

# Equilibrium Time Correlation Functions from Irreversible Transformations in Trajectory Space<sup>†</sup>

Phillip L. Geissler<sup>\*,‡</sup>

Department of Chemistry, Massachusetts Institute of Technology, Cambridge, Massachusetts 02139

Christoph Dellago

Institute for Experimental Physics, University of Vienna, Boltzmannngasse 5, 1090 Vienna, Austria

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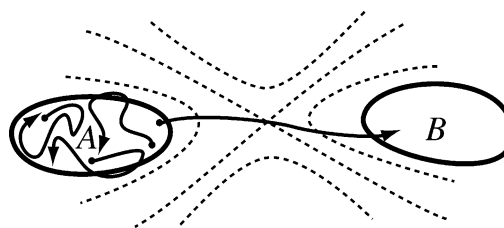
We present a new identity for the statistical mechanics of trajectories, showing that a distribution of irreversible transformations between ensembles of trajectories is sufficient to determine equilibrium time correlation functions. This general and exact result extends to the dynamical realm recently derived connections between thermodynamic free energies and statistics out of equilibrium. We focus on the specific application to population correlation functions characterizing chemical kinetics. In this context we use the identity to compute reaction rate constants through appropriate averaging of an effective work to switch from nonreactive to reactive trajectory ensembles. There is in principle no restriction on how quickly this switching of ensembles is performed. We demonstrate the practicality of such a calculation for a model isomerization in dense solvent.

## I. Introduction

The most interesting dynamical features of a complex system are often much slower than the basic microscopic motions that advance them. For instance, the characteristic time scale of protein folding ( $\sim 1$  s for a typical protein) greatly exceeds that of torsional rotations along the polymer backbone ( $\sim 100$  ps). Other examples of processes exhibiting widely different time scales include nucleation of first order phase transitions, chemical reaction in solution, dynamics near a glass transition, and transport in and on solids. Such a separation of important time scales seriously hinders the study of dynamical mechanisms. Experiments cannot usually resolve the molecular fluctuations that drive condensed phase dynamics. Computer simulations, on the other hand, can feasibly generate trajectories only a few orders of magnitude longer than the duration of microscopic fluctuations, making long-time behavior elusive.

One common source of disparate time scales is the presence of dynamical bottlenecks between basins of attraction in phase space. Figure 1 depicts some microstates in such a basin, A (e.g., a protein's unfolded state), and trajectories emanating from each. If free energy barriers separating A from adjacent basins are much larger than typical thermal excitations, then only a very small fraction of trajectories will escape A to end in some other metastable state, B (e.g., the protein's native state), within microscopic correlation times. Many computational schemes have been devised to explore the important but infrequently visited transition state region. Most presume knowledge of mechanism,<sup>1</sup> assume that saddle points of the potential energy surface coincide with dynamical bottlenecks,<sup>2</sup> or introduce artificial dynamical rules.<sup>3–6</sup> More systematic strategies focus on the rare short trajectories that exhibit transitions of interest.<sup>7–9</sup>

We make these ideas quantitative by defining a partition function for the restricted ensemble of microstates in A whose



**Figure 1.** Several trajectories originating in a basin of attraction A. Free energy contours (dashed lines) indicate a bottleneck between A and a second basin B. The vast majority of short trajectories do not surmount this free energy barrier and thus do not connect the two basins.

trajectories of length  $t$  end in B,

$$Z_{AB}(t) = \int dx_0 \rho(x_0) h_A[x_0] h_B[x_t(x_0)] \quad (1)$$

For the moment we imagine that dynamics are deterministic, so that each phase space point  $x_0$  uniquely specifies a trajectory, represented here as an ordered sequence of microstates separated by a time step  $\Delta t$ ,  $x(t) = \{x_0, x_{\Delta t}, x_{2\Delta t}, \dots, x_t\}$ . In eq 1  $\rho(x)$  is an equilibrium probability density, for example, the canonical distribution function  $\rho(x) \propto e^{-E(x)/k_B T}$ . The functions  $h_A$  and  $h_B$  project onto A and B, respectively; i.e.,  $h_i[x]$  is unity for  $x$  in state  $i$  and otherwise vanishes. We now compare  $Z_{AB}(t)$  with the partition function for the entire basin,  $Z_A = \int dx_0 \rho(x_0) h_A[x_0]$ . The logarithm of their ratio determines a free energy difference between the two ensembles,  $\Delta F(t) \equiv -k_B T \ln[Z_{AB}(t)/Z_A]$ , that depends parametrically on time. Although free energy is typically conceived as a static quantity,  $\Delta F(t)$  is directly related to an equilibrium time correlation function,

$$C(t) \equiv \frac{\langle h_A[x_0] h_B[x_t(x_0)] \rangle}{\langle h_A \rangle} = \exp[-\Delta F(t)/k_B T] \quad (2)$$

where angled brackets denote an average over the equilibrium distribution  $\rho(x)$ . The approach of  $C(t)$  to its equilibrium value

