Entropy-energy decomposition from nonequilibrium work trajectories

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We derive expressions for the equilibrium entropy and energy changes in the context of the Jarzynski equality relating nonequilibrium work to equilibrium free energy. The derivation is based on a stochastic path integral technique that reweights paths at different temperatures. Stochastic dynamics generated by either a Langevin equation or a Metropolis Monte Carlo scheme are treated. The approach enables the entropy-energy decomposition from trajectories evolving at a single-temperature and does not require simulations or measurements at two or more temperatures. Both finite difference and analytical formulae are derived. Testing is performed on a prototypical model system and the method is compared with existing thermodynamic integration and thermodynamic perturbation approaches for entropy-energy decomposition. The new formulae are also put in the context of more general, dynamics-independent expressions that derive from either a fluctuation theorem or the Feynman–Kac theorem. © *2008 American Institute of Physics.*
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I. INTRODUCTION

The ability to calculate separately the enthalpic and entropic contributions to the free energy change of condensed-matter processes is central to the understanding of their underlying driving forces. For example, the relatively small free energy of protein folding or of ligand binding often is the result of a near cancellation of much larger entropy and enthalpy (or more precisely for canonical ensemble conditions, energy) changes.[1,2] In instances involving hydration, energy-entropy decomposition can help discriminate between distinct mechanisms for processes with similar free energy changes.[3] Furthermore, comparing experimentally measured energy and entropy values with those calculated from molecular simulations can aid in the improvement of empirical force fields or implicit solvent models used by the simulations.

Traditionally, most applications of free energy calculations have been pursued either in the framework of thermodynamic integration[4] (TI) or in that of thermodynamic perturbation (TP).[5] Recently, a new free energy formulation has been introduced by Jarzynski;[6] it derives from a remarkable equality between the exponential average of nonequilibrium work values over an ensemble of trajectories straddling two states and the equilibrium free energy difference between those states.

While energy-entropy decompositions of the free energy change have been derived for both TI (Ref. 7) and TP,[8] no such formalism has been presented for the Jarzynski equality (JE). The purpose of the present paper is to provide that. After briefly reviewing the existing TP and TI-based energy-entropy decompositions, we derive our new JE formulation,

implement it numerically in two incarnations, and apply it, together with TI and TP for comparison, to a prototypical model system.

II. ENERGY-ENTROPY DECOMPOSITION USING TI AND TP

Consider a system transformation from an initial state 0 to a final state 1, parameterized by an external coupling variable $\lambda = 0 \rightarrow 1$ which defines the hybrid potential energy of the system, $V_\lambda = (1-\lambda)V_0 + \lambda V_1$, where the subscripts refer to the system's state, with the hybrid system being actually simulated. The basic thermodynamic relationships

$$\Delta U = \partial(\beta \Delta F)/\partial \beta,$$
$$T\Delta S = \beta(\partial \Delta F/\partial \beta), \tag{1}$$

with $\beta = (k_B T)^{-1}$, are the starting points for all three concerned methods (TI, TP, JE) to compute the energy, U, and the entropy, S, components of the Helmholtz free energy change $\Delta F = \Delta U - T\Delta S$ between states 0 and 1.

TI uses an integral expression for the Helmholtz free energy change, $\Delta F = \int_0^1 d\lambda \langle \partial V_\lambda / \partial \lambda \rangle_\lambda$, (where $\langle \ldots \rangle_\lambda$ denotes canonical-ensemble averaging at fixed λ), together with Eqs. (1) to obtain the energy and entropy changes (see Ref. 7)

$$\Delta U = \Delta F + \beta \int_0^1 d\lambda \left[\left\langle \frac{\partial V}{\partial \lambda} \right\rangle_\lambda \langle V \rangle_\lambda - \left\langle \frac{\partial V}{\partial \lambda} V \right\rangle_\lambda \right] \tag{2}$$

and

$$T\Delta S = \beta \int_0^1 d\lambda \left[\left\langle \frac{\partial V}{\partial \lambda} \right\rangle_\lambda \langle V \rangle_\lambda - \left\langle \frac{\partial V}{\partial \lambda} V \right\rangle_\lambda \right]. \tag{3}$$

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The TP formalism is based on expressing the free energy difference between two values of λ as an ensemble average at one λ value, $\Delta F = F_{\lambda'} - F_\lambda = -\beta^{-1} \ln \langle \exp(-\beta[V_{\lambda'} - V_\lambda]) \rangle_\lambda$.

