Biased Sampling of Nonequilibrium Trajectories: Can Fast Switching Simulations Outperform Conventional Free Energy Calculation Methods?†

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We have investigated the maximum computational efficiency of reversible work calculations that change control parameters in a finite amount of time. Because relevant nonequilibrium averages are slow to converge, a bias on the sampling of trajectories can be beneficial. Such a bias, however, can also be employed in conventional methods for computing reversible work, such as thermodynamic integration or umbrella sampling. We present numerical results for a simple one-dimensional model and for a Widom insertion in a soft sphere liquid, indicating that, with an appropriately chosen bias, conventional methods are in fact more efficient. We describe an analogy between nonequilibrium dynamics and mappings between equilibrium ensembles, which suggests that the practical inferiority of fast switching is quite general. Finally, we discuss the relevance of adiabatic invariants in slowly driven Hamiltonian systems for the application of Jarzynski's theorem.

I. Introduction

According to the second law of thermodynamics, the average work $\langle W \rangle$ done when changing a constraint, or control parameter, on a system initially in thermal equilibrium is larger than the Helmholtz free energy difference ΔF between the two equilibrium states corresponding to the initial and final value of the constraint,

$$\langle W \rangle \geq \Delta F \tag{1}$$

The equality holds when the change is carried out reversibly so that equilibrium is maintained at all times. A few years ago, Jarzynski extended this result by showing that the equilibrium free energy difference can be expressed as an exponential average of the work performed on the system during, in general, irreversible transformations:[1−3]

$$\exp(-\beta \Delta F) = \langle \exp(-\beta W) \rangle \tag{2}$$

Here, $\beta = 1/k_B T$ is the inverse temperature and k_B is Boltzmann's constant. The angled brackets $\langle \cdots \rangle$ in eq 2 denote an average over an ensemble of nonequilibrium transformation processes initiated from equilibrium states.

The Jarzynski theorem introduces a new way of calculating equilibrium free energy differences. Conventional methods, used in a variety of fields ranging from biology to materials science, mostly follow one of two strategies: either the transformation between the states of interest is carried out instantaneously as in Zwanzig's perturbative treatment,[4] or the constraint on the system is changed "infinitely" slowly (i.e., the change is slower than any important relaxation process) as in Kirkwood's coupling parameter method (also known as thermodynamic integration).[5] The fast switching approach suggested by Jarzynski's theorem, in which changes of the control parameter can be carried out at a finite, nonzero rate, can be considered as intermediate between these two limiting cases. From a computational point of view, the question naturally arises as to how the efficiency of the fast switching methods compares to the efficiency of conventional approaches such as umbrella sampling or thermodynamic integration. This question is the subject of this paper.

In the thermodynamic integration scheme free energy differences are determined from equilibrium averages calculated at different values of the control parameter.[6] Effectively, this corresponds to integrating a single, very long trajectory along which the control parameter is changed very slowly. In contrast, the fast switching approach based on Jarzynski's identity requires integration of many short trajectories during which the control parameter is changed from its value in one equilibrium state to that of the other equilibrium state. Because the computational cost of determining molecular dynamics trajectories is proportional to their length, simulation methods based on short trajectories would seem to be advantageous. This benefit, however, might be outweighed by the necessity of generating many, albeit computationally inexpensive, short trajectories. It has been demonstrated that, if the control parameter is changed sufficiently slowly, the product of the trajectory length τ and the number N of trajectories needed to obtain a given accuracy for the reversible work is independent of τ in a straightforward implementation of the fast switching method.[7,8] The benefit and cost of driving a system at small but nonzero rate are thus evenly balanced, and from a computational point of view it does not matter whether one chooses to generate many short trajectories or a few long ones. Hummer has shown that this ambivalence is valid when the variance of the work is less than $(k_B T)^2$.[9]

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The situation is different if the control parameter is switched rapidly. In this case the work distribution is centered at values large compared to the free energy difference. To see why this creates numerical problems, we rewrite the average in eq 2 as an integral over the work distribution:

$$\exp(-\beta\Delta F) = \int \mathrm{d}W\, P(W) \exp(-\beta W) \tag{3}$$

In general, the integrand on the right-hand side, $P(W)\exp(-\beta W)$, is peaked at work values very different from the average work $\langle W\rangle$. Values of the work W contributing significantly to the integral in the above equation belong to the low-W wing of the work distribution $P(W)$ and are generated only very rarely in a straightforward fast switching simulation. As a consequence, the statistical errors in the free energy difference estimated from a finite sample of fast switching trajectories can be very large. One expects these errors to be most severe for very short trajectories.

These numerical difficulties are analogous to the problems encountered when calculating free energy differences using Zwanzig's approach:[10]

$$\exp(-\beta\Delta F) = \int \mathrm{d}x\, P(x) \exp(-\beta\Delta E) \tag{4}$$

where $P(x)$ is the phase space distribution of the initial equilibrium state and ΔE is the difference between the energy of microstate x in the final state and its energy in the initial state. Indeed, eq 4 is just the $\tau \to 0$ limit of eq 3. Practical problems arise for simple Boltzmann sampling of $P(x)$ when large values of $P(x)\exp(-\beta\Delta E)$ do not coincide with typical microstates of the initial ensemble. Non-Boltzmann sampling techniques provide a way to circumvent such problems. In umbrella sampling, for instance, the simulation is biased such that the systems visits all relevant parts of configuration space with uniform frequency.[11,12] Appropriate corrections for this bias guarantee that the correct ensemble averages are calculated.

A similar approach can be used to alleviate the numerical problems occurring in fast switching simulations. Recently, Sun has introduced a novel methodology in which the ensemble of fast switching nonequilibrium trajectories is sampled with a non-Boltzmann bias.[13] In this generalization of thermodynamic integration from configuration space to the space of trajectories, pathways are generated with a likelihood depending on the work associated with them. Pathways with work values contributing significantly to the exponential average are preferentially sampled, reducing the statistical errors considerably.[13] Because in Sun's approach the path probability explicitly depends on the work done on the system, the trajectories cannot be simply generated by initiating them from equilibrium initial conditions. Instead, the pathways are generated with path sampling algorithms developed for the simulation of rare, but important events.[14−16] In the same spirit, Ytreberg and Zuckerman have applied umbrella sampling to fast switching trajectories generated with path sampling methods.[17] Similar approaches were also suggested by Athènes.[18] In Ytreberg and Zuckerman's method, an explicit bias function favors generation of trajectories carrying low weight but contributing significantly to the exponential work average. Other methods, such as flat histogram sampling,[19] multiple histogram algorithms[20] or multicanonical techniques,[21] can be combined with path sampling for the evaluation of Jarzynki's exponential average.

Although the biased path sampling methods mentioned above can considerably increase the efficiency of the fast switching approach, the question remains whether these algorithms can compete with conventional approaches such as umbrella sampling or thermodynamic integration. After all, in Zwanzig's exponential averaging the change of the control parameter is carried out instantaneously, and equations of motion need not be integrated at all. In the present paper we address this question and present a detailed analysis of the numerical cost of fast switching simulations. Numerical evidence obtained for two Hamiltonian systems indicates that current algorithms based on the Jarzynski identity are in general inferior to conventional algorithms.

The remainder of this paper is organized as follows. In section II we review the statistical mechanics underlying Jarzynski's identity. In section III we describe an uncustomary view of fast switching that reveals in simple terms how it might improve upon standard methods. In section IV we outline the biased sampling of nonequilibrium pathways. Expressions for the statistical error made in such biased simulations are derived in section V. We apply these results to a schematic example in section VI and to two model systems in section VII. The effect of adiabatic invariants on the work distributions of Hamiltonian systems in the limit of slow switching is discussed in section VIII. Conclusions are given in section IX.

II. Jarzynski's Identity

Consider a Hamiltonian $H(x, \lambda)$ depending on x, the microscopic state of the system, and a constraint (or control parameter) λ imposed on the system. For a given value of λ and temperature T the Helmholtz free energy of the system is given by

$$F_\lambda(\beta) = -k_\mathrm{B}T \ln Q_\lambda \tag{5}$$

where

$$Q_\lambda(\beta) = \int \mathrm{d}x \exp[-\beta H(x, \lambda)] \tag{6}$$

is the partition function. Because we are interested only in free energy *differences* we have omitted factors that do not depend on λ, including those making the partition function dimensionless. The free energy difference between two systems corresponding to two different values of the control parameter, λ_A and λ_B, is

$$\Delta F = F_{\lambda_B} - F_{\lambda_A} = -k_\mathrm{B}T \ln \frac{Q_{\lambda_B}}{Q_{\lambda_A}} \tag{7}$$

Here and in the following we omit the argument β for the free energy and the partition function to simplify the notation. The free energy difference ΔF, or equivalently the work to reversibly change the control parameter from λ_A to λ_B, is the central quantity considered in this paper.

In the fast switching approach the control parameter is switched from its initial value λ_A to its final value λ_B in finite time. Because energy depends on the control parameter λ, work W is performed on the system:

$$W[x(t), \lambda(t)] = \int \mathrm{d}t\, \dot{\lambda} \left(\frac{\partial H}{\partial \lambda}\right)_{x=x(t)} \tag{8}$$

The notation $W[x(t), \lambda(t)]$ indicates that the work performed along a given trajectory $x(t)$ depends on the whole trajectory and on the time dependence $\lambda(t)$ of the control parameter. Jarzynski's theorem states that the free energy difference ΔF is related to the statistics of work accumulated along trajectories starting from canonically distributed initial conditions, $\rho(x_0) =$

$\exp[-\beta H(x_0, \lambda_A)]/Q_{\lambda_A}$, and evolving according to the time dependent Hamiltonian $H[x, \lambda(t)]$:

$$\exp(-\beta\Delta F) = \int \mathcal{D}x(t)\, P[x(t)] \exp\{-\beta W[x(t)]\} \quad (9)$$

Here, $P[x(t)]$ is the statistical weight of pathway $x(t)$. We have dropped the explicit dependence of P and W on $\lambda(t)$. The notation used in the above expression implies a sum over all pathways weighted with their probability to occur. Equation 9 can be evaluated as an average over an ensemble of pathways obtained by integrating the system's equations of motion with initial conditions drawn from the equilibrium distribution $\rho(x_0)$.

