Computing free energy differences using conditioned diffusions

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Abstract.
We derive a Crooks-Jarzynski-type identity for computing free energy differences between metastable states that is based on nonequilibrium diffusion processes. Furthermore we outline a brief derivation of an infinite-dimensional stochastic partial differential equation that can be used to efficiently generate the ensemble of trajectories connecting the metastable states.

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INTRODUCTION

Given a system assuming states $x \in \mathscr{X} \subseteq \mathbb{R}^d$ with the energy $V(x)$, the free energy at temperature $\varepsilon > 0$ as a function of a scalar reaction coordinate $\Phi(x)$ is defined as

$$F(\xi) = -\varepsilon \ln \int_{\mathscr{X}} \exp(-\varepsilon^{-1} V(x)) \delta(\Phi(x) - \xi) dx . \tag{1}$$

Given that $x \in \mathscr{X}$ follows the Boltzmann distribution $\rho \propto \exp(-\varepsilon^{-1} V)$, the free energy is just the marginal distribution in $\Phi(x)$. However estimating the marginal numerically from samples of ρ may be prohibitively expensive, e.g., when V has large barriers in the direction of Φ. Therefore we dismiss this option and propose a different scheme that employs realizations of the overdamped Langevin equation

$$dX_\tau = f(X_\tau, \tau) d\tau + \sqrt{2\varepsilon} dW_\tau , \quad \tau \in [0, T] \tag{2}$$

subject to the boundary conditions (see Fig. 1)

$$\Phi(X_0) = \xi_A \quad \text{and} \quad \Phi(X_T) = \xi_B . \tag{3}$$

The vector field $f(x, \tau) = -\nabla V(x) + g(x, \tau)$ is assumed to be smooth with the time-dependent part g being such that the process hits the level set $\{\Phi(x) = \xi_B\}$ at time T; without loss of generality we set $T = 1$.

As we will demostrate below, the free energy difference $\Delta F = F(\xi_B) - F(\xi_A)$ can be computed as the weighted average (cf. [1, 2, 3])

$$\Delta F = -\varepsilon \ln \mathbf{E} \left[\exp \left(-\varepsilon^{-1} \int_0^1 g(X_\tau, \tau) \circ dX_\tau \right) \right] \tag{4}$$

where "$\circ$" means integration in the sense of Stratonovich and $\mathbf{E}[\cdot]$ denotes the expectation over all (bridge) paths that solve the conditioned Langevin equation (2)–(3).

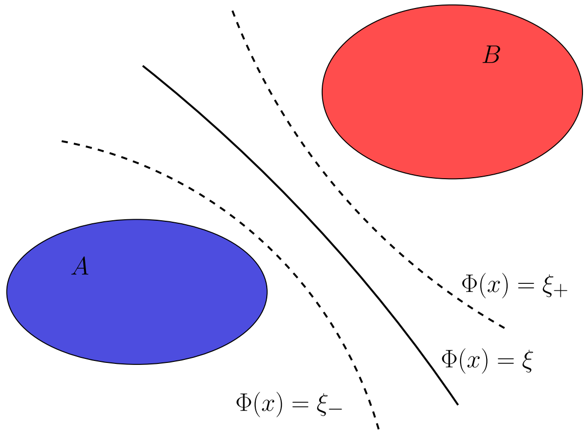

FIGURE 1. Boundaries of metastable states A and B as level sets of the reaction coordinate Φ.

DERIVATION: EULER'S METHOD

Our derivation of (4) is based on the discrete Euler-Maruyama approximation of (2),

$$X_{k+1} = X_k + \Delta\tau f(X_k, \tau_k) + \sqrt{2\varepsilon\Delta\tau}\,\eta_{k+1}\,, \quad k = 0, \ldots, n-1\,. \tag{5}$$

Here $\Delta\tau = 1/n$ and $\eta_k \sim \mathcal{N}(0, I)$ are i.i.d. distributed Gaussian random variables.

We call $\mathbf{P}_n(x) = \text{Prob}\,[X_0 = x_0, X_1 = x_1, \ldots, X_n = x_n]$ the joint distribution of the path $x = \{x_0, x_1, \ldots, x_n\} \subset \mathscr{X}$. Assuming that the x_0 follow the Boltzmann distribution ρ conditional on $\Phi(x_0) = \xi_A$, the distribution of the paths is readily shown to be

$$\mathbf{P}_n(x) \propto \rho(x_0|\xi_A) \exp\left(-\frac{\Delta\tau}{4\varepsilon}\sum_{k=0}^{n-1}\left|\frac{x_{k+1}-x_k}{\Delta\tau} - f(x_k, \tau_k)\right|^2\right)\delta(\Phi(x_n) - \xi_B)\,.$$

We are interested in the likelihood ratio of forward and backward paths. To this end we introduce $\tilde{\mathbf{P}}_n(x) = \mathbf{P}_n(\tilde{x})$ as the distribution of the reversed paths $\tilde{x} = \{x_n, x_{n-1}, \ldots, x_0\} \subset \mathscr{X}$ with $x_n \sim \rho(\cdot|\xi_B)$. By the smoothness of f, the forward measure $\mathbf{P}_n$ has a density with respect to $\tilde{\mathbf{P}}_n$ that is is given in terms of their Radon-Nikodym derivative,

$$\psi_n(x) = \exp\left(\varepsilon^{-1}(\Delta V + W_n(x))\right)\exp\left(-\varepsilon^{-1}\Delta F\right)\,. \tag{6}$$

