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Nonadiabatic force matching for alchemical free-energy estimation

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We propose a method to compute free-energy differences from nonadiabatic alchemical transformations using flow-based generative models. The method, nonadiabatic force matching, hinges on estimating the dissipation along an alchemical switching process in terms of a nonadiabatic force field that can be learned through stochastic flow matching. The learned field can be used in conjunction with short-time trajectory data to evaluate upper and lower bounds on the alchemical free energy that variationally converge to the exact value if the field is optimal. Applying the method to evaluate the alchemical free energy of atomistic models shows that it can substantially reduce the simulation cost of a free-energy estimate at negligible loss of accuracy when compared with thermodynamic integration.

INTRODUCTION

Computational schemes for accurate, high-throughput free-energy estimation are highly coveted and could enable scientific breakthroughs in materials design [1] and drug discovery [2]. Presently, widespread methods adopt an alchemical approach, in which the state of a system is transformed along a thermodynamic path that connects the two equilibrium states, A and B, between which the free-energy difference ΔF is sought [3]. Changes in the system’s state are driven by a switching potential $U(\mathbf{x}, \lambda)$, where the switch λ runs from λ_A to λ_B and indexes a family of equilibrium probability densities

$$\pi(\mathbf{x}, \lambda) \equiv \exp\{\beta[F(\lambda) - U(\mathbf{x}, \lambda)]\} \quad (1)$$

over system configurations \mathbf{x} , with β^{-1} the temperature times Boltzmann’s constant and $F(\lambda)$ the absolute Helmholtz free energy at λ . If the system is driven at a slow enough rate to prevent dissipation throughout the switching, the free-energy difference between its end states is [4]

$$\Delta F \equiv F(\lambda_B) - F(\lambda_A) = \int_{\lambda_A}^{\lambda_B} d\lambda \langle \partial_\lambda U \rangle_\lambda \quad (2)$$

where the angled brackets $\langle \cdot \rangle_\lambda$ denote a configurational average under the probability density in Eq. (1). The duration of this adiabatic alchemical transformation approaches the quasistatic limit, exceeding the system’s longest relaxation timescales and allowing it to reach equilibrium at every λ .

Free-energy estimation by numerical evaluation of Eq. (2), known as thermodynamic integration (TI), underpins the computation of solubility curves and binding affinities for molecular systems of modest size [5, 6]. However, TI entails sampling a locus of high-dimensional, multi-modal equilibrium states along the thermodynamic path [7], and is seldom tractable at the scale of modern campaigns for drug discovery and materials design. An alternative avenue for free-energy estimation is suggested by Jarzynski’s work theorem [8]

$$\exp(-\beta\Delta F) = \langle \exp(-\beta\mathcal{W}_\tau) \rangle \quad (3)$$

which relates ΔF to the work \mathcal{W}_τ done on the system to drive it through the thermodynamic path via a switching process of duration τ . The expression in angled brackets $\langle \cdot \rangle$ in Eq. (3) denotes an average over nonequilibrium work measurements; its evaluation enables free-energy estimation from nonadiabatic alchemical transformations, which are those whose duration is short compared to the quasistatic limit. Seeking computational expediency beyond that of TI without sacrificing accuracy, a flurry of schemes have emerged to evaluate Eq. (3) with maximum efficiency and minimum bias [9–12].

Naive evaluation of Jarzynski’s equality in Eq. (3) is far from efficient, as converging the exponential average on its right-hand side often requires exponentially many work measurements [13]. Instead, modern schemes for free-energy estimation based on Jarzynski’s equality target the exponentially rare work measurements that dominate the average, deploying probabilistic generative modeling techniques [14–17] to mine quasi-adiabatic paths connecting states A and B [18–23]. To address scenarios where such paths are intractable due to computational limitations, it is desirable to extend generative modeling approaches to free-energy estimation that leverage typical nonequilibrium work measurements from simulation or experiment [24–28]. Necessary to this end are theoretical perspectives that clarify the dissipative contributions to the exponential average in Eq. (3) in terms of quantities that can be estimated from readily accessible trajectory data.

In this article, we examine flow matching models (FMMs) as an emergent platform for dissipative free-energy estimation. After formulating an alchemical interpretation of the FMM archetype and laying out the stochastic thermodynamics of the nonadiabatic transformation that it induces, we elucidate descriptors of the dissipation incurred along the transformation that yield sharp bounds on the free-energy difference. The bounds are saturated by a flow field that extends a stationary analogue introduced in Ref. 29 to evaluate log-likelihood functions for active systems, and that can be learned by training a FMM. Numerical demonstrations on atomistic models of fast-growth solvation and of Frenkel–Ladd solid formation confirm that, given a nonadiabatic alchemical transformation and an associated FMM, our variational bounds can produce a free-energy estimate with comparable accuracy to TI at a substantially reduced simulation cost.

