The Journal of Chemical Physics

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Cite as: J. Chem. Phys. **124**, 044113 (2006); https://doi.org/10.1063/1.2162874
Submitted: 15 July 2005 . Accepted: 28 November 2005 . Published Online: 30 January 2006

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Equilibrium free energies from fast-switching trajectories with large time steps

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(Received 15 July 2005; accepted 28 November 2005; published online 30 January 2006)

Jarzynski's [Phys. Rev. Lett. **78**, 2690 (1997)] identity for the free-energy difference between two equilibrium states can be viewed as a special case of a more general procedure based on phase-space mappings. Solving a system's equation of motion by approximate means generates a mapping that is perfectly valid for this purpose, regardless of how closely the solution mimics true time evolution. We exploit this fact, using crudely dynamical trajectories to compute free-energy differences that are in principle exact. Numerical simulations show that Newton's equation can be discretized to low order over very large time steps (limited only by the computer's ability to represent resulting values of dynamical variables) without sacrificing thermodynamic accuracy. For computing the reversible work required to move a particle through a dense liquid, these calculations are more efficient than conventional fast-switching simulations by more than an order of magnitude. We also explore consequences of the phase-space mapping perspective for systems at equilibrium, deriving an exact expression for the statistics of energy fluctuations in simulated conservative systems. © *2006 American Institute of Physics*. [DOI: 10.1063/1.2162874]

I. INTRODUCTION

The maximum work theorem, a consequence of the second law of thermodynamics, states that the amount of work performed by a thermodynamic system during a transformation from a specific initial state A to a specific final state B is less than the free-energy difference between the two states.[1] The work W is maximum and equal to the free-energy difference, or *reversible work*, if the transformation is carried out reversibly. Equivalently, the average work performed on a system during such a transformation is bounded from below by the free-energy difference ΔF,

$$\langle W \rangle \geqslant \Delta F. \tag{1}$$

The notation $\langle \cdots \rangle$ implies an average over many in general irreversible transformations initiated in an equilibrium state. (For macroscopic systems every individual transformation will require the same amount of work but for small systems work fluctuations occur.) Remarkably, the inequality (1) can be turned into an equality by considering exponential averages,[2]

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

where $\beta = 1/k_B T$ is the inverse temperature and k_B is Boltzmann's constant. This identity, proven by Jarzynski[2] and later by Crooks[3] under very general conditions, relates the statistics of irreversible work to equilibrium free-energy differences.

The Jarzynski identity can be used to calculate free-energy differences in computer simulations of molecular systems.[4–8] In statistical mechanical terms the free-energy difference $\Delta F = F_B - F_A$ between a system at temperature T with Hamiltonian $\mathcal{H}_B(x)$ and another one at the same temperature with Hamiltonian $\mathcal{H}_A(x)$ is given by

$$\Delta F = -k_B T \ln \frac{\int dx \exp\{-\beta \mathcal{H}_B(x)\}}{\int dx \exp\{-\beta \mathcal{H}_A(x)\}} = -k_B T \ln \frac{Q_B}{Q_A}, \tag{3}$$

where the integration extends over the entire phase space and $x = \{q, p\}$ includes the positions q and momenta p of all particles. In the above equation, Q_A and Q_B are the canonical partition functions of systems A and B. To calculate ΔF using Jarzynski's identity we introduce a parameter-dependent Hamiltonian $\mathcal{H}(x, \lambda)$ defined such that $\mathcal{H}_A$ and $\mathcal{H}_B$ are obtained for particular values of the control parameter, $\mathcal{H}(x, \lambda_A) = \mathcal{H}_A(x)$ and $\mathcal{H}(x, \lambda_B) = \mathcal{H}_B(x)$. By switching the control parameter λ from λ_A to λ_B we can continuously transform $\mathcal{H}_A(x)$ into $\mathcal{H}_B(x)$. If this is done over a time τ, while the system evolves from particular initial conditions x_0, the work performed on the system is

$$W = \int_0^\tau dt \left(\frac{\partial \mathcal{H}}{\partial \lambda} \right) \dot{\lambda}. \tag{4}$$

Its value depends on the initial conditions x_0 and on the particular way the control parameter $\lambda(t)$ is switched from its initial to its final value. According to Jarzynski's identity, the free-energy difference can be evaluated by averaging the work exponential $e^{-\beta W}$ over many such transformations. Specifically, this average is performed over a canonical distribution of initial conditions in the initial equilibrium state,

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$$\exp(-\beta\Delta F) = \int dx_0 \rho(x_0) \exp\{-\beta W(x_0)\}, \tag{5}$$

where $\rho(x_0) = \exp\{-\beta\mathcal{H}_A(x_0)\}/Q_A$.

In fast-switching simulations based on the Jarzynski identity, nonequilibrium trajectories are generated by approximately integrating the equation of motion, typically through a truncated Taylor expansion of the time-evolving phase-space point $x(t)$. The fidelity of trajectories obtained in this way to true microscopic dynamics is determined by the time interval over which a low-order Taylor expansion is assumed to be accurate. Usually, the time step is chosen to be small, so that the total energy is nearly conserved when control parameters are held constant (in an isolated system).[9,10] In this paper we show that fast-switching trajectories integrated with large time steps, while perhaps poor simulations of dynamics suffice to compute *exact* free-energy differences. This new approach, which can increase the efficiency of fast-switching simulations by up to two orders of magnitude, is based on a generalization of Jarzynski's identity for general phase-space mappings.[11,12] Jarzynski's original expression corresponds to the particular phase-space mapping provided by the dynamical propagator. His result is valid, however, for any invertible phase-space mapping. One could just as well use a concatenation of highly approximate molecular-dynamics steps, the result of integrating equations of motion to low order over large time intervals, to map points in phase space. Although such large time step trajectories are not accurate dynamical pathways, expressions for the free energy remain exact. Due to the reduced cost of large time step trajectories, a considerable efficiency increase is possible.

The remainder of the paper is organized as follows. The formalism and the justification of the large time step approach are presented in Sec. II. The efficiency of the resulting algorithm is discussed in Sec. III. In Sec. IV we demonstrate the validity of this algorithm by calculating the reversible work for transformations in three different model systems. In Sec. V we discuss our results and show that our method remains valid also for stochastic mappings. Conclusions are given in Sec. VI.

II. FORMALISM

A. Jarzynski's identity for phase-space mappings

The deterministic time evolution of a classical many-particle system can be viewed as mapping every point in phase space to another: a system initially at x_0 will be located at $x_t = \phi_t(x_0)$ after a time t. The function ϕ_t is called the *propagator* of the system. Since the system evolves deterministically the point x_t is completely determined by the initial conditions x_0. The time reversibility of the equations of motion further ensures that such a mapping is invertible, i.e., that from x_t the corresponding starting point x_0 can be uniquely determined, $x_0 = \phi_{-t}(x_t)$.

Consider now a general invertible and differentiable mapping,

$$x' = \phi(x), \tag{6}$$

that maps phase-space point x into phase-space point x'. Here, the mapping $\phi(x)$ takes the place of the propagator $\phi_t(x)$. For such mappings Jarzynski has derived an expression akin to the nonequilibrium work theorem.[12] To introduce the necessary notation we rederive this result. For this purpose we consider the definition of the free-energy difference,

$$\exp(-\beta\Delta F) = \frac{Q_B}{Q_A} = \frac{\int dx' \exp\{-\beta\mathcal{H}(x', \lambda_B)\}}{Q_A}. \tag{7}$$

Multiplying and dividing the integrand in the above equation with $\exp\{-\beta\mathcal{H}(\phi^{-1}(x'), \lambda_A)\}$ we obtain

$$\exp(-\beta\Delta F) = \int dx' \frac{\exp\{-\beta\mathcal{H}(\phi^{-1}(x'), \lambda_A)\}}{Q_A} \times \exp\{-\beta[\mathcal{H}(x', \lambda_B) - \mathcal{H}(\phi^{-1}(x'), \lambda_A)]\}. \tag{8}$$

A change of integration variables from x' to $x = \phi^{-1}(x')$ yields

$$\exp(-\beta\Delta F) = \int dx \left|\frac{\partial\phi(x)}{\partial x}\right| \frac{\exp\{-\beta\mathcal{H}(x, \lambda_A)\}}{Q_A} \times \exp\{-\beta[\mathcal{H}(\phi(x), \lambda_B) - \mathcal{H}(x, \lambda_A)]\}, \tag{9}$$

where $|\partial\phi(x)/\partial x|$ is the Jacobian determinant of the mapping $\phi(x)$. The above equation suggests generalizing the definition of work,

$$W_\phi = \mathcal{H}(\phi(x), \lambda_B) - \mathcal{H}(x, \lambda_A) - k_B T \ln\left|\frac{\partial\phi(x)}{\partial x}\right|. \tag{10}$$

This "work" includes the energy change caused by switching the control parameter from λ_A to λ_B. In addition W_ϕ includes a term involving the Jacobian of $\phi(x)$, which can be viewed as the work necessary to compress or expand the phase-space volume when applying the mapping $\phi(x)$. This entropic contribution can be interpreted as "heat" absorbed during the mapping. In fact, if we choose the mapping to be the system's propagator, this term is exactly the heat. In this interpretation, Eq. (10) is nothing other than an expression of the first law of thermodynamics. We note that redefinitions of the work also appear in algorithms that bias the sampling of trajectories in favor of low work values.[13] The Jacobian term appearing in Eq. (10), however, follows from properties of the phase-space mapping rather than from a work bias.