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<sup>‡</sup> Current address: Department of Chemistry, University of California at Berkeley, CA 94720.

determines the phenomenological kinetics of transitions from A to B:<sup>10</sup>

$$C(t) \sim k_{AB}t \quad \text{for} \quad \tau_{\text{mol}} < t \ll \tau_{\text{rxn}} \quad (3)$$

Here,  $\tau_{\text{mol}}$  is the time scale characterizing microscopic motions, and  $\tau_{\text{rxn}} = (k_{AB} + k_{BA})^{-1}$  is the reaction time depending on the forward and backward reaction rate constants  $k_{AB}$  and  $k_{BA}$ . The unusual partition function  $Z_{AB}(t)$  thus connects the thermodynamic concept of free energy to intrinsically dynamical quantities such as rate constants.

To clarify this connection in principle, and to make it useful in practice, we along with others have developed a statistical mechanics of trajectories, in close analogy to the familiar statistical mechanics of individual microstates.<sup>7,11,12</sup> Ensembles of trajectories, weighted by their frequency of occurrence, form the basis for this approach. The probability density of observing a particular pathway  $x(t)$  at equilibrium depends in general on the distribution of initial conditions  $\rho(x_0)$ , and on transition probabilities  $p(x \rightarrow x')$  for each step in time:

$$P_{\text{equ}}[x(t)] = \rho(x_0) \prod_{i=0}^{t/\Delta t - 1} p(x_{i\Delta t} \rightarrow x_{(i+1)\Delta t}) \quad (4)$$

Integrating the path distribution  $P_{\text{equ}}[x(t)]$  over all possible pathways consistent with relevant constraints generates the analogue of a partition function,  $\mathcal{Z}(t)$ . For the ensemble of trajectories whose initial points lie in A,  $\mathcal{Z}_A(t) = \int \mathcal{D}x(t) P_{\text{equ}}[x(t)] h_A(x_0)$ . (The notation  $\int \mathcal{D}x(t)$  represents integration over all phase space points comprising a trajectory of length  $t$ . Resemblance to conventional path integrals is intentional, but integration over a discrete set of phase space points here ensures that issues of measure are not problematic.) Further constraining trajectories to end in B at time  $t$  gives  $\mathcal{Z}_{AB}(t) = \int \mathcal{D}x(t) P_{\text{equ}}[x(t)] h_A(x_0) h_B(x_t)$ . For deterministic dynamics, transition probabilities are Dirac delta functions, and  $\mathcal{Z}_{AB}(t)$  reduces to the function  $Z_{AB}(t)$  in eq 1. For stochastic dynamics (e.g., Langevin or Monte Carlo), however, transition probabilities may have finite widths. In this case,  $Z_{AB}(t)$  is not well-defined, because initial conditions do not uniquely specify trajectories. The path ensemble “partition function”  $\mathcal{Z}_{AB}(t)$ , however, remains meaningful.

Within this perspective thermodynamic quantities related to partition functions have analogous meaning for trajectories. For example,  $-\ln[\mathcal{Z}_{AB}(t)/\mathcal{Z}_A(t)]$  is effectively the “free energy” difference between the ensemble of all trajectories originating in A and the ensemble including only reactive trajectories, those that originate in A and end in B. As a result of this connection, many standard techniques of statistical mechanics have analogous utility. Importance sampling can be used to focus on rare trajectories of interest, such as those executing transitions between basins of attraction. This transition path sampling technique, in effect a biased random walk through the space of all dynamical paths, has been applied to several very slow but important processes in complex systems.<sup>13–16</sup> Other analogies to equilibrium thermodynamics have been revealed and exploited, primarily toward the end of determining reaction rates and mechanisms.<sup>17–19</sup> In this article we show that connections between the statistical mechanics of trajectories and that of microstates exist even *out* of equilibrium. We do so by deriving in section IV a dynamical version of the nonequilibrium identity recently presented by Jarzynski.<sup>20</sup> To establish this result, we must first generalize concepts of mechanical work and phase space evolution to the space of trajectories, as described in

sections II and III. We present a numerical application of the new identity in section V and discuss its implications in section VI.

## II. “Work” in Trajectory Space

Jarzynski’s identity relates differences in equilibrium free energy, or reversible work  $W_{\text{rev}}$ , to repeated irreversible transformations between the corresponding ensembles. This exact relationship amends Clausius’s inequality,  $\bar{W} \geq W_{\text{rev}}$ , profoundly. It is convenient to define mechanical work,  $W$ , in terms of a time-dependent potential energy function,  $E(x, \tau)$ , which drives changes of ensemble. If the dependence of  $E$  on  $x$  changes in  $N$  sudden steps at times  $\tau_i$ ,

$$E(x, \tau) = E^{(i)}(x) \quad \tau_{i-1} < \tau \leq \tau_i \quad (5)$$

then  $W$  is just the total of energy accumulated at each step:

$$W = \sum_{i=0}^{N-1} [E^{(i+1)}(x_{\tau_i}) - E^{(i)}(x_{\tau_i})] \quad (6)$$

A corollary to the first and second laws of thermodynamics, Clausius’s inequality establishes the average (denoted by an overbar) of expended work over many realizations of an irreversible process as an upper bound on  $W_{\text{rev}}$ . Jarzynski’s result, on the other hand,

$$\overline{\exp[-W/k_B T]} = \exp(-W_{\text{rev}}/k_B T) \quad (7)$$

shows how to properly average over nonequilibrium realizations so that  $W_{\text{rev}}$  is obtained exactly.<sup>20</sup>