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THE STOCHASTIC THERMODYNAMICS OF FLOW MATCHING MODELS

FMMs learn a two-sided mapping between distributions of *data* and *noise* that allows generating samples from either distribution by transporting samples from the other. The mapping is comprised of a pair of stochastic processes, of which the *forward* process is given and the *backward* process is its learned time-reversal [30]. Here we specify an alchemical FMM paradigm in which the map is determined by a switch $\lambda(t)$ of duration τ with the boundary values $\lambda(t=0) \equiv \lambda_A$ and $\lambda(t=\tau) \equiv \lambda_B$, and where the forward process

$$d\mathbf{x}_t = -\beta D \nabla U(\mathbf{x}_t, \lambda(t)) dt + \sqrt{2D} d\mathbf{w}_t \quad (4)$$

has an initial configuration \mathbf{x}_0 drawn from the data distribution with density $\pi(\mathbf{x}, \lambda_A)$. Here and throughout, D denotes a diffusion coefficient, $\{\mathbf{w}_t\}_{t=0}^\tau$ a standard Brownian motion, and $U(\mathbf{x}_t, \lambda(t))$ the switching potential introduced in Eq. (1). The forward process in Eq. (4) maps the data distribution onto the noise distribution with density $\rho(\mathbf{x}, \tau) \equiv \langle \delta(\mathbf{x}_\tau - \mathbf{x}) \rangle$, where δ is the Dirac delta and where the angled brackets $\langle \cdot \rangle$ denote an average over realizations of the forward process. The noise density satisfies the Fokker–Planck equation

$$\partial_t \rho(\mathbf{x}, t) = -\nabla \cdot [D \nabla V(\mathbf{x}, t) \rho(\mathbf{x}, t)] \quad (5)$$

subject to the initial condition $\rho(\mathbf{x}, t=0) \equiv \pi(\mathbf{x}, \lambda_A)$, and the nonadiabatic potential

$$V(\mathbf{x}, t) \equiv -\ln \frac{\rho(\mathbf{x}, t)}{\pi(\mathbf{x}, \lambda(t))} \quad (6)$$

advects probability density from state A toward state B. Figure 1 illustrates the alchemical FMM specified herein.

Physically, the forward process in Eq. (4) corresponds to a nonadiabatic alchemical transformation where a system, initially at thermal equilibrium in state A, is mechanically driven toward state B in an irreversible manner. Although this transformation occurs far from equilibrium, the free-energy difference ΔF remains well-defined within the framework of stochastic thermodynamics [31, 32]. By the first law, the change of energy along the transformation is

$$\Delta U \equiv \langle U(\mathbf{x}_\tau, \lambda(\tau)) - U(\mathbf{x}_0, \lambda(0)) \rangle = \langle \mathcal{W}_\tau \rangle - \langle \mathcal{Q}_\tau \rangle \quad (7)$$

with

$$\mathcal{W}_\tau \equiv \int_0^\tau dt \partial_t U(\mathbf{x}_t, \lambda(t)) \quad (8a)$$

$$\mathcal{Q}_\tau \equiv - \int_0^\tau d\mathbf{x}_t \circ \nabla U(\mathbf{x}_t, \lambda(t)) \quad (8b)$$

the work exerted on the system and the heat dissipated by the system, respectively, along a realization of the process. Using Eq. (1), the first equality in Eq. (7) reduces to an expression for the Helmholtz free-energy difference, namely (SI, Section I)