This, together with the finite difference, T-derivative form of Eqs. (1), leads to the TP version for the energy and entropy changes (see Ref. 8)

$$\Delta U = U_{\lambda'} - U_\lambda \simeq \frac{k_B T^2}{2\Delta T} \ln \left\langle \frac{\left\langle \exp\left[\frac{-V_{\lambda'}}{k_B(T+\Delta T)} + \frac{V_\lambda}{k_B T} \right] \right\rangle_{\lambda,T}}{\left\langle \exp\left[\frac{-V_{\lambda'}}{k_B(T-\Delta T)} + \frac{V_\lambda}{k_B T} \right] \right\rangle_{\lambda,T}} \frac{\langle e^{-L_- V_\lambda} \rangle_{\lambda,T}}{\langle e^{-L_+ V_\lambda} \rangle_{\lambda,T}} \right\rangle \tag{4}$$

and

$$T\Delta S = T(S_{\lambda'} - S_\lambda) \simeq k_B \ln \langle \exp(-\beta[V_{\lambda'} - V_\lambda]) \rangle_{\lambda,T} + \frac{k_B T}{2\Delta T} \ln \left\langle \frac{\left\langle \exp\left[\frac{-V_{\lambda'}}{k_B(T+\Delta T)} + \frac{V_\lambda}{k_B T} \right] \right\rangle_{\lambda,T}}{\left\langle \exp\left[\frac{-V_{\lambda'}}{k_B(T-\Delta T)} + \frac{V_\lambda}{k_B T} \right] \right\rangle_{\lambda,T}} \frac{\langle e^{-L_- V_\lambda} \rangle_{\lambda,T}}{\langle e^{-L_+ V_\lambda} \rangle_{\lambda,T}} \right\rangle, \tag{5}$$

where $L_\pm = 1/k_B(T \pm \Delta T) - 1/k_B T$ and the averages are taken at T and λ. In practice, the total energy and entropy changes between $\lambda = 0$ and 1 are obtained by summing the ΔU and ΔS values in Eqs. (4) and (5) over a number of adjacent λ pairs covering the interval [0, 1].

III. DERIVATION FROM THE JARZYNSKI EQUALITY BY REWEIGHTING

Jarzynski's free energy method is based on the nonequilibrium work theorem

$$\langle \exp(-\beta W) \rangle = \exp(-\beta \Delta F), \tag{6}$$

where $W = \int_0^1 (\partial V/\partial \lambda) d\lambda$ is the work performed during switching from states 0 to 1 on a finite classical system in contact with a heat reservoir and the brackets denote ensemble averaging. In its practical implementations, one generates, from canonically distributed initial conformations, N_s finite time (hence, nonequilibrium) repetitions of the λ-switching process, records the nonequilibrium work W_i on the system during the ith trajectory and uses $\Delta F = -\beta^{-1} \ln(1/N_s \sum_{i=1}^{N_s}) \exp(-\beta W_i)$ to compute the free energy difference. Adaptation of such a scheme can also lead to expressions for free energy profiles along specified coordinates.[9] Alternatively, the same strategy can be used in repetitive single-molecule manipulation experiments by recording work from force-extension measurements.[9,10]

As in TP (which can be regarded as the instantaneous-switch equivalent of JE), our JE-based derivation for the energy and entropy follows from the temperature derivatives of the free energy. From Eqs. (1) and (6), $\Delta U = -\partial \ln \langle \exp(-\beta W) \rangle / \partial \beta$ and $T\Delta S = -\beta \partial (\beta^{-1} \ln \langle \exp(-\beta W) \rangle) / \partial \beta$, which, expressed as finite differences, yields

$$\Delta U \simeq -\frac{\ln \langle \exp(-\beta_+ W) \rangle_{\beta_+} - \ln \langle \exp(-\beta_- W) \rangle_{\beta_-}}{2\Delta \beta} \tag{7}$$

and

$$T\Delta S \simeq -\beta \left[\frac{\ln \langle \exp(-\beta_+ W) \rangle_{\beta_+}}{2\Delta \beta \beta_+} - \frac{\ln \langle \exp(-\beta_- W) \rangle_{\beta_-}}{2\Delta \beta \beta_-} \right], \tag{8}$$

where $\beta_\pm = \beta \pm \Delta \beta$ and the index of the bracket denotes the inverse temperature of both the initial distribution of points and the subsequent trajectory bundle. As in TP, the gist is to run simulations at β, but to calculate, by perturbative reweighting, the averages $\langle \dots \rangle_{\beta_\pm}$ that one would have gotten if the simulation would have been run at β_+ or β_-.

