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Free Energy Computation by Controlled Langevin Dynamics

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Abstract

We propose a nonequilibrium sampling method for computing free energy profiles along a given reaction coordinate. The method consists of two parts: a controlled Langevin sampler that generates nonequilibrium bridge paths conditioned by the reaction coordinate, and Jarzynski's formula for reweighting the paths. Our derivation of the equations of motion of the sampler is based on stochastic perturbation of a controlled dissipative Hamiltonian system, for which we prove Jarzynski's identity as a special case of the Feynman-Kac formula. We illustrate our method by means of a suitable numerical example and briefly discuss issues of optimally choosing the control protocol for the reaction coordinate.

Keywords: Free Energy sampling, Stochastic Langevin dynamics, Jarzynski's identity, Optimal control

1. Introduction

Given a system assuming states $x \in \mathcal{X}$ with the energy $H(x)$, the total free energy can be defined as [1]

$$F = -\beta^{-1} \ln Z, \quad Z = \int_{\mathcal{X}} \exp(-\beta H(x)) dx,$$

where $\beta > 0$ denotes the system's inverse temperature. Jarzynski's equality [2, 3] relates the free energy difference

$$\Delta F = -\beta^{-1} \ln \left(\frac{Z_1}{Z_0} \right)$$

between two equilibrium states of a system given by an unperturbed energy function $H = H_0$ and its perturbation H_1 with the work W done on the system under the perturbation: Suppose we set $H_\xi = (1-\xi)H_0 + \xi H_1$ with $\xi \in [0, 1]$, and assume we set a protocol that describes how the system evolves from $\xi = 0$ to $\xi = 1$ (see [4, 5]). If, initially, the states $x \in \mathcal{X}$ are distributed according to the equilibrium distribution $\exp(-\beta H_0)$ then, by the second law of thermodynamics, it follows that $\mathbf{E}W \geq \Delta F$ where W is the total work done on the system and $\mathbf{E}$ denotes the average over all possible realizations of the transition from H_0 to H_1; equality is attained if the transition is infinitely slow (i.e., adiabatically). Jarzynski's equality now asserts that

$$\Delta F = -\beta^{-1} \ln \mathbf{E}[\exp(-\beta W)] .$$

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Although controversial, Jarzynski's equality can be unambiguously derived when the underlying dynamics are diffusive, in which case the identity turns out to be an instance of the Feynman-Kac formula; for a critical discussion of possible issues and different notions of free energy see, e.g., [6, 7] and the references therein. Here, we wish to point out that, in this context, one must be careful when relating and applying Jarzynski's equality to pulling experiments (either in computer simulations or single-molecule pulling experiments,) since it tacitly assumes that the initial values are randomly distributed according to the Boltzmann distribution $\exp(-\beta H_0)$, which is typically not available.

In this paper we address the problem of computing *conditional* free energy profiles along a reaction coordinate for the *unperturbed system*, rather than total free energy differences between perturbed and unperturbed system. That is, for a given function of the coordinates (typically some of the configurations), $\phi(x)$, we consider the quantity

$$F(\xi) = -\beta^{-1} \ln Z(\xi), \quad Z(\xi) = \int_{\mathcal{X}} \exp(-\beta H(x)) \delta(\phi(x) - \xi)\, dx\,.$$

As sampling the Boltzmann distribution is prohibitively expensive, conditional free energy profiles are often computed by thermodynamic integration [8]. Thermodynamic integration exploits the fact that the derivative of F can be recast as a conditional average over a generalized force f (see Section 2.1),

$$F'(\xi) = -\beta^{-1} \frac{1}{Z(\xi)} \int_{\mathcal{X}} f(x) \exp(-\beta H(x)) \delta(\phi(x) - \xi)\, dx\,,$$

which is why the free energy is also termed *potential of mean force*. In comparison to the full Boltzmann distribution, the conditional distributions are relatively cheap to evaluate, for the reaction coordinate is typically the "slowest" variable in the system (see Figure 1 below). In practical terms this means that one has to discretize the reaction coordinate and sample each of the grid points. The free energy profile is then reconstructed by integration,