$$\Delta F = \Delta U - \beta^{-1} [\Delta S + D_{\text{KL}}(\tau)] \quad (9)$$

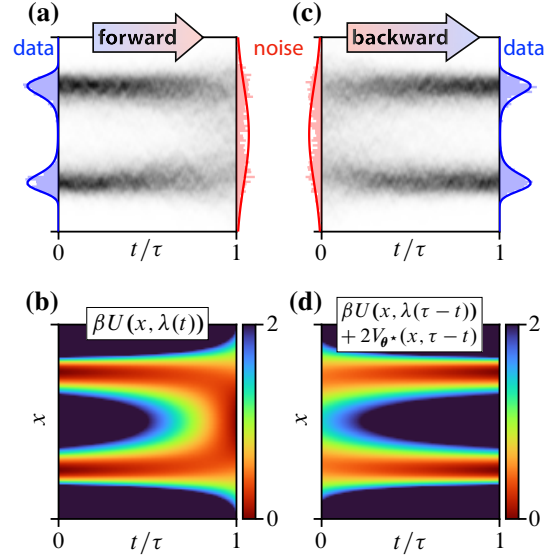


FIG. 1. A flow matching model for nonadiabatic alchemical free-energy estimation (a) Sample realizations of the forward process that drives a system from state A, a bimodal distribution, toward state B, a Gaussian distribution, according to a switch $\lambda(t)$ of duration τ . (b) The switching potential $\beta U(\mathbf{x}, \lambda(t))$ drives the system away from a bimodal distribution and toward a Gaussian distribution. (c) The backward process, using the learned nonadiabatic potential $V_{\theta^*}(\mathbf{x}, t)$, stochastically reverses the transition driven by the switching potential. (d) The nonadiabatic switching potential $\beta U(\mathbf{x}, \lambda(\tau-t)) + 2V_{\theta^*}(\mathbf{x}, \tau-t)$ restores the system to a bimodal distribution.

where $\Delta S \equiv \langle -\ln[\rho(\mathbf{x}_\tau, \tau)/\pi(\mathbf{x}_0, \lambda_A)] \rangle$ is the entropy change of the system along the transformation; the Kullback–Leibler (KL) divergence

$$D_{\text{KL}}(t) \equiv \left\langle \ln \frac{\rho(\mathbf{x}_t, t)}{\pi(\mathbf{x}_t, \lambda(t))} \right\rangle = \langle -V(\mathbf{x}_t, t) \rangle \quad (10)$$

quantifies the nonadiabatic lag between the state of the system at each time $t \in [0, \tau]$ and its counterpart in the quasistatic limit [33, 34]. The second law of thermodynamics provides a decomposition of ΔS through an entropy balance that clarifies Eq. (9) [35, 36]. Since the system evolves at a fixed temperature, entropy changes in the ideal, implicit bath are reversible; we find (SI, Section II)

$$\Delta S = \left\langle \int_0^\tau dt D |\nabla V(\mathbf{x}_t, t)|^2 \right\rangle - \beta \langle \mathcal{Q}_\tau \rangle \quad (11)$$

where the first term is the entropy produced along the transformation, which is nonnegative, and the second is the dissipated heat introduced in Eq. (7). Combining Eqs. (7) and (9) to (11), we finally obtain

$$\Delta F = \langle \mathcal{W}_\tau \rangle - \beta^{-1} \left\langle \int_0^\tau dt D |\nabla V(\mathbf{x}_t, t)|^2 - V(\mathbf{x}_\tau, \tau) \right\rangle \quad (12)$$

an equality relating ΔF to the dissipation along a nonadiabatic alchemical transformation from state A toward state B.

Equation (12) furnishes a refinement of Jensen’s bound on Jarzynski’s equality in Eq. (3),

$$\Delta F \leq \langle \mathcal{W}_\tau \rangle \quad (13)$$

in that it explicitly states the dissipative terms that close the gap from Jensen’s bound, rendering the inequality an equality. These terms depend on the nonadiabatic potential $V(\mathbf{x}, t)$ in Eq. (6), whose gradient can be regressed from the forward process by minimizing the loss function (SI, Section III)

$$\ell(\theta) \equiv \left\langle \int_0^\tau dt D |\nabla V_\theta(\mathbf{x}_t, t)|^2 - 2 \int_0^\tau d\mathbf{x}_t \circ \nabla V_\theta(\mathbf{x}_t, t) \right\rangle \quad (14)$$

with respect to the parameters θ of the differentiable ansatz V_θ . If $\theta^* \equiv \arg \min \ell(\theta)$ are optimal parameters, then the optimal nonadiabatic potential V_{θ^*} satisfies

$$V(\mathbf{x}, t) = V_{\theta^*}(\mathbf{x}, t) - \ln \langle \exp[V_{\theta^*}(\mathbf{x}_t, t)] \rangle \quad (15)$$

where the cumulant shift ensures correct normalization. For the initial condition in Eq. (5), the optimal nonadiabatic potential must satisfy the boundary condition $V_{\theta^*}(\mathbf{x}, t=0) \equiv 0$, which may be built into the ansatz or enforced through regularization during training. While numerical estimation of the exponential average in Eq. 15 can be computationally challenging, it acts as a time-dependent baseline that can be incorporated into, and trained alongside, the ansatz for $V(\mathbf{x}, t)$.

