

# 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  $x \in \mathcal{X} \subseteq \mathbb{R}^d$  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

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

Given that  $x \in \mathcal{X}$  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  $\rho$  may be prohibitively expensive, e.g., when  $V$  has large barriers in the direction of  $\Phi$ . Therefore we dismiss this option and propose a different scheme that employs realizations of the overdamped Langevin equation

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

subject to the boundary conditions (see Fig. 1)

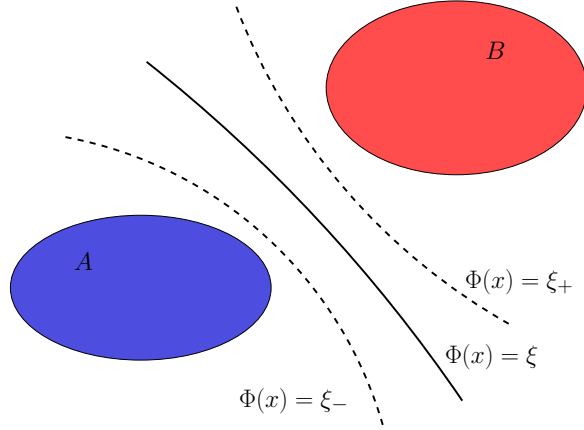
$$\Phi(X_0) = \xi_A \quad \text{and} \quad \Phi(X_T) = \xi_B. \quad (3)$$

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

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

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  $\Phi$ .

### DERIVATION: EULER'S METHOD

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

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

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

We call  $\mathbf{P}_n(x) = \text{Prob}[X_0 = x_0, X_1 = x_1, \dots, X_n = x_n]$  the joint distribution of the path  $x = \{x_0, x_1, \dots, x_n\} \subset \mathcal{X}$ . Assuming that the  $x_0$  follow the Boltzmann distribution  $\rho$  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  $\tilde{x} = \{x_n, x_{n-1}, \dots, x_0\} \subset \mathcal{X}$  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 given in terms of their Radon-Nikodym derivative,

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

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

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

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

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

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  $n \rightarrow \infty$ .

## 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

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

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  $\Sigma = \{x \in \mathcal{X}^{n+1} : \Phi(x_0) = \xi_A, \Phi(x_n) = \xi_B\} \subset \mathcal{X}^{n+1}$  of admissible paths. Conversely,  $\exp(-\varepsilon^{-1}\Delta\tau\varphi)$  is the stationary distribution of the Langevin equation [4]

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

where  $Q_s = (q_0(s), \dots, q_n(s))$  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  $n \rightarrow \infty$  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

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

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  $\mathcal{X}$ .

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

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