$$F(\xi) - F(0) = \int_0^{\xi} F'(\zeta)\, d\zeta\,.$$

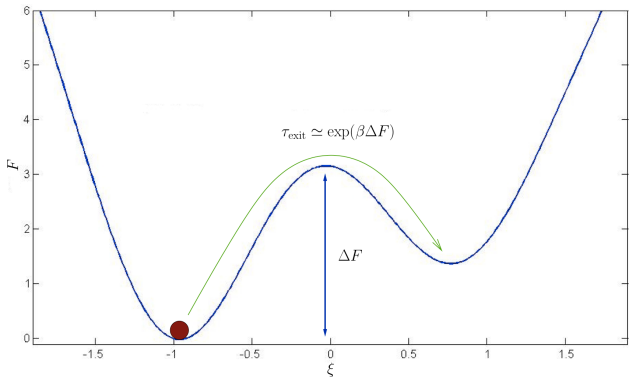

Figure 1: Sampling the free energy is slowed down by large energy barriers in the direction of the reaction coordinate.

Here we adopt a different strategy: rather than constraining the reaction coordinate to the grid points we let it vary continuously. More specifically, we design a sampling scheme that allows for arbitrarily controlling ξ and prove a Jarzynski equality for the exponential reweighting of the trajectories. When the reactions coordinate is moved adiabatically, i.e., infinitely slowly, the method converges to thermodynamic integration (or a continuous variant thereof). Our approach is based on degenerate diffusions of Langevin type and is similar to the method proposed in [9] for non-degenerate diffusions (overdamped Langevin); in the overdamped limit our method reduces to the method in [9]. Although beyond the scope of this article, an obvious extension of the sampling scheme would involve its reformulation as an optimal control problem so as to obtain estimators that have, e.g., minimum variance or optimal rates of convergence. We briefly discuss these issues at the end of the article.

The paper is organized as follows. In Section 2, we state the equations of motion of the stochastic Langevin sampler and prove the analogue of Jarzynski's equality by means of Feynman-Kac formula. Section 3 contains the numerical example: a 4-dimensional system with slow and fast coordinates. We conclude with an outlook for further improvement in Section 4.

2. Controlled Langevin dynamics

Let $H\colon \mathcal{X} \to \mathbb{R},\ \mathcal{X} \subseteq \mathbb{R}^{2n}$ be the Hamiltonian

$$H(x_1, x_2) = \frac{1}{2}|x_2|^2 + V(x_1)\,. \tag{1}$$

where here and in the following we shall use the shorthand $x = (x_1, x_2)$ with $x_i = (x_i^1, \ldots, x_i^n)$. The function V is assumed to be smooth, bounded below and to satisfy the usual growth conditions at infinity. We consider dynamics of Langevin type, viz.,

$$dX(t) = (J - D)\nabla H(X(t))dt + S\,dW(t)\,, \quad X(0) = x \tag{2}$$

with the constant coefficient matrices

$$J = \begin{pmatrix} 0 & I \\ -I & 0 \end{pmatrix}, \quad D = \begin{pmatrix} 0 & 0 \\ 0 & \gamma \end{pmatrix} \quad S = \begin{pmatrix} 0 \\ \sigma \end{pmatrix}.$$

Suppose we are given a smooth reaction coordinate $\phi(x) := \phi(x_1)$ with $|\nabla\phi| \neq 0$ almost everywhere.[1] We want to perturb the Langevin dynamics (2) systematically by adding a force acting along the reaction coordinate. To this end, we adopt ideas from [10] and introduce the projected Hamiltonian

$$\tilde{H}(x) = H(x_1, P(x_1)x_2)\,. \tag{3}$$

with

$$P = I - \frac{\nabla\phi\nabla\phi^T}{|\nabla\phi|^2}\,.$$

It can be readily checked that $P^2 = P$ and $P = P^T$, hence P is the orthogonal projection onto the codimension-1 kernel of $\nabla\phi$. The thus defined Hamiltonian has the property that, when substituted into (2), it makes ϕ a conserved quantity under the dynamics, i.e., $d\phi(X_1(t)) = 0$. We can go one step further and add a control force that allows for controlling the value of ϕ arbitrarily. This yields a Langevin equation of the form

$$dX(t) = ((J - D)\nabla\tilde{H}(X(t)) + u(t)B(X(t)))dt + S\,dW(t)\,, \quad X(0) = x \tag{4}$$

with the control $u\colon \mathbb{R}^+ \to \mathbb{R}$ and the vector field $B\colon \mathcal{X} \to \mathbb{R}^{2n}$ given by

$$B(x) = \begin{pmatrix} \nabla\phi(x_1)/|\nabla\phi(x_1)|^2 \\ 0 \end{pmatrix}.$$