Taken together, Eqs. (12), (14) and (15) suggest a scheme to estimate ΔF by training an FMM to quantify the dissipation along a nonadiabatic alchemical transformation. Given an ensemble of realizations of the forward process, a nonadiabatic potential ansatz $V_\theta(\mathbf{x}, t)$ can be trained by minimizing Eq. (14), shifted according to Eq. (15), and plugged into Eq. (12) to obtain a free-energy estimate. If the learned nonadiabatic potential is optimal, then this procedure yields a statistically unbiased estimate of ΔF at no greater simulation cost than evaluating the work bound in Eq. (13).

FLOW MATCHING MODELS ENABLE VARIATIONAL FREE-ENERGY ESTIMATION

Since the exact nonadiabatic potential in Eq. (6) is seldom known, unbiased free-energy estimation with Eq. (12) is all but intractable in realistic applications. Here, we argue that the forward and backward processes that comprise an alchemical FMM are associated with variational upper and lower bounds on ΔF . These bounds control the systematic bias incurred by a suboptimal nonadiabatic potential and, by virtue of their variational character, are simultaneously saturated by the equality in Eq. (12) for an optimal potential.

Probabilistic inference in FMMs is achieved through a map from noise to data that is enabled by a learned flow field. In alchemical FMMs, this map is effected by the backward process

$$d\mathbf{x}_t = -D[\beta \nabla U(\mathbf{x}_t, \lambda(\tau-t)) + 2\nabla V_\theta(\mathbf{x}_t, \tau-t)] dt + \sqrt{2D} d\mathbf{w}_t \quad (16)$$

where the role of the flow field falls on the learned nonadiabatic force $-\nabla V_\theta$. A physical system evolving under the backward process has an initial configuration \mathbf{x}_0 drawn from the noise distribution with density $\rho(\mathbf{x}, \tau)$ and is driven by the time-reversed switch $\lambda(\tau-t)$ toward the equilibrium distribution at state A. If the learned nonadiabatic force is optimal, then the backward process maps the system directly onto state A, enabling the generation of equilibrium samples through the time-reversed nonadiabatic alchemical transformation.

A connection between the backward process and the free-energy difference ΔF can be gleaned from the flexible trainability of FMMs through either flow matching or minimization of the relative entropy between forward and backward processes [37]. Specifically, the nonadiabatic potential V_θ that enters the backward process can be trained by minimizing the loss in Eq. (14) or by minimizing the *backward* Kullback-Leibler (KL) divergence

$$\left\langle -\ln \frac{d\mathbb{P}_\tau[\{\mathbf{x}_{\tau-t}\}_{t=0}^\tau]}{d\mathbb{P}_{\theta, \tau}[\{\mathbf{x}_t\}_{t=0}^\tau]} \right\rangle_\theta \geq 0 \quad (17)$$

between forward and backward path ensembles, where the symbol $d\mathbb{P}_\tau[\{\mathbf{x}_{\tau-t}\}_{t=0}^\tau]/d\mathbb{P}_{\theta, \tau}[\{\mathbf{x}_t\}_{t=0}^\tau]$ denotes the likelihood of a backward trajectory $\{\mathbf{x}_t\}_{t=0}^\tau$ relative to that of its time-reversal $\{\mathbf{x}_{\tau-t}\}_{t=0}^\tau$, and the angled brackets $\langle \cdot \rangle_\theta$ denote an average over realizations. The relative likelihood takes the form (SI, Section IV)

$$\frac{d\mathbb{P}_\tau[\{\mathbf{x}_{\tau-t}\}_{t=0}^\tau]}{d\mathbb{P}_{\theta, \tau}[\{\mathbf{x}_t\}_{t=0}^\tau]} = \exp[V(\mathbf{x}_0, \tau) - \beta(\overline{\mathcal{W}}_\tau + \Delta F) - \overline{\mathcal{S}}_{\theta, \tau}] \quad (18)$$

where the reverse-time work and surprisal are given by

$$\overline{\mathcal{W}}_\tau \equiv \int_0^\tau dt \partial_t U(\mathbf{x}_t, \lambda(\tau-t)) \quad (19a)$$

$$\overline{\mathcal{S}}_{\theta, \tau} \equiv \int_0^\tau dt D |\nabla V_\theta(\mathbf{x}_t, \tau-t)|^2 - \sqrt{2D} d\mathbf{w}_t \cdot \nabla V_\theta(\mathbf{x}_t, \tau-t) \quad (19b)$$