Using the work definition (10) we can rewrite Eq. (9) as

$$\exp(-\beta\Delta F) = \int dx \frac{\exp\{-\beta\mathcal{H}(x, \lambda_A)\}}{Q_A} \exp\{-\beta W_\phi(x)\} \tag{11}$$

or, as an average over the initial equilibrium distribution,

$$\exp(-\beta\Delta F) = \langle \exp\{-\beta W_\phi(x)\} \rangle. \tag{12}$$

This equation can be viewed as a generalization of Jarzynski's identity. If the mapping is chosen to be the propagator

$\phi_t(x)$ of Newtonian dynamics, the work W_ϕ equals the physical work W carried out on the system as it evolves from x_0 to x_t,

$$W = \mathcal{H}(x_t, \lambda_B) - \mathcal{H}(x_0, \lambda_A), \tag{13}$$

and Eq. (12) reduces to Jarzynski's identity. In deriving this result we have exploited the fact that Newtonian dynamics conserves phase-space volume—even when a control parameter changes with time, the Jacobian appearing in the definition of W_ϕ [Eq. (10)] is unity.

B. Long time step trajectories

Instead of the propagator ϕ_t, we can choose a sequence of molecular-dynamics steps as our mapping. Each of these steps, which are designed to approximate the time evolution of the system over a small time interval Δt, maps a phase point x_i into a phase point x_{i+1}. Equation (12) can be applied to a map defined by n such steps, together taking the initial point x_0 into a final point $x_n = \phi_n(x_0)$. The expression for the work W_ϕ is particularly simple for integrators such as the Verlet algorithm, which both conserve phase-space volume and are time reversible.[9,10] In this case the Jacobian of the mapping is unity, and, according to Eq. (10),

$$W_\phi(x_0) = \mathcal{H}(x_n, \lambda_B) - \mathcal{H}(x_0, \lambda_A), \tag{14}$$

so that

$$e^{-\beta \Delta F} = \langle \exp\{-\beta[\mathcal{H}(x_n, \lambda_B) - \mathcal{H}(x_0, \lambda_A)]\}\rangle. \tag{15}$$

This relation is exact regardless of the size of the time step Δt used in applying these integrators.

Equation (15) suggests the following algorithm. (1) A canonical distribution $\rho(x_0)$ of initial conditions is sampled with a Monte Carlo procedure or with an appropriately thermostated molecular-dynamics simulation. (Note that in the latter case a sufficiently small time step must be used in order to preserve the correct equilibrium distribution.) (2) These initial conditions are then used as starting points for fast-switching trajectories obtained by repeated application of the Verlet algorithm. (3) During the integration the control parameter is changed from λ_A to λ_B. Since Eq. (15) is exact for any size of the time step Δt, the chosen integration time step can be arbitrarily large, provided that the variables specifying the state of the system (for instance, positions and momenta of all particles) retain values that do not exceed the range that a computer can represent. We call this limit the *stability limit*. For each trajectory the energy difference $W = \mathcal{H}(x_n, \lambda_B) - \mathcal{H}(x_0, \lambda_A)$ is determined and used to calculate the exponential average appearing in Eq. (15). Since large time step trajectories are computationally less expensive, this algorithm holds promise to increase the efficiency of fast-switching free-energy calculations. Whether this is actually the case depends on how the work distribution is modified by the increase in time step length. In Sec. III we describe how to analyze the efficiency of fast-switching simulations with large time steps.

C. Stochastic dynamics

Often the dynamics of model molecular systems evolve by stochastic equations of motion. Common examples include the Langevin equation,[14]

$$\begin{aligned} \dot{q} &= p/m, \\ \dot{p} &= -\frac{\partial \mathcal{H}}{\partial q} - \gamma p + \eta(t), \end{aligned} \tag{16}$$

where γ is a friction coefficient and $\eta(t)$ is a fluctuating random force, the deterministic dynamics coupled to stochastic thermostats, such as the Andersen thermostat.[15] It has been shown that the Jarzinsky relation remains valid also in these cases.[3,16] In this section we discuss the question whether the large time step approach discussed in the previous section can be applied to stochastic dynamics as well.

We describe the stochastic component of these dynamics through a "noise history" $\eta(t)$. In the case of Langevin dynamics the noise history is, as the notation suggests, the trajectory of the random force. For a given realization of $\eta(t)$, the time evolution of a stochastic system can be regarded as deterministic, and we may write

$$x_t = \phi[x_0; \eta(t)], \tag{17}$$

where the second argument in the deterministic map indicates its dependence on the noise history $\eta(t)$. Since this mapping is invertible and differentiable, Eq. (12) applies for any particular noise history,

$$\exp(-\beta \Delta F) = \int dx \rho(x) \exp\{-\beta W_\phi[x; \eta(t)]\}, \tag{18}$$

where we have averaged over canonically distributed initial conditions and

$$\begin{aligned} W_\phi[x; \eta(t)] = {} & \mathcal{H}(\phi[x; \eta(t)], \lambda_B) - \mathcal{H}(x, \lambda_A) \\ & - k_B T \ln \left| \frac{\partial \phi[x; \eta(t)]}{\partial x} \right|. \end{aligned} \tag{19}$$

The result above is valid for any noise-dependent map $\phi[x_0; \eta(t)]$, so we are free to choose a mapping comprised of repeated application of Brownian dynamics steps[9] with arbitrary step size. Because the result of averaging $\exp\{-\beta W_\phi[x; \eta(t)]\}$ over initial conditions is completely independent of $\eta(t)$, the remaining average over noise histories is trivial, yielding

$$\begin{aligned} \exp(-\beta \Delta F) = {} & \int \mathcal{D}\eta(t) \int dx P[\eta(t)] \rho(x) \\ & \times \exp\{-\beta W_\phi[x; \eta(t)]\}. \end{aligned} \tag{20}$$

Here, the notation $\int \mathcal{D}\eta(t)$ indicates summation over all noise histories and $P[\eta(t)]$ is the probability distribution for observing a particular realization.

Interestingly, the above derivation implies that Eq. (20) can be applied to mappings with a completely arbitrary stochastic component. In particular, it is not necessary that the magnitude of stochastic fluctuations be related in any way to the rate of dissipation. In order to preserve a canonical dis-

tribution, the Langevin equation must be supplemented with such a constraint on the statistics of $\eta(t)$ (henceforth assumed to be Gaussian white noise):

$$\langle \eta(t)\,\eta(t')\rangle = 2k_{\mathrm{B}}T\gamma\delta(t-t'). \tag{21}$$

This fluctuation-dissipation relation, ensuring detailed balance, is a necessary condition for the applicability of Jarzynski's original identity concerning the exponential average of work defined in the conventional way. Obtaining that result from Eq. (20) is not nearly as straightforward as was the analogous task for deterministic dynamics. For stochastic mappings the Jacobian determinant does not directly correspond to heat, even in the limit of small time step size. Instead, for a trajectory of length τ,

$$\lim_{\Delta t\to 0}\left|\frac{\partial\phi[x;\eta(t)]}{\partial x}\right| = e^{-n_f\gamma\tau}, \tag{22}$$

where n_f is the number of momentum degrees of freedom. The volume of a phase-space element evolving under Langevin dynamics thus decays steadily as time evolves and has no contribution from the fluctuating random force. Mathematically, this phase-space compression arises from the systematic damping of kinetic energy through the friction term in Eq. (16). Physically, its cancellation of contributions from heat $\mathcal{Q}$ in the exponential average of Eq. (20) is a subtle consequence of detailed balance. Crooks has shown that, for trajectories generated by any balanced dynamical rules, $e^{-\beta\mathcal{Q}}$ is equivalent to the ratio of probability densities of forward and time-reversed pathways. This ratio is closely related to a mapping's Jacobian, as will be shown in Sec. V.