Lemma 2.1. *The solutions of (4) satisfy $d\phi(X_1(t)) = u(t)\,dt$.*

Proof. The position component $X_1(t) = (X_1^1(t), \ldots, X_1^n(t))$ in (4) reads

$$dX_1(t) = (P(X_1(t))X_2(t) + u(t)B(X(t)))\,dt\,. \tag{5}$$

Thus, Ito's formula for the derivative of $\phi(X_1(t))$ is just standard chain rule. Using (5),

$$\begin{aligned}\frac{d\phi}{dt} &= \nabla\phi(X_1(t))^T \left(P(X_1(t))X_2(t) + u(t)\nabla\phi(X_1(t))/|\nabla\phi(X_1(t))|^2\right) \\ &= \nabla\phi(X_1(t))^T P(X_1(t))X_2(t) + u(t),\end{aligned}$$

where the first term vanishes by definition of P. □

[1] We shall use the notation $\nabla\phi$ to denote the n-dimensional gradient of ϕ with respect to the argument x_1, but also the gradient in $\mathbb{R}^{2n}$, i.e., the derivative with respect to all the coordinates (x_1, x_2). The meaning should be clear from the context.

Fokker-Planck equation and stationary distribution. The backward-Kolmogorov generator of the Langevin dynamics (4) reads

$$L = \frac{1}{2} S S^T : \nabla^2 + (J - D)\nabla \tilde{H}(x) \cdot \nabla + u(t) B(x) \cdot \nabla, \tag{6}$$

where $x \cdot y = x^T y$ and $A : B = \mathrm{tr}(A^T B)$ denote the usual inner products between vectors and matrices. In the absence of forcing, $u = 0$, and if $2D = \beta S S^T$, the unconditioned Boltzmann distribution $\rho \propto \exp(-\beta \tilde{H})$ is a stationary distribution and solves $L^* \rho = 0$ where L^* is the formal adjoint in $L^2(dx)$.

The space $L^2(dx)$ is somewhat unnatural, however, for the force-free Langevin dynamics has ϕ as an integral. Hence the dynamics never leave the level set $\phi^{-1}(\cdot) \times \mathbb{R}^n$ from which they have started. Instead, it appears natural to define all quantities with respect to the invariant volume element of the corresponding deterministic Hamiltonian system (i.e., for $D, S = 0$) given by the family of measures

$$d\lambda_\xi(x) = \delta(\phi(x_1) - \xi)\, dx\,.$$

If we define $L^2(d\lambda_\xi)$ to be the Hilbert space that is equipped with the scalar product

$$(f, g)_\xi = \int_{\phi^{-1}(\xi) \times \mathbb{R}^n} f g \, d\lambda_\xi\,,$$

then the following statement holds.

Lemma 2.2. *For $u = 0$, the formal adjoint in $L^2(d\lambda_\xi)$ has the form*

$$L^*_{u=0} = \frac{1}{2} S S^T : \nabla^2 - (J - D)\nabla \tilde{H}(x) \cdot \nabla + D : \nabla^2 \tilde{H}\,. \tag{7}$$

Proof. Setting $u = 0$ in (6), we have to show that $(Lf, g)_\xi = (f, L^* g)_\xi$ with the operator L^* as given above (we omit all discussions concerning boundary conditions.) It is clear that the first term in (7) is the adjoint of the first term in (6). It remains

$$\begin{aligned}
&\int_{\phi^{-1}(\xi) \times \mathbb{R}^n} g\, (J - D)\nabla \tilde{H}(x) \cdot \nabla f \, d\lambda_\xi \\
= \; & - \int_{\phi^{-1}(\xi) \times \mathbb{R}^n} f\, \nabla \cdot \left\{ (J - D)\nabla \tilde{H}(x) g\, \delta(\phi(x_1) - \xi) \right\} dx \\
= \; & - \int_{\phi^{-1}(\xi) \times \mathbb{R}^n} f \left\{ (J - D)\nabla \tilde{H}(x) \cdot \nabla g - (D : \nabla^2 \tilde{H}(x) \right\} \delta(\phi(x_1) - \xi)\, dx\,,
\end{aligned}$$

where, in the second equality, we have used the fact that all terms involving $\nabla\phi$ vanish since ϕ is a conserved quantity and so the vector field $(J - D)\nabla \tilde{H}$ is perpendicular to $\nabla\phi$ (here understood as a gradient in $\mathbb{R}^{2n}$). □

The next lemma is a straight consequence.