We extend the concept of mechanical work to trajectory space by introducing a path “energy” function,  $\mathcal{E}[x(t)]$ , that plays a role analogous to that of  $E(x, \tau)$  above. A change in the dependence of  $\mathcal{E}$  on trajectory  $x(t)$  should reflect a change in path ensemble. For a given path distribution  $P[x(t)]$  and associated “partition function”  $\mathcal{Z}(t)$ , we therefore define

$$\mathcal{E}[x(t)] = -\ln\{P[x(t)]\mathcal{Z}(t)\} \quad (8)$$

so that  $e^{-\mathcal{E}}$  has the form of an unnormalized Boltzmann factor. For the transition path ensemble  $P_{AB}[x(t)] \equiv P_{\text{equ}}[x(t)] h_A(x_0) h_B(x_t)/\mathcal{Z}_{AB}(t)$ , for instance, the path energy is  $\mathcal{E}[x(t)] = -\ln\{P_{\text{equ}}[x(t)] h_A(x_0) h_B(x_t)\}$ . The path energy is analogous to the action in path integral theory.

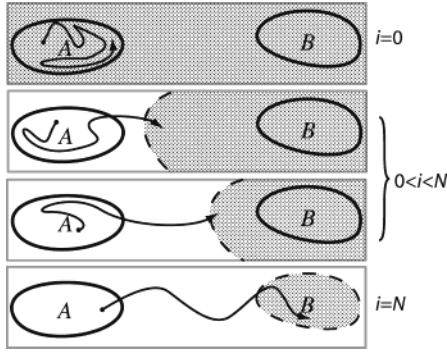
The natural extension of work, corresponding to a change of path ensemble in  $N$  sudden steps, is then an accumulated “energy”

$$\mathcal{W} = \sum_{i=0}^{N-1} (\mathcal{E}^{(i+1)}[x^{(i)}(t)] - \mathcal{E}^{(i)}[x^{(i)}(t)]) \quad (9)$$

With these generalizations the reasoning used to derive eq 7 in, e.g., ref 21 applies transparently to transformations in trajectory space. In particular, averaging the exponential of eq 9 over many realizations of a transformation yields a result for ensembles of trajectories that is identical in form to Jarzynski’s.

## III. “Dynamics” in Trajectory Space

A specific set of rules for sampling dynamical paths constitutes a “dynamics” in trajectory space. We emphasize that a system’s natural dynamics, governing the time evolution within individual trajectories, are not modified by this set of evolution rules, which determines a sequence of trajectories, such as that



**Figure 2.** Schematic depiction of one possible sequence of trajectories of the model system described in the main text. Shaded regions are areas where the biasing potential  $U(x, \lambda^{(i)})$  is not much greater than unity. At step  $i = 0$ , this region encompasses all of phase space, because the trajectory endpoint is unbiased. As  $i$  increases toward  $N$ , however, the region shrinks to include only state B.

depicted in Figure 2. Viewing the exploration of trajectory space as a random walk, we represent a particular set of rules using transition matrices,  $\{\mathbf{M}^{(0)}, \mathbf{M}^{(1)}, \dots, \mathbf{M}^{(N)}\}$ , that independently conserve path distributions  $\{P^{(0)}, P^{(1)}, \dots, P^{(N)}\}$ :

$$\int \mathcal{D} x(t) M^{(i)}[x(t) \rightarrow x'(t)] P^{(i)}[x(t)] = P^{(i)}[x'(t)] \quad (10)$$

Matrix elements  $M^{(i)}[x(t) \rightarrow x'(t)]$  express the probability that a walker situated at path  $x(t)$  at step  $i - 1$  will reside at path  $x'(t)$  at step  $i$ . In transforming between two trajectory ensembles, path distributions conserved by the initial and final steps should clearly describe the initial and final ensembles, respectively. The identity we derive in the following section is in principle independent of the choice of  $\mathbf{M}^{(i)}$  at intermediate steps. Crooks has shown that the exact form of phase space dynamics is analogously arbitrary for Jarzynski's identity.<sup>21</sup>

The reader may note that one choice of trajectory space "dynamics" is provided by simply following the natural evolution of a system over many multiples of the trajectory length  $t$ . This choice amounts to using the final microstate state of one trajectory segment as an initial condition for the next. Though valid, such an approach is not useful for our purpose, because it is not amenable to a bias in sampling. Imposing a bias on the sampling of trajectories is essential for switching between path ensembles.