The practical utility of our large time step result for free-energy differences is compromised in the specific case of Langevin dynamics by at least two issues. First, the rapid decay of $|\partial\phi[x;\eta(t)]/\partial x|$ could damp all but the largest fluctuations, making convergence of the average in Eq. (20) problematic. Second, an exact calculation of the Jacobian for large time steps is cumbersome when many degrees of freedom interact. The insensitivity in Eq. (20) to the form of stochastic noise might be exploited to offset these problems, but it is not obvious how to do so.

III. EFFICIENCY ANALYSIS

In a straightforward application of the fast-switching procedure, the free-energy difference ΔF is estimated from a finite sample of N trajectories originating from canonically distributed initial conditions. Here we assume that these initial conditions are statistically uncorrelated samples. Defining

$$X \equiv \exp(-\beta W_\phi), \tag{23}$$

we can write the free-energy difference for finite N as

$$\Delta\bar{F}_N \equiv -k_{\mathrm{B}}T\ln\bar{X}_N, \tag{24}$$

where $\bar{X}_N$ is the average of X over N independent trajectories:

$$\bar{X}_N \equiv \frac{1}{N}\sum_{i=1}^{N} X^{(i)}. \tag{25}$$

Here, $X^{(i)}$ is the value of X obtained from the ith trajectory. We now repeat this entire procedure M times (generating a total of MN trajectories) and average over all M resulting free-energy estimates $\Delta\bar{F}_N^{(j)}$. The limiting result of this protocol is

$$\langle\Delta\bar{F}_N\rangle \equiv \lim_{M\to\infty}\frac{1}{M}\sum_{j=1}^{M}\Delta\bar{F}_N^{(j)}. \tag{26}$$

Due to the nonlinearity of the logarithm relating the average $\bar{X}_N$ to the free-energy estimate $\bar{F}_N$ [see Eq. (24)], $\langle\Delta\bar{F}_N\rangle$ differs from the true free-energy difference ΔF even in the limit of infinitely many repetitions. For sufficiently large N this deviation, or bias, is given by,[11,17,18]

$$b_N \equiv \langle\Delta\bar{F}_N\rangle - \Delta F = \frac{k_{\mathrm{B}}T}{2N}\frac{\langle(\delta X)^2\rangle}{\langle X\rangle^2}, \tag{27}$$

where the fluctuation $\delta X \equiv X - \langle X\rangle$ is the deviation of X from its average value. This equation is obtained by expanding the logarithm in Eq. (24) in powers of relative fluctuations of $\bar{X}_N$ and truncating the expansion after the quadratic term. Expression (27) for the bias is valid only for a large number N of repetitions. This limit, however, is often not attainable in practice for interesting systems. Kofke and co-workers have shown that, in this small sample size regime, the bias can be estimated by considering the wings of the work distribution.[19–21]

In addition to the systematic bias, we must account for random error in each free-energy estimate $\bar{F}_N^{(j)}$. Assuming the statistical errors of different samples to be uncorrelated, and denoting their variance as

$$\sigma_N^2 \equiv \langle[\Delta\bar{F}_N - \langle\Delta\bar{F}_N\rangle]^2\rangle, \tag{28}$$

we obtain the total mean-squared deviation from the true free-energy difference,

$$\epsilon_N^2 \equiv \langle[\Delta\bar{F}_N - \Delta F]^2\rangle = b_N^2 + \sigma_N^2. \tag{29}$$

Note that the bias decays with sample size as $b_N \propto 1/N$ for large N, while the scale of random error decays only as $\sigma_N \propto 1/\sqrt{N}$. Thus, for sufficiently large N only the statistical errors in the free-energy estimate are relevant, and we can safely approximate

$$\epsilon_N^2 = \sigma_N^2 = \frac{k_{\mathrm{B}}^2T^2}{N}\frac{\langle(\delta X)^2\rangle}{\langle X\rangle^2}. \tag{30}$$

For small sample sizes N, however, the bias can dominate the total error. For the model applications presented in Sec. IV of this paper, it will therefore be important to consider the effect of large time steps on the bias. We will do so by computing $\langle\Delta\bar{F}_N\rangle$ from representative samples with a finite number of repetitions.

From Eq. (30) one can determine the number of trajectories N_ϵ necessary to obtain a certain level of error ϵ,

$$N_\epsilon = \frac{k_B^2 T^2}{\epsilon^2} \frac{\langle (\delta X)^2 \rangle}{\langle X \rangle^2}. \tag{31}$$

The computational cost of each trajectory is roughly proportional to the number of required force calculations and hence proportional to the number of steps $n=\tau/\Delta t$ necessary to generate a trajectory of length τ. Neglecting the cost of the generation of initial conditions we can thus define a normalized computational cost,

$$C_{\mathrm{CPU}} \equiv n \frac{\langle (\delta X)^2 \rangle}{\langle X \rangle^2} = \frac{\tau}{\Delta t} \frac{\langle (\delta X)^2 \rangle}{\langle X \rangle^2}. \tag{32}$$

This computational cost C_{CPU} is the CPU time required to obtain an accuracy in the free energy of $\epsilon = k_B T$ measured in units of the CPU time required to carry out one single molecular-dynamics time step. Note that while $\langle X \rangle$ is independent of the step size Δt, the mean-square fluctuations $\langle (\delta X)^2 \rangle$ depend on it. To determine an optimal time step size for a fast-switching free-energy calculation, we must minimize the entire quantity C_{CPU}. In the following section we will present calculations of this normalized CPU time as a function of the step size Δt for two different models.

IV. NUMERICAL RESULTS

A. One-dimensional system

We first study the effect of large time step integration for a simple model introduced by Sun.[7] In this one-dimensional model a point particle of unit mass moves in a potential that depends on a control parameter λ. The Hamiltonian for the system as a function of the position q and the momentum p of the moving particle is

$$\mathcal{H}(q,p;\lambda) = \frac{1}{2}p^2 + q^4 - 16(1-\lambda)q^2. \tag{33}$$

Here, all quantities are scaled to be unitless. For $\lambda=0$ the potential has two symmetric minima located at $q=\pm\sqrt{8}$ separated by a barrier of height $\Delta E=64$ located at $q=0$. For $\lambda=1$ the potential-energy function reduces to a single quartic well. For a given value of the control parameter λ the partition function is $\int dq dp \exp\{-\beta \mathcal{H}(q,p,\lambda)\}$. The free-energy difference between the two states corresponding to $\lambda=1$ and $\lambda=0$, respectively, can be calculated analytically to be $62.9407 k_B T$.[11]

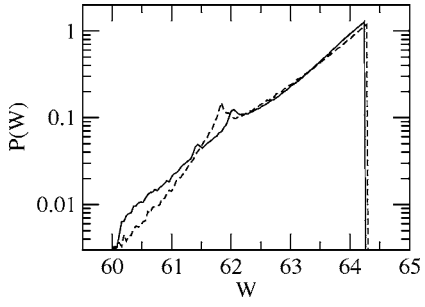

FIG. 1. Work distributions $P(W)$ obtained for the Sun model for a trajectory length $\tau=10$ and step sizes $\Delta t=0.1$ (solid line) and 0.01 (dashed line). Work distributions for all time steps smaller than $\Delta t=0.01$ are indistinguishable from the distribution for $\Delta t=0.01$ on the scale of the figure.

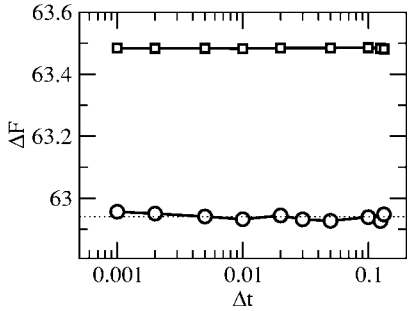

FIG. 2. Free-energy differences (circles) obtained for the Sun model from fast-switching trajectories of length $\tau=10$ with different step sizes Δt. The dotted line denotes the exact free-energy difference. Also shown is the average work $\langle W \rangle$ (squares).

