Single-ensemble nonequilibrium path-sampling estimates of free energy differences

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We introduce a straightforward, single-ensemble, path sampling approach to calculate free energy differences based on Jarzynski’s relation. For a two-dimensional “toy” test system, the new (minimally optimized) method performs roughly one hundred times faster than either optimized “traditional” Jarzynski calculations or conventional thermodynamic integration. The simplicity of the underlying formalism suggests the approach will find broad applicability in molecular systems.

The estimation of free energy differences $\Delta F$ in molecular systems is important for a wide variety of applications including virtual screening for drug design, determination of the solubility of small molecules, and binding affinities of ligands to proteins. Jarzynski recently introduced a general non-equilibrium approach to computing $\Delta F$, but the technique never has been shown superior to more traditional equilibrium calculations (e.g., Refs. 1, 2, 3, 4, 5, 6, 7, 8, 9). Here, we introduce a potential route for dramatically faster non-equilibrium $\Delta F$ calculations.

Many previous workers have attempted to improve non-equilibrium $\Delta F$ estimates. Hummer studied the optimization of non-equilibrium simulation 2, and Jarzynski introduced “targeted free energy perturbation” to improve configurational sampling 13. Improvement of configurational sampling in $\Delta F$ calculations has also been the focus of studies by McCammon and collaborators 6, Karplus and collaborators 14, and van Gunsteren and collaborators 15. Schulten and collaborators used Jarzynski’s approach for steered molecular dynamics simulations 3, Ytreberg and Zuckerman 16, and Zuckerman and Woolf 17, have developed methods for more efficient use of non-equilibrium data for $\Delta F$ calculation.

In an important advance of direct relevance to the present report, Sun suggested the use of a path sampling approach to evaluate $\Delta F$ via Jarzynski’s relation, with a formalism that essentially entails thermodynamic integration in (inverse) temperature space 18. Sun reported impressive efficiency gains. However, multiple path sampling ensembles were required even for simple systems.

The approach outlined below builds on several sources. Jarzynski defined the non-equilibrium approach 19, and Pratt introduced the seminal concept of sampling dynamic paths with equilibrium tools 20. Chandler and collaborators supplied Monte Carlo path sampling moves for effective implementation of the Pratt approach 18, 19, 20, and Sun suggested that path sampling ensembles could be used to evaluate Jarzynski’s relation. Finally, Zuckerman and Woolf employed a direct formalism for path-based estimates of arbitrary quantities, which is key to our single-ensemble protocol 21.

In outline, this report first sketches Jarzynski’s relation and shows how it can be re-written using importance sampling of paths. The path sampling procedure used in our method is then described. Finally, we present our results and a discussion.

Following the usual formalism to define the $\Delta F$ calculation, we consider two systems or distinct states that are defined by Hamiltonians $H_0(\vec{x})$ and $H_1(\vec{x})$, where $\vec{x}$ is a set of configurational coordinates. By introducing a parameter $\lambda$, a hybrid Hamiltonian can be constructed, e.g., $H(\lambda; \vec{x}) = H_0(\vec{x}) + \lambda[H_1(\vec{x}) - H_0(\vec{x})]$. Jarzynski showed that arbitrarily rapid, non-equilibrium switches from $\lambda = 0$ to $\lambda = 1$ can be used to calculate the equilibrium free energy difference $\Delta F = \Delta F_{\lambda=0 \rightarrow 1}$. To this end, one considers switching trajectories that combine increments in $\lambda$ with “traditional” dynamics (such as Monte Carlo or Langevin dynamics) in $\vec{x}$-space at fixed $\lambda$ values. Thus, a trajectory with $n$ $\lambda$-steps is given by

$$Z_n = \{(\lambda_0 = 0, \vec{x}_0), (\lambda_1, \vec{x}_0), (\lambda_1, \vec{x}_1), (\lambda_2, \vec{x}_1), \ldots, (\lambda_n, \vec{x}_n)\}, \quad (\lambda_2, \vec{x}_2), \ldots, (\lambda_{n-1}, \vec{x}_{n-1}), (\lambda_n = 1, \vec{x}_{n-1})\right\} \quad (1)$$

where it should be noted that increments (steps) from $\lambda_i$ to $\lambda_{i+1}$ are performed at a fixed conformation $\vec{x}_i$, and the initial $\vec{x}_0$ is drawn from the $H_0$ distribution. For simplicity we have assumed only a single dynamics step at each fixed $\lambda_i$, from $\vec{x}_{i-1}$ to $\vec{x}_i$, is performed, but multiple steps can be performed within the Jarzynski formalism.