Corollary 2.3. *The family of probability measures*

$$d\mu_\xi = \frac{\exp(-\beta \tilde{H})}{\tilde{Z}(\xi)}\, d\lambda_\xi\,, \quad \tilde{Z}(\xi) = \int \exp(-\beta \tilde{H})\, d\lambda_\xi$$

is invariant under the zero-force Langevin dynamics (i.e., for $u = 0$).

Proof. Let $f \in C^{2,1}(\phi^{-1}(\xi) \times \mathbb{R}^n, \mathbb{R}^+)$ be the solution of the Cauchy problem

$$\frac{\partial}{\partial t} f(x, t) = L f(x, t)\,, \quad f(x, 0) = g(x)\,.$$

By definition, μ_ξ is an invariant measure if

$$\int f(x,t)\, d\mu_\xi(x) = \int f(x,0)\, d\mu_\xi(x)\,.$$

If f solves the Cauchy problem above, it is sufficient to show

$$\int Lf\, d\mu_\xi = 0\,.$$

By Lemma 2.2, it follows that

$$\int Lf\, d\mu_\xi = \int f(L^* \exp(-\beta\tilde{H}))\, d\lambda_\xi\,,$$

where the right integral vanishes since $L^* \exp(-\beta\tilde{H}) = 0$ if $2D = \beta S S^T$. □

2.1. Free energy and Jarzynski's equality

We introduce the conditional free energy as the function

$$\tilde{F}(\xi) = -\beta^{-1} \ln \tilde{Z}(\xi)\,, \quad \tilde{Z}(\xi) = \int \exp(-\beta\tilde{H}(x))\delta(\phi(x) - \xi)\, dx\,, \tag{8}$$

where the integration is over a suitable subspace of $\phi^{-1}(\xi) \times \mathbb{R}^n$ so that the integral exists (note that because of the projection, the kinetic energy part of $\tilde{H}$ has one flat direction). A more familiar expression is obtained upon integrating out the momenta which leads to the following result.

Lemma 2.4. *Up to additive constants, $\tilde{F}$ equals the standard free energy*

$$F(\xi) = -\beta^{-1} \ln Z(\xi)\,, \quad Z(\xi) = \int \exp(-\beta V(x_1))\delta(\phi(x_1) - \xi)\, dx_1\,. \tag{9}$$

Proof. We may set $\beta = 1$ without loss of generality. Now let $Q(x_1) \in \mathbb{R}^{n\times(n-1)}$ with $Q^T Q = I$ be a family of orthogonal matrices whose columns span the admissible momentum subspace. We introduce the new momenta $q = Q^T x_2$ and $p = n^T x_2$ where $n = \nabla\phi/|\nabla\phi|$ denotes the outer unit normal to $\phi^{-1}(\xi)$. Now $I = QQ^T + nn^T$ which entails $x_2 = Qq + np$. Doing a change of variables in the expression for the partition function Z and integrating only over the admissible momenta $x_2 = Qq$ yields

$$\begin{aligned}
\tilde{Z}(\xi) &= \int \exp(-\tilde{H}(x_1, q))\delta(\phi(x_1) - \xi)\, dx_1 dq \\
&= \int \exp\left(-\frac{1}{2}|q|^2 - V(x_1)\right)\delta(\phi(x_1) - \xi)\, dx_1 dq \\
&= C \int \exp(-V(x_1))\delta(\phi(x_1) - \xi)\, dx_1\,,
\end{aligned}$$

which completes the proof. □

Differentiating the free energy (8) it follows upon integration by parts and using the formal identity (which can be made precise using the co-area formula [11])

$$\frac{\partial}{\partial\xi}\delta(\phi - \xi) = -|\nabla\phi|^{-2}\nabla\phi \cdot \nabla\delta(\phi - \xi)\,,$$

that the derivative of the free energy can be expressed as a conditional expectation with respect to the invariant measure of the process, namely,

$$\tilde{F}'(\xi) = \int f\, d\mu_\xi\,, \quad f = \frac{\nabla V \cdot \nabla\phi}{|\nabla\phi|^2} - \beta^{-1}\nabla \cdot \left(\frac{\nabla\phi}{|\nabla\phi|^2}\right),$$

where, again, the momentum integration must be suitably restricted. Consequently, we may sample the derivative of $\tilde{F}$ (or, equivalently, F) by computing the conditional expectations for various values of ξ, from which the free energy profile can be eventually recovered by integration, viz.,

$$F(\xi) - F(0) = \int_0^\xi \tilde{F}'(\zeta)\, d\zeta\,.$$

The idea of the forced Langevin equation is to let $\xi = \xi(t)$ vary with rate $u(t)$ and compute the free energy as a suitably weighted nonequilibrium average of the exerted work. We will need the following identity that again is an instance of the co-area formula (cf. [9]).