For this model we carried out fast-switching simulations using different time steps Δt ranging from $\Delta t=0.002$ to $\Delta t=0.1$. The equations of motion were integrated with the velocity Verlet algorithm,[9,10] yielding positions q_t and momenta p_t as a function of time t. For this model the Verlet algorithm becomes unstable for time steps larger than $\Delta t=0.1$. In all cases the total trajectory length was $\tau=10$, corresponding to a transformation sufficiently gradual to allow accurate calculation of the free-energy difference and of the mean-square fluctuations $\langle (\delta X)^2 \rangle$. For each time step size we integrated 10^6 trajectories from initial conditions sampled from a canonical distribution (with $\lambda=0$) using a Monte Carlo procedure. Along the trajectories the control parameter was varied from its initial to its final value. More precisely, after each velocity Verlet step, carried out at constant λ, the control parameter was increased by $1/n$, where $n=\tau/\Delta t$ is the number of time steps in the trajectory. At the end of each trajectory the work $W=\mathcal{H}(q_\tau,p_\tau;1)-\mathcal{H}(q_0,p_0;0)$ was calculated and added to the exponential average. (Note that, when advancing time in large steps, it is important to use this generalized definition of work rather than summing estimates of the physical work performed during each stepwise change of the control parameter.)

Work distributions $P(W)$ obtained for different step sizes Δt (and hence for different numbers of steps per trajectory) are shown in Fig. 1. $P(W)$ deviates visibly from its small time step limit only for the largest step size, $\Delta t=0.1$. These differences originate in the inaccuracy of the integration algorithm for large step sizes. Even though the work distribution varies with the size of integration steps, the resulting free energies show no step size dependence (see Fig. 2),

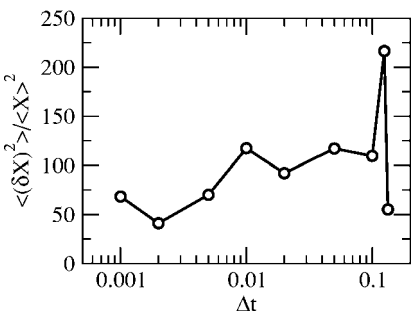

FIG. 3. Relative fluctuations $\langle (\delta X)^2 \rangle / \langle X \rangle^2$ for the Sun model as a function of the step size Δt.

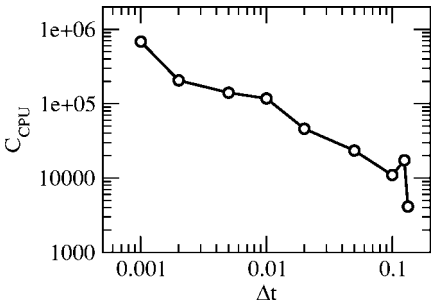

FIG. 4. Normalized CPU time C_{CPU} for the Sun model as a function of the step size Δt for $k_{\mathrm{B}}T=1$. For all step sizes the total trajectory length was $\tau=1$. This result indicates that for this model the computational cost of a free-energy calculation with a given error decreases for increasing step size until the stability limit is reached.

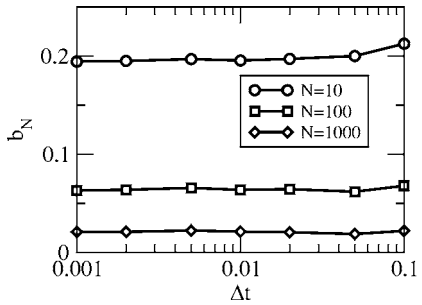

FIG. 5. Bias b_N as a function of the integration time step Δt in the Sun model obtained for sample sizes $N=10$, $N=100$, and $N=1000$ and a total trajectory length of $\tau=10$. In all three cases the bias is essentially unaffected by the integration time step.

provided the stability limit of the integration algorithm is not exceeded.

To quantify the statistical error in the free-energy estimates shown in Fig. 2 we have calculated the relative fluctuations $\langle(\delta X)^2\rangle/\langle X\rangle^2$, which according to Eq. (30) determine the mean-squared error ϵ_N^2. These relative fluctuations are plotted in Fig. 3. The irregular shape of this curve reflects changes in the features (such as the peak near $W=62$) of the work distributions shown in Fig. 1.

The computational cost C_{CPU} follows from the relative fluctuations and is shown as a function of the step size in Fig. 4. Over the range of time steps depicted in the figure the computational cost decreases from about 10^6 to about 10^4. Thus, the fast-switching simulation can be accelerated by two orders of magnitude if the conservative step size of $\Delta t=0.001$ is replaced by a step size $\Delta t=0.1$ near the stability limit. Although in the latter case the equations of motion are not faithfully solved (see Sec. V, Fig. 14), the expression for the free energy remains exact.

As mentioned in Sec. III, the total error of the free-energy difference obtained from a fast-switching simulation can be dominated by the bias b_N. To gauge the efficiency increase of our approach it is therefore important to study the effect of the large time step integration on the bias. Since the work distribution is not strongly affected by the time step as long as the integration remains stable (see Fig. 1), one does not expect the bias to change dramatically as the time step is increased. The same conclusion can be drawn in a more quantitative way by noting that, as shown in Fig. 3, the relative fluctuations $\langle(\delta X)^2\rangle/\langle X^2\rangle$ do not vary strongly over the whole range of step sizes Δt. Since, according to Eq. (27), these fluctuations determine the magnitude of the bias for large sample size N, the bias b_N should depend only weakly on the step size. The explicit calculations of the bias as a function of the step size for different sample sizes N shown in Fig. 5 indicate that this is indeed the case for the Sun model. Thus, the bias is not negatively affected by the use of large integration time steps.

B. Dragged particle in Lennard-Jones fluid

Our second example involves a system with many degrees of freedom and is therefore likely to be more relevant for typical molecular systems of interest. Specifically, we tested the large time step version of the Jarzynski identity for a particle dragged through a Lennard-Jones fluid. In these simulations, a tagged particle is coupled to a harmonic trap whose minimum is shifted from one position to another while the system evolves in time. If this process is carried out at a finite rate, work is performed on the system by the moving trap. Nevertheless, the free-energy difference between the two states corresponding to the initial and final positions of the trap vanishes due to symmetry.

The time-dependent Hamiltonian for our M-particle system is

$$\mathcal{H}(p,q,t)=\sum_{i=1}^{M}\frac{\mathbf{p}_i^2}{2m_i}+\sum_{i<j}^{M}v(r_{ij})+\frac{k}{2}(\mathbf{r}_1-\mathbf{R}(t))^2, \tag{34}$$

where $\mathbf{p}_i$ is the momentum of particle i, $\mathbf{r}_i$ is the position of particle i, r_{ij} is the distance between particles i and j, and the second sum on the right-hand side extends over all particle pairs. The particles interact via the Lennard-Jones potential,

$$v(r)=4\varepsilon\left[\left(\frac{\sigma}{r}\right)^{12}-\left(\frac{\sigma}{r}\right)^{6}\right]. \tag{35}$$

Here, ε and σ are parameters describing the depth of the potential well and the interaction range of the strongly repulsive core, respectively. The last term in Eq. (34) describes the potential energy of one particular particle (we arbitrarily pick particle 1) in a harmonic trap with force constant k. In Eq. (34) $\mathbf{R}(t)$ denotes the time-dependent position of the trap's minimum, which is moved from the origin in the x direction with constant speed v,

$$\mathbf{R}(t)=\mathbf{e}_x vt, \tag{36}$$

where $\mathbf{e}_x$ is the unit vector in the x direction. During a total time τ the trap is displaced by an amount $L=v\tau$. While the trap's minimum roughly determines the position of particle 1, this particle does fluctuate about $\mathbf{R}(t)$. The work W performed on the system along a particular trajectory from $\{q_0,p_0\}$ to $\{q_\tau,p_\tau\}$ is given by

$$W_\phi=\mathcal{H}(q_\tau,p_\tau;\tau)-\mathcal{H}(q_0,p_0;0). \tag{37}$$

Since the free energy of the system does not depend on the trap's location, $\Delta F=0$, the exponential work average carried out over many realizations of this process is

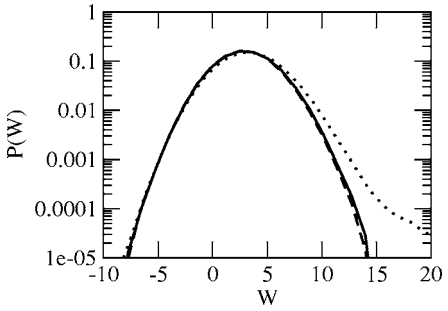

FIG. 6. Work distributions $P(W)$ for a particle dragged through a Lennard-Jones fluid for step size $\Delta t=0.001\sigma(\varepsilon/m)^{1/2}$ (solid line), step size $\Delta t=0.015\sigma(\varepsilon/m)^{1/2}$ (dashed line), and step size $\Delta t=0.02\sigma(\varepsilon/m)^{1/2}$ (dotted line).

$$\langle \exp(-\beta W_{\phi})\rangle = \exp(-\beta \Delta F) = 1. \tag{38}$$

Here, angular brackets indicate a canonical average for a fixed position of the trap.