Finally, the work performed on the system during a switching trajectory is

$$W(Z_n) = \sum_{i=0}^{n-1} [H(\lambda_{i+1}; \vec{x}_i) - H(\lambda_i; \vec{x}_i)], \quad (2)$$

and transcribing the Jarzynski relation into path language, the free energy difference can be written as

$$e^{-\beta \Delta F} = \int dZ_n \mathcal{Q}(Z_n) e^{-\beta W(Z_n)} / \int dZ_n \mathcal{Q}(Z_n), \quad (3)$$

where $\beta = 1/k_B T$, $dZ_n$ denotes integration over all possible trajectories, and $\mathcal{Q}(Z_n)$ is proportional to the probability of occurrence of trajectory $Z_n$. $\mathcal{Q}(Z_n)$ depends on the dynamics employed and will be specified below for the overdamped Langevin case.
In “standard” non-equilibrium simulation, the integral need never be considered since trajectories — and the associated work values — are automatically generated with the proper frequency (i.e., proportional to $Q(Z_n)$).

In this case, the Jarzynski relation provides an estimate for $\Delta F$ for a set of work values \{W_1, W_2, ..., W_N\} given by

$$\Delta F \doteq \Delta F_{\text{Jarz}} \equiv -\frac{1}{\beta} \ln \left[ \frac{1}{N} \sum_{i=1}^{N} e^{-\beta W_i} \right], \quad (4)$$

where the “$\doteq$” denotes a computational estimate. Since the relationships in Eqs. 3 and 4 are valid for an arbitrary number $n$ of $\lambda$-steps, switches may be performed very rapidly. The apparent advantage of these “fast-growth” (small $n$) calculations is that very little computational time is spent generating trajectories, and thus $\Delta F_{\text{Jarz}}$ can be generated with very little CPU time. However, in practice, unless there is sufficient overlap between the states described by $H_0(\vec{x})$ and $H_1(\vec{x})$, $\Delta F_{\text{Jarz}}$ will be biased, often by many $k_B T$. This bias is due to the nonlinear nature of Eq. (4) where the smallest, and thus rarest, work values dominate the average. Additionally, CPU time must be invested in generating the equilibrium distribution for $H_0$.

This study uses importance sampling of switching trajectories to sample dominant but rare work values more frequently, without the need to sample the $H_0$ equilibrium distribution. We combine the sampling strategy of Sun et al. with the simple formalism used by Zuckerman and Woolf, as we consider an alternative distribution of switching trajectories $D(Z_n)$. Then, with no loss of generality, Eq. 3 can be written as

$$e^{-\beta \Delta F} = \frac{\int dZ_n \left[ Q(Z_n)/D(Z_n) \right] e^{-\beta W(Z_n)}}{\int dZ_n \left[ Q(Z_n)/D(Z_n) \right]} = \frac{\sum D Q(Z_n) e^{-\beta W(Z_n)}/D(Z_n)}{\sum D Q(Z_n)/D(Z_n)} \quad (5)$$

where the only condition is that $D(Z_n) \neq 0$ anywhere. The shorthand $\sum D$ indicates a sum over trajectories generated according to $D(Z_n)$.

Since the fundamental idea behind the importance sampling in Eq. 3 is to generate trajectories — and hence work values — according to $D(Z_n)$, the choice $D$ is critical. We choose $D(Z_n)$ to favor trajectories with important work values, namely,

$$D(Z_n) = Q(Z_n) e^{-\frac{1}{2} \beta W(Z_n)}, \quad (6)$$

As will be seen below in Eq. 7, this choice appears to balance convergence difficulties between the numerator and denominator of Eq. 3. We note that Sun also employed the distribution as one among several used for an indirect calculation of $\Delta F_{\text{Jarz}}$. While it is not obvious that the choice is optimal in general, other forms for $D(Z_n)$ have been tested by the authors and provided no improvement. By comparison with 3, the $\beta/2$ in 6 embodies double the temperature.