respectively. Due to the nonnegativity of the KL divergence, one infers from Eqs. (17) and (18) the relation (SI, Section V A)

$$\Delta F \geq \langle -\overline{\mathcal{W}}_\tau \rangle_\theta - \beta^{-1} \left\langle \int_0^\tau dt D |\nabla V_\theta(\mathbf{x}_t, \tau-t)|^2 \right\rangle_\theta + \beta^{-1} [\langle V_\theta(\mathbf{x}_0, \tau) \rangle_\theta - \ln \langle \exp[V_\theta(\mathbf{x}_0, \tau)] \rangle_\theta] \quad (20)$$

which provides a *backward variational bound* on ΔF in terms of the work done and the dissipation incurred along the backward process. A similar argument starting from the *forward* KL divergence between forward and backward processes yields the separate relation (SI, Section V B)

$$\Delta F \leq \langle \mathcal{W}_\tau \rangle - \beta^{-1} \left\langle \int_0^\tau dt D |\nabla V_\theta(\mathbf{x}_t, t)|^2 \right\rangle + \beta^{-1} [\langle V_\theta(\mathbf{x}_\tau, \tau) \rangle - \ln \langle \exp[V_\theta(\mathbf{x}_\tau, \tau)] \rangle] \quad (21)$$

and thus recasts Eq. (12) as the saturated case of a *forward variational bound* on the free-energy difference.

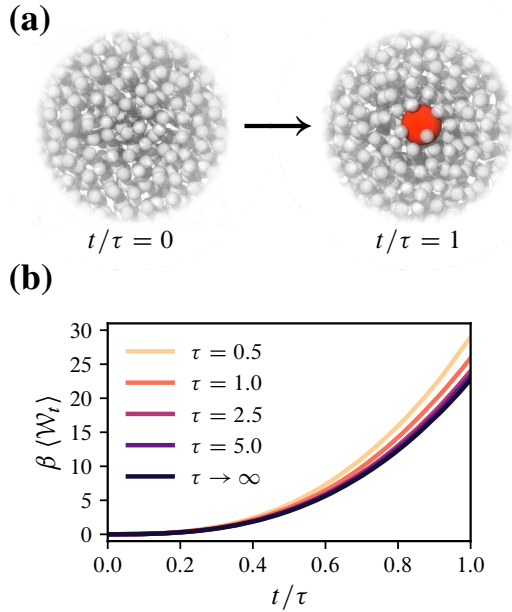


FIG. 2. Alchemical solvation in a WCA liquid. **(a)** Configuration snapshots along the alchemical path of a growing solute (red) within a WCA solvent (gray). **(b)** Estimates of the cumulative work done on the system to grow the solute at various rates τ^{-1} , compared to adiabatic growth at the quasistatic limit (black).

The variational lower and upper bounds on ΔF in Eqs. (20) and (21) are both saturated by the optimal nonadiabatic potential $V_{\theta^*}(\mathbf{x}, t)$ that satisfies Eq. (15) (SI, Section IV). Away from saturation, these inequalities provide a confidence interval for the free-energy difference that can be systematically narrowed through refinement of the nonadiabatic potential ansatz. It is worth noting that a free-energy estimate obtained by evaluating the backward variational bound in Eq. (20) can itself be systematically improved through the application of reinforcement learning schemes to saturate the inequality [38, 39].

EFFICIENCY GAINS FROM NONADIABATIC FLOW MATCHING FOR FREE-ENERGY ESTIMATION

We provide a numerical demonstration of alchemical FMMs for free-energy estimation by evaluating the backward variational bound in Eq. (20) on atomistic test problems. We use a simple linear switch $\lambda(t) \equiv (1-t/\tau)\lambda_A + (t/\tau)\lambda_B$, where $\lambda_A \equiv 0$ and $\lambda_B \equiv 1$ respectively index the equilibrium states A and B at the endpoints of the alchemical transformation. This switch recovers the quasistatic limit as $\tau \rightarrow \infty$, allowing us to compare the simulation cost to evaluate the backward variational bound in Eq. (20) with that of the TI estimator in Eq. (2). We set the diffusion coefficient to unity and use the Euler–Maruyama integrator [40] with integration stepsizes up to 5×10^{-5} time units to estimate forward and backward trajectories by solving Eq. (4) and Eq. (16), respectively.