We have carried out a fast-switching procedure for $M=108$ particles of unit mass in a three-dimensional, cubic simulation box with periodic boundary conditions. The fluid's density, $\rho=0.8\sigma^{-3}$, is roughly that at the triple point, and its initial temperature places it in the liquid phase. Canonically distributed initial conditions were generated by a molecular-dynamics simulation, employing an Andersen thermostat at temperature $k_BT/\varepsilon=1.0$,[15] with the trap fixed at the origin. For the generation of initial conditions, the equations of motions were integrated with the velocity Verlet algorithm and a time step of $dt=0.001\sigma(\varepsilon/m)^{1/2}$. The state of the system was recorded every 50 steps along this equilibrium trajectory, providing an ensemble of 5×10^5 initial conditions for the fast-switching procedure.

From these initial conditions we generated fast-switching trajectories of total length $\tau=1.2\sigma(\varepsilon/m)^{1/2}$ with different time steps ranging from $\Delta t=0.001\sigma(\varepsilon/m)^{1/2}$ to $\Delta t=0.02\sigma(\varepsilon/m)^{1/2}$. The corresponding pathways ranged in number of steps from $n=1200$ to $n=60$, respectively. In each case the total displacement of the trap from its initial to its final position was $L=0.5\sigma$ corresponding to a velocity of $\nu=5/12(m/\varepsilon)^{1/2}$. The velocity Verlet algorithm without thermostat was used to integrate Newton's equations of motion. Along these trajectories the particle trap was displaced stepwise by a small distance L/n after each molecular-dynamics step. Work distributions obtained in this manner are shown in Fig. 6 for three different step sizes. Free-energy differences ΔF and the average work W calculated in these simulations are depicted in Fig. 7.

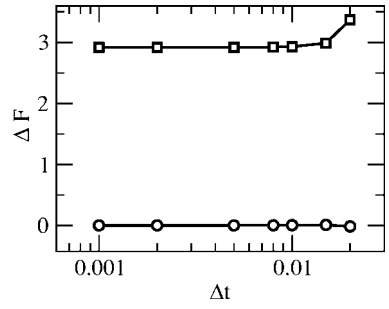

FIG. 7. Free-energy differences (circles) for a particle dragged through a Lennard-Jones fluid as a function of step size Δt. The trajectory length was $\tau=1.2\sigma(\varepsilon/m)^{1/2}$ for all step sizes. Also shown is the average work $\langle W\rangle$ (squares).

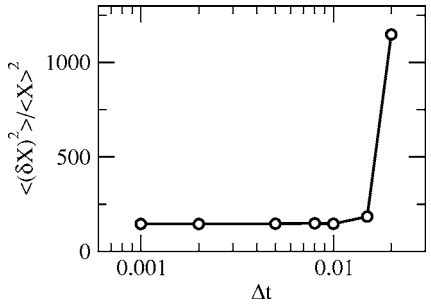

FIG. 8. Relative fluctuations $\langle(\delta X)^2\rangle/\langle X\rangle^2$ for the particle dragged through a Lennard-Jones fluid as a function of the step size Δt.

We used the relative fluctuations $\langle(\delta X)^2\rangle/\langle X\rangle^2$ (see Fig. 8) to calculate the normalized CPU time C_{CPU}, which is plotted in Fig. 9. The computational effort required to obtain a specific accuracy decreases with increasing step size until the largest value, $\Delta t=0.02\sigma(\varepsilon/m)^{1/2}$. Just as in the schematic one-dimensional example, the most efficient fast-switching calculation for dragging a particle through a dense fluid is obtained for step sizes close to the stability limit.

As in the case of Sun's model the work distribution for the dragged Lennard-Jones particle does not vary considerably over a wide range of time steps (see Fig. 6). Accordingly, the bias b_N should not depend strongly on the step size. For large sample sizes N this follows quantitatively from the fact that the relative fluctuations $\langle(\delta X)^2\rangle/\langle X^2\rangle$ are essentially constant up to a step size of $\Delta t=0.015\sigma(\varepsilon/m)^{1/2}$. That this is true also for small sample sizes N can be seen in Fig. 10, which shows the bias as a function of the step size for three different sample sizes. Thus, also for the particle dragged through a soft-sphere liquid the bias is not negatively affected by the size of the time step as long as one does not exceed the stability limit.

C. Multiharmonic model

The final model we have investigated with large time step trajectories is a multiharmonic model, proposed by Wu and Kofke as a prototype for asymmetric transformations.[22]

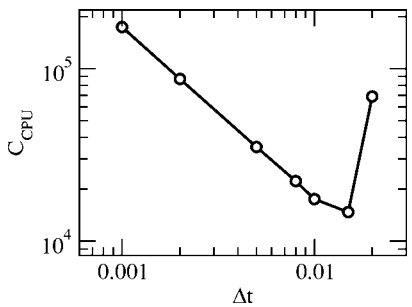

FIG. 9. Normalized CPU time C_{CPU} for the particle dragged through a Lennard-Jones fluid of $M=108$ particles at a density $\rho=0.8\sigma^{-3}$ as a function of the step size Δt at $k_BT/\varepsilon=1$. The particle is dragged through the fluid by a parabolic potential with force constant $k=10^3(\varepsilon/\sigma^2)$ moving at constant speed $\nu=5/12(m/\varepsilon)^{1/2}$. For all step sizes the total trajectory length was $\tau=1.2\sigma(\varepsilon/m)^{1/2}$. Also for this model the cost of a free-energy calculation decreases up to step sizes just short of the stability limit.

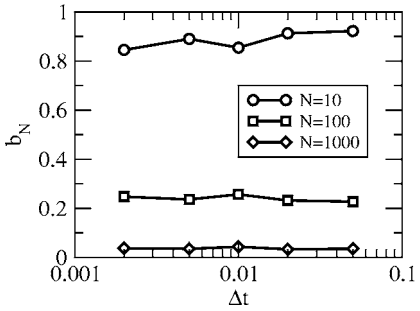

FIG. 10. Bias b_N as a function of the integration time step Δt for the dragged particle obtained for sample sizes $N=10$, $N=100$, and $N=1000$ and a total trajectory length of $\tau=1.2\sigma(\varepsilon/m)^{1/2}$. In all three cases the bias is essentially unaffected by the integration time step.

Here, the equilibrium distributions of initial and final states are simply one dimensional and Gaussian, but with different means and variances:

$$\mathcal{H}(q,p;\lambda_A)=\frac{1}{2m}p^2+\frac{1}{2}\alpha_A q^2, \tag{39}$$

$$\mathcal{H}(q,p;\lambda_B)=\frac{1}{2m}p^2+\frac{1}{2}\alpha_B (q-q_B)^2, \tag{40}$$

where m is the mass, α_A and α_B are the restoring force constants of the two states, and q_B is the displacement between them.

When computing free-energy differences in a standard fashion through Zwanzig's formula,

$$e^{-\beta\Delta F}=\langle\exp\{-\beta[\mathcal{H}(q,p;\lambda_B)-\mathcal{H}(q,p;\lambda_A)]\}\rangle_A \tag{41}$$

$$=\langle\exp\{-\beta[\mathcal{H}(q,p;\lambda_A)-\mathcal{H}(q,p;\lambda_B)]\}\rangle_B, \tag{42}$$

one may choose to evaluate either Eq. (41) or Eq. (42), i.e., to sample configurations either from equilibrium state A or from equilibrium state B. Here, angled brackets with subscript A or B denote equilibrium averages in states A and B, respectively. Lu and Kofke have shown that it is generally advantageous to sample the state with larger variance.[19] In that case less extensive sampling of low-probability microstates is needed to obtain an estimate of ΔF that is not strongly biased. It is reasonable to expect that similar logic applies to fast-switching calculations, since Eqs. (41) and (42) are, in effect, expressions of Jarzynski's identity for infinitely rapid transformations. Surprisingly, with large time steps, this expectation is not always correct.