Combining Eqs. 5 and 6, the free energy estimate for our single-ensemble path sampling (SEPS) method is given by the new relation

$$\Delta F \doteq \Delta F_{\text{SEPS}} \equiv -\frac{1}{\beta} \ln \left[ \sum D e^{-\frac{1}{2} \beta W} \right]/\left[ \sum D e^{\frac{1}{2} \beta W} \right]. \quad (7)$$

We now specify $Q(Z_n)$ from Eq. 7 which is required for the path sampling performed below. We assume overdamped Langevin (Brownian) dynamics is used at fixed $\lambda$ values. Single-step distributions for $\Delta \vec{x}_i = \vec{x}_i - \vec{x}_{i-1}$ are thus Gaussian, with a variance given by $\sigma^2 = 2 \Delta t/m \gamma$, where $m$ is the mass of the particle and $\gamma$ is the friction coefficient of the medium (e.g., Ref. 23). Combining the Brownian distributions with that for $\lambda = 0$ leads to the full trajectory weight

$$Q(Z_n) = e^{-\beta H_0(\vec{x}_0)} \prod_{i=1}^{n-1} e^{-\Delta x_i - \Delta x_{i-1}' t/m \gamma/\beta} (2\pi \sigma^2)^{d/2} \quad (8)$$

where $\Delta x_{i}' = -d H(\lambda_i; \vec{x}_i-1)/m \gamma t$ is proportional to the force and time step, and $d$ is the dimensionality of the conformational space $\vec{x}$. Note that if deterministic dynamics (e.g., Verlet) is used then $Q(Z_n) = e^{-\beta H_0(\vec{x}_0)}$.

To calculate the free energy estimate $\Delta F_{\text{SEPS}}$ in Eq. 7, switching trajectories must be generated according to $D(Z_n)$. This is readily accomplished using the path sampling approach proposed by Pratt et al., where entire trajectories (paths) are generated and then accepted or rejected based upon a suitable Monte Carlo criterion. Trial moves in path space are generated following Chandler and coworkers.

Putting the pieces together, we estimate $\Delta F$ by sampling trajectories according to $D(Z_n)$ in Eq. 7 using the following steps (c.f. Ref. 23): (i) Generate an arbitrary initial reference trajectory by switching the system from $\lambda = 0 \rightarrow 1$. Calculate the work $W$ done on the system during the switch. (ii) Pick a random $\lambda$ value along the reference trajectory and make a random phase-space displacement. For Brownian dynamics this corresponds to a random shift in position. Generate a trial trajectory by “shooting” forward (increment $\lambda$) and backward (decrement $\lambda$). Calculate the trial work done on the system $W'$. (iii) Accept this new trajectory according to the Metropolis criterion: $\min[1, Q e^{-\frac{1}{2} \beta W'}/Q e^{-\frac{1}{2} \beta W}]$, with $Q$ from Eq. 8. (iv) If accepted, the trial trajectory becomes the current reference trajectory. If rejected, the current reference trajectory remains unchanged. Whether accepted or rejected, the current reference trajectory is then used in Eq. 7. Repeat from step (ii).

It should be noted that to obtain good sampling, as in any Monte Carlo simulation, equilibrium must be attained before averages are calculated. Using the path sampling procedure above, we accomplish this by check-
ing the running average work every 20 accepted trajectories for convergence within 0.01 $k_B T$.

As a test problem, we consider a two-dimensional system (Fig. 1) switched from a single well to a double well:

$H_0(x, y) = (x + 2)^2 + y^2,$

$H_1(x, y) = \frac{1}{10} \left\{ ((x - 1)^2 - y^2)^2 + 10(x^2 - 5)^2 + (x + y)^4 + (x - y)^4 \right\}. \quad (9)$

Figure 1 clearly demonstrates why estimating $\Delta F$ for this system is expected to be difficult: the significant barrier in $H_1$ will prevent sufficient configurational sampling of the dominant minimum at $H_1(2, 0)$ for short trajectories. Thus ordinary fast-growth Jarzynski estimates will substantially overestimate $\Delta F$. Similarly, equilibrium approaches like thermodynamic integration (TI) will require long simulation times to surmount the barrier.

For this system, the free energy difference was estimated using the Jarzynski method given by $\Delta F_{\text{Jarz}}$ in Eq. (7), by the SEPS method given by $\Delta F_{\text{seps}}$ in Eq. (7), as well as by conventional TI. Trajectories for all estimates were generated using Brownian dynamics with parameters $\beta = \gamma = m = 1$, and $\Delta t = 0.001$.