III. A Static Perspective

Although the dynamical implications of Jarzynski's identity are profound, it is instructive for the purpose of assessing computational efficiency to adopt a nondynamical view of eq 2. Such a counterintuitive perspective results from viewing time evolution,

$$x_t = \exp[i\int_0^t \mathrm{d}t' L(t')]x_0$$

(where L is the classical Liouville operator) as a special example of mapping points in phase space,

$$x' = \phi(x) \quad (10)$$

We require only that $\phi(x)$ is invertible, so that a function $\phi^{-1}[\phi(x)] = x$ exists for all x. Such a mapping transforms an equilibrium ensemble A into a new ensemble A' characterized by the phase space distribution

$$P_{A'}(x) = Q_{\lambda_A}{}^{-1} \exp\{-\beta H[\phi^{-1}(x), \lambda_A]\}\left|\frac{\partial\phi^{-1}(x)}{\partial x}\right| \quad (11)$$

We define a new energy function

$$H'(x, \lambda_A) = H[\phi^{-1}(x), \lambda_A] - k_\mathrm{B}T \ln\left|\frac{\partial\phi^{-1}(x)}{\partial x}\right| \quad (12)$$

such that A' is simply an equilibrium canonical ensemble with distribution

$$P_{A'} = \exp[-\beta H'(x, \lambda_A)]/Q'_{\lambda_A} \quad (13)$$

and partition function

$$\begin{aligned} Q'_{\lambda_A} &= \int \mathrm{d}x \exp[-\beta H'(x,\lambda_A)] \\ &= Q_{\lambda_A} \end{aligned} \quad (14)$$

The second line of eq 14 results from inserting eq 12 for H' and changing integration variables from x to $x' = \phi^{-1}(x)$.

The work required to reversibly switch from A to another equilibrium state B is of course independent of the path taken between them. We may thus proceed through any intermediate state, including A':

$$\Delta F = (F_{\lambda_B} - F'_{\lambda_A}) + (F'_{\lambda_A} - F_{\lambda_A}) \quad (15)$$

Because $Q'_{\lambda_A} = Q_{\lambda_A}$, the free energy F'_{λ_A} of ensemble A' is identical to that of A. Using Zwanzig's result eq 4 for the second step of this transformation, $A' \rightarrow B$,we obtain

$$\mathrm{e}^{-\beta\Delta F} = \exp[-\beta(F_{\lambda_B} - F'_{\lambda_A})] \quad (16)$$

$$= \langle \exp\{-\beta[H(x, \lambda_B) - H'(x, \lambda_A)]\}\rangle' \quad (17)$$

The primed average is carried out over the equilibrium distribution $P_{A'}(x)$ of the intermediate ensemble A'.

With the above manipulations we have devised a generic two-step procedure for switching between equilibrium ensembles A and B that involves only equilibrium states. The first step converts A to A' by mapping points in phase space, with no change in free energy. The second step converts A' to B, with a reversible work determined by the exponential average of their energy difference. For the trivial choice $\phi(x) = x$, A is unchanged in the first step, and the procedure reduces to a standard application of Zwanzig's formula.

For the choice of dynamical mapping, $x_t = \phi(x_0)$, eq 17 becomes Jarzynski's identity, because

$$H(x_t, \lambda_B) - H'(x_t, \lambda_A) = H(x_t, \lambda_B) - H(x_0, \lambda_A) \quad (18)$$

is exactly the work expended over the course of a trajectory beginning at x_0 and ending at x_t. Here, we have used the fact that $|\partial\phi^{-1}(x)/\partial x| = 1$ for Hamiltonian systems. One could view this route to Jarzynski's identity, drawing only on standard results of equilibrium statistical mechanics, as an explanation for the familiar form of eq 2, the exponential average of an energy difference.

The Jacobian associated with a complicated mapping of many variables is often a difficult object to compute. In some cases it can be propagated numerically in time along with positions and momenta. The equations of motion for Nose-Hoover dynamics, for instance, permit such a calculation. For very simple mappings, on the other hand, we may evaluate $|\partial\phi(x)/\partial x|^{-1}$ explicitly. An example is momentum rescaling, $p'_i = \gamma p_i$. Applying this transformation to $3M$ translational degrees of freedom yields

$$H'(r^{(M)}, p^{(M)}) = H(r^{(M)}, \gamma^{-1}p^{(M)}) + 3Mk_\mathrm{B}T \ln\gamma \quad (19)$$

where $r^{(M)}$ and $p^{(M)}$ denote $3M$-dimensional configuration and momentum vectors specifying a microscopic state. The final term in eq 19 indicates that "mechanical" work is therefore required to compress phase space volume elements.

The results of this section do not apply to stochastic time evolution (a nonunique mapping), often used in particle systems to emulate the influence of a heat bath. It is thus interesting to note that one role of such a bath can be mimicked by periodically rescaling momenta as a system is driven from equilibrium. For $\gamma < 1$, this procedure in effect dissipates heat, although its contribution in eq 19 is formally accounted as work.

The proof we have offered for a slightly generalized form of Jarzynski's identity differs little in structure from his original analysis. Our primary purpose in presenting it is to highlight the formal and practical equivalence between implementing eq 2 and standard methods for computing reversible work. The numerical difficulties arising from switching ensembles at a finite rate are *precisely* those that plague instantaneous switching. Without umbrella sampling the most severe of these problems arises from poor statistical overlap between ensembles. The potential power of finite-time switching lies in abating the degree of this difficulty. To be specific, imagine that initial and final ensembles A and B overlap poorly. A straightforward application of eq 4 will converge very slowly in this case. A useful mapping transforms A into an intermediate ensemble A' whose overlap with B is greatly improved. In this case, an

estimate of eq 17 with Boltzmann sampling will converge much more quickly. Adiabatically slow switching can be viewed as an ideal mapping that associates the most highly weighted microstates of *A* with those of *B*. One can expect that the improvement of statistical overlap lessens as the length of switching trajectories decreases. The question addressed in this paper is whether the numerical benefit of such mappings generally outweighs the cost of generating them.

As mentioned in the Introduction, the analogy with equilibrium calculations also allows application of non-Boltzmann sampling to overcome practical numerical problems. In the following sections we describe this application in detail and quantify its statistical errors. In example problems these errors are relatively insensitive to the extent of overlap between ensembles for an optimal choice of bias. For this reason, finite-time switching, which serves only to increase this overlap, provides little advantage to offset its numerical cost.

IV. Work Biased Path Sampling

To alleviate the numerical difficulties arising when applying Jarzynski's identity to a rapidly changing control parameter, one can rewrite eq 9, introducing a bias function (or umbrella function) $\pi[x(t)]$ as suggested by Ytreberg and Zuckerman:[17]

$$e^{-\beta\Delta F} = \frac{\int \mathcal{D}x(t)\, P[x(t)]\, \pi[x(t)] \left[\dfrac{e^{-\beta W[x(t)]}}{\pi[x(t)]}\right]}{\int \mathcal{D}x(t)\, P[x(t)]\, \pi[x(t)] \left[\dfrac{1}{\pi[x(t)]}\right]} \tag{20}$$

$$= \frac{\langle e^{-\beta W[x(t)]}/\pi[x(t)]\rangle_\pi}{\langle 1/\pi[x(t)]\rangle_\pi} \tag{21}$$

The notation $\langle\cdots\rangle_\pi$ denotes an average over the path distribution $P[x(t)]\ \pi[x(t)]$. For an observable $A[x(t)]$ depending on the pathway $x(t)$ this average is given by

$$\langle A[x(t)]\rangle_\pi \equiv \frac{\int \mathcal{D}x(t)\, P[x(t)]\, \pi[x(t)]\, A[x(t)]}{\int \mathcal{D}x(t)\, P[x(t)]\, \pi[x(t)]} \tag{22}$$

If the bias function $\pi[x(t)]$ is chosen such that it covers all important regions in path space, the statistical error of both the numerator and the denominator in eq 20 can be kept small.

To calculate such path averages, one must generate pathways according to the biased ensemble $P[x(t)]\ \pi[x(t)]$. In contrast to the original path ensemble $P[x(t)]$, however, the biased ensemble cannot be sampled by simply generating initial conditions and evolving them in time according to dynamical rules, because the bias function $\pi[x(t)]$ may depend on the entire pathway. Instead, as suggested by Sun,[13] one can use path sampling techniques to impose a desired bias. In this approach, originally developed to find rare, reactive pathways in complex systems,[15] a biased random walk is carried out in trajectory space such that pathways are generated according to their weight in the biased ensemble. For this purpose, one generates a new path from an old one using algorithms described in ref 15. One then accepts or rejects the new path depending on its weight relative to the weight of the old path. In doing so, the Metropolis algorithm is used to ensure that the detailed balance condition is obeyed and the correct path ensemble is sampled. Repeating this operation many times, one generates a Markov chain of pathways occurring with their weight in the biased path ensemble.

If the bias function $\pi[x(t)]$ and the observable $A[x(t)]$ depend on the pathway only through the work $W[x(t)]$, i.e., $\pi = \pi[W[x(t)]]$ and $A = A[W[x(t)]]$, it is convenient to express the average in the biased ensemble using integrals over the work distribution $P(\tilde{W}) = \int \mathcal{D}x(t)\ P[x(t)]\delta(\tilde{W} - W[x(t)])$:

$$\langle A\rangle_\pi \equiv \frac{\int \mathrm{d}W\, P(W)\, \pi(W)\, A(W)}{\int \mathrm{d}W\, P(W)\, \pi(W)} \tag{23}$$

This expression will be useful in the following discussion of the errors made when calculating Jarzynski's exponential average in a biased path sampling simulation.