WCA monomer solvation

As a canonical benchmark problem, we consider the free energy to solvate a point particle in a three-dimensional Weeks–Chandler–Andersen (WCA) solvent. In our simulations, the solvent is comprised by $N = 512$ point particles with positions $\{\mathbf{x}_i\}_{i=1}^N$, their interactions governed by the pairwise energy function

$$u_{\text{WCA}}(\mathbf{x}_i, \mathbf{x}_j | \sigma) \equiv 4\epsilon (r_{ij}^{-12} - r_{ij}^{-6} + 1/4) \mathbf{1}\{r_{ij} \leq 2^{1/6}\} \quad (22)$$

with σ the solvent size, ϵ the interaction energy scale, $r_{ij} \equiv |\mathbf{x}_j - \mathbf{x}_i|/\sigma$ the dimensionless distance between particles i and j , and $\mathbf{1}\{r_{ij} \leq \cdot\}$ a distance cutoff indicator. The solvent occupies a periodic cubic box with a side length of 8.110σ and is held at a temperature that corresponds to $\beta^{-1} = 1.214\epsilon$. These parameters define the equilibrium distribution of the system at state A, whose density is proportional to the Boltzmann factor $\exp[-\beta \sum_{i<j} u_{\text{WCA}}(\mathbf{x}_i, \mathbf{x}_j | \sigma)]$, where the sum runs over solvent atom pairs.

The alchemical path to the solvated state starts with the insertion of a small solute into a random pocket of the equilibrium solvent. The free-energetic cost of this operation, which we neglect, is well captured by a Poisson point process approximation of Widom’s scheme that takes advantage of the solute’s small size at insertion [41, 42]. Once inserted, the solute grows from its initial size, $\sigma_A \equiv 0.02\sigma$, to its final size, $\sigma_B \equiv 2\sigma$, while interacting with the surrounding solvent. For this σ_A , the expected free energy from Widom insertion is much less than the thermal energy. Solute-solvent interactions are also governed by the energy function in Eq. (22), but involve a switch-dependent interaction lengthscale

$$\sigma_S(t) \equiv \sqrt{[\sigma_A(1-\lambda(t)) + \sigma_B\lambda(t)]\sigma} \quad (23)$$

that dictates the solute size. With the solute position given by \mathbf{x}_S , the switching potential takes the form

$$U(\mathbf{x}, \lambda(t)) \equiv \sum_{i<j} u_{\text{WCA}}(\mathbf{x}_i, \mathbf{x}_j | \sigma) + \sum_i u_{\text{WCA}}(\mathbf{x}_i, \mathbf{x}_S | \sigma_S(t)) \quad (24)$$

where $\mathbf{x} \equiv \text{vec}(\{\mathbf{x}_S\}, \{\mathbf{x}_i\}_{i=1}^N)$ is the solvated configuration. The alchemical path to the solvated state is illustrated in Fig. 2a, which contains simulation snapshots taken along a solute growth trajectory obtained from the forward process in Eq. (4) with the potential in Eq. (24).

Fig. 2b shows Monte Carlo estimates of the mean accumulated work $\langle \mathcal{W}_t \rangle$ done on the system to enact solute growth up to each time $t \in [0, \tau]$ during the nonadiabatic alchemical transformation. The work is computed at growth rates τ^{-1} spanning an order of magnitude, and separately for a quasistatic growth rate via trapezoidal quadrature of Eq. (2) on a 21-point grid along the switching schedule with a uniform grid spacing of 0.05. The cumulative work estimates, obtained by averaging 100 Euler–Maruyama solutions of Eq. (4) at each growth rate, exhibit negligible variance and accrue smoothly along the thermodynamic path, suggesting that the