For $\Delta F_{\text{Jarz}}$, to generate uncorrelated initial configurations $\vec{x}_0$, the system was run at $\lambda = 0$ for $N_{\text{eq}}$ steps between switching trajectories. For $H_0$ given by (9), it was determined that $N_{\text{eq}} = 10,000$, and that smaller values of $N_{\text{eq}}$ introduce bias in $\Delta F_{\text{Jarz}}$. Given $N_{\text{eq}}$, moreover, we optimized $\Delta F_{\text{Jarz}}$ by varying the number $n$ of $\lambda$-steps in Eqs. (11) and (12). We found that $n = 100,000$ was most efficient.

Trajectories for $\Delta F_{\text{seps}}$ were generated as described above. Specifically, perturbations to the selected state $\vec{x}_i$ of the reference trajectory (step (ii) above) were chosen from a Gaussian distribution of width 50.0$\sigma$, giving an acceptance ratio of $1 - 2\%$. Smaller perturbations were also highly successful. The SEPS procedure is not optimized in the sense that only a simple type of trial move (termed “shooting”) was employed, and we used strict path-equilibration criteria. Optimization methods are currently under investigation by the authors.

For comparison to an equilibrium approach, “textbook” thermodynamic integration (TI) simulations were performed with identical Brownian parameters and 10 $\lambda$-steps, with 25% of data discarded for equilibration. This well-known approach is described in many sources (e.g., Ref. [22]) and is not detailed here. Since no optimization was performed, we refer to this method as “conventional TI.”

To compare the efficiency of the SEPS approach with other methods, in Fig. 2 we plot $\Delta F$ estimates for the SEPS, Jarzynski, and TI methods as a function of the total CPU time needed generate the estimates. The circles show the results of the SEPS method using 10 $\lambda$-steps. The results of the Jarzynski method for a very short trajectory (10 $\lambda$-steps, squares) and the most efficient trajectory length (100,000 $\lambda$-steps, triangles) are also shown. TI estimates based on 10 $\lambda$ increments are shown as diamonds. The exact answer of $\Delta F = 6.55 k_B T$ is shown as a solid horizontal line. Each data point represents the mean estimate, with standard deviations given by the error bars, based on 100 independent estimates of $\Delta F$ for each method.

As expected, Fig. 2 shows that for fast-growth work values (10 $\lambda$-steps, squares), the Jarzynski method incorrectly estimates the free energy difference as $\Delta F_{\text{Jarz}} \approx 13 k_B T$. As the number of $\lambda$-steps increases, the stan-
standard Jarzynski trajectories begin to “see” the minimum at $H_{1}(2,0)$ and the correct $\Delta F$ is obtained. Since the highest efficiency for the standard Jarzynski method was obtained using 100,000 $\lambda$-steps (triangles), we consider this curve to be the optimized Jarzynski method for the test system. The unoptimized, conventional TI calculations are of comparable efficiency to the traditional Jarzynski estimates.

The SEPS method, by contrast, correctly estimates the free energy quickly and accurately, even for very short trajectories (10 $\lambda$-steps). One can quantitatively compare estimates from each method by noting that the estimate for the SEPS method $\Delta F_{\text{seps}}(t \approx 1500\text{ s})$ is slightly more accurate than $\Delta F_{\text{J}}(t \approx 500,000\text{ s})$, implying a roughly 100-fold speed-up of SEPS over the other methods.

Compared to “standard” Jarzynski calculation, the SEPS approach has several advantages: (a) important, rare trajectories with small work values are favored; (b) no CPU time is spent acquiring an equilibrium ensemble at $\lambda = 0$; and (c) path-sampling moves that are capable of surmounting barriers may be used. In other words, the SEPS approach focuses CPU time on the important regions of $(\lambda; \bar{x})$ space — this also contrasts with TI and other equilibrium approaches which attempt to sample the full space.

To summarize, we have described a rapid and straightforward method for estimating free energy differences $\Delta F$, using a single-ensemble path sampling (SEPS) approach. We also have carefully quantified the numerical efficiency of the approach. Without extensive optimization, the SEPS method generates $\Delta F$ estimates over 100$\times$ more efficiently than “standard” Jarzynski and conventional thermodynamic integration calculations, for the two-dimensional test system considered here. Our approach relies on an extremely simple importance sampling formalism, and therefore appears to be readily extendable to molecular systems. This extension — which will require addressing issues of memory for trajectory storage — is currently underway. We will also optimize the SEPS approach via alternative importance sampling distributions, and path-sampling trial moves.

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