#### IV. "Out of Equilibrium" in Trajectory Space

Given a set of  $N$  transition matrices governing a random walk through path space, the probability of observing a particular sequence of trajectories,  $\mathcal{X}(N, t) = \{x^{(0)}(t), x^{(1)}(t), \dots, x^{(N)}(t)\}$ , is

$$\mathcal{P}[\mathcal{X}(N, t)] = P^{(0)}[x^{(0)}(t)] \prod_{i=0}^{N-1} M^{(i+1)}[x^{(i)}(t) \rightarrow x^{(i+1)}(t)] \quad (11)$$

This weight, a complete description of the random walk's statistics, determines averages of sequence-dependent quantities,  $\mathcal{Y}[\mathcal{X}(N, t); \{\mathbf{M}^{(i)}\}]$ , over many realizations of the walk:

$$\bar{\mathcal{Y}} = \sum_{\mathcal{X}(N, t)} \mathcal{P}[\mathcal{X}(N, t)] \mathcal{Y}[\mathcal{X}(N, t); \{\mathbf{M}^{(i)}\}] \quad (12)$$

The sum in eq 12 runs over all possible path sequences of length  $N$ . In general such an average depends on the choice of  $\mathbf{M}^{(i)}$  and is therefore sensitive to the way in which ensembles are transformed.

We focus attention on the special case

$$\mathcal{Y} = e^{-\mathcal{W}} \quad (13)$$

$$= \frac{\mathcal{Z}^{(N)}(t)}{\mathcal{Z}^{(0)}(t)} \prod_{i=0}^{N-1} \frac{P^{(i+1)}[x^{(i)}(t)]}{P^{(i)}[x^{(i)}(t)]} \quad (14)$$

where we have used definitions (8) and (9) for path energy and path work, respectively. All but the initial and final factors of  $\mathcal{Z}^{(i)}(t)$  arising from eqs 8 and 9 have been canceled in eq 14.<sup>22</sup> The surviving ratio of "partition functions"  $\mathcal{Z}^{(N)}(t)/\mathcal{Z}^{(0)}(t)$  is the exponential of an effective *reversible* work,  $\mathcal{W}_{\text{rev}}$ , to change from the initial to final path ensemble. In the spirit of ref 21 the remaining product in eq 14 could be viewed as the exponential of work in excess of  $\mathcal{W}_{\text{rev}}$ ,

$$\mathcal{W}'_{\text{d}} = \mathcal{W} - \mathcal{W}'_{\text{rev}} \quad (15)$$

$$= - \sum_{i=0}^{N-1} \ln(P^{(i+1)}[x^{(i)}(t)]/P^{(i)}[x^{(i)}(t)]) \quad (16)$$

which is "dissipated" due to the irreversibility of transforming between ensembles in a finite number of steps.  $\mathcal{W}'_{\text{d}}$  clearly vanishes in the limit of a transformation so gradual that path distributions at steps  $i$  and  $i + 1$  are identical.

Averaging eq 14 over all possible realizations of the random walk with the aid of eqs 11 and 12, we obtain

$$\begin{aligned} \overline{e^{-\mathcal{W}}} &= \frac{\mathcal{Z}^{(N)}(t)}{\mathcal{Z}^{(0)}(t)} \sum_{\mathcal{X}(N, t)} P^{(0)}[x^{(0)}(t)] \prod_{i=0}^{N-1} M^{(i+1)}[x^{(i)}(t) \rightarrow x^{(i+1)}(t)] \\ &\quad \times \frac{P^{(i+1)}[x^{(i)}(t)]}{P^{(i)}[x^{(i)}(t)]} \quad (17) \end{aligned}$$

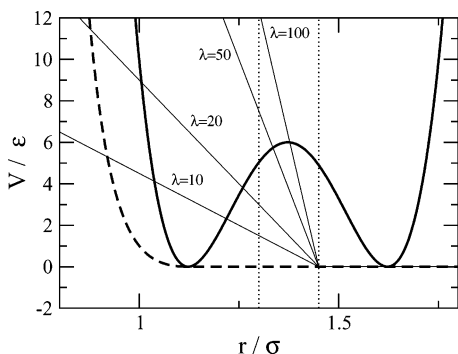
The initial path  $x^{(0)}(t)$  appears in only one term of the product in eq 17 and can be integrated out easily

$$\begin{aligned} \int \mathcal{D} x^{(0)}(t) P^{(0)}[x^{(0)}(t)] M^{(1)}[x^{(0)}(t) \rightarrow x^{(1)}(t)] \frac{P^{(1)}[x^{(0)}(t)]}{P^{(0)}[x^{(0)}(t)]} = \\ P^{(1)}[x^{(1)}(t)] \quad (18) \end{aligned}$$

because  $M^{(1)}$  conserves the distribution  $P^{(1)}$  by definition. With the elimination of  $x^{(0)}(t)$  the sum over trajectory sequences from eq 17 has the same form as the original sum, but for a path sequence of length  $N - 1$  beginning with  $i = 1$ . The new initial path  $x^{(1)}(t)$  can therefore be integrated out in exactly the same way. We iterate this procedure until a single integral remains,  $\int \mathcal{D} x^{(0)}(t) P^{(0)}[x^{(0)}(t)]$ , which gives unity because path distributions are normalized. As a result,  $\overline{e^{-\mathcal{W}'_{\text{d}}}} = 1$  (as Crooks has demonstrated for conversions between ensembles of microstates<sup>21</sup>), leaving

$$\overline{e^{-\mathcal{W}}} = \frac{\mathcal{Z}^{(N)}(t)}{\mathcal{Z}^{(0)}(t)} \quad (19)$$