V. Error Analysis

An efficiency analysis of the biased path sampling algorithm described in the previous section requires an estimation of the (statistical and systematic) errors made in computer simulations of finite length. In this section we derive expressions for such errors in terms of the statistics of work and the bias function used in the simulation. To simplify the notation, we introduce the variables

$$X \equiv \exp(-\beta W)/\pi(W) \qquad \text{and} \qquad Y \equiv 1/\pi(W) \tag{24}$$

The estimate of the free energy obtained according to eq 20 from *N* fast switching pathways is

$$\Delta\bar{F}_N \equiv -k_B T \ln \frac{\bar{X}_N}{\bar{Y}_N} \tag{25}$$

where $\bar{X}_N$ and $\bar{Y}_N$ are the averages of *X* and *Y* over the *N* samples of the simulation,

$$X_N \equiv \frac{1}{N}\sum_{i=1}^{N} X^{(i)} \qquad \text{and} \qquad Y_N \equiv \frac{1}{N}\sum_{i=1}^{N} Y^{(i)} \tag{26}$$

Here, $X^{(i)}$ and $Y^{(i)}$ are the values of *X* and *Y* associated with the *i*-th path sampled from the biased ensemble, $P[x(t)]\ \pi[x(t)]$.

Due to the nonlinearity of the logarithm, this estimator for the free energy is biased; i.e., the average over *M* estimators $\Delta\bar{F}_N^{(j)}$,

$$\langle\Delta\bar{F}_N\rangle \equiv \lim_{M\to\infty} \frac{1}{M}\sum_{j=1}^{M} \Delta\bar{F}_N^{(j)} \tag{27}$$

does not converge toward the true free energy difference in the limit $M \to \infty$. The deviation from this limit,

$$b_N \equiv \langle\Delta\bar{F}_N\rangle - \Delta F \tag{28}$$

is called the bias. In addition to this systematic deviation, the estimator $\Delta\bar{F}_N$ is affected by statistical errors as quantified by the variance,

$$\sigma_N{}^2 \equiv \langle[\Delta\bar{F}_N - \langle\Delta\bar{F}_N\rangle]^2\rangle = \langle(\Delta\bar{F}_N)^2\rangle - \langle\Delta\bar{F}_N\rangle^2 \tag{29}$$

The mean squared deviation of the estimator $\Delta\bar{F}_N$ from the true free energy difference ΔF is given by

$$\epsilon_N{}^2 \equiv \langle[\Delta\bar{F}_N - \Delta F]^2\rangle = b_N{}^2 + \sigma_N{}^2 \tag{30}$$

The quantity $\epsilon_N{}^2$ is also called the mean squared error.

In the limit of large *N* the relative deviations $\delta\bar{X}_N$ and $\delta\bar{Y}_N$ from their averages,

$$\delta\bar{X}_N = \bar{X}_N - \langle X\rangle_\pi \qquad \text{and} \qquad \delta\bar{Y}_N = \bar{Y}_N - \langle\bar{Y}\rangle_\pi \quad (31)$$

are small and we can expand the logarithm in eq 25 around $\langle X\rangle/\langle Y\rangle$. Truncating after the quadratic term (the linear terms vanish after averaging) and assuming that all samples are statistically independent, we obtain

$$b_N = \frac{k_B T}{2N}\left[\frac{\langle(\delta X)^2\rangle_\pi}{\langle X\rangle_\pi^2} - \frac{\langle(\delta Y)^2\rangle_\pi}{\langle Y\rangle_\pi^2}\right] \quad (32)$$

where the fluctuations δX and δY are given by

$$\delta X \equiv X - \langle X\rangle \qquad \text{and} \qquad \delta Y \equiv Y - \langle Y\rangle \quad (33)$$

To determine large-N expressions for the variance σ_N and the mean squared error ϵ_N, we proceed in a similar way, but we truncate the expansion of the logarithm in eq 25 after the linear term. In this approximation the bias vanishes and the variance and the mean squared error are identical:

$$\epsilon_N^2 = \sigma_N^2 = \frac{k_B^2 T^2}{N}\alpha^2 \quad (34)$$

where α depends on the work statistics $P(W)$, the bias function π, but not on the number of samples N,

$$\alpha^2 \equiv \frac{\langle(\delta X)^2\rangle_\pi}{\langle X\rangle_\pi^2} + \frac{\langle(\delta Y)^2\rangle_\pi}{\langle Y\rangle_\pi^2} - 2\frac{\langle\delta X\delta Y\rangle_\pi}{\langle X\rangle\langle Y\rangle_\pi} \quad (35)$$

In the absence of a bias function π these expressions for the bias and the variance become identical to those derived in refs 22 and 23 for the analysis of straightforward fast switching simulations.

For a given (normalized) distribution of work, $P(W)$, and a given bias function, $\pi(W)$, all expressions necessary to calculate the bias b_N, the variance σ_N, and the mean squared error ϵ_N can be evaluated numerically as integrals over the work:

$$\mathrm{I} = \int \mathrm{d}W\, P(W)\, \pi(W) \quad (36)$$

$$\langle X\rangle_\pi = \frac{1}{I}\int \mathrm{d}W\, P(W)\exp(-\beta W) \quad (37)$$

$$\langle Y\rangle_\pi = \frac{1}{I} \quad (38)$$

$$\langle X^2\rangle_\pi = \frac{1}{I}\int \mathrm{d}W\, P(W)\left[\frac{\exp(-2\beta W)}{\pi(W)}\right] \quad (39)$$

$$\langle Y^2\rangle_\pi = \frac{1}{I}\int \mathrm{d}W\, P(W)\left[\frac{1}{\pi(W)}\right] \quad (40)$$

$$\langle XY\rangle_\pi = \frac{1}{I}\int \mathrm{d}W\, P(W)\left[\frac{\exp(-\beta W)}{\pi(W)}\right] \quad (41)$$

In the next two sections we use these expressions to calculate the bias and the mean squared errors of the free energy for a Gaussian work distribution, for a transformation of a simple one-dimensional model, and for a particle insertion in a soft sphere fluid.

VI. Schematic Example

To explore the merit of non-Boltzmann sampling as described above, we consider first the simple case in which the work distribution is Gaussian:

$$P(W) = (2\pi\Delta^2)^{-1/2}\exp\left[-\frac{(W - W_0)^2}{2\Delta^2}\right]$$

This choice allows explicit evaluation of eqs 36−41 for simple forms of $\pi(W)$. We focus on broad distributions (i.e., poor overlap between the dynamically mapped ensemble A' and the final state B), $\beta\Delta \gg 1$.

In the absence of bias, $\pi(W) = 1$, corresponding to straightforward fast switching, the mean squared error is given by

$$N(\beta\epsilon_N)^2 = \mathrm{e}^{(\beta\Delta)^2} - 1 \approx \mathrm{e}^{(\beta\Delta)^2} \quad (42)$$

as shown and discussed in refs 22 and 23. The bias suggested by Zuckerman and Ytreberg, $\pi(W) = \exp(-\beta W/2)$, yields a similar dependence of sampling error on switching rate:

$$N(\beta\epsilon_N)^2 = 2\mathrm{e}^{(\beta\Delta)^2/4}(1 - \mathrm{e}^{-(\beta\Delta)^2/2}) \approx 2\mathrm{e}^{(\beta\Delta)^2/4} \quad (43)$$

Because these results depend strongly on the variance of $P(W)$, a mapping that reduces Δ (in effect, improving overlap between ensembles) is extremely beneficial. The potentially rapid growth of error with increasing switching rate makes it likely that computational efficiency will be maximal for a finite value of ν.

The situation is quite different for the choice $\pi(W) = 1/P(W)$, which renders sampling uniform over a desired range of work. In this case Gaussian integration yields

$$N(\beta\epsilon_N)^2 = \frac{I}{\sqrt{\pi}\Delta}[1 - \mathrm{e}^{-(\beta\Delta)^2/4}] \approx \frac{I}{\sqrt{\pi}\Delta} \quad (44)$$

Here, I is simply the range of W sampled. As we will discuss later, an accurate estimate of ΔF requires that sampling includes the maxima of both $P(W)$ and $P(W)\mathrm{e}^{-\beta W}$, which occur at W_0 and $W_0 - \beta\Delta^2$, respectively. With $I = \beta\Delta^2$, we have $N(\beta\epsilon_N)^2 \approx \beta\Delta/\sqrt{\pi}$. Compared to the mean squared error with no bias or with Zuckerman and Ytreberg's bias, this result grows very weakly with $\beta\Delta$. As a result, non-Boltzmann sampling with the bias $\pi(W) = 1/P(W)$ is essentially immune to the pathology of poorly overlapping ensembles. There are of course other sources of statistical error in sampling broad, uniform distributions, but they are generally inconsequential compared to the errors described by eq 34. If the growth of Δ with increasing switching rate ν is less than linear, total computational cost is minimized for $\nu = \infty$. Switching over a finite time interval in this case inevitably degrades computational efficiency.

VII. Results

We have carried out the error analysis described in section V for two transformations taking place in Hamiltonian systems: the change from a one-dimensional double well potential to a single well potential and the gradual Widom insertion of a particle into a soft sphere fluid. In both cases we consider systems evolving according to Hamilton's equations of motion. The initial conditions are canonically distributed. Physically, we imagine that the initial state is prepared by coupling the system to a heat bath. The system is then separated from the heat bath and the change of the control parameter is carried out for the isolated system.

Because Hamilton's equations of motion are deterministic, the path integrals appearing in section V can be written as integrals over initial conditions x_0, e.g.,

$$\exp(-\beta\Delta F) = \int \mathrm{d}x_0\, \rho(x_0) \exp\{-\beta W(x_0)\} \qquad (45)$$

Although we do not consider an example system with nondeterministic dynamics in this paper, the path sampling algorithms we have described can be employed to sample stochastic paths equally as well as deterministic trajectories. The error formulas derived in section V are also appropriate for stochastic dynamics.

A. One-Dimensional Model. We first analyze the performance of biased path sampling methods for a one-dimensional particle of unit mass moving in a simple potential. The parameter-dependent Hamiltonian defining this model introduced by Sun[13] is

$$H[q, p, \lambda(t)] = \frac{p^2}{2} + q^4 - 16(1-\lambda)q^2 \qquad (46)$$

where p denotes the momentum of the particle and q is its position. Both the coordinate and the momentum are scaled to be unitless. For $\lambda = 0$ the potential energy as a function of q is a double well with minima located at $q = \pm\sqrt{8}$ and separated by a barrier of height 64 located at $q = 0$. For $\lambda = 1$ the potential has a single well. The free energy difference $\Delta F = F_1 - F_0$ can be calculated analytically. For $\beta = 1$ we obtain

$$\Delta F = \ln \frac{\pi e^{32}(I_{-1/4}(32) + I_{1/4}(32))}{\sqrt{2}\Gamma(5/4)} = 62.9407 \qquad (47)$$

where Γ denotes the gamma function and $I_{-1/4}$ and $I_{1/4}$ are modified Bessel functions of the first kind.