Here $\Delta V = V(x_n) - V(x_0)$ and

$$W_n(x) = \frac{1}{2}\sum_{k=0}^{n-1}(x_{k+1} - x_k)\cdot(f(x_k, \tau_k) + f(x_{k+1}, \tau_{k+1})) + \mathscr{O}(|\Delta\tau|)$$

is the Stratonovich approximation of the stochastic work integral, i.e.,

$$\lim_{n\to\infty} W_n(x) = -\Delta V + \int_0^1 g(X_\tau, \tau)\circ dX_\tau \quad (\Delta\tau \to 0,\, n\Delta\tau = 1)\,.$$

The free energy difference in (6) pops up as a boundary term, $\exp(-\varepsilon^{-1}\Delta F) = Z_B/Z_A$, with Z_A and Z_B normalizing the conditional distributions for forward and backward paths. Upon noting that both $\mathbf{P}_n$ and $\tilde{\mathbf{P}}_n$ are probability measures, (6) entails (4) as $n \to \infty$.

AN INFINITE-DIMENSIONAL LANGEVIN SAMPLER

Now comes our main result: To evaluate the expectation in (4) we have to generate the ensemble of bridge paths. For this purpose we introduce the auxiliary potential

$$\varphi = \Delta\tau^{-1}V(x_0) + \frac{1}{4}\sum_{k=0}^{n-1}\left|\frac{x_{k+1}-x_k}{\Delta\tau} + f(x_k,\tau_k)\right|^2 + \Delta\tau^{-1}\varepsilon\left(\ln|\nabla\Phi(x_0)| + \ln|\nabla\Phi(x_n)|\right),$$

so that $\exp(-\varepsilon^{-1}\Delta\tau\varphi)$ is the density of $\mathbf{P}_n$ with respect to the surface element on the image space $\Sigma = \{x \in \mathscr{X}^{n+1} \colon \Phi(x_0) = \xi_A, \Phi(x_n) = \xi_B\} \subset \mathscr{X}^{n+1}$ of admissible paths. Conversely, $\exp(-\varepsilon^{-1}\Delta\tau\varphi)$ is the stationary distribution of the Langevin equation [4]

$$dQ_s = -\left(\nabla\varphi(Q_s) + \nabla\sigma(Q_s)\lambda^T\right)ds + \sqrt{2\varepsilon\Delta\tau^{-1}}dW_s\,, \quad \sigma(Q_s) = 0 \tag{7}$$

where $Q_s = (q_0(s),\ldots,q_n(s))$ and $\lambda = (\lambda_1,\lambda_2)$ labels the Lagrange multipliers determined by the constraint $\sigma = 0$, the latter being shorthand for $\Phi(q_0) = \xi_A$ and $\Phi(q_n) = \xi_B$.

Using formal arguments (that can be made rigorous using Girsanov's theorem), we can take the limit $n \to \infty$ which turns the Langevin sampler (7) into a stochastic partial differential equation (SPDE) for bridge paths [5]. If we denote the continuous path by $\gamma = \gamma(\tau,s)$ with $\tau \in [0,1]$ now being the "spatial" variable, our SPDE reads

$$\begin{aligned}
\frac{\partial\gamma}{\partial s} &= \frac{1}{2}\frac{\partial^2\gamma}{\partial\tau^2} - \frac{1}{2}\left(\nabla f f + \varepsilon\nabla(\nabla\cdot f)\right) + \sqrt{2\varepsilon}\,\frac{\partial W}{\partial s} && \forall(\tau,s)\in[0,1]\times(0,\infty)\\
\Phi(\gamma) = \xi_A\,,\ \left(\frac{\partial\gamma}{\partial s}\right)^{\parallel} &= (2\varepsilon Sn - f)^{\parallel} && \forall(\tau,t)\in\{0\}\times(0,\infty)\\
\Phi(\gamma) = \xi_B\,,\ \left(\frac{\partial\gamma}{\partial s}\right)^{\parallel} &= (f - 2\varepsilon Sn)^{\parallel} && \forall(\tau,t)\in\{1\}\times(0,\infty)\\
\gamma &= \gamma_0 && \forall(\tau,s)\in[0,1]\times\{0\}
\end{aligned} \tag{8}$$

where $\partial W/\partial s$ is space-time white noise and we have introduced the various shorthands: $n = \nabla\Phi/|\nabla\Phi|$ for the unit normal to the level sets $\{\Phi(x) = \xi\}$, $f^{\parallel} = (I - n\otimes n)f$ for the vector field f tangent to the level sets, and $S = \nabla^2\Phi/|\nabla\Phi|$ for the shape operator (second fundamental form) of $\{\Phi(x) = \xi\}$ understood as a submanifold of $\mathscr{X}$.

Note that although γ lives in $\mathscr{X} \subseteq \mathbb{R}^d$, which may be high-dimensional, its two arguments are scalar variables (namely, arc length τ and time s). Methods for numerically solving SPDEs such as (8) are discussed in, e.g., [6].

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