Unlike in TP, however, the β-perturbation formula that constitutes the centerpiece of the finite difference approximation is not trivial for JE. Importantly, the perturbation formula used by TP [see Eqs. (4) and (5)], is, in effect, a reweighting procedure. One divides, for a given λ, each sample by the weight with which it was generated in the ensemble run at β and multiplies by the weight $\exp(-\beta' V(x))$ that the sampled conformation x would have at $\beta' = 1/k_B(T \pm \Delta T)$, the desired inverse temperature. This reweighting ratio is thus a function of x. In contrast, in JE the work $W[X(t)]$, that appears in the averages involved in Eqs. (7) and (8), is a functional of the trajectory $X(t)$, rather than a function of a point x. We thereby need a functional generalization of the weight for the space of trajectories.

In the case of Langevin dynamics this generalization is offered by the Wiener formalism of stochastic path integrals. Consider, without loss of generality, the overdamped Langevin equation,

$$0 = -m\gamma \dot{x} + F(x) + \xi(t), \tag{9}$$

where m is the mass, x is the position, $F(x)$ is the force derived from the potential V, and ξ is white noise with zero mean and obeying a fluctuation-dissipation relation, $\langle \xi(t)\xi(t') \rangle = 2k_B T m \gamma \delta(t-t')$, with T as the absolute temperature and γ as the friction. For such dynamics, the weight of a trajectory is given by

$$\mathcal{P}_\beta[X(t)] \propto \exp(-\mathcal{S}_\beta[X(t)]), \tag{10}$$

where $\mathcal{S}_\beta[X(t)] = (\beta/4m\gamma)\int_0^t (m\gamma\dot{x} + \nabla V)^2 dt'$ is the Onsager–Machlup action functional[11] at inverse temperature β; its computation in the present work (see Sec. V) involved the Itô discretization,[12] for which the functional Jacobian of the transformation from noise to conformational coordinates is constant[13] (see also Ref. 14). Probability functionals akin to the one in Eq. (10) have previously been used for reweighting ensembles of trajectories generated with a distinct dynamical propagator than that of the system of interest.[15–19]

In the case of trajectories that are propagated by a Monte Carlo scheme for which suggested steps are accepted or rejected based on a Metropolis criterion,[20] the weight of each trajectory is the product of the likelihood of each step in the trajectory: $\mathcal{P}_\beta[X(t)] \propto \Pi_j p_j$, where

$$p_j = \begin{cases} \min(1, \exp(-\beta\Delta V)), & \text{if step accepted} \\ 1 - \exp(-\beta\Delta V), & \text{otherwise} \end{cases} \tag{11}$$

with ΔV the potential energy change during the suggested step.

The central quantity needed to recover the correct average of any functional observable at $\beta_\pm$ from the actual trajectories at β by applying reweighting is

$$\frac{\mathcal{P}_{\beta_\pm}}{\mathcal{P}_\beta} \equiv \Phi_{\text{traj}}[X_i(t)], \tag{12}$$

a correction functional for the relative weight that a particular trajectory $X_i(t)$ would have at $\beta_\pm$ if it would pass exactly through the same x points as those of a trajectory generated at β. Using it, in the practical application of the JE-based ΔU and ΔS formulae in Eqs. (7) and (8), all trajectories are generated at β, then, reweighed at $\beta_\pm$. For example, to calculate $\langle \exp(-\beta_\pm W)\rangle_{\beta_\pm}$ from an actual evolution of trajectories at β, one can use the reweighting formula

$$\langle \exp(-\beta_\pm W)\rangle_{\beta_\pm} = \frac{\sum_{i=1}^{N_s} \exp(-\beta_\pm W_i)\phi_{\text{eq}}(x_{0i})\Phi_{\text{traj}}[X_i(t)]}{\sum_{i=1}^{N_s} \phi_{\text{eq}}(x_{0i})\Phi_{\text{traj}}[X_i(t)]}, \tag{13}$$

where the summation index i labels N_s (nonequilibrium) trajectories simulated at β and originating from canonically distributed points x_{0i}, and $\phi_{\text{eq}}(x_{0i})$ is a correction factor for the equilibrium weight of the initial point of each trajectory, $\phi_{\text{eq}}(x_{0i}) = \exp(-\beta_\pm V(x_{0i}))/\exp(-\beta V(x_{0i}))$.