The right-hand side of eq 19, a ratio of trajectory ensemble partition functions, is the exponential of a difference in effective free energies of initial and final path ensembles. The left-hand side is an average over *irreversible* transformations in a path sequence of finite length. Equation 19 is thus the dynamical analogue of Jarzynski's identity. Remarkably, as in the case of



**Figure 3.** Intramolecular ( $V_{dw}(r)$ , solid line) and intermolecular ( $V_{WCA}(r)$ , dashed line) potential energy for the model isomerization. The parameters determining height and width of the double-well potential are  $h = 6\epsilon$  and  $R = 0.25\sigma$ . The thin lines denote the “drawbridge” constraining potential and are labeled from  $\lambda = 10$  to  $\lambda = 100$  according to their slopes. The limits  $r_A$  and  $r_B$  for states A and B, respectively, are denoted with vertical dotted lines.

eq 7, this result is independent of the procedure used to switch ensembles (i.e., independent of  $\mathbf{M}^{(i)}$  for  $0 < i < N$ ).

By choosing  $P^{(0)}[x(t)] = P_{\text{equ}}[x(t)]$  and  $P^{(N)}[x(t)] = P_{\text{equ}}[x(t)]$ , one can in principle calculate the equilibrium average of any dynamical function  $\mathcal{Z}^{(N)}(t) = \int \mathcal{D}x(t) P_{\text{equ}}[x(t)] w[x(t)]$  in this way. Recall that the notation  $x(t)$  represents an entire trajectory, so that  $w[x(t)]$  could be, for example, the product of an arbitrary number of observables,  $A(t_1) A(t_2) \dots A(t_n)$ , at arbitrary times  $t_1 < t_2 < \dots < t_n < t$ . Because  $\mathcal{Z}^{(N)}(t)$  is used to construct probabilities, however, we must have  $w[x(t)] > 0$  for all  $x(t)$ . This condition is automatically satisfied for the population functions appearing in eq 1. Other applications could well involve observables  $A[x(t)]$  with indefinite sign. In these cases a generating function  $w[x(t)] = \exp\{\phi A[x(t)]\}$  could be used to compute averages  $\langle A[x(t)] \rangle$  by evaluating the derivative of  $\exp\{\phi A[x(t)]\}$  with respect to the auxiliary variable  $\phi$  at  $\phi = 0$ . Such a calculation is possible in principle but would clearly be cumbersome in practice.

## V. Application to Isomerization

We illustrate the practical utility of eq 19 by using it to calculate the kinetics of a model reaction, namely the isomerization of a diatomic solute in dense solvent.<sup>17,23</sup> This two-dimensional model consists of  $M$  point particles of unit mass interacting via the purely repulsive Weeks–Chandler–Anderson potential,

$$V_{WCA}(r) = \begin{cases} 4\epsilon \left[ \left( \frac{\sigma}{r} \right)^{12} - \left( \frac{\sigma}{r} \right)^6 \right] + \epsilon & \text{for } r \leq r_{WCA} \equiv 2^{1/6}\sigma \\ 0 & \text{for } r > r_{WCA} \end{cases} \quad (20)$$

where  $r$  is the interparticle distance, and  $\epsilon$  and  $\sigma$  are parameters specifying the strength and the interaction radius of the potential, respectively. In addition, two of the  $M$  particles form a dimer and are bound to each other by a double-well potential

$$V_{dw}(r) = h \left[ 1 - \frac{(r - r_{WCA} - R)^2}{R^2} \right]^2 \quad (21)$$

where  $h$  denotes the height of the potential energy barrier separating the potential energy minima located at intramolecular distances of  $r_{WCA} = 2^{1/6}\sigma$  and  $r_{WCA} + 2R$ . The interaction potentials  $V_{WCA}(r)$  and  $V_{dw}(r)$  are depicted in Figure 3. All numerical simulations presented in this paper were obtained for  $M = 9$  at a particle density of  $\rho = 0.6\sigma^{-2}$  and for parameters

$h = 6\epsilon$  and  $R = 0.25\sigma$ . The simulations were carried out in the microcanonical ensemble at a total energy of  $E = 9\epsilon$ .