Corollary 2.5. *For a suitable test function $\varphi \in C^\infty(\phi^{-1}(\xi) \times \mathbb{R}^n)$ we have*

$$\frac{\partial}{\partial \xi} \int \varphi \exp(-\beta \tilde{H})\, d\lambda_\xi = \int \left(\frac{\nabla \varphi \cdot \nabla \phi}{|\nabla \phi|^2} - \beta f \varphi \right) \exp(-\beta \tilde{H})\, d\lambda_\xi\,,$$

with the convention $\nabla \phi \in \mathbb{R}^{2n}$ (and the x_2-component being zero).

Now comes our main result.

Theorem 2.6. *Let $\phi(X(t)) = \xi(t)$ vary with rate $\xi'(t) = u(t)$ and let the random variable*

$$W(\tau) = \int_0^\tau f(X(t))u(t)\, dt\,, \tag{10}$$

denote the nonequilibrium work exerted by the forcing. Assume furthermore that at $t = 0$, X is distributed according to

$$X(t=0) \sim \mu_{\xi(0)} = \frac{\exp\left(-\beta \tilde{H}\right)}{\tilde{Z}(\xi(0)} \, \delta(\phi - \xi(0)).$$

Then

$$\exp(-\beta \Delta F) = \mathbf{E}[\exp(-\beta W(\tau))]\,, \quad \Delta F = F(\xi(\tau)) - F(\xi(0)). \tag{11}$$

Proof. Let $w \in C^{2,1}(\phi^{-1}(\xi) \times \mathbb{R}^n, \mathbb{R}^+) \cap C^{0,1}(\mathbb{R}^{2n}, \mathbb{R}^+)$ solve the backward equation

$$\frac{\partial}{\partial t} w(x,t) = (\beta f u(t) - L) w(x,t)\,, \quad w(x,\tau) = \varphi(x)$$

which, by the Feynman-Kac formula [12], is of the form

$$w(x,t) = \mathbf{E}_x \left[\varphi(X(\tau)) \exp\left(-\beta \int_t^\tau f(X(s))u(s)\, ds \right) \right].$$

Here $\mathbf{E}_x$ is understood as the expectation of the argument over all Brownian paths conditioned on $X(t) = x$. It follows from Corollary 2.5 that

$$\begin{aligned}
&\frac{d}{dt} \int w(x,t) \exp(-\beta \tilde{H})\, d\lambda_{\xi(t)} \\
&\quad = \int \left((\beta f u(t) - L) w + \xi'(t) \left(\frac{\nabla w \cdot \nabla \phi}{|\nabla \phi|^2} - \beta f w \right) \right) \exp(-\beta \tilde{H})\, d\lambda_{\xi(t)} \\
&\quad = \int \left(-Lw + u(t) \frac{\nabla w \cdot \nabla \phi}{|\nabla \phi|^2} \right) \exp(-\beta \tilde{H})\, d\lambda_{\xi(t)} \\
&\quad = \int (-Lw + u(t) B \cdot \nabla w) \exp(-\beta \tilde{H}) \delta(\phi - \xi(t))\, dx \\
&\quad = -\int (L_{u=0} w) \exp(-\beta \tilde{H}) \delta(\phi - \xi(t))\, dx\,,
\end{aligned}$$