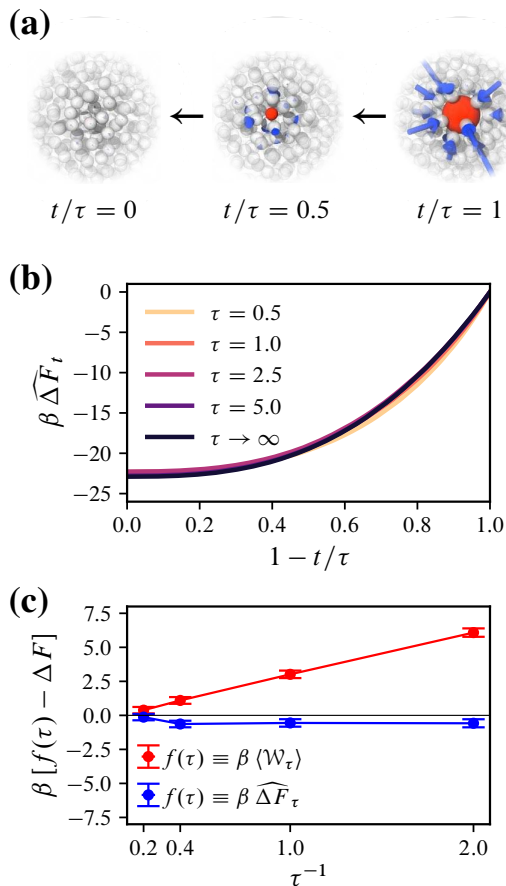


FIG. 3. WCA solvation free energies from nonadiabatic force matching. (a) Snapshots from a realization of the backward process, where the solute growth is reversed by the nonadiabatic switching potential. (b) The cumulative free-energy differences estimated from the denoised solute growth (colored) closely match the quasistatic limit (black). (c) Accuracy of solvation free-energy estimates as a function of solute growth rate τ^{-1} .

excess work, $\langle \mathcal{W}_t \rangle - [F(\lambda(t)) - F(\lambda(0))]$, arises from localized energy fluctuations throughout the growth process. The leading-order role of this excess work is to rectify solvation-shell fluctuations that contend with solute growth.

In general, physical insight into the role of excess work informs the design of efficiently trainable nonadiabatic potential ansätze for accurate free-energy estimation. We use an ansatz that captures energetic fluctuations due to solute-solvent interactions along the solute growth direction while ignoring higher-order contributions due to solvent-solvent interactions. The ansatz is comprised of a Behler-style neural forcefield [43] whose inputs are N solute-solvent pair distances $\{\phi(|\mathbf{x}_s - \mathbf{x}_i|/\sigma)\}_{i=1}^N$, where

$$\phi(r) \equiv \frac{1}{2} [1 + \cos(\pi r^2/4)] \exp(-r^2/4) \mathbf{1}\{r \leq 2\} \quad (25)$$

is a symmetry function that encodes short-ranged, rotationally invariant, repulsive interactions between the solute and the solvent [44]. These inputs are passed to a shallow, fully-connected

neural network (NN) with N neurons in the input layer, $4N$ neurons in a hidden layer, and a scalar output layer that yields the nonadiabatic potential $V_\theta(\mathbf{x}, t)$. To ensure that the learned potential satisfies the boundary condition $V_\theta(\mathbf{x}, t=0) \equiv 0$, the NN inputs are multiplied by the instantaneous switching value $\lambda(t)$, the linear bias of each layer is fixed at zero, and exponential linear units [45] are used as activation functions in all layers. The layer weights θ are optimized by minimizing the loss in Eq. (14) with the Adam optimizer [46], and the optimal nonadiabatic potential $V_{\theta^*}(\mathbf{x}, t)$ is used to produce 100 statistically independent Euler–Maruyama solutions of Eq. (16) at each growth rate, each initialized at the final configuration along a corresponding solution of Eq. (4).

Snapshots taken along a trajectory of the learned backward process are shown in Fig. 3a, where the blue arrows show how the optimal nonadiabatic force $-\nabla V_{\theta^*}(\mathbf{x}, t)$ drives solvent particles to fill the vacancy left by the solute as it shrinks in reverse time. By construction, this force is localized around the solute’s closest solvation shell throughout the switching process. Although this may result in a reasonable approximation of the fluctuating velocity field near the quasistatic limit, it rapidly degrades as the field delocalizes at solute growth rates faster than those considered here. A total of 100 independent backward trajectories are used to evaluate an estimator of Eq. (20),

$$\widehat{\Delta F}_t \equiv \langle -\overline{\mathcal{W}}_t \rangle_\theta - \beta^{-1} \langle \overline{\mathcal{S}}_{\theta,t} \rangle_\theta + \beta^{-1} \langle V_\theta(\mathbf{x}_t, \tau-t) \rangle_\theta \quad (26)$$

for times t within the duration of the nonadiabatic alchemical transformation. This estimator excludes the cumulant shift in Eq. (20), which we found to be negligible in our calculations. The results, shown in Fig. 3b, illustrate that the variational free-energy bound is closely saturated across the range of transition durations. Comparing the accuracy of the variational bound in Eq. (20) with the work bound in Eq. (13), as done in Fig. 3c, shows that the trajectory duration required to saturate the variational free-energy estimate is between 1-2 orders of magnitude shorter than that required to approach the quasistatic limit, which in turn suggests that the backward variational bound attains a commensurate reduction in simulation cost relative to TI.