As in the case of Sun's model, we switched between energy functions corresponding to states A and B linearly in time. Specifically, at time step n,

$$\mathcal{H}^{(n)}(q,p)=\frac{n\Delta t}{\tau}\mathcal{H}(q,p;\lambda_B)+\left(1-\frac{n\Delta t}{\tau}\right)\mathcal{H}(q,p;\lambda_A). \tag{43}$$

We chose units of length ($\sqrt{k_BT/\alpha_A}$), time ($\sqrt{m/\alpha_A}$), and energy (k_BT) such that $\langle q^2\rangle_A=1$ and $\langle p^2\rangle=1$. In those units the mean position and variance in state B were $q_B=5$ and $\langle(q-q_B)^2\rangle_B=0.25$, the duration of switching trajectories was $\tau=5$, and time steps ranged from $\Delta t=0.005$ to 1.05. With these time steps an appreciable amount of work is dissipated both

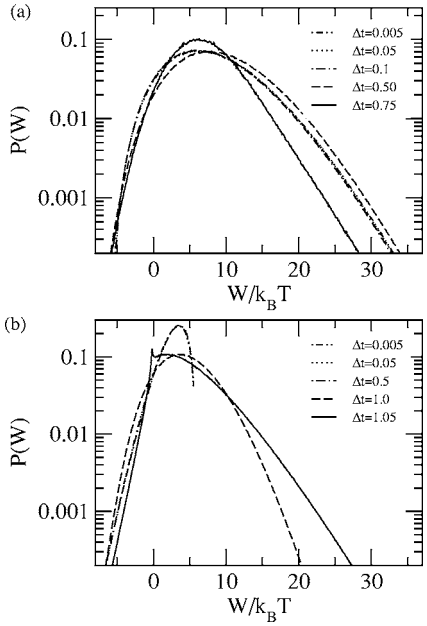

FIG. 11. Work distributions $P(W)$ for the multiharmonic model. Results for the forward transformation (from the state with higher entropy to the state with lower entropy) are shown in (a) for several values of the integration time step Δt. Results for the reverse transformation are shown in (b).

forwards ($\langle W\rangle_{\text{forw}}-\Delta F=7.5k_BT$, $7.4k_BT$, $7.3k_BT$, $8.6k_BT$, and $6.4k_BT$for time steps $\tau=0.005$, 0.05, 0.1, 0.5, and 0.75, respectively) and backwards ($\langle W\rangle_{\text{back}}+\Delta F=3.3k_BT$, $3.3k_BT$, $3.4k_BT$, $5.2k_BT$, and $5.5k_BT$ for time steps $\tau=0.005$, 0.05, 0.5, 1.0, and 1.05, respectively).

In the multiharmonic model, the final phase-space point $x_\tau=(q_\tau,p_\tau)$ of a fast-switching trajectory is a linear function of initial conditions $x_0=(q_\tau,p_0)$, even when the restoring force constant varies in time. As a result, time evolution can be represented in simple matrix form:

$$x_\tau=\mathbf{A}\cdot x_0+\mathbf{b}. \tag{44}$$

The elements of $\mathbf{A}$ and $\mathbf{b}$ can be evaluated by repeated application of the Verlet algorithm for any given value of Δt. Since the work W_ϕ depends only on x_τ and x_0, no further dynamical information is needed to apply Jarzynski's identity. The simplicity of generating trajectories according to Eq. (44) allows exhaustive sampling of the work distribution.

Because the magnitude of forces increases only linearly with displacements in the multiharmonic model, numerical stability can be maintained even with very large time steps. For the largest step sizes we have considered, $\Delta t\approx 1$, a full period of oscillation in state A is completed in only a handful of steps. Trajectories can be generated for still larger step sizes, but they bear little resemblance to true dynamical pathways. A broad range of fast-switching behavior is evident in the work distributions we determined by Wang-Landau sampling.[23] Figure 11 shows $P(W)$ for both forward and backward transformations. In both cases the shape of $P(W)$ changes near $\Delta t\approx 1$. Most significantly, the distributions develop long tails on the side of negative work that decay only slightly faster than $e^{\beta W}$. For the purpose of computing free-

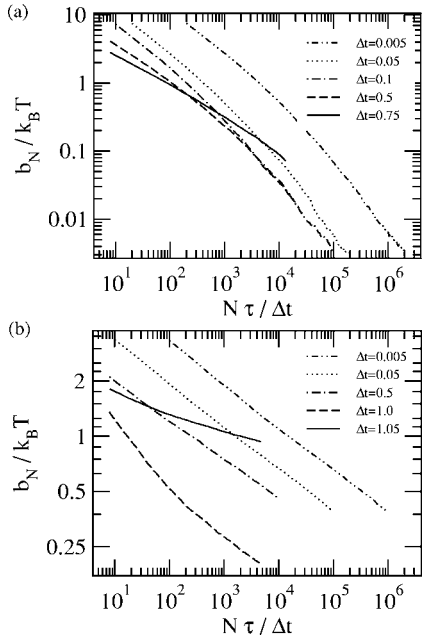

FIG. 12. Average bias b_N in the estimate of reversible work from averaging over a finite set of fast-switching trajectories. Results for the forward (a) and backward (b) transformations are plotted against computational effort, i.e., the number of integration steps required to obtain N trajectories of length τ.

energy differences, sampling $P(W)$ sufficiently to evaluate $\langle e^{-\beta W} \rangle$ becomes problematic well before numerical instabilities arise.

The breadth of $P(W)$ for large time steps gives rise to an unusual dependence of computational efficiency on sample size N. The bias b_N was computed explicitly for this model by drawing N random samples from the appropriate work distribution, and then averaging over many realizations. The corresponding computational cost for integrating N trajectories is proportional to $N\tau/\Delta t$. [Although Eq. (44) rendered our computational effort independent of Δt, such a simplification is rarely available for nonlinear systems of physical interest.] Figure 12 shows the average bias as a function of this cost.

Over the entire range of computational effort studied, the smallest bias is obtained for time steps of order unity. For most time step sizes in the forward transformation, b_N reaches the expected asymptotic N^{-1} decay described by Eq. (27). The mean-squared random error σ_N^2 behaves in a very similar fashion for this range of step sizes. For both sources of error, the use of large time steps is more beneficial the more limited are available computational resources. Results for the backward transformation are more unexpected. An asymptotic scaling of b_N (and of mean-squared statistical error) with sample size is evident in Fig. 12(b), but the decay is noticeably more gradual than N^{-1}. This unconventional scaling is a product of the very long, nearly exponential tail of $P(W)$.

Comparing Figs. 12(a) and 12(b), we can assess the more pragmatic direction for fast-switching calculations. When computational resources are plentiful, switching in the forward direction minimizes errors, as would be expected from the analysis of Kofke and co-workers and from the slower decay of b_N for backward transformations. When resources are scant, however, errors are smaller for switching in the backward direction. For static free-energy calculations, the greater entropy of state A degrades the accuracy of averages performed in equilibrium state B by conferring great importance on low-probability microstates. The advantage of a backward transformation for dynamical calculations is that larger time steps can be tolerated without changing the shape of $P(W)$. Increasing entropy in the multiharmonic model corresponds to softening of linear restoring forces. In the forward direction, the magnitude of potential-energy gradients increases with time, and large time steps incur greater deviations from true dynamical paths. By contrast, in the backward direction these gradients become less severe as the transformation proceeds, mitigating the effect of integration errors. This peculiar behavior may be limited to very simple models, where entropy is directly related to the stiffness of forces. But in situations where increasing entropy does entail gentler forces, and a small number of force evaluations can be afforded, the wisest application of Jarzynski's identity may, in fact, begin in the state with lower entropy.

V. DISCUSSION

Molecular-dynamics simulations carried out with large time steps do not faithfully reproduce the dynamics of any system with configuration-dependent forces. If such large time steps are used in the generation of fast-switching trajectories to calculate free-energy differences on the basis of Jarzynski's identity, integration errors lead to work distributions differing from those obtained in the small time step limit. Nevertheless, as we have shown in Sec. II, the Jarzynski identity remains exactly valid in principle for time steps of arbitrary size. As a practical matter the stability limit provides an upper bound to the step size. Since the computational cost of molecular-dynamics trajectories is proportional to the number of integration steps, large time steps can be beneficial. Whether an increase of computational efficiency can really be achieved depends on how the relative squared fluctuations $\langle (\delta X)^2 \rangle / \langle X \rangle^2$ scale with the size of the integration time step. If these fluctuations increase with Δt sublinearly, using large time steps is advantageous.

In both of the numerical examples presented in Sec. IV, increasing the size of the time step well beyond the range appropriate for equilibrium simulations proved favorable. Resulting efficiency increases reached up to two orders of magnitude. Here we ask more generally, and with complex molecular systems in mind, what circumstances should allow large time step integration to improve upon fast-switching simulations. To answer that question it is convenient to write the work W performed on the system during the transformation as sum of two parts. This separation is particularly natural if the control parameter λ is changed stepwise, i.e., if each step is performed at constant λ and is followed by an increase in the control parameter by an increment $\Delta\lambda = 1/n$.