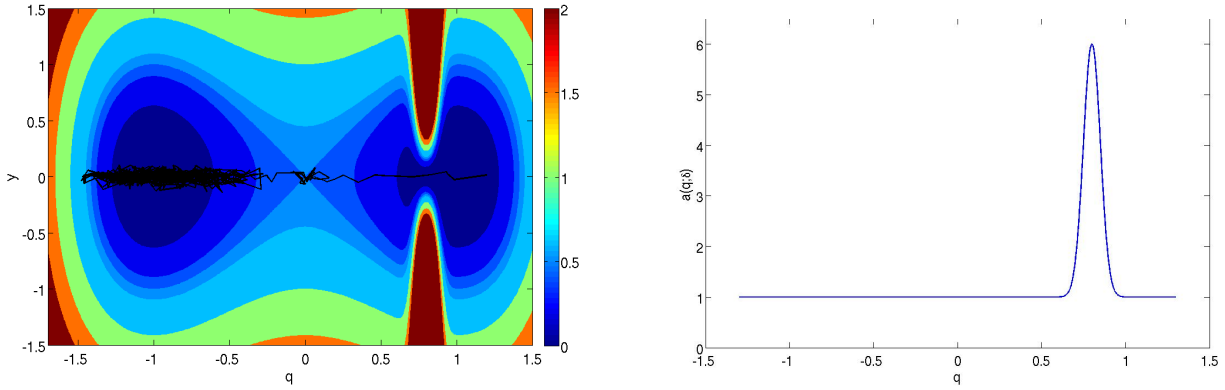

Figure 2: **Left Panel**: Contour lines of the potential $V(q, y)$, with $\epsilon = 0.1$, $\delta^{-2} = 200$. Superimposed a sample trajectory of the Langevin dynamics, with $Q_0 = -1.2$, $\beta = 0.5$ and integrated numerically using an Euler-Maruyama method, with $h = 0.000125$ and a total number of integration steps $N \approx 1.3\text{x}10^6$. **Right Panel**: Normal frequency $a(q;\delta)$, with $\delta^{-2} = 200$.

where the last integral is zero by Lemma 2.2. It follows that

$$\int w(x,\tau)\exp(-\beta\tilde{H})\,d\lambda_{\xi(\tau)} = \int w(x,0)\,\exp(-\beta\tilde{H})\,d\lambda_{\xi(0)}\,,$$

which, using $w(x,\tau) = \varphi(x)$, the Feynman-Kac formula and the definition of the work W, implies

$$\begin{aligned}\int \varphi\,\exp(-\beta\tilde{H})\,d\lambda_{\xi(\tau)} &= \int \mathbf{E}_x\left[\varphi(X(\tau))\exp\left(-\beta W(\tau)\right)\right]\exp(-\beta\tilde{H})\,d\lambda_{\xi(0)} \\ &= \tilde{Z}(\xi(0))\,\mathbf{E}\left[\varphi(X(\tau))\exp\left(-\beta W(\tau)\right)\right].\end{aligned}$$

The last equality follows since we have assumed that initially the dynamics are distributed according to $\mu_{\xi(0)}$. Finally, setting $\varphi = 1$ and exploiting that

$$\frac{\tilde{Z}(\xi(\tau))}{\tilde{Z}(\xi(0))} = \exp(-\beta\Delta\tilde{F})\,, \quad \tilde{Z}(\xi) = \int \exp(-\beta\tilde{H})\,d\lambda_\xi\,,$$

yields Jarzynski's equality (11) for $\Delta\tilde{F}$. But $\Delta F = \Delta\tilde{F}$ by Lemma 2.4, thus proving the assertion. □

3. Numerical illustration

As a test example we consider the stiff potential

$$V(x_1) = \frac{1}{2}(q^2-1)^2 + \frac{1}{2\epsilon^2}(a(q;\delta))^2 y^2\,, \quad \epsilon \in (0,1]$$

with $x_1 = (q, y) \in \mathbb{R}^2$ and the normal frequency

$$a(q;\delta) = 1 + 5\exp\left[\left(\frac{q-q_0}{\delta}\right)^2\right], \quad q_0 = 0.8\,.$$

Setting $\phi(x_1) = q$ and abbreviating the conjugate momenta as $x_2 = (p, r)$, the projected Hamiltonian assumes the simple expression

$$\tilde{H}(x) = \frac{1}{2}r^2 + V(q,y)\,, \quad x = (q,y,p,r)\,.$$

In Figure 2 we have plotted the level curves of the potential, superimposed with a sample trajectory of the (non-constrained) Langevin dynamics. One can observe that trajectories move along the q coordinate while remaining close to $y = 0$ if $\epsilon \ll 1$. The free energy along the (slow) q coordinate (remember that here $\xi = q$) can be computed explicitly, namely,

$$F(\xi) = \frac{1}{2}(\xi^2 - 1)^2 + \beta^{-1} \ln a(\xi; \delta).$$

For values of $q \ll q_0$ where $a(q; \delta) \approx 1$, the q and y dynamics are almost decoupled, whereas for values of $q \approx q_0$ the normal frequency grows creating an *entropic barrier* proportional to the temperature β^{-1}. The problem then becomes numerically stiff and one must take sufficiently small time steps so as to resolve the fast y-dynamics, while transitions between the two minima, located at $q \approx -1$ and $q \approx 1$, are rare.