We now consider a control parameter varying linearly in time, $\lambda(t) = \nu t$, where $\nu = 1/\tau$ is the switching rate. For an instantaneous switch, i.e., an infinite switching rate, the system has no time to respond to the change of λ and the work performed on the system is simply the difference in potential energy at the position of the system, $W(q) = 16q^2$. In this case the work distribution can be determined analytically by a transformation of variables from q to W. For $W \geq 0$

$$P(W, \nu = \infty) = \frac{\exp\{-(W^2/16^2 - W)\}}{4\sqrt{W}\pi e^{32}(I_{-1/4}(32) + I_{1/4}(32))} \qquad (48)$$

The $1/\sqrt{W}$-singularity at $W = 0$ arises from the vanishing derivative of $W(q)$ at $q = 0$.

For finite switching rates the work distributions must be determined numerically. We calculated work distributions with switching rates ranging from $\nu = 0.0005$ to $\nu = 500$. Some of these distributions are shown in Figure 1. For $\nu \leq 0.01$ we calculated the work distribution using straightforward fast switching with 10^5 ($\nu = 0.0001$) to 10^7 ($\nu = 0.01$) trajectories. Equations of motion were integrated using the velocity Verlet algorithm[10] with a time step $\Delta t = 0.002$. Initial positions q were generated with a Metropolis Monte Carlo procedure and initial momenta p were drawn from an appropriate Boltzmann distribution.

For $\nu \geq 0.02$ we calculated the work distributions with biased path sampling. For each switching rate we sampled 10^6 pathways generated with the shooting method. In this approach, a point along a given pathway is first chosen at random. Then, the momentum at this point is slightly changed by adding a random perturbation. Equations of motion are integrated forward and backward in time starting from this point. The newly generated pathway is finally accepted or rejected according to the ratio of its weight to the weight of the old path. We chose the magnitude of momentum displacements to obtain an average acceptance rate of about 50%. We determined the bias used in our path sampling simulations iteratively: We first carried out a simulation without bias to determine the work distribution in the peak region. From this distribution we extrapolated a bias to make less likely values of the work accessible to the simulation. After at most 2 iterations we obtained an umbrella function covering the entire relevant range of work.

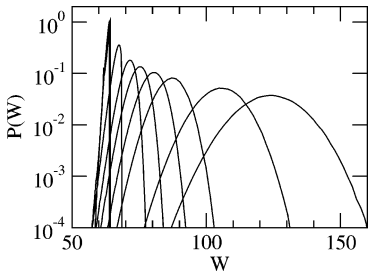

Figure 1. Work distributions $P(W)$ for Sun's model for the switching rates $\nu = 0.001$, 0.1, 1.0, 1.25, 1.42, 1.66, 2.0, 3.33, and 10.0 (from left to right). The work distributions for $\nu = 0.001$, 0.1, and 1.0 were calculated by straightforward fast switching from canonically distributed initial conditions while the other distributions were calculated with biased path sampling.

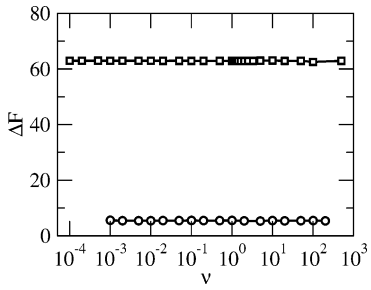

Figure 2. Free energy difference ΔF as a function of the switching rate obtained for the Sun model (squares) and the gradual Widom insertion (circles) from integrals over the work distribution, $\Delta F = \int \mathrm{d}W\, P(W) \exp(-\beta W)$.

As can be seen in Figure 1 the work distributions for the Sun model at low switching rates are narrow and centered at small work values. For faster switching the distributions become wider and are shifted toward higher work values. Note that even for infinitely slow switching the work distribution does not become a delta function. This is a consequence of the existence of adiabatic invariants in Hamiltonian systems, as will be discussed in section VIII. In contrast, the width of the work distribution goes to zero in the slow switching (linear response) limit if a thermostat is coupled to the system as is frequently done in molecular simulations.[6] As discussed below this fact has important implications for the efficieny of fast switching simulations.

Free energy differences ΔF obtained for Sun's model determined by numerical integration over the calculated work distributions (see eq 3) are displayed in Figure 2 (squares). These results indicate that for all switching rates considered in this study the work distributions are known in a sufficiently wide range to permit an accurate calculation of the free energy difference through Jarzynski's identity. To estimate the impor-

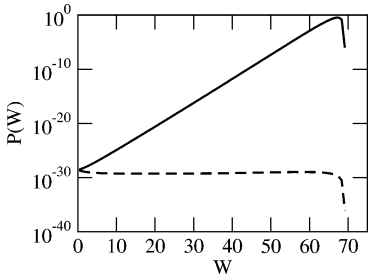

Figure 3. Work distributions $P(W)$ (solid line) and $P(W)\exp(-\beta W)$ (dashed line) as functions of the work W for Sun's model with a switching rate of $\nu = 1.0$.

tant range of W in advance, one could also generate trajectories for the reverse process, in which the control parameter is changed from λ_B to λ_A.[24] The work distribution $P_{\mathrm{rev}}(W)$ for the reverse process is related to the work distribution of the forward process by Crook's identity, $P_{\mathrm{rev}}(-W) = P(W)\exp(-\beta W)$.[2] Thus, $P_{\mathrm{rev}}(-W)$ is peaked exactly where the integrand appearing in Jarzynki's identity is peaked. For an accurate calculation of the free energy difference, the umbrella function should span the region in path space corresponding to pathways with work values in the range between the peaks of $P_{\mathrm{rev}}(-W)$ and $P(W)$.

The origin of numerical difficulties encountered in straightforward applications of the fast switching method is exemplified by the curves shown in Figure 3. Here, the solid line is the work distribution $P(W)$ for a switching rate of $\nu = 1$ and the dashed line is $P(W)\exp(-\beta W)$, the integrand appearing on the right-hand side of eq 3. Although the work distribution $P(W)$ is strongly peaked at work values around $W \approx 67$, the product $P(W)\exp(-\beta W)$ (with a maximum at $W = 0$) is almost flat up to $W \approx 65$. Hence, all work values in the range from $W = 0$ to $W \approx 70$ significantly contribute to the exponential average. In a straightforward fast switching simulation only trajectories with work values close to the peak of $P(W)$ are generated with high probability, causing large statistical uncertainties in the free energy estimate. Path sampling simulations with an appropriate bias, however, focuses on the most important trajectories, yielding accurate free energies differences.

From the calculated work distributions we can estimate the errors occurring in biased path sampling simulations for any bias function $\pi(W)$. Here we consider idealized path sampling simulations in which consecutive pathways are statistically independent from each other. In any practical simulations, however, correlations persist for several sampling steps. More than one path sampling move needs to be carried out in order obtain a statistically independent pathway, increasing the computational cost of calculating free energy differences with a desired level of accuracy. Such correlations can be taken into account in our efficiency analysis, but for simplicity we neglect them at this point.

Through numerical evaluation of the integrals (36)−(41), we have calculated the mean squared error ϵ_N^2 according to eq 34 for all switching rates. The normalized root-mean-squared error, $\epsilon_N\sqrt{N} = k_{\mathrm{B}}T\alpha$, is shown in Figure 4 as a function of the switching rate for different bias functions $\pi(W)$. Without a bias (dotted line) the error is small for slow switching but then grows very quickly once the switching rate exceeds $\nu = 10^{-2}$. The bias function $\pi(W) = \exp(-\beta W/2)$ introduced by Ytreberg and Zuckerman[17] keeps the error small to slightly larger switching rates but yields large errors for switching rates beyond $\nu = 0.1$. Small errors (solid line) are obtained over the whole range of switching rates for a bias proportional to the inverse of the work

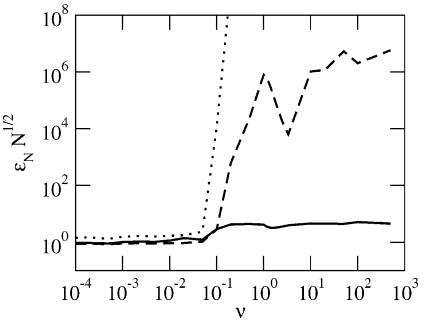

Figure 4. Root mean squared error ϵ_N times the square root of the sample size as a function of the switching rate ν for the Sun model calculated with the bias $1/P(W)$ (solid line), the bias $\exp(-0.5\beta W)$ (dashed line), and no bias (dotted line).

distribution, $\pi(W) = 1/P(W)$, over a range of work. More precisely, this bias is defined by

$$\pi(W) = \begin{cases} 1/P(W) & W_{\mathrm{min}} \le W \le W_{\mathrm{max}}, \\ 1/P(W_{\mathrm{min}}) & W < W_{\mathrm{min}}, \\ 1/P(W_{\mathrm{max}}) & W > W_{\mathrm{max}} \end{cases} \tag{49}$$

We have determined W_{min} and W_{max} by requiring that at these values $P(W)$ and $\exp(-\beta W)P(W)$, respectively, are less than a certain fraction of their peak values. For this bias function the sampled work distribution is flat in the range $W_{\mathrm{min}} < W < W_{\mathrm{max}}$. For all bias functions the normalized mean squared error converges to a well-defined value both in the limits of very large and very small switching rates. This is due to the fact that in these limits the work distribution $P(W)$ converges toward limiting distributions. Hence, the integrals over the work distribution determining the mean squared error are constant once these limiting distributions are reached. Note that for systems coupled to a heat bath during the switching procedure, this is not the case in the slow switching limit. For such systems, the variance of the work distribution depends linearly on the switching rate[7] and, hence, the work distribution converges toward a δ-function centered at the free energy difference for $\nu \to 0$.