We define the first contribution to the generalized work W_ϕ as the change in energy due to the changes in control parameter for fixed phase points,

$$W_\lambda \equiv \sum_{i=1}^{n} \mathcal{H}[x_i, i\Delta\lambda] - \mathcal{H}[x_i, (i-1)\Delta\lambda]. \tag{45}$$

Here, x_i is the phase-space point reached after i integration steps starting from phase-space point x_0. In Crooks's considerations of systems out of equilibrium, W_λ is precisely the physical work exerted by the change of control parameter.[3]

In a system that evolves according to Newton's equations with a time-independent potential-energy function, the total energy is a constant of the motion. But when these equations are integrated approximately over finite time steps, the energy of the system is not perfectly conserved. Summing the energy changes due to integration error in the intervals between stepwise increases of λ, we obtain the other contribution to W_ϕ:

$$W_\epsilon \equiv \sum_{i=0}^{n-1} \mathcal{H}[x_{i+1}, i\Delta\lambda] - \mathcal{H}[x_i, i\Delta\lambda]. \tag{46}$$

To summarize our decomposition of W_ϕ, the work W_λ involves changes in control parameter at fixed phase-space points, while the less physical contribution W_ϵ involves changes in the phase-space point at constant control parameter. The total work performed during the transformation is the sum of these two quantities,

$$W = W_\lambda + W_\epsilon. \tag{47}$$

In the limit of very small time steps, the energy of the system is conserved whenever λ is constant. In this case, the "error" work W_ϵ vanishes and the entire work is caused by changes in the control parameter $W = W_\lambda$. If a system is driven away from equilibrium by a stepwise increase of the control parameter, the error work serves as a simple measure for the accuracy of approximate numerical integration.

Neglecting correlations between W_λ and W_ϵ for the moment, we can write

$$\langle \exp(-\beta \Delta W) \rangle = \langle \exp(-\beta W_\lambda) \rangle \langle \exp(-\beta W_\epsilon) \rangle. \tag{48}$$

Accordingly, the free-energy change is the sum of two terms originating from W_λ and W_ϵ,

$$\Delta F = \Delta F_\lambda + \Delta F_\epsilon = -k_B T \ln\langle e^{-\beta W_\lambda} \rangle - k_B T \ln\langle e^{-\beta W_\epsilon} \rangle. \tag{49}$$

This separation of the free-energy difference into two terms related to W_λ and W_ϵ, respectively, is only strictly valid if fluctuations in

$$X_\lambda \equiv \exp(-\beta W_\lambda) \quad \text{and} \quad X_\epsilon \equiv \exp(-\beta W_\epsilon) \tag{50}$$

are statistically independent. This supposition cannot be assumed *a priori* to be the case. For the two models treated numerically in this study we have calculated the correlation

$$C_{\lambda\epsilon} \equiv \frac{\langle \delta X_\lambda \delta X_\epsilon \rangle}{\sqrt{\langle (\delta X_\lambda)^2 \rangle \langle (\delta X_\epsilon)^2 \rangle}}, \tag{51}$$

where $\delta X_\lambda \equiv X_\lambda - \langle X_\lambda \rangle$ and $\delta X_\epsilon \equiv X_\epsilon - \langle X_\epsilon \rangle$. This coefficient quantifies correlations between the two variables X_λ and X_ϵ. While in the absence of correlations $C_{\lambda\epsilon}=0$, perfect correlation (anticorrelation) leads to $C_{\lambda\epsilon}=1$ ($C_{\lambda\epsilon}=-1$). Correlations computed numerically for the Sun model are depicted in Fig. 13 as a function of the time step Δt. For all time step sizes X_λ and X_ϵ are only weakly (anti)correlated. The assumption of statistical independence is justified in these cases.

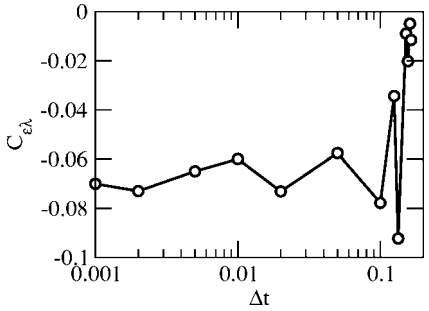

FIG. 13. Correlations $C_{\epsilon\lambda}$ between control parameter work and integration error work as a function of the step size for the Sun model.

Under the same assumption the statistical error of a fast-switching free-energy calculation with large time steps can also be written as the sum of two distinct contributions. Absent correlations between W_λ and W_ϵ [Eq. (30)] become

$$\epsilon_N^2 = \frac{k_B^2 T^2}{N} \left[\frac{\langle (\delta X_\lambda)^2 \rangle}{\langle X_\lambda \rangle^2} + \frac{\langle (\delta X_\epsilon)^2 \rangle}{\langle X_\epsilon \rangle^2} \right]. \tag{52}$$

Thus, the total mean-squared error is the sum of the mean-squared errors of the free energies related to the control parameter work and the integration error work, respectively. One potentially substantial difference between these two error contributions is their dependence on system size. Often, the control parameter λ acts only on a small subset of the system's degrees of freedom. In calculating the chemical potential of an electrically neutral species by particle insertion, for instance, the solute interacts only with a small number of other particles near the insertion point. Similarly, the transformation of a residue of a protein into another one mainly affects only a local group of interactions. In such cases, the work W_λ resulting directly from changes in the control parameter quickly saturates with growing system size. The work W_ϵ, originating in the inaccuracy of the integration algorithm, has a different system size dependence. Since all degrees of freedom contribute to the integration error, W_ϵ is expected to grow linearly with the system size. Thus, for sufficiently large systems the second term on the right-hand side of Eq. (52) might become dominating for long time steps, thus limiting the maximally possible efficiency gain. (It is for similar reasons that hybrid Monte Carlo molecular-dynamics simulations decline efficiency for large systems.[24]) But as long as the integration error is small compared to work done by changes in control parameter, using large time steps should remain advantageous.

In our discussion of the efficiency of the large time step fast-switching approach we have so far neglected the computational cost associated with generating initial conditions. Often, starting points for the fast-switching trajectories are generated with an appropriately thermostated molecular-dynamics simulation. It is important that these simulations are carried out with a time step of conventionally small size. Otherwise the distribution of initial conditions can differ

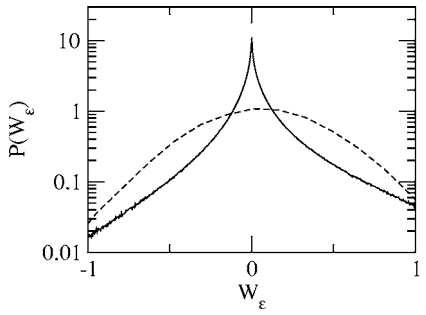

FIG. 14. Distributions $P(W_\epsilon)$ of the integration error W_ϵ at constant control parameter. Solid line: Sun model for $\lambda=0$, $\tau=10$, and $\Delta t=4/30$; dashed line: Lennard-Jones fluid with one particle in fixed trap, $\tau=1.2\sigma(\epsilon/m)^{1/2}$, and $\Delta t=0.015\sigma(\epsilon/m)^{1/2}$.

from the necessary canonical one. Thus, the large time step approach can reduce only the computational cost associated with generating the nonequilibrium trajectories. This latter contribution is dominant by far in most cases.

The issues discussed in this paper have some interesting implications for molecular-dynamics simulations carried out at equilibrium as well. If the control parameter λ is not changed as the system evolves in time, no work W_λ is done on the system. In this case the free-energy difference ΔF also vanishes, since initial and final Hamiltonians are identical. Nevertheless, due to the imperfection of a finite time step integration algorithm, the energy is not strictly conserved, and some error work W_ϵ is performed. According to Eq. (15) the statistics of such energy errors obeys

$$\langle \exp(-\beta W_\epsilon)\rangle = 1. \tag{53}$$

This result implies that the distribution of integration errors cannot be symmetric about $W_\epsilon=0$. Rather, positive errors are in loose terms more likely than negative ones. For a Gaussian error distribution, Eq. (53) relates the average error to the width of the error distribution,

$$\langle W_\epsilon\rangle = \frac{1}{2}\beta^2\sigma_\epsilon^2. \tag{54}$$

For more complicated error distributions, this same result is obtained from a cumulant expansion of Eq. (53) truncated after the second term. Thus, for an error distribution that is Gaussian and/or sufficiently narrow, the average error is positive. This demonstration that the average energy of a simulated canonical ensemble drifts upward with time makes no reference to the details of molecular interactions.