In order to compute the free energy profile by means of nonequilibrium trajectories, we integrate numerically the forced Langevin dynamics with a simple Euler-Maruyama scheme

$$X_{n+1} = h(J - D)\nabla \tilde{H}(X_n) + hBu_n + \sqrt{h} S \zeta_{n+1}\,, \quad \zeta_n \sim \mathcal{N}(0, 1)$$

where $B = (1, 0, 0, 0)^T$ and $u_n = u(nh)$; here $h > 0$ denotes the integration time step. At this point one could think of using a more sophisticated numerical integrator (higher order, symplectic integrator, etc.) but since we are dealing with a relatively simple system, we have simply chosen the time step h sufficiently small such that the Euler scheme is stable in the *fast* direction (in this example the y-coordinate.) In this case, Euler-Maruyama is a first order numerical scheme (in a weak sense) [13] which will estimate the desired distributions in a sufficiently accurate way.

We have chosen parameters $D = \mathrm{diag}(0, 0, 10, 10)$ and $S = \sqrt{2\beta^{-1}D}$. Then, given a protocol $\xi'(t) = u(t)$, we simulate M independent trajectories with initial values $(Q_0, P_0) = (\xi(0), 0)$ fixed and $(Y_0, R_0) = (y, r)$ distributed according to $\mu_{\xi(0)}$,

$$y \sim \mathcal{N}(0, \beta^{-1}(\epsilon / a(q; \delta))^2)\,, \quad r \sim \mathcal{N}(0, \beta^{-1} I)\,.$$

The expectation in (11) is computed with the estimator

$$\Delta F_M^h = -\beta^{-1} \ln \frac{1}{M} \sum_{k=1}^{M} \exp(-\beta \hat{W}_k^h(\tau))\,, \tag{12}$$

that converges to ΔF as $h \to 0$ and $M \to \infty$. Here $\hat{W}^h$ denotes the discrete approximation to the work integral (10) that is obtained by, e.g., a trapezoidal rule,

$$\hat{W}^h(\tau) = -\frac{h}{2} u_{N(\tau)} \left.\frac{\partial V}{\partial q}\right|_{X_{1,N(\tau)}} - h \sum_{n=1}^{N(\tau)-1} u_n \left.\frac{\partial V}{\partial q}\right|_{X_{1,n}}\,, \quad (u_0 = 0)$$

where $N(\tau)$ is given by the terminal condition $\tau = Nh$. The free energy profile is then computed as follows: We notice in (11) that the final time τ can be any deterministic time. If we set, without loss of generality, the value of the free energy at the starting point Q_0, $F(Q_0) = 0$, we can set sampling windows along the trajectory from $t = 0$ to the terminal time $t = \tau$ and compute the accumulated work up to time τ. The free energy $F(\xi) = \Delta F$ at the point $\xi = Q_N$ is then simply estimated using (12). In Figure 3 we show numerical results for the estimation of the free energy for different values of β. We have chosen $Q_0 = -1.2$ and $u_n = 1.2\omega \sin(\omega nh)$, with $\omega Nh = \pi$, so that the terminal point of the integration is $Q_N = 1.2$. As we see, the estimated free energy reproduces the exact profile rather accurately, including the entropic barrier at $q = 0.8$.

4. Outlook and conclusions

We have introduced a nonequilibrium sampling method for computing free energy profiles using controlled (degenerate) diffusions. Specifically, we have proved Jarzinsky's equality for a certain class of controlled Langevin processes using the Feynman-Kac formula and illustrated the method by means of a numerical example.