Equations (7) and (8) constitute the JE equivalent of the TP Eqs. (4) and (5); both sets involve finite differences. In addition to expressing the necessary β derivatives using a finite difference approximation, it is possible in the case of Langevin dynamics to take the required derivative analytically when starting from an expression for ΔU into which the appropriate reweighting factor relative to some other inverse temperature β' has already been included. The full reweighting factor can thus be expressed as

$$\phi_{\text{eq}}(x_0)\Phi[X(t)] = \exp((\beta - \beta')\mathcal{A}[X(t)]), \tag{14}$$

where $\mathcal{A}[X(t)] = V(x_0) + (1/4m\gamma)\int_0^t (m\gamma\dot{x} + \nabla V)^2 dt'$. The change in energy as a function of β' can then be expressed in terms of an ensemble path average taken at β,

$$\Delta U(\beta') = -\frac{\partial}{\partial\beta'}\ln\frac{\langle \exp-(\beta'W - (\beta' - \beta)\mathcal{A})\rangle_\beta}{\langle \exp(-(\beta' - \beta)\mathcal{A})\rangle_\beta}. \tag{15}$$

Since W and $\mathcal{A}$ are independent of β', the derivative with respect to β' can be taken directly (see the Appendix), yielding a general formula for ΔU as a function of the inverse temperature, β', based on an ensemble average of trajectories sampled at β. This formula is exact in principle for any value of β', but will converge poorly for values of β' far from β when relevant trajectories at the two temperatures do not overlap. When evaluated at $\beta' = \beta$, the formula simplifies to

$$\Delta U = \frac{\langle (W + \mathcal{A})\exp(-\beta W)\rangle_\beta}{\langle \exp(-\beta W)\rangle_\beta} - \langle \mathcal{A}\rangle_\beta, \tag{16}$$

a formula for ΔU at the inverse sampling temperature, β, that does not rely on a finite difference approximation.

The same procedure applied to the calculation of ΔS yields the result

$$T\Delta S = \frac{\langle (W + \mathcal{A})\exp(-\beta W)\rangle}{\langle \exp(-\beta W)\rangle} - \langle \mathcal{A}\rangle + \frac{\ln\langle \exp(-\beta W)\rangle}{\beta}, \tag{17}$$

which recovers the difference between the expression for ΔU in Eq. (16) and the JE expression for ΔF. We note that a similar procedure as the one used by us for JE, when applied to TP, can derive the analytical derivative TP expressions for ΔU and ΔS,[21] which can be shown[22] to be the $\Delta T \to 0$ limit of the finite difference TP formulae. We also note that our procedure to extract $\Delta U - \Delta S$, either analytically or as finite differences, can be applied to ΔF expressions that use forward and backward switching, derived by Bennett for TP (Ref. 23) and generalized by Crooks for nonequilibrium.[24]

Equations (7), (8), (16), and (17) present the finite difference and, respectively, the analytical derivative JE-reweighting formulae for calculating equilibrium energy and entropy components from irreversible (nonequilibrium) work trajectories performed at a single temperature. They have been derived using the relationships involving β derivatives of the free energy given in Eq. (1).

IV. DERIVATION FROM A FLUCTUATION THEOREM

A nonequilibrium expression for ΔU that is distinct from the JE reweighting-based ones derived in the previous section follows from a fluctuation theorem (FT)-based relation derived by Crooks[24]

$$\langle f[x(\tau)]e^{-\beta W_d}\rangle_{\text{neq}} = \langle f[x(\tau)]\rangle_{\text{eq}}, \tag{18}$$

where $f[x(\tau)]$ is function of the final state of the trajectory. The left-hand side is an average over nonequilibrium trajectories and the right-hand side is an equilibrium average for the final state of the system. In the special case when $f[x(\tau)] = V(x)$ one obtains
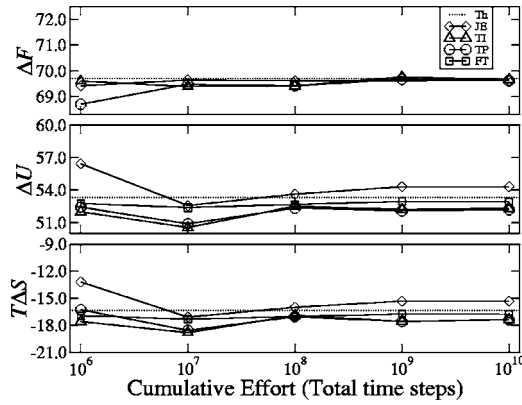
FIG. 1. The calculated ΔF, ΔU, and $T\Delta S$ of Sun's model using Jarzynski's, TI, TP, and FT methods compared to the exact theoretical value (dotted line). For TI, the λ interval [0, 1] was divided into ten subintervals. At each λ, trajectories were run for a number of time steps $N_l=10^5$, 10^6, 10^7, 10^8, or 10^9. The integral in Eqs. (2) and (3) used a trapezoidal numerical summation scheme. Similarly for TP, simulations were carried out in ten subdivisions of the λ interval. To perform the JE and FT calculations, we run $N_s=10^3$, 10^4, 10^5, 10^6, or 10^7 trajectories with ($N_l=1000$) steps each. The time step used in all trajectory was $dt=0.01$ and the kT used was 65.0 with $\Delta T=0.5$ for TP and $\Delta\beta=0.0005$ for the finite difference JE.