We have verified Eq. (53) both for the Sun model and for the Lennard-Jones fluid. In both cases we have determined the distribution $P(W_\epsilon)$ of the integration error W_ϵ for a large integration step Δt and constant λ. The averages were carried out in the respective canonical ensembles corresponding to $\lambda=0$. Two typical distributions are shown in Fig. 14. For the Sun model (solid line) $P(W_\epsilon)$ is strongly non-Gaussian and asymmetric about $W_\epsilon=0$, with positive errors more likely than negative ones. While the average error of $\langle W_\epsilon\rangle=0.041$ is clearly positive, the exponential average $\langle \exp(-\beta W_\epsilon)\rangle$ is unity with high accuracy. For the Lennard-Jones fluid with one particle in a fixed trap the distribution of integration errors is approximately Gaussian, with an average of $\langle W_\epsilon\rangle=0.064$. Also in this case the exponential work average is unity.

Formulating changes in control parameter as a sequence of discrete steps is also convenient for demonstrating the equivalence between our identity for stochastic mappings, Eq. (20), and Jarzynski's original identity. During periods when λ is fixed, stochastic evolution subject to a suitable fluctuation-dissipation relation, such as Eq. (21), satisfies detailed balance in the small time step limit. Specifically,

$$\rho_i(x)p(x\to x') = \rho_i(x')\hat{p}(x'\to x), \tag{55}$$

where $\rho_i(x)\propto\exp[-\beta\mathcal{H}(x,i\Delta\lambda)]$ is the canonical distribution corresponding to the Hamiltonian $\mathcal{H}(x,i\Delta\lambda)$ at step i, and $p_i(x\to x')$ is the noise-averaged probability for a phase-space point x at the beginning of a constant-λ interval to evolve into phase-space point x' at the end of the interval. The caret in Eq. (55) indicates *time reversal*, so that $\hat{p}(x'\to x)$ is the probability for x' to evolve into x under dynamics running backward in time. For Langevin dynamics, time reversal can be achieved simply by inverting the signs of all momenta contained in phase-space points x and x'. For a given noise history, such transition probabilities are specified by the deterministic map $\phi[x;\eta(t)]$. We can thus rewrite Eq. (55) as

$$e^{-\beta\mathcal{H}(x,i\Delta\lambda)}\langle\delta(x'-\phi[x;\eta(t)])\rangle_\eta = e^{-\beta\mathcal{H}(x',i\Delta\lambda)}\left\langle \delta(x'-\phi[x;\eta(t)])\left|\frac{\partial\phi[x;\eta(t)]}{\partial x}\right|\right\rangle_\eta, \tag{56}$$

where angled brackets with a subscript η denote an average over realizations of the noise history.

From the condition of detailed balance, we now obtain a general identity for averages involving the Jacobian determinant. We begin by multiplying Eq. (56) by an arbitrary function $f(x,x')$ of two phase-space points, and then integrate over x', yielding

$$\langle f(x,\phi[x;\eta(t)])\rangle_\eta = \left\langle f(x,\phi[x;\eta(t)]) \times e^{-\beta[\mathcal{H}(\phi[x;\eta(t)],i\Delta\lambda)-\mathcal{H}(x,i\Delta\lambda)]} \times\left|\frac{\partial\phi[x;\eta(t)]}{\partial x}\right|\right\rangle_\eta. \tag{57}$$

This result holds for any period during which the control parameter is held constant, i.e., while no physical work is done on a system. Since we have assumed here that equations of motion are integrated with an infinitesimally small time step, the error work vanishes as well. The energy change $\mathcal{H}(\phi[x;\eta(t)],i\Delta\lambda)-\mathcal{H}(x,i\Delta\lambda)$ in Eq. (57) is thus identically the heat $\mathcal{Q}_i$ absorbed from the bath during the ith time interval. Equation (57) states that the Jacobian determinant and $e^{-\beta\mathcal{Q}}$ negate one another in averages over noise history.

This proof is completed by decomposing the total change in energy along a trajectory into contributions from physical work W_λ (accumulated over many discrete steps in control parameter at fixed phase-space point) and heat (accumulated over many intervals during which the phase-space point evolves at fixed λ):

$$\mathcal{H}(\phi[x;\eta(t)],\lambda_B)-\mathcal{H}(x,\lambda_A)=W_\lambda+\mathcal{Q}, \tag{58}$$

$$\mathcal{Q}=\sum_{i=0}^{n-1}\mathcal{H}[x_{i+1},i\Delta\lambda]-\mathcal{H}[x_i,i\Delta\lambda]. \tag{59}$$

We have retained the definition of physical work from Eq. (46). Note that heat in the case of stochastic dynamics is defined in precisely the same way as error work was defined for deterministic dynamics propagated in an approximate way. Recalling the generalized definition of work W_ϕ and applying the identity (57) with $f(x,x')=\exp\{-\beta(\mathcal{H}[x',i\Delta\lambda]-\mathcal{H}[x',(i-1)\Delta\lambda])\}$ for each constant-λ interval, we finally have

$$\langle e^{-\beta W_\phi}\rangle_\eta=\left\langle e^{-\beta W_\lambda}e^{-\beta\mathcal{Q}}\left|\frac{\partial\phi[x;\eta(t)]}{\partial x}\right|\right\rangle_\eta=\langle e^{-\beta W_\lambda}\rangle_\eta. \tag{60}$$

This equivalence, together with Eq. (20), completes an alternative route to Jarzynski's identity for systems evolving stochastically under the constraint of detailed balance.

The consequence of detailed balance expressed in this way has interesting implications for energy fluctuations of stochastic systems at equilibrium (i.e., with fixed control parameter). With the choice $f(x,x')=1$, we have for the specific case of Langevin dynamics [see Eq. (22)]

$$\langle e^{-\beta\mathcal{Q}}\rangle=e^{n_f\gamma\tau} \tag{61}$$

along trajectories of length τ. This identity stands in stark contrast to the corresponding exponential average of energy fluctuations under norm-conserving deterministic mappings [Eq. (53)]. The long-time divergence in Eq. (61) would be expected for a system which asymptotically loses all memory of its initial conditions. In that case, the exponential average factorizes in the long-time limit:

$$\langle e^{-\beta\mathcal{Q}}\rangle\approx\langle e^{\beta\mathcal{H}(x_0)}\rangle\langle e^{-\beta\mathcal{H}(x_\tau)}\rangle. \tag{62}$$

The first factor on the right-hand side of Eq. (62) averages a quantity that negates the effect of Boltzmann weighting, and is proportional to the entire phase-space volume. Since the range of possible momenta is unbound even in a system with finite volume, a divergent result is inevitable once correlations have decayed completely. We anticipate similarly unbounded growth of exponentially averaged energy fluctuations for many classes of stochastic dynamics, such as Monte Carlo sampling. That the analogous average is fixed at unity for deterministic propagation rules with unit Jacobian such as the Verlet algorithm indicates that errors arising from finite time step size do not disrupt substantial correlations with initial conditions.

VI. CONCLUSION

By considering general invertible phase-space mappings we have demonstrated that the Jarzynski relation remains exactly valid for nonequilibirum trajectories generated with large time steps, provided the work performed on the system is defined appropriately. For integration algorithms that conserve phase-space volume, such as the Verlet algorithm, this definition is particularly simple. Here, the work just equals the energy difference between the final and initial states of the trajectory. Simulating dynamics with a larger time step requires fewer integration steps to generate a trajectory of given length, and therefore lower computational cost. Numerical simulations indicate that optimum efficiency is achieved for time steps just short of the stability limit. Compared to simulations with time steps of conventional size, the long time step approach can yield improvements in efficiency of one or more orders of magnitude.

Despite the low cost of large time step trajectories, the approach presented in this paper is not capable of overcoming the statistical difficulties related to the exponential averaging required in the application of the Jarzynski equation. These problems, familiar from free-energy perturbation calculations,[19] arise from the strong nonlinearity of the exponential function. Particularly at high switching rates the average in Eq. (2) can be dominated by low work values, yielding large but rare contributions to the average. Recently, several authors have put forward algorithms designed to circumvent these difficulties by biasing the sampling towards trajectories with important work values.[7,8,13,25] Whether such biased sampling methodologies can outperform conventional free-energy calculations is presently unclear. It will be interesting to see if the fast-switching approach can be improved, by combining the long time step method of this paper with such biased path sampling methodologies, to the point that it is computationally competitive with other free-energy calculation techniques, such as umbrella sampling, thermodynamic integration, or flat histogram sampling.

ACKNOWLEDGMENT

This work was supported by the Austrian Science Fund (FWF) under Grant No. P17178-N02.

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