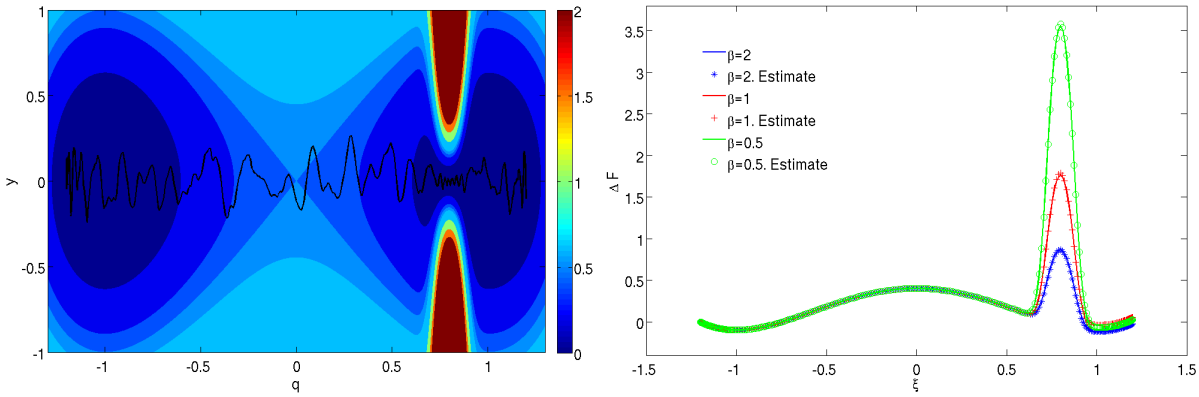

Figure 3: **Left Panel**. Sample trajectory of the forced Langevin dynamics, with $\beta = 1$, $\epsilon = 0.1$, $\omega = 0.2$. Superimposed are the contour lines of the potential $V(q, y)$. **Right Panel**. Solid lines: Exact free energy $F(q)$ for different values of β. Markers: Free energy estimates computed by means of nonequilibrium trajectories and equation (11). $\omega = 0.2$, $h = 0.000125$, $\tau \approx 15.7$ for a total number of integration steps $N = 126\,500$, $M = 5000$ independent trajectories.

An obvious question now is how the performance of the Langevin sampler can be improved by changing the protocol. For our choice of a sinusoidal control function, we have tried various parameters (i.e., different values of ω), as well as different protocols (i.e., not sinusoidal) without showing much effect in the estimate of the free energy or the sample variance of said estimate. Even given the simple example, one would expect that better results are obtained if the reaction coordinate moves slowly, so that the remaining variables can equilibrate adiabatically. We have performed different numerical experiments (not shown here) in which we have varied not only the "shape" of the protocol, but also the "speed" at which the protocol pulls the slow q-coordinate toward its final state. These experiments, however, do not show a convincing improvement or worsening of the estimation of the free energy.

Clearly, the quality of the estimation can always be improved by adding more samples, but this strategy could be an expensive one. For the estimate of the expected value of the exponential work in (12), one should expect a improvement in the Monte Carlo error as $O(1/\sqrt{M})$ where M is the number of independent realizations of the process, while the error in the numerical integration should decrease as $O(h)$ where h is the numerical time step in the Euler-Maruyama scheme. However, it follows from Jensen's inequality that the finite sample estimator (12) overestimates the correct free energy. Hence one may seek instead to design a control law that minimizes the expectation subject to fixed terminal condition at $t = \tau$ when $\xi(\tau)$ reaches its predetermined value. Problems of this kind are known as *risk-sensitive control problems* (see [14]). For our purpose, a reasonable optimal control task would be to maximize the exponential work functional over a suitable space U of admissible controls, viz.,

$$I^\sigma(u; x, \tau) = \max_{u \in U} \mathbf{E}_x \left[\exp\left(-\frac{2}{\sigma^2} \int_0^\tau f(X^\sigma(s)) u(s)\, ds \right) \right]$$

subject to

$$dX^\sigma(t) = ((J - D)\nabla \tilde{H}(X^\sigma(t)) + u(t) B(X^\sigma(t)))dt + S\, dW(t)\,, \quad X^\sigma(0) = x$$

with the non-zero block of S being σI and $2D = \sigma^2 I$. The work functional has the advantage of involving all its moments, in other words, it also controls the variance of the estimator (see [15]). Here $\sigma > 0$ is a small parameter that controls the temperature of the system (there is no need for a nonequilibrium method at high temperature as the free energy can easily be computed by a histogram). One can then show, exploiting a result from [16], that $I^\sigma \sim \exp(V/\sigma)$ asymptotically as $\sigma \to 0$ where V is the value function of a certain differential game.

Of course, the optimal steering protocol strategy does not come for free, and users often will decide to increase the sample size rather than solving a complicated nonlinear optimal control problem. However, we believe that

experimenting with simple systems may give insight into good control strategies in more general cases, and even for single-molecule experiments (cf. [4]).

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