$$\langle V(x)\rangle_{\lambda=1} = \langle V(x(t))e^{-\beta W_d}\rangle = \frac{\langle V(x(t))e^{-\beta W}\rangle}{\langle e^{-\beta W}\rangle}. \tag{19}$$

Using this expression for the energy of the final state, ΔU can be written as

$$\Delta U = \frac{\langle V(x(t))e^{-\beta W}\rangle}{\langle e^{-\beta W}\rangle} - \langle V(x(0))\rangle, \tag{20}$$

with the $T\Delta S$ expression being simply the difference between the earlier ΔU and the ΔF formula in Eq. (6). We note that the FT derivation does not require a Langevin or Monte Carlo propagation in particular, and can be used with deterministic Hamiltonian dynamics (although convergence problems for deterministic switching free energy calculations have been reported[25,26]).

Equation (19) can also be derived from the Feynman–Kac theorem[27] as follows. Beginning from Eq. (4) in Ref. 9,

$$\frac{e^{-\beta V(x,t)}}{\int e^{-\beta V(x',0)}dx'} = \langle \delta(x - x_t)e^{-\beta W}\rangle, \tag{21}$$

both sides are multiplied by $V(x)$ and integrated with respect to x, yielding

$$\frac{\int V(x)e^{-\beta V(x,t)}dx}{\int e^{-\beta V(x',0)}dx'} = \langle V(x,t)e^{-\beta W}\rangle. \tag{22}$$

The left-hand side is multiplied the trivial factor $\int e^{-\beta V(x,t)}dx / \int e^{-\beta V(x,t)}dx$, the numerator becomes $\langle V(x)\rangle_{\lambda=1}$ and the denominator becomes $e^{\beta\Delta F}$. Simple algebraic rearrangement and substitution using the Jarzynski identity yields Eq. (19).

V. TESTS ON MODEL SYSTEM EXAMPLE

To showcase the nonequilibrium JE reweighting-based and FT-based methods, we present them together with calculations using TP and TI for a model system introduced by Sun,[28] which has become prototypical for tests of various methods using the Jarzynski equality.[25] The model describes the system transformation from a bistable ($\lambda=0$) to a uniwell ($\lambda=1$) potential,

$$V_\lambda(x) = x^4 - 16(1 - \lambda)x^2, \tag{23}$$

for which exact ΔU and ΔS values could be calculated analytically from the partition function, thereby allowing us to estimate both the statistical error and the bias (see Tables II and III).

The calculated values of ΔF, ΔU, and ΔS using the JE, TI, and TP methods are illustrated in Fig. 1 and, as seen, agree with the respective theoretical values derived analytically. Moreover, for any of the three quantities, i.e., for ΔF, ΔU, and ΔS, all three methods (i.e., TI, TP, and JE) yielded similar accuracies for the same amount of CPU time. A point regarding the relative precision of the calculation of ΔU, ΔS versus that of ΔF using our method with the similar relative precision for TI and TP is worth making here. While the statistical error in all three quantities decays with $1/\sqrt{N}$, where N is the number of independent samples, for all three methods the relative error in ΔS and ΔU was an order of magnitude larger than that in ΔF. This is in accord with previous TI and TP entropy and energy calculations which report, invariably, less accurate estimates than those for the free energy,[29,30] typically by more than an order of magnitude. This is because, unlike ΔF estimates, which require only the average of a potential difference (or a derivative), in either the case of TI or TP, ΔS and ΔU estimation depends on the reliability of computing small differences between averages of two (or several) relatively larger numbers. In the case of ΔF, on the other hand, only a single averaging is required. As for TI and TP, this also holds true for our JE-

TABLE I. Biases and standard deviations for each of four methods used to calculate ΔF.