To determine the numerical cost required to obtain a given accuracy in the free energy difference, we must take into account the cost associated with the generation of each trajectory. Because the trajectories are generated with molecular dynamics simulation this cost is proportional to the trajectory length. Hence, the number N of trajectories that can be generated with a given amount of CPU time is proportional to ν. This leads us to define a mean squared error per CPU time (see eq 34),

$$\epsilon_{\mathrm{CPU}}^2 \equiv \frac{k_{\mathrm{B}}{}^2T^2}{\nu}\alpha^2 \tag{50}$$

where the CPU time is effectively measured in units of the CPU time necessary to generate a trajectory of length $\tau = 1$. With this definition $\epsilon_{\mathrm{CPU}} = \epsilon_N\sqrt{N/\nu}$ The error per CPU time is shown in Figure 5 for different bias functions $\pi(W)$. For all bias functions the error per CPU time is a decreasing function of ν beyond a certain switching rate. Although both without a bias and with the Ytreberg−Zuckerman bias the error per CPU time has a minimum for switching rates close to $\nu = 0.1$, the error per CPU time for the $1/P(W)$ bias decreases almost monotonically over the whole range of switching rates considered here. Hence, in this case instantaneous switching, i.e., conventional umbrella sampling, yields the highest efficiency. Thermostated systems behave differently for small switching

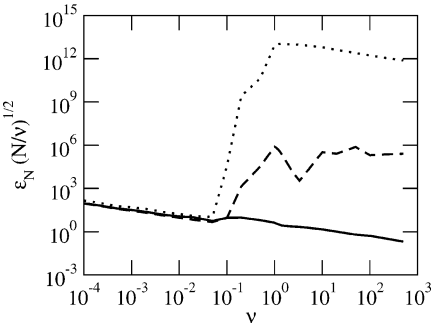

Figure 5. Error per CPU time, $\epsilon_N\sqrt{N/\nu}$, as a function of the switching rate ν for the Sun model calculated with the bias $1/P(W)$ (solid line), the bias $\exp(-0.5\beta W)$ (dashed line), and no bias (dotted line).

rates. In this case the error per CPU time reaches a constant value in the limit of small switching rates. Thus, for such systems, the efficieny ceases to be a function of the switching rate in the linear response regime.[9]

For the largest switching rate shown in Figure 5 ($\nu = 500$) the transformation is performed in one single step. In this case the work distribution has reached its limiting form of instantaneous switching. Thus, the error per CPU time in a conventional umbrella sampling simulation equals the error shown at $\nu = 500$ in Figure 5 (provided that the computational cost of generating a new configuration in an umbrella sampling simulation is roughly equal to the cost of a single molecular dynamics step).

For all error estimates discussed in the previous paragraphs we have assumed that all pathways are statistically independent from each other. In real path sampling simulations, however, correlations persist for a certain number of sampling steps, increasing the statistical error. To take correlations into account, we have calculated the autocorrelation function of the work, $\langle W(0)\ W(n)\rangle$, as a function of the number of sampling steps, n, for different switching rates. In all cases this correlation function decays approximately exponentially from its initial to its asymptotic value, $\langle W(0)\ W(n)\rangle \approx \langle W\rangle^2 + \exp(-n/n_c)(\langle W^2\rangle - \langle W\rangle^2)$. The parameter n_c can be interpreted as the number of path moves necessary to obtain a statistically independent pathway. Thus, the cost of an independent trajectory is increased by a factor of n_c with respect to the correlation free case. We have determined n_c for switching rates ranging from $\nu = 0.1$ to $\nu = 100.0$ in simulations with the bias function $\pi(W) = 1/P(W)$. Calculated values lie between $n_c \approx 5$ and $n_c \approx 90\,000$. Because shooting moves depend on the natural divergence of nearby trajectories in phase space, path sampling is most efficient when trajectory lengths are comparable to the time scales characterizing chaos. In the case of very fast switching, i.e., very short trajectories, the effect of this divergence is small, and slowly decaying correlations should be expected. Most likely, long correlation times in the short trajectory limit can be reduced by introducing new path moves involving position changes in addition to the momentum changes of the shooting algorithm.

Taking correlations into account, the mean squared error per CPU time becomes

$$\epsilon^2_{\mathrm{CPU}} \equiv \frac{{k_B}^2 T^2 n_c}{\nu}\alpha^2 \tag{51}$$

This error is shown in Figure 6 as solid line. For comparison we have also plotted the error per CPU time for straightforward fast switching simulations (dashed line), for which we have assumed no correlations ($n_c = 1$). The correlations in the path

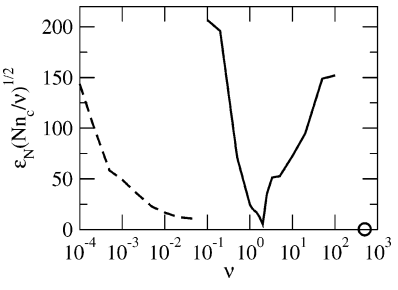

Figure 6. Error per CPU time, $\epsilon_N\sqrt{Nn_c/\nu}$ with correlations taken into account as a function of the switching rate ν for the Sun model for a bias of $1/P(W)$ (solid line) and without bias (dashed line). The symbol in the lower right corner denotes error per CPU time with correlations taken into account in an umbrella sampling Monte Carlo simulation.

sampling simulations make these free energy calculations considerably more expensive for high switching rates. The error per CPU time now has a minimum at $\nu = 2$ but grows for larger switching rate due to the stronger correlations for shorter pathways. Neglecting correlations, path simulations with bias $1/P(W)$ are more efficient than straightforward fast switching simulations for all switching rates $\nu > 1$. With correlations taken into account, biased path sampling is competitive with straightforward fast switching only in a narrow regime around $\nu = 2$. The correlation-corrected error per CPU time is lowest by far, however, for conventional umbrella sampling (circle in the lower right corner of Figure 6). We have plotted this result at a switching rate corresponding to a transformation taking place in one single molecular dynamics time step.

B. Gradual Widom Insertion. As a further example we calculated the chemical potential of a soft sphere fluid. This test case was considered by Jarzynski to illustrate the performance of straightforward fast switching simulations.[25] The model system consists of M identical, classical particles of mass m in three dimensions, interacting via the potential energy $U(r^{(M)})$. Here $r^{(M)}$ is a $3M$-dimensional vector specifying all particle coordinates. The system is enclosed in a constant volume V and is in contact with a heat bath at temperature T. (Note that in the context of the fast switching algorithm this is the temperature of the ensemble of initial conditions rather than a temperature which is maintained constant during the nonequilibrium transformation. In all our simulations the fast switching trajectories are calculated by integration of the Newtonian equations of motion without any coupling to a thermostat.) The chemical potential for such a system is defined as the derivative of the Helmholtz free energy $F(M, V, T)$ with respect to the particle number M,[6]

$$\mu \equiv \left(\frac{\partial F(M, V, T)}{\partial M}\right)_{V,T} \tag{52}$$

The Helmholtz free energy is

$$F(M, V, T) = -k_B T \ln Q(M, V, T) \tag{53}$$

where the partition function $Q(M, V, T)$ is given by

$$Q(M, V, T) = \frac{1}{\Lambda^{3M} M!}\int \mathrm{d}r^{(M)} \exp[-\beta U(r^{(M)})] \tag{54}$$

In contrast to the earlier definition of the partition function (see eq 6) this definition includes all proper (classical) factors. In the above equation, $\Lambda = (h^2/2\pi m k_B T)^{1/2}$ is the thermal wavelength and h is Planck's constant. The free energy can be separated into an ideal gas contribution and an excess part:

$$F(M, V, T) = F_{id}(M, V, T) + F_{ex}(M, V, T) \tag{55}$$

with

$$F_{id} = -k_B T \ln\left(\frac{V^M}{\Lambda^{3M} M!}\right) \tag{56}$$

$$F_{ex} = -k_B T \ln\left[\frac{1}{V^M}\int dr^{(M)} \exp[-\beta U(r^{(M)})]\right] \tag{57}$$

For large M the derivative with respect to the particle number can be written as a difference,

$$\mu = F(M+1, V, T) - F(M, V, T) \tag{58}$$

The chemical potential also separates naturally into an ideal gas contribution and an excess part:

$$\mu = \mu_{id} + \mu_{ex} \tag{59}$$

where

$$\mu_{id} = -k_B T \ln\left(\frac{V/\Lambda^3}{M+1}\right) \tag{60}$$

$$\mu_{ex} = -k_B T \ln\left[\frac{\int dr^{(M+1)} \exp[-\beta U(r^{(M+1)})]}{V\int dr^{(M)} \exp[-\beta U(r^{(M)})]}\right] \tag{61}$$

Though the ideal contribution μ_{id} to the chemical potential can be calculated analytically, the excess part μ_{ex} must be determined numerically. To do that, we rewrite the above expression for μ_{ex} as

$$\mu_{ex} = -k_B T \ln\left[\frac{\int dr^{(M+1)} \exp[-\beta U(r^{(M+1)})]}{\int dr^{(M+1)} \exp[-\beta U(r^{(M)})]}\right] \tag{62}$$

Note that here both the numerator and the denominator contain integrals over the $3(M+1)$-dimensional configuration space. The numerator is the configurational partition function for the full $M+1$ particle system, and the denominator is the partition function for a system of $M+1$ particles of which only the first M particles interact with each other through the potential energy $U(r^{(M)})$. Particle $M+1$ is an ideal particle that does not interact with the other particles. Thus the excess chemical potential can be viewed as the reversible work necessary to "switch on" the interactions between particle $M+1$ and all other particles.

Equation 62 is the basis for Widom's particle insertion method for calculating chemical potential.[6,26] In this approach, a canonical Monte Carlo (or molecular dynamics) simulation is carried out for the M particle system. Periodically, the particle $M+1$ is inserted at a random position drawn from a uniform distribution in the volume V. Averaging the exponential of the energy difference $\Delta U \equiv U(r^{(M+1)}) - U(r^{(M)})$, one then obtains the excess chemical potential from

$$\mu_{ex} = -k_B T \ln\frac{1}{V}\int dr_{M+1} \langle \exp(-\beta \Delta U)\rangle_M \tag{63}$$

where the integral over the coordinates of particle $M+1$ is evaluated by random insertions. The notation $\langle\cdots\rangle_M$ refers to a canonical average in the system with M particles.

