unbiased calculation to achieve this level of improvement in accuracy (due to the slow convergence at large inaccuracies).

As with most free-energy methods, performance depends on the nature of the phase-space overlap of the reference and target systems, and the choice of a specific Rosenbluth-NEW approach should be made with this factor in mind. The λ-bias and hybrid-bias samplings are most suitable for the extreme-subset cases, in which the phase space of the target system is a small subset of the phase space of the reference (Fig. 3); pure λ-bias is not particularly effective for the partial and nonoverlap cases (Fig. 5, C,D). Configuration-bias sampling is better than NEW in every case when equilibration cycles are applied between steps in λ (Figs. 4 and 6). The degree of improvement depends on the ability of the system to equilibrate quickly enough to provide independent configuration samples for use by the method, and this factor can accentuate the importance of the reference-target phase-space overlap (Fig. 7). In this regard it would be helpful to have a means to quantify the degree of phase-space overlap of two systems. Presently no such measure is available (or at least not developed in the context of free-energy calculations), and we feel that efforts to establish an easily applied metric would be worthwhile.

The biasing methods have been presented here using a very general formalism, and there is significant room to fine tune their performance as more is learned about them. Less obviously, we think that a useful extension of the ideas presented here would result in a method that does not require prespecification of the number of λ steps (the parameter n). In this way the work process could proceed at its own pace from A to B, and not be forced to become the B system at some arbitrarily specified λ step. Certainly an important next step also is the application of the method to practical free-energy calculations, such as those related to solvation, molecular transformations, intermolecular binding, and so on.

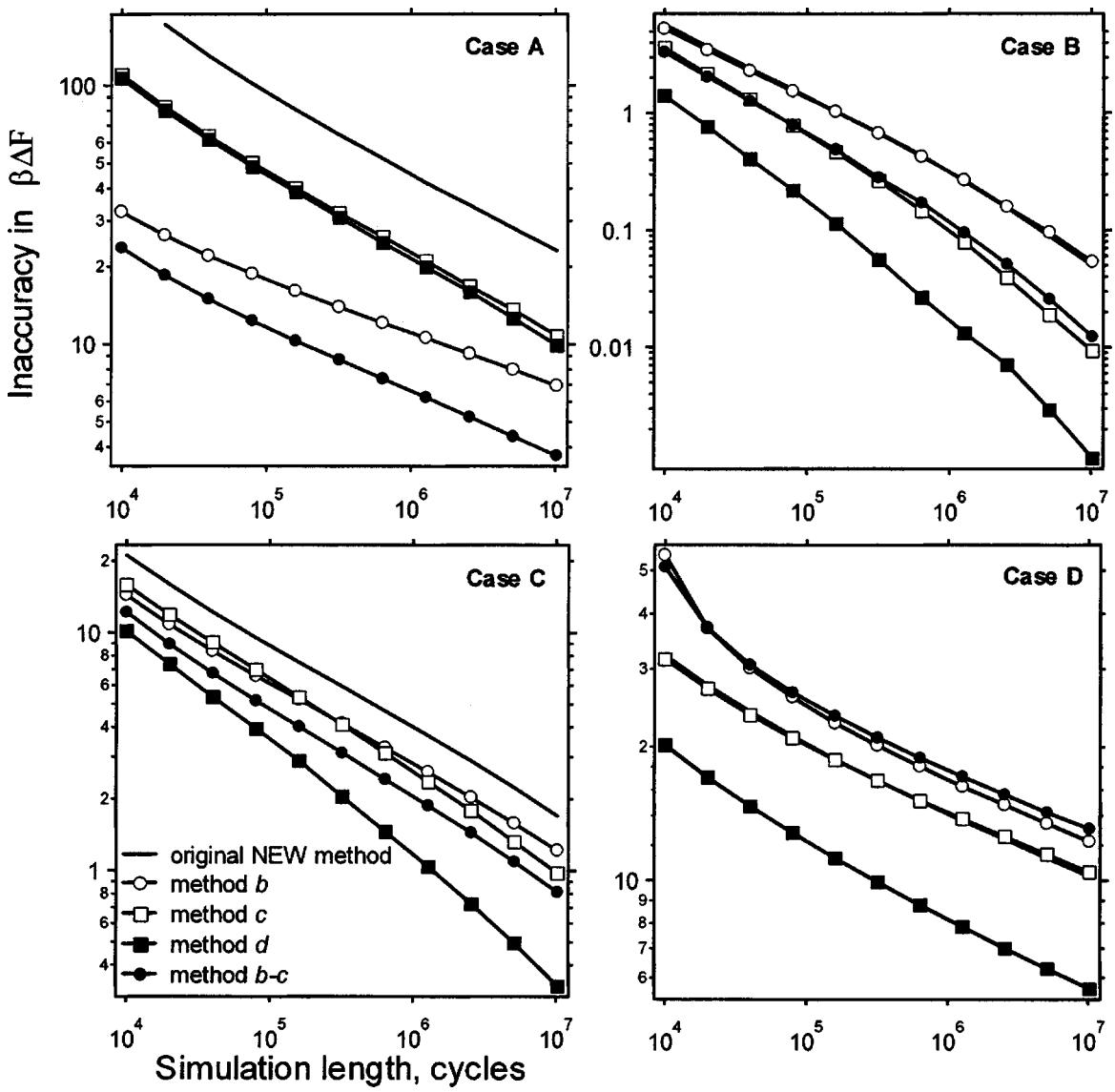

FIG. 7. Same as Fig. 5, except results are computed using a Markov Monte Carlo process to generate configurations, rather than generating them from direct sampling of a Gaussian distribution. For the abscissa, "cycles" means the quantity $n \times M \times m \times t$, where t is the number of MC trial moves. In all cases $m \times t = 1000$; for methods involving configuration bias, $m = 10$, while for the other methods $m = 1$. For case B results from the original NEW method and method *b* are almost indistinguishable; in case D the results from the original NEW method and method *c* are almost indistinguishable.

ACKNOWLEDGMENTS

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