| | Monte Carlo | | | | | | Langevin | |
| | TI | | TP | | JE | | JE | |
Steps	δ	σ	δ	σ	δ	σ	δ	σ
10^5	0.0205968	0.306957	0.0157416	0.261254	0.0103407	0.294198	0.0250241	3.66951
10^6	0.0162808	0.0928635	0.000758978	0.0833433	0.000402889	0.087341	0.0741598	1.17113
10^7	0.0177693	0.0296191	0.000196086	0.0261185	0.000923003	0.0300394	0.0369018	0.356863
10^8	0.0175085	0.00953593	0.000462176	0.00855994	0.00010989	0.00963731	0.0329407	0.117901

TABLE II. Biases and standard deviations for each of six methods (TI, TP, JE reweighting using Langevin or Monte Carlo, and FT using Langevin or Monte Carlo) employed to calculate ΔU.

| | Monte Carlo | | | | | | | | Langevin | | | |
| | TI | | TP | | FT | | JE | | FT | | JE | |
Steps	δ	σ	δ	σ	δ	σ	δ	σ	δ	σ	δ	σ
10^5	0.03591	0.35444	0.00821	0.23262	0.12473	5.69595	0.17021	3.64620	0.25044	5.60621	0.01534	75.6854
10^6	0.03148	0.11162	0.00061	0.07604	0.08878	1.75686	0.03279	1.16295	0.01468	1.78501	1.68585	24.0913
10^7	0.02908	0.03494	0.00011	0.02343	0.03784	0.56125	0.02647	0.38602	0.00411	0.54892	1.57726	7.24880
10^8	0.02747	0.01125	0.00048	0.00734	0.00456	0.17885	0.01132	0.11999	0.01117	0.18624	1.89812	2.25615

derived ΔU and ΔS estimates [viz. Eqs. (7), (8), (16), and (17)] and for our FT estimates [viz. Eq. (20)], which similarly involve differences of averages.

As for TI and TP, for JE it is also because of this distinction that energy/entropy estimates can be orders of magnitude less accurate than their free energy counterpart.

The results from calculations of ΔF, ΔU, and $T\Delta S$ are presented in Tables I–III. Bias was calculated as $\delta = |\hat{\bar{x}}(N) - x|$, where x is the exact value of ΔF, ΔU, or $T\Delta S$, and $\hat{\bar{x}}(N)$ is the average calculated from $N=1000$ trial estimates each consisting of the specified number of trajectory steps. Since each estimator is exact in principle, bias is the result of either insufficient convergence (given the limited number of 1000 trials) or is due to numerical error. The standard deviation is calculated as the square root of the sample variance $\sigma^2 = (1/N)\Sigma_{i=1}^{N}(\hat{x}_i - \hat{\bar{x}}(N))^2$ again calculated on the basis of $N=1000$ trials. The convergence of bias and standard deviation are plotted for ΔU in Figs. 2 and 3.

In this test β has been set to $1/50$; for reference, the maximum barrier height of the model (i.e., when $\lambda=0$) is, in equivalent units, 64. For the simple system presented here, TP had the best performance. The total steps in each TI simulation were evenly divided between 20 simulations at distinct values of λ, ranging from 0 to 1 and integration over λ was performed using a trapezoidal scheme. TI converged quickly, but was less accurate that TP due to the low accuracy of the integral over λ.

For the nonequilibrium JE and FT methods, individual nonequilibrium trajectories were 1000 steps long, both for Monte Carlo (MC) and Langevin sampling. For the latter propagation scheme, γ was set to 100, and in the case of JE reweighting, $\Delta\beta$ was set to 0.0001. JE was competitive as a method for calculating ΔF, particularly when MC sampling was used. JE and FT methods of calculating ΔU and $T\Delta S$

were competitive with TI and TP, but fared less well when Langevin sampling was used. The relatively poor performance obtained in this case was a result of a broader distribution of sampled work values, which caused slower convergence, and by additional bias introduced by the numerical properties of the estimator in Eq. (13) for Langevin propagation (see Fig. 2).

All methods involving MC sampling produced reasonable performance, achieving results well within a percent relative convergence after 10^8 MC steps (exact values of ΔF, ΔU, and $T\Delta S$ are 65.8878, 53.1957, and -12.6921). However, it is important to stress that the relative performance is expected to be strongly model dependent. Our conclusions might not be generalized for other systems or conditions or when comparing to yet other methods (for example, the Bennett acceptance ratio method,[23] which is technically distinct from either TI or TP, has also been recently used[31] and extended[32]). It is likely that there might not be an overall best method, but rather that various methods may be good for various systems or observables. For example, when comparing the calculation of ΔF using JE, Bennett's acceptance-rejection method, and TI, it was found that each of those three methods performed more efficiently than the others in at least one situation examined.[33] This is expected to extend also to the estimation derived here for the components of ΔF.