The diatomic molecule can reside in two states, A (with small intramolecular separation  $r < r_A$ ) and B (for which  $r > r_B$ ), separated from each other by a potential energy barrier. If the barrier is high compared to  $k_B T$ , transitions between the two states are rare. The relevant correlation function describing the kinetics of such isomerizations,  $C(t)$  in eq 2, is obtained from eq 19 by selecting as initial and final path distributions  $P^{(0)}[x(t)] = P_{\text{equ}}[x(t)] h_A(x_0)/\mathcal{Z}_A(t)$  and  $P^{(N)}[x(t)] = P_{\text{equ}}[x(t)] h_B(x_t)/\mathcal{Z}_{AB}(t)$ , respectively. To convert an ensemble of trajectories unconstrained at time  $t$  into an ensemble of reactive trajectories switching from isomer A to isomer B, we make the arbitrary choice for steps  $0 < i < N$

$$P^{(i)}[x(t)] \equiv \frac{P_{\text{equ}}[x(t)] h_A(x_0) \exp[-U(x_i, \lambda^{(i)})]}{\mathcal{Z}^{(i)}(t)} \quad (22)$$

where  $\mathcal{Z}^{(i)}(t)$  is determined by normalization and

$$U(x, \lambda) \equiv \lambda[r_B - r(x)][1 - h_B(x)] \quad (23)$$

The corresponding path “energy” function is

$$\mathcal{G}^{(i)}[x(t)] = -\ln(P_{\text{equ}}[x(t)] h_A(x_0)) + U(x_i, \lambda^{(i)}) \quad (24)$$

and the effective work required for the conversion is simply

$$\mathcal{W} = \sum_{i=0}^{N-1} (U(x_i, \lambda^{(i+1)}) - U(x_i, \lambda^{(i)})) \quad (25)$$

The function  $U(x, \lambda)$  is thus an effective potential whose exponential interpolates smoothly between 1 (for  $\lambda = 0$ ) and  $h_B[x]$  (for  $\lambda = \infty$ ). This “potential”  $U(x, \lambda)$  acts as a drawbridge (anchored at  $r(x) = r_B$ ) that, when lifted, pulls trajectory endpoints into B (see Figure 3). We emphasize again that this bias, or pull, acts on the *sampling* of trajectories rather than on the trajectories themselves. Here, we let  $\lambda^{(i)}$  vary linearly with  $i$ , i.e.,  $\lambda^{(i)} = \lambda_{\text{max}} i / (N - 1)$  for  $i < N$ , and  $\lambda^{(N)} = \infty$ . In all our simulations  $\lambda_{\text{max}} = 100$ , and  $r_A = 1.30\sigma$  and  $r_B = 1.45\sigma$ .

To evaluate  $C(t)$ , we must finally determine rules for evolution in trajectory space that are consistent with the chosen bias functions. For this purpose we adapt the methods of transition path sampling, a Metropolis Monte Carlo sampling of trajectories.<sup>12,24</sup> Specifically, we construct trial moves  $x(t) \rightarrow x'(t)$  by the shooting and shifting algorithms described in Ref 12, and accept them at step  $i$  with probability

$$P_{\text{acc}}^{(i)}[x(t) \rightarrow x'(t)] = \min \left[ 1, \frac{P_{\text{equ}}[x'(t)] w^{(i)}[x'(t)]}{P_{\text{equ}}[x(t)] w^{(i)}[x(t)]} \right] \quad (26)$$

where  $w^{(i)}[x(t)] = h_A(x_0) \exp[-U(x_i, \lambda^{(i)})]$ . The corresponding transition matrices  $\mathbf{M}^{(i)}$  conserve path distributions  $P^{(i)}[x(t)]$  by construction.

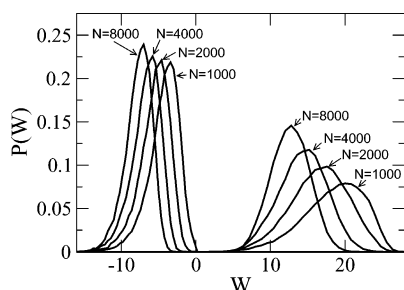
Results for  $C(t)$  computed by averaging  $e^{-\mathcal{W}}$  over many realizations of the path ensemble conversion are given in Table 1. We have focused on a single value of  $t = 0.8(m\sigma^2/\epsilon)^{1/2}$  but have considered several values of  $N$  in the range  $10^3$ – $10^4$ . Corresponding distributions of effective work are plotted in Figure 4. Our numerical results bear out the validity of eq 19. Although the mean “work”,  $\overline{\mathcal{W}}$ , is very different for different values of  $N$ , the estimates of  $\Delta F(t) = -\ln(\overline{e^{-\mathcal{W}}})$  are indeed identical within statistical error of a few percent. Moreover,