Whereas, in the Widom method, particles are inserted instantaneously at random positions, one can apply Jarzynski's idea and insert particles gradually by turning on its interactions with the other particles at a finite rate. For this purpose one defines a parameter-dependent potential energy $U[r^{(M+1)}, \lambda]$ which equals $U[r^{(M)}]$ for $\lambda = 0$ and $U[r^{(M+1)}]$ for $\lambda = 1$. The control parameter varies from $\lambda = 0$ to $\lambda = 1$ in time τ according to a certain time dependence $\lambda(t)$. From the statistics of work W performed on the system during many such switching processes the chemical potential can be determined (see eq 2):

$$\exp(-\beta \mu_{ex}) = \langle \exp(-\beta W)\rangle \tag{64}$$

where the average is taken over the ensemble of fast switching trajectories. For infinite switching rate this expression reduces to the Widom expression.

We have performed straightforward fast switching and biased path sampling for a system of 32 soft particles in a periodically replicated box, interacting via a modified Lennard-Jones potential. For a pair of particles separated by a distance r the standard Lennard-Jones potential is

$$\phi_{LJ}(r) = 4\epsilon\left[\left(\frac{\sigma}{r}\right)^{12} - \left(\frac{\sigma}{r}\right)^{6}\right] \tag{65}$$

where ϵ is the depth of the potential and σ is the van der Waals diameter of the particles. To avoid problems with diverging energies due to particle overlap and infinite interaction radii, we use Jarzynski's modification of the Lennard-Jones potential:[25]

$$\phi(r) = \begin{cases} a - br^2 & \text{if } 0 \le r \le 0.8\sigma, \\ \phi_{LJ} + c(r - r_c) - d & \text{if } 0.8\sigma \le r \le r_c, \\ 0 & \text{if } r_c \le r \end{cases} \tag{66}$$

The cutoff radius r_c is half the box length and the parameters a, b, c, and d were chosen such that the potential and its first derivative are continuous everywhere. All our simulations were carried out for a particle number (including the particle that does not interact with the other particles at $\lambda = 0$) $M + 1 = 32$, a density $\rho = (M+1)/V = 0.8\sigma^{-3}$, and a temperature corresponding to $k_B T/\epsilon = 1.0$ (this is the temperature of the initial conditions). At this density the side length of the cubic simulation box is $L = 3.420\sigma$ and the interaction parameters are $r_c = 1.710\sigma$, $a = 327.2\epsilon$, $b = 474.4\epsilon/\sigma^2$, $c = -0.516\epsilon/\sigma$, and $d = -0.154\epsilon$. Equations of motion were integrated with the velocity Verlet algorithm with a step size of $\Delta t = 0.0005\sigma(m/\epsilon)^{1/2}$.

The parameter λ is used to turn on the interaction of particle $M+1$ with the other M particles:

$$U[r^{(M+1)}, \lambda] \equiv \sum_{i\neq j}^{M} \phi(r_{ij}) + \lambda \sum_{i}^{M} \phi(r_{i(M+1)}) \tag{67}$$

where r_{ij} is the distance between particles i and j. In all our simulations the time dependence of λ is

$$\lambda(t) = (t/\tau)^2 \tag{68}$$

where $\tau = 1/\nu$ is the trajectory length and ν is the switching rate.

We first calculated the work distribution for this gradual Widom insertion using straightforward fast switching. For this purpose we generated canonically distributed initial conditions by molecular dynamics simulation of the system coupled to a heat bath through an Andersen thermostat.[27] The collision frequency per particle for the Andersen thermostat was $0.02(\epsilon/m\sigma^2)^{1/2}$. For each initial configuration we selected random velocities from a Maxwell−Boltzmann distribution and inte-

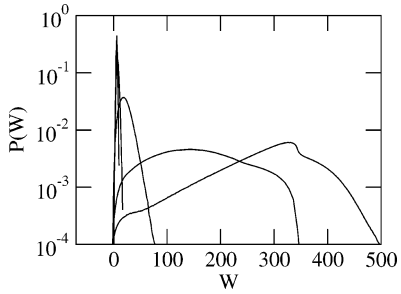

Figure 7. Work distributions $P(W)$ for the gradual Widom insertion for switching rates $\nu = 0.001$, 0.01, 0.1, 1.0, 10.0, and $100.0(\epsilon/m\sigma^2)^{1/2}$ (from left to right).

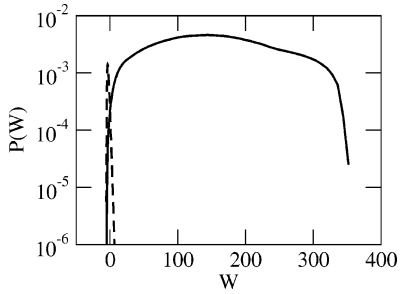

Figure 8. Work distribution $P(W)$ (solid line) and the function $P(W)$ $\exp(-\beta W)$ (dashed line) as a function of the work W for the gradual Widom insertion with a switching rate of $\nu = 10.0(\epsilon/m\sigma^2)^{1/2}$.

grated the time dependent Hamiltonian equations of motion for the isolated system. We calculated work distributions $P(W)$ for switching rates ranging from $\nu = 0.001(\epsilon/m\sigma^2)^{1/2}$ to $\nu = 200\text{-}(\epsilon/m\sigma^2)^{1/2}$ generating from 250 (for $\nu = 0.001(\epsilon/m\sigma^2)^{1/2}$) to 50 $\times 10^6$ (for $\nu = 200(\epsilon/m\sigma^2)^{1/2}$) trajectories. For the switching rates from $\nu = 0.2(\epsilon/m\sigma^2)^{1/2}$ to $\nu = 200(\epsilon/m\sigma^2)^{1/2}$ we extended the work distributions toward very small work values using biased path sampling. For this purpose we extrapolated the work distributions obtained from straightforward fast switching into the small W range and used the extrapolated distributions to construct a bias for path sampling. These simulations were limited to the small W range. The complete work distribution was finally obtained by matching the work distributions computed in biased path sampling simulations with those from straightforward fast switching runs.

With this strategy we were able to calculate work distributions down to sufficiently small work values such that an error analysis was possible. Some of these distributions are shown in Figure 7. Though for high switching rates the work distributions are broad and extend to large work values, for slow switching the work distributions are narrow and peaked at work values near the free energy difference. The work distribution $P(W)$ for a switching rate of $\nu = 10.0(\epsilon/m\sigma^2)^{1/2}$ (solid line) is shown in Figure 8 along with $P(W)$ $\exp(-\beta W)$. Because $P(W)$ $\exp(-\beta W)$ is nonnegligible only in the small W tail of $P(W)$, statistical errors in reversible work are large for straightforward fast switching simulations.

From the simulations described above we have also calculated the free energy difference ΔF as a function of the control parameter λ. For $0 < \lambda < 1$ this is the reversible work required to partially turn on the interactions of particle $M + 1$ with the other particles. Figure 9 shows $\Delta F(\lambda)$ obtained from simulations carried out for different switching rates ranging from $\nu = 0.001\text{-}(\epsilon/m\sigma^2)^{1/2}$ to $\nu = 10.0(\epsilon/m\sigma^2)^{1/2}$. As expected, all curves coincide, indicating that a sufficient number of trajectories has been generated to obtain an accurate free energy estimate. Interestingly, $\Delta F(\lambda)$ has a maximum at about $\lambda \approx 0.35$. Thus, an amount

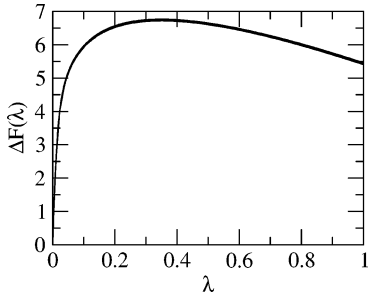

Figure 9. Free energy difference ΔF as a function of the parameter λ calculated using the Jarzynski equality for different switching rates ranging from $\nu = 0.001(\epsilon/m\sigma^2)^{1/2}$ to $\nu = 10.0(\epsilon/m\sigma^2)^{1/2}$ for the gradual Widom insertion. The value of ΔF for $\lambda = 1$ is the chemical potential μ.

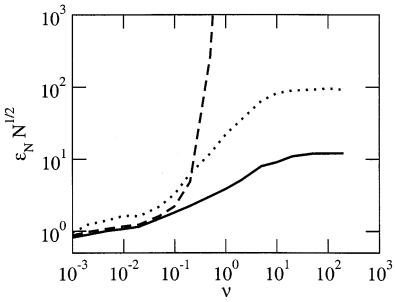

Figure 10. Root mean squared error ϵ_N times the square root of the sample size as a function of the switching rate ν for the gradual Widom insertion calculated with the bias $1/P(W)$ (solid line), the bias $\exp(-0.5\beta W)$ (dashed line), and no bias (dotted line).

of work 6.73 $k_B T$ must be expended to reversibly change the control parameter λ from 0 to 0.35. Increasing it further from 0.35 to 1.0, an amount of work 1.28 $k_B T$ is returned by the system. The free energy difference at $\lambda = 1$ is the excess chemical potential, $\mu_{ex} = 5.45\ k_B T$.

Using the work distributions calculated with straightforward fast switching and biased path sampling simulations, we have carried out an error analysis for different bias functions. The results of this analysis are presented in Figure 10. As in the case of Sun's one-dimensional model, the error in the free energy estimate obtained without a bias (dotted line) is small only for low switching rates. For switching rates $\nu > 0.1(\epsilon/m\sigma^2)^{1/2}$, the system naturally relaxes over time scales much longer than τ and cannot adapt to the perturbation as the particle is inserted. Statistical error thus grows very quickly with increasing ν. Smaller errors are obtained for slow switching for the bias function $\pi(W) = \exp(-0.5\beta W)$ (dashed line). For growing switching rate, however, the error quickly grows and, interestingly, eventually exceeds the error for the bias free case. For the bias $\pi(W) = 1/P(W)$ (solid line) the computed error depends weakly on ν over the whole range of switching rates. At the highest switching rates we have examined, the error reaches a plateau in all three cases indicating that the work distribution has reached its limiting form for instantaneous insertions. At low switching rates the error maintains significant dependence on switching rate. Thus, the corresponding work distributions still differ from the limiting distribution expected for an adiabatically driven Hamiltonian system (see section VIII).