VI. CONCLUDING DISCUSSION

We have presented and tested two nonequilibrium formulations (one based on perturbative temperature reweighting and the other on a fluctuation theorem) that enable the calculation of the energy and entropy components of the equilibrium Helmholtz free energy difference between two states from nonequilibrium transformations, extending thus

TABLE III. Biases and standard deviations for each of six methods used to calculate $T\Delta S$.

| | Monte Carlo | | | | | | | | Langevin | | | |
| | TI | | TP | | FT | | JE | | FT | | JE | |
Steps	δ	σ	δ	σ	δ	σ	δ	σ	δ	σ	δ	σ
10^5	0.01531	0.41363	0.00753	0.18191	0.11439	5.69481	0.18055	3.64778	0.22542	5.73306	0.04036	75.4346
10^6	0.01520	0.12946	0.00137	0.05698	0.08837	1.75570	0.03239	1.16263	0.08884	1.90158	1.76001	24.0265
10^7	0.01131	0.04158	0.00009	0.01783	0.03692	0.56169	0.02554	0.38664	0.03279	0.56872	1.61416	7.23693
10^8	0.00996	0.01316	0.00002	0.00585	0.00445	0.17938	0.01121	0.12025	0.04411	0.18575	1.93106	2.25252
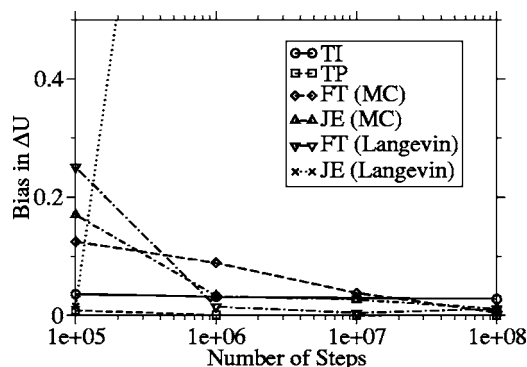
FIG. 2. Convergence of ΔU as calculated by various methods. JE denotes the analytic version of the non-equilibrium reweighting procedure, with either MC or Langevin dynamics. Note that, while the Langevin result does converge to the theoretical value, it does so after order of magnitude longer times and has a large bias.

the common use of the formalism behind the use Jarzynski equality or fluctuation theorems for free energies to also treat entropic and energetic contributions.

While this extension provides a novel method to compute equilibrium ΔS and ΔU in nonequilibrium molecular dynamics or Monte Carlo simulations, it would be of additional usefulness to employ it in the analysis of single-molecule experiments. For example, Hummer and Szabo[9] have shown how one can utilize the Jarzynski equality in the context of single-molecule pulling to reconstruct the free energy profile $\Delta F(\xi)$ along the pulling coordinate ξ employed in the experiment; a version of such a JE-based approach has been used by Liphardt *et al.*[34] to analyze folding free energies using force-extension curves obtained by unfolding ribonucleic acid (RNA). The fluctuation theorem also has been used with single molecule experiments to recover RNA folding free energy differences.[35] Applications of the new JE- and FT-based energy-entropy methods presented by us here would provide a new approach to probing the entropy-energy contribution to the folding free energy landscape[36] or to resolve between entropic[37] and enthalpic[38] models for dynamic disorder in proteins. Moreover, by gauging individual trajectory weights [cf. Eq. (10)], the approach might offer insights into $\Delta U - \Delta S$ compensation for folding at the single-molecule level.[39]

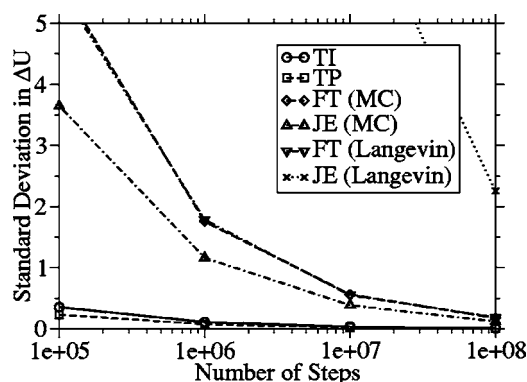However, although applying the method to molecular

FIG. 3. Standard deviation in ΔU, based on $N = 1000$ trials, each consisting of the specified number of time steps. Method labels same as in Fig. 2.