**TABLE 1: Path Free Energy  $F(t)$  and Population Correlation Function  $C(t)^a$** 

$N$	$C^f(t)$	$F^f(t)$	$C^b(t)$	$F^b(t)$
1000	$5.52 \times 10^{-5}$	9.80	$7.35 \times 10^{-5}$	9.52
2000	$4.82 \times 10^{-5}$	9.94	$5.01 \times 10^{-5}$	9.90
4000	$5.11 \times 10^{-5}$	9.88	$4.91 \times 10^{-5}$	9.92
8000	$5.23 \times 10^{-5}$	9.86	$4.95 \times 10^{-5}$	9.91
US	$6.55 \times 10^{-5}$	9.63		
TI	$5.27 \times 10^{-5}$	9.85		

<sup>a</sup> Using the identity (19), we determined  $F(t)$  and  $C(t)$  at  $t = 0.8(m\sigma^2/\epsilon)^{1/2}$  for the model dimer isomerization with several sequence lengths  $N$ . For each  $N$ ,  $5 \times 10^4$  transformations were carried out and reactive and nonreactive path ensembles were interconverted in both forward [ $C^f(t)$ ,  $F^f(t)$ ] and backward [ $C^b(t)$ ,  $F^b(t)$ ] directions. Results obtained from path sampling calculations using umbrella sampling (US)<sup>25</sup> and thermodynamic integration (TI)<sup>26</sup> are included for comparison.



**Figure 4.** Distributions of effective work  $\mathcal{W}$  to transform an ensemble of trajectories beginning in isomer A to an ensemble switching from isomer A to isomer B. The distributions peaked at positive values of  $\mathcal{W}$  correspond to path “compressions” in which the biasing potential was gradually applied (raising the drawbridge). The distributions peaked at negative values of  $\mathcal{W}$ , on the other hand, result from simulations in which the biasing potential was gradually released (lowering the drawbridge).

results obtained by path “compression” (switching from non-reactive to reactive path ensembles, with primarily positive values of  $\mathcal{W}$ ) and path “expansion” (switching from reactive to nonreactive path ensembles, with primarily negative values of  $\mathcal{W}$ ) agree within the same accuracy, indicating a sufficient sampling of path space. During the path “compression” runs, a certain fraction of final trajectories  $x^{(N)}(t)$  do not have endpoints in the final region B. Because  $\lambda^{(N)} = \infty$ , in such cases the effective potential  $U(x_i^{(N)}, \lambda^{(N)})$  and work  $\mathcal{W}$  are infinite, and the corresponding contribution to the average  $e^{-\mathcal{W}}$  vanishes.

## VI. Discussion and Conclusion

The computational effort expended in the calculations presented in the previous section is comparable to that of calculating  $C(t)$  (to similar accuracy) with the methods of transition path sampling alone (i.e., implementing a quasi-reversible change of trajectory ensemble). In light of applications of Jarzynski’s identity,<sup>27–29</sup> this observation is not surprising. On one hand, these nonequilibrium relations provide computational savings by allowing fast switching between ensembles. On the other hand, the averages in eqs 7 and 19 can be slow to converge.<sup>30</sup> Although the distributions of  $\mathcal{W}$  plotted in Figure 4 are not especially broad, the corresponding distributions of  $e^{-\mathcal{W}}$  have substantial weight in the wings.

As a result, a small fraction of path sequences can dominate the average. Significant effort is thus spent exploring regions of sequence space with little quantitative importance. In these cases a bias that guides sampling to path sequences with large values of  $e^{-\mathcal{W}}$  would be advantageous. Sun has shown how to facilitate applications of Jarzynski’s identity in an analogous

fashion.<sup>31</sup> Specifically, he used methods of path sampling to properly apply a bias that focuses attention on pathways contributing most strongly to the nonequilibrium average. Generalizing such an approach to the sampling of path sequences is formally straightforward, but complicated in practice. The standard trial moves of path sampling are most efficient for dynamics in which particle momenta can be changed by an arbitrarily small amount. The “dynamics” in trajectory space we have described, however, lacks an analogue of momentum. It would thus be difficult to generate trial path sequences that are sufficiently similar to existing sequences to ensure a reasonable acceptance probability in Sun’s scheme.

In summary, ensembles of trajectories provide a natural description of many slow and dynamically heterogeneous phenomena. Their response to applied constraints and perturbations readily provide dynamical information on equilibrium fluctuations that might otherwise become manifest only at very long times during the course of a system’s natural evolution (e.g., the time scale of inverse reaction rates). We have shown that quantitative measures of such fluctuations can be captured by arbitrarily sudden changes of ensemble. Performing computationally inexpensive, rapid transformations, however, has a drawback in that many realizations of a perturbation may be necessary to obtain reliable averages. We expect that importance sampling techniques can abate this cost, but they must await further advances in the methodology of transition path sampling.