As in the previous example, we computed error per CPU time by taking into account the cost of generating molecular dynamics trajectories. Results of this analysis are displayed in Figure 11 as a function of the switching rate. for the bias $\pi(W) = \exp(-0.5\beta W)$ (dashed line) the error per CPU time is minimum at

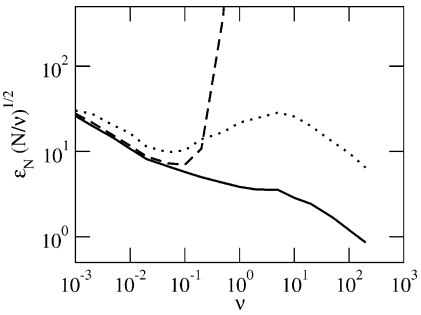

Figure 11. Normalized error per CPU time, $\epsilon_N\sqrt{N/\nu}$, as a function of the switching rate ν for the gradual Widom insertion calculated with the bias $1/P(W)$ (solid line), the bias $\exp(-0.5\beta W)$ (dashed line), and no bias (dotted line).

a switching rate of about $0.1(\epsilon/m\sigma^2)^{1/2}$. For smaller switching rates the error per CPU time increases with decreasing ν. This observation contradicts the expectation that for small switching rates the variance of the work distribution is inversely proportional to the trajectory length τ.[9,28] If that were true, the error per CPU time would be constant for switching rates below a certain threshold. In fact, this is what is found for systems coupled to a heat bath during the switching process. Why this expectation, however, is not valid for strictly Hamiltonian dynamics is explained in section VIII by considering adiabatic invariants.

Both without bias (dotted line) and for the bias $\pi(W) = 1/P(W)$ (solid line) the error per CPU time is minimum for the largest switching rate considered. This implies that, neglecting correlations, instantaneous switching (i.e., conventional umbrella sampling) is more efficient than any biased path sampling simulations with pathways of finite length. In drawing this conclusion, we have assumed that one Monte Carlo step and one molecular dynamics step have approximately the same cost. Furthermore, correlations between successive samples are likely to be more problematic for path sampling than for regular umbrella sampling (see section VIIA). We therefore expect the practical superiority of standard methods of equilibrium statistical mechanics to be further enhanced when correlations are taken into account.

VIII. Adiabatic Invariants

If an external parameter λ of an ergodic Hamiltonian system is changed very slowly, then certain quantities known as *adiabatic invariants* remain conserved.[29] In the case of a one-dimensional pendulum, for instance, the ratio of the energy E and the square root of the length l of the pendulum is exactly conserved in the limit of an infinitely slow change in l. The conserved quantity $E/\sqrt{l}$ is just the action

$$I(E, \lambda) = \frac{1}{2\pi} \oint p dq \tag{69}$$

i.e., the phase space volume enclosed by a surface of constant energy, $H(q, p, \lambda) = E$.[30,31] In other words, a slow change of an external parameter λ from $\lambda(0)$ to $\lambda(\tau)$ maps an energy shell of the initial Hamiltonian into a unique energy shell of the final Hamiltonian (namely, the energy shell enclosing the same phase volume). Known as the Ehrenfest adiabatic invariant, the action is conserved for all slowly driven Hamiltonian systems with one degree of freedom.

This result can be extended to higher dimensions. As observed by Hertz,[32,33] an adiabatic transformation uniquely maps an energy shell of an ergodic Hamiltonian system into another

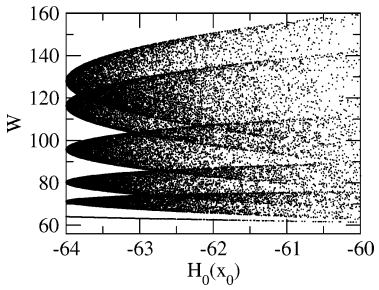

Figure 12. Scatter plot of work values as a function of the initial energy for different switching rates for Sun's model. Each point in the plot corresponds to a single trajectory started from an initial state x_0 with energy $H(x_0)$ and along which the work W has been performed on the system during the transformation. The parabolically shaped sets of points have been performed on the system during the transformation. The parabolically shaped sets of points have been obtained for six different switching rates decreasing from top to bottom. For small switching rates adiabatic invariance leads to an almost unique dependence of the work from the initial energy.

energy shell. Although the energy of the system changes when the external parameter λ is varied, it does so in the same way for all initial conditions lying on an energy shell of the initial Hamiltonian provided the variation of λ is carried out sufficiently slowly. As a result, the energy $E_\tau = H(x_\tau(x_0), \lambda(\tau))$ of the system at the end of a slow transformation of duration τ is a unique function of the initial energy $E_0 = H(x_0, \lambda(0))$ and it is independent of the specific initial phase point x_0. Furthermore, Liouville's theorem implies that the phase space volume $\Omega(E)$ enclosed by an energy shell is conserved by the system's dynamics. Hence, the entropy $S(E) = k_B \ln \Omega(E)$ does not change during an adiabatic transformation.[34] Exploiting this fact, Watanabe and Reinhardt devised a method to calculate entropies (and hence free energies) of classical fluids from adiabatic switching molecular dynamics simulations.[35] Recently, Adib generalized this approach and showed how to determine entropy differences from fast switching trajectories forced by ergostats to maintain constant energy.[36]

For isolated Hamiltonian systems the existence of the Hertz invariant has a strong effect on the distribution of work performed on the system during transformation of the external parameter λ in the slow switching limit.[8] In this case, the system never thermalizes and for each value of the external parameter the phase space distribution deviates from the canonical distribution. In general, the work performed on the system differs from the free energy difference even in the limit of infinitely slow switching. It is important to note, however, that Jarzynski's equality still holds.

In the slow switching limit the energy E_τ of the system at the end of a transformation of duration τ is a unique function of the initial energy E_0 only, $E_\tau(E_0)$. Therefore, all trajectories initiated on a given energy shell with energy E_0 will accumulate the same amount of work,

$$W(E_0) = E_\tau(E_0) - E_0 \tag{70}$$

The work as a function of the initial energy is shown in Figure 12 at different switching rates for Sun's model. For higher switching rates there is no one-to-one relation between the work and the initial energy and for each E_0 the work W is distributed over a wide range. As the switching rate decreases the correlation between W and E_0 becomes stronger. In the limit of infinitely slow switching, W uniquely depends on E_0 (line at the bottom of the plot). Using this result, we can express the work distribution in terms of the density of states of the initial system.

In general, the work distribution $P(W)$ for an ensemble of (deterministic) trajectories with canonically distributed initial conditions x_0 is given by

$$P(\tilde{W}) = \int \mathrm{d}x_0 \, \mathrm{e}^{-\beta H[x_0,\lambda(0)]} \delta[\tilde{W} - W(x_0)]/Q_0 \qquad (71)$$

where $Q_0 = \int \mathrm{d}x_0 \exp(-\beta H[x_0, \lambda(0)])$. Inserting a factor of unity, $1 = \int \mathrm{d}E_0 \; \delta[E_0 - H(x_0, \lambda(0))]$, exchanging the order of integration, and using relation (70) we obtain

$$P(\tilde{W}) = \int \mathrm{d}E_0 \, \mathrm{e}^{-\beta E_0} g(E_0) \delta[\tilde{W} - W(E_0)]/Q_0 \qquad (72)$$

where

$$g(E) \equiv \int \mathrm{d}x_0 \; \delta(E - H[x_0, \lambda(0)]) \qquad (73)$$

is the density of states corresponding to the initial Hamiltonian. Because the final energy of the system after a slow switching transformation is a unique function of its initial energy, $E_\tau = E_\tau(E_0)$ and the time reversibility of Hamilton's equations of motion implies that E_0 is a unique function of E_τ, the work $W(E_0) = E_\tau(E_0) - E_0$ is a *monotonic* function of the initial energy E_0. Therefore, we can transform variables from E_0 to W and carry out the integration in eq 7 obtaining

$$P(W) = \left|\frac{\mathrm{d}W}{\mathrm{d}E_0}\right|^{-1}_{\mathrm{E}_0 = E_0(W)} g(E_0(W)) \mathrm{e}^{-\beta E_0(W)}/Q_0 \qquad (74)$$

or, equivalently,

$$P(W) = \left|\frac{\mathrm{d}W}{\mathrm{d}E_0}\right|^{-1}_{E_0 = E_0(W)} P_E(E_0(W)) \qquad (75)$$

where $P_E(E) \equiv \int \mathrm{d}x_0 \exp(-\beta H[x_0, \lambda(0)]) \delta(E - H[x_0, \lambda(0)])/Q_0$ is the energy distribution in the canonical ensemble of initial conditions.

Equation 75 implies that the work distribution for isolated Hamiltonian systems subject to a changing external parameter converges toward a well-defined limiting distribution in the limit of adiabatic switching. In general, this distribution has a finite width. As discussed above, this fact has strong implications for the efficiency of fast switching simulations in the adiabatic limit. In contrast, the width of the work distribution for systems in contact with a heat reservoir during the transformation, converges toward zero in the limit of vanishing switching rate. For such systems, the work W performed on the system in the infinitely slow switching limit is equal to the free energy difference ΔF for all trajectories. Isolated Hamiltonian systems do not behave in this way. Figure 13, which displays a work distribution obtained with very small switching rate for the 1d-model discussed in section VIIA, illustrates the finite width of $P(W)$ in the limit of slow switching.