LJ solid formation

To illustrate the utility of flow matching for free-energy estimation in solids, we compute the free energy to form a Lennard–Jones (LJ) solid from a harmonic face-centered cubic (FCC) crystal. We simulate a periodic super-lattice with $5 \times 5 \times 5$ FCC unit cells or, equivalently, $N = 500$ lattice sites with positions $\mathbf{x}_O \equiv \text{vec}(\{\mathbf{x}_{O,i}\}_{i=1}^N)$, of which one is kept frozen to fix the center of mass of the lattice [47]. The unit cell side-length is 1.462σ , where σ sets the interaction length-scale, and the lattice is held at a temperature that corresponds to $\beta^{-1} = \epsilon$, where ϵ sets the interaction energy scale. The harmonic FCC lattice is alchemically evolved toward a LJ solid via the Frenkel–Ladd potential [48]

$$U(\mathbf{x}, \lambda(t)) \equiv \frac{\kappa}{2} (1 - \lambda(t)) |\mathbf{x} - \mathbf{x}_O|^2 + \lambda(t) U_{\text{LJ}}(\mathbf{x}) \quad (27)$$

where $\mathbf{x} \equiv \text{vec}(\{\mathbf{x}_i\}_{i=1}^N)$ is the fluctuating configuration of the lattice, $U_{\text{LJ}}(\mathbf{x}) \equiv \sum_{i<j} u_{\text{LJ}}(\mathbf{x}_i, \mathbf{x}_j)$ the LJ potential with the pairwise energy function

$$u_{\text{LJ}}(\mathbf{x}_i, \mathbf{x}_j) \equiv 4\epsilon [(|\mathbf{x}_j - \mathbf{x}_i|/\sigma)^{-12} - (|\mathbf{x}_j - \mathbf{x}_i|/\sigma)^{-6}] \quad (28)$$

truncated and shifted to zero at pairwise distances $|\mathbf{x}_j - \mathbf{x}_i| \geq 2.7\sigma$ [49], and $\kappa \equiv 100\epsilon/\sigma^2$ the stiffness constant of the harmonic crystal.

Fig. 4a gives trajectory snapshots for the alchemical transformation from a harmonic crystal to the LJ lattice, with the red lines indicating the displacement of each particle from its FCC lattice site. Monte Carlo estimates of the work done on the system *per lattice site*, $\langle W_t \rangle/N$, up to each time $t \in [0, \tau]$ are shown in Fig. 4b for switching rates τ^{-1} spanning two orders of magnitude. At each lattice relaxation rate, 100 statistically independent Euler–Maruyama solutions of the forward process in Eq. (4) are used to estimate the cumulative work done on the system, which stores excess energy in lattice modes that cannot be dispersed within the timescale of the alchemical transformation. The cumulative work in the quasistatic limit as $\tau^{-1} \rightarrow 0$, also shown in Fig. 4b, was approximated by averaging over trajectories of duration $\tau = 10$, resulting in a ground-truth estimate of ΔF that is comparable in accuracy to TI with a fine quadrature grid. For this system, the free-energy difference is well-approximated by the cumulative work [Eq. (13)] at remarkably short durations. Because the fluctuating lattice configuration remains sharply concentrated around the mode of the adiabatic alchemical distribution, nonadiabatic fluctuations are rendered a higher-order effect.

This observation has important consequences for variational free-energy estimation as shown in Fig. 4c, where the estimator in Eq. (26) is evaluated with the *constant* nonadiabatic potential ansatz $V_\theta(\mathbf{x}, t) \equiv 0$ using 100 Euler–Maruyama solutions of the backward process in Eq. (16), initialized with the final nonequilibrium distribution sampled by the forward trajectories. In alignment with our expectation that the exact nonadiabatic potential is roughly constant along the nonadiabatic alchemical transformation, the estimator in Eq. (26) with a constant potential closely follows the variational free-energy bound in Eq. (20) across a wide range of transition durations. In contrast, the work bound in Eq. (13) is approximately thrice as biased across the range of alchemical switching rates τ^{-1} , as seen in Fig. 4d. Thus in this example, simply using the backward variational bound without training an FMM significantly reduces the error of nonadiabatic free-energy estimation.

CONCLUDING REMARKS

We present a stochastic-thermodynamic framework for free-energy estimation along a nonadiabatic alchemical transformation that hinges on training a flow-based generative model. Within this framework, we derive variational estimators for the free-energy difference that, coupled with an efficient neural ansatz for the nonadiabatic force field, can reduce the simulation cost of a statistically unbiased free-energy estimate by orders of magnitude relative to methods that operate within the quasistatic limit, such as thermodynamic integration. In our