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## References and Notes

- (1) Anderson, J. B. *J. Chem. Phys.* **1973**, *58*, 4684. Bennett, C. H. In *Algorithms for Chemical Computations*; Christoffersen R. E., Ed.; American Chemical Society: Washington, DC, 1977; pp 63–97. Chandler, D. *J. Chem. Phys.* **1978**, *68*, 2959.
- (2) Doye, J. P. K.; Wales, D. J. *J. Phys. D* **1997**, *40*, 194.
- (3) Elber, R.; Karplus, M. *Chem. Phys. Lett.* **1987**, *139*, 375. Elber, R.; Meller, J.; Olender, R. *J. Phys. Chem. B* **1999**, *103*, 899.
- (4) Henkelman, G.; Johansson, G.; Jónsson, H. In *Progress on Theoretical Chemistry and Physics*; Schwartz, S. D., Ed.; Kluwer Academic Publishers: Dordrecht, The Netherlands, 2000.
- (5) Laio, A.; Parrinello, M. *Proc. Natl. Acad. Sci. U.S.A.* **2002**, *99*, 12562.
- (6) Voter, A. F.; Montalenti, F.; German, T. C. *Annu. Rev. Mater. Res.* **2002**, *32*, 321.
- (7) Dellago, C.; Bolhuis, P. G.; Csajka, F. S.; Chandler, D. *J. Chem. Phys.* **1998**, *108*, 1964.
- (8) Ren, W.; E, W.; Vanden-Eijnden, E. *Phys. Rev. B* **2002**, *66*, 052301.
- (9) Corcelli, S. A.; Rahman, J. A.; Tully, J. C. *J. Chem. Phys.* **2003**, *118*, 1085.
- (10) Chandler, D. *Introduction to Modern Statistical Mechanics*; Oxford University Press: Oxford, U.K., 1987.
- (11) Bolhuis, P. G.; Chandler, D.; Dellago, C.; Geissler, P. L. *Annu. Rev. Phys. Chem.* **2002**, *53*, 291.
- (12) Dellago, C.; Bolhuis, P. G.; Geissler, P. L. *Adv. Chem. Phys.* **2002**, *123*, 1.
- (13) Geissler, P. L.; Dellago, C.; Chandler, D.; Hutter, J.; Parrinello, M. *Science* **2001**, *291*, 2121.
- (14) Bolhuis, P. G.; Dellago, C.; Chandler, D. *Proc. Natl. Acad. Sci. U.S.A.* **2000**, *97*, 5877.
- (15) Ensing, B.; Baerends, E. J. *J. Phys. Chem.* **2002**, *106*, 7902.
- (16) Rodriguez, J.; Moreina, G.; Laria, D. *Chem. Phys. Lett.* **2002**, *356*, 147.
- (17) Dellago, C.; Bolhuis, P. G.; Chandler, D. *J. Chem. Phys.* **1999**, *110*, 6617.
- (18) Vlucht, T. J. H.; Smit, B. *Phys. Chem. Commun.* **2001**, *2*, 11.
- (19) Dellago, C.; Geissler, P. L. *Proceedings of “The Monte Carlo Method in the Physical Sciences: Celebrating the 50th anniversary of the Metropolis algorithm”*; AIP Conference Proceedings; AIP: Melville, NY, 2003; Vol. 690, p 192.
- (20) Jarzynski, C. *Phys. Rev. Lett.* **1997**, *78*, 2690.
- (21) Crooks, G. E. *J. Stat. Phys.* **1998**, *90*, 1481.

- (22) The cancellation of partition functions leading to eq 14 is made possible by defining an energy function that preserves the form of a canonical distribution. A formally analogous cancellation has been described for kinetic Monte Carlo trajectories biased in such a way that only the endpoint probabilities are modified [Cai, W.; Kalos, M. H.; de Koning, M.; Bulatov, V. V. *Phys. Rev. E* **2002**, *66*, 046703].
- (23) Straub, J. E.; Borkovec, M.; Berne, B. J. *J. Chem. Phys.* **1988**, *89*, 4833.
- (24) Metropolis, N.; Metropolis, A. W.; Rosenbluth, M. N.; Teller, A. H.; Teller, E. *J. Chem. Phys.* **1953**, *21*, 1087.
- (25) Dellago, C.; Bolhuis, P. G.; Chandler, D. *J. Chem. Phys.* **1999**, *110*, 6617.
- (26) Dellago, C.; Geissler, P. L. *Proceedings of "The Monte Carlo Method in the Physical Sciences: Celebrating the 50th anniversary of the Metropolis algorithm"*; AIP Conference Proceedings; AIP: Melville, NY, 2003; Vol. 690.
- (27) Hummer, G.; Szabo, A. *Proc. Natl. Acad. Sci. U.S.A.* **2001**, *98*, 3658; Liphardt, J.; Dumont, S.; Smith, S. B.; Tinoco, I.; Bustamante, C. *Science* **2002**, *296*, 1832.
- (28) Hendrix, D. A.; Jarzynski, C. *J. Chem. Phys.* **2001**, *114*, 5974.
- (29) Hummer, G. *J. Chem. Phys.* **2001**, *114*, 7330.
- (30) Gore, J.; Ritort, F.; Bustamante, C. *Proc. Natl. Acad. Sci.* **2003**, *100*, 12564.
- (31) Sun, S. X. *J. Chem. Phys.* **2003**, *118*, 5769.