If the system is coupled to a heat bath during the switching procedure, the work done on the system in the slow switching (linear response) limit is a sum of many small, essentially uncorrelated contributions. In this case the work distribution is Gaussian with a variance inversely proportional to the switching time.[7] This can be demonstrated as follows. Consider a system evolving in time while the control parameter is slowly switched from its initial value λ_A to its final value λ_B. Imagine further that the parameter λ is switched in n small instantaneous steps and after each change in λ the system evolves for a time $\Delta\tau$ at constant λ. The time interval $\Delta\tau$ is selected such that the system can thermalize and correlations are lost before the next step in λ is carried out. At each change of λ work is performed on the system. Because the system is given time to thermalize at each value of λ, the average work done on the system at a small change $\Delta\lambda = (\lambda_B - \lambda_A)/n$ is

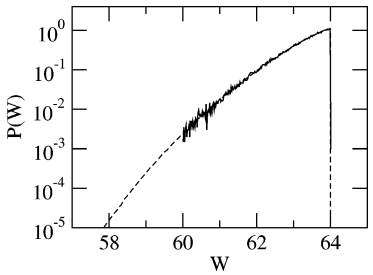

Figure 13. Work distributions $P(W)$ for Sun's model obtained from a straightforward switching simulation with trajectories of length $\tau = 10^4$ (solid line) and from eq 75 (dashed line). The function $W(E_0)$ necessary for the evaluation of the expression in eq 75, was obtained numerically by starting trajectories of length $\tau = 2 \times 10^5$ from phase points with evenly spaced energies. Increasing the number of steps by a factor of two did not change the results on the scale shown in the figure. The distribution $P_{E_0}(E)$ can be determined analytically for this simple one-dimensional model.

$$\langle \Delta W \rangle_\lambda = \int \mathrm{d}x \frac{\exp[-\beta H(x, \lambda)]}{Q} \left[\Delta\lambda \frac{\partial H(x, \lambda)}{\partial \lambda}\right] \qquad (76)$$

$$= \Delta\lambda \left\langle \frac{\partial H}{\partial \lambda} \right\rangle_\lambda \qquad (77)$$

where $\langle \cdots \rangle_\lambda$ denotes a canonical ensemble average with control parameter λ and we have approximated the difference $H(x, \lambda + \Delta\lambda) - H(x, \lambda)$ by $\Delta\lambda(\partial H/\partial\lambda)$. The average of the total work is the sum of the work averages at each step,

$$\langle W \rangle = \sum_\lambda \Delta\lambda \left\langle \frac{\partial H}{\partial \lambda} \right\rangle_\lambda \qquad (78)$$

$$\approx \int_{\lambda_A}^{\lambda_B} d\lambda \left\langle \frac{\partial H}{\partial \lambda} \right\rangle_\lambda = \Delta F \qquad (79)$$

where we have approximated the sum by an integral. Similarly, the average of the work squared at each step is given by

$$\langle (\Delta W)^2{}_\lambda \rangle = (\Delta\lambda)^2 \left\langle \left(\frac{\partial H}{\partial \lambda} \right)^2 \right\rangle_\lambda \qquad (80)$$

yielding a variance of

$$\langle (\delta \Delta W)^2 \rangle_\lambda = \langle (\Delta W)^2 \rangle_\lambda - \langle \Delta W \rangle_\lambda{}^2 = (\Delta\lambda)^2 \left[\left\langle \left(\frac{\partial H}{\partial \lambda} \right)^2 \right\rangle_\lambda - \left\langle \frac{\partial H}{\partial \lambda} \right\rangle_\lambda{}^2 \right] \qquad (81)$$

According to the central limit theorem[37] the sum of independent random variables has Gaussian distribution with a variance equal to the sum of the variances of the random variables. Hence, the variance of the total work is given by the sum of the work variances at each step of the process:

$$\langle (\delta W)^2 \rangle = \sum_\lambda \langle (\delta \Delta W)^2 \rangle \approx \Delta\lambda \int d\lambda \left[\left\langle \left(\frac{\partial H}{\partial \lambda} \right)^2 \right\rangle_\lambda - \left\langle \frac{\partial H}{\partial \lambda} \right\rangle_\lambda{}^2 \right] \qquad (82)$$

Because the integral on the right-hand side of the above equation is a number independent of the number of steps n, and $\Delta\lambda = (\lambda_B - \lambda_A)/n = (\lambda_B - \lambda_A)\Delta\tau/\tau$, we finally obtain

$$\langle(\delta W)^2\rangle \propto \frac{1}{\tau} \tag{83}$$

For isolated Hamiltonian systems and low switching rates the total work W performed along a certain trajectory cannot be viewed as resulting from many independent contributions. Rather, due to the existence of adiabatic invariants, the total work is a unique function of the initial energy. Therefore, we expect deviations from the above relation for isolated Hamiltonian systems in the linear response limit. The variance of the work distribution as a function of the switching rate (dashed line) is shown in Figure 14 for the gradual Widom insertion in the 32 particle soft sphere system. Clearly, the variance is not proportional to $1/\tau$ (dotted line) but flattens for decreasing switching rates and seems to converge toward a constant. This behavior is consistent with the finite width expected for the work distribution in the slow switching limit when adiabatic invariance becomes manifest (see eq 75).

Although for isolated Hamiltonian systems the variance does not scale with $1/\tau$, the work distributions do become Gaussian in the case of slow switching. For Gaussian work distributions Jarzynski's equation requires that

$$\beta\langle W_d\rangle = \frac{1}{2}\beta^2[\langle W^2\rangle - \langle W\rangle^2] \tag{84}$$

where $W_d = W - \Delta F$ is the dissipative work. Figure 14 shows $\beta\langle W_d\rangle$ (solid line) and $(1/2)\beta^2[\langle W^2\rangle - \langle W\rangle^2]$ (dashed line) as functions of the switching rate. Equation 84 is obeyed in the low switching rate (linear response) limit. The Gaussian form of the work distribution is most likely due to the approximately Gaussian nature of the energy distribution $P(E) = g(E)\exp(-\beta E)$ for many-particle systems at thermal equilibrium. It follows from eq 75 that this feature leads to a Gaussian work distribution, provided the function $|dW/dE_0|$ changes only weakly in the important energy range. Interestingly, the peak of a Gaussian work distribution for an isolated Hamiltonian system does not in general coincide with the reversible work, even in the limit of slow change. Because the system is unable to thermalize, the phase space distribution prepared by adiabatically slow switching differs from a canonical distribution with the final value of the control parameter. The mean of a Gaussian work distribution for slow switching is thus offset from the true free energy difference by the amount of work required to reversibly transform the final, nonthermal distribution into its thermal counterpart.

IX. Conclusions

The Jarzynski theorem is one of the few general exact results known for nonequilibrium processes. From a computational point of view its attractiveness stems from the promise of more efficient free energy calculations. For low switching rates, however, computer simulations based on a straightforward application of Jarzynski's theorem do not lead to performance increases with respect to conventional methods such as thermodynamic integration. More precisely, the average errors of a free energy estimate obtained from a few long trajectories or many short trajectories are the same for the same amount of CPU time (provided the system is not driven far away from equilibrium).[9] In the linear response limit the only advantage of fast switching simulations compared to thermodynamic integration is the improved error estimation and easier parallelizability.[9]

The above conclusion is valid only if the system can thermalize while the control parameter is changed. In molecular simulations such a thermalization is often achieved by coupling a thermostat to the equations of motion. For isolated Hamiltonian systems, however, this is not the case. For such systems, the work distribution approaches a limiting functional form with finite width (rather than collapsing to a delta-function) even for vanishing switching rate due to the existence of adiabatic invariants. As a consequence, the expected error for a given number of samples becomes constant for switching rates below a certain value. As a peculiarity of Hamiltonian systems evolving without contact to a heat bath, the error per CPU time then diverges as $1/\nu$ instead of reaching a constant value as in the case of thermalizing systems.

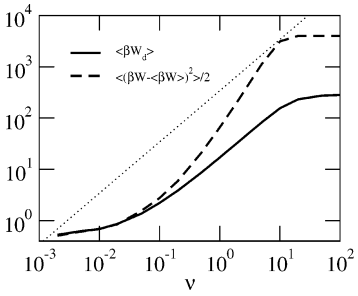

Figure 14. Average dissipative work (solid line) and work fluctuations (dashed line) as a function of the switching rate for the gradual Widom insertion in the 32-particle soft sphere fluid. Because the system evolves according to Newton's equations of motion and is isolated during the transformation, both curves deviate from the linear dependence on the swithing rate (dotted line) expected for thermalizing systems (see eq 83).

For larger switching rates straightforward fast switching simulations become less efficient due to statistical inaccuracies related to the exponential averaging. Biased path sampling schemes,[13,17] designed to sample nonequilibrium pathways with rare but important work values, can help to overcome these practical difficulties. But there is no guarantee that these algorithms can compete with conventional methods. The error analyses we have carried out for a simple one-dimensional model and a Widom particle insertion in a soft sphere fluid indicate that, provided knowledge of a good bias function, optimal efficiency is obtained for instantaneous switching.

We expect that this result, demonstrated numerically for two specific examples, holds quite generally. Because adiabatic invariants are not relevant for fast switching, systems in contact with a heat bath should be no exception. If the switching rate is increased beyond the range where the system can adapt to the change in the control parameter, the work distribution reaches a limiting form. In this regime, where the work distribution is essentially identical to the work distribution obtained for instantaneous switching, the error expected for a given number of samples ceases to be a function of the switching rate. The computational cost of generating a trajectory, however, keeps decreasing with increasing switching rate. For this reason, the error per CPU time is smallest for instantaneous switching. In this limit, the biased path sampling scheme reduces to conventional umbrella sampling.

Put another way, the phase space mapping provided by Hamiltonian trajectories of length τ is useful only to the extent that the distribution of microstates at time τ overlaps the final equilibrium state more extensively than the original equilibrium state does. Such improvement of overlap can be reasonably expected only when τ is comparable to or larger than a system's basic relaxation times, as reflected by the approach of $P(W)$ to a limiting form. Moreover, the benefit provided by improved statistical overlap is only mild when a good bias function is

known. The cost of generating fast switching trajectories is therefore accompanied by little statistical gain.

Our conclusion that conventional umbrella sampling is superior to the fast switching approach hinges on the possibility of finding good biasing functions. Recently, simulations methods such as Wang−Landau sampling have been developed to systematically find optimum bias functions. We are thus led to the conclusion that simulation methods based on the Jarzynski equation do not offer any efficiency gain compared to conventional umbrella sampling and thermodynamic integration. It remains to be seen if more sophisticated fast switching methodologies can be developed to surpass the efficacy of standard methods.

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