dynamics simulations is straightforward, single-molecule force-extension experiments do not record all the information necessary in order to calculate the statistical reweighting factor, Φ_{traj}, in Eq. (12) for each trajectory. This is because the weight of a trajectory will depend, in principle, on the displacements and potential gradients for all degrees of freedom of the system, while only displacements along the pulling coordinate are recorded. Since the temperature dependence of the free energy is accounted for by the temperature dependence of the weight, by discarding information about certain degrees of freedom, their contribution to the temperature dependence of the free energy is lost. Calculation of the entropy and energy contributions to the free energy along a single dimension, while neglecting other degrees of freedom, provides no more information than can be derived from the free energy profile analysis of Hummer and Szabo described earlier.[9] But if it were possible to monitor motion along some important second coordinate,[40] the reweighting strategy could be applied in order to determine the entropy and enthalpy due to motion in that second direction as they vary along the pulling coordinate. It is conceivable that motion along a second coordinate could be monitored, concomitantly with pulling, by the inclusion of fluorescence resonance energy transfer (FRET) labels in the molecule to be studied.[41,42] Additionally, even assuming that sufficiently resolved displacement information could be calculated on the basis of the FRET signal, some approximation would have to be made to account for the potential gradient which could not be directly measured.

Similarly to JE-based ΔF calculations, only low work values make significant contributions to the JE-based ΔS and ΔU calculations presented here. These values are statistically rare, particularly when the spread of the work distribution exceeds $K_B T$. As such, for switching rates in the linear-response regime, the efficiency of JE can be similar to that of TP or TI.[25,43] However, the advantage of JE lies in its trivial parallelization and therefore in a decrease of the actual computing time. Moreover, enhanced path sampling techniques that favor generation of low work trajectories[28,44] could aid in devising more efficient algorithms when using the present $\Delta U - \Delta S$ decomposition.

The equations derived here for the Helmholtz free energy can be generalized to deconvolute the enthalpy and entropy components of the Gibbs free energy in the isobaric-isothermal ensemble implementations of the Jarzynski equality.[26,45] It would also be interesting to explore how the JE-derived entropy formulae derived here connect with entropy-production along single-molecule trajectories[39,46,47] or with microcanonical entropies from isoenergetic nonequilibrium processes.[48]

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APPENDIX: DERIVATION USING ANALYTICAL DERIVATIVES

Setting $f = \langle \exp(-\beta' W - (\beta' - \beta)\mathcal{A}) \rangle_\beta$ and $g = \langle \exp(-(\beta' - \beta)\mathcal{A} \rangle_\beta$, Eq. (14) becomes

$$\Delta U(\beta') = -\frac{\partial}{\partial \beta'} \ln(f/g). \tag{A1}$$

Taking the derivative with respect to β' yields

$$\Delta U(\beta') = \frac{1}{g}\frac{\partial g}{\partial \beta'} - \frac{1}{f}\frac{\partial f}{\partial \beta'}. \tag{A2}$$

Because W and $\mathcal{A}$ are independent of β', the derivatives of f and g can be taken directly

$$\frac{\partial f}{\partial \beta'} = \langle (-W - \mathcal{A})\exp(-\beta' W - (\beta' - \beta)\mathcal{A}) \rangle_\beta \tag{A3}$$

and

$$\frac{\partial g}{\partial \beta'} = \langle -\mathcal{A}\exp(-(\beta' - \beta)\mathcal{A}) \rangle_\beta. \tag{A4}$$

Hence,

$$\Delta U(\beta') = \frac{\langle -\mathcal{A}\exp(-(\beta' - \beta)\mathcal{A}) \rangle_\beta}{\langle \exp(-(\beta' - \beta)\mathcal{A} \rangle_\beta} - \frac{\langle (-W - \mathcal{A})\exp(-\beta' W - (\beta' - \beta)\mathcal{A}) \rangle_\beta}{\langle \exp(-\beta' W - (\beta' - \beta)\mathcal{A}) \rangle_\beta}. \tag{A5}$$

This is a general equation for ΔU as a function of β' in terms of an ensemble path average at β. Now that we have exploited the β' dependence of the reweighting factor in order to take the required derivatives, the function can be evaluated at $\beta' = \beta$ yielding the simplified equation

$$\Delta U(\beta) = \frac{\langle (W + \mathcal{A})\exp(-\beta W) \rangle_\beta}{\langle \exp(-\beta W) \rangle_\beta} - \langle \mathcal{A} \rangle_\beta. \tag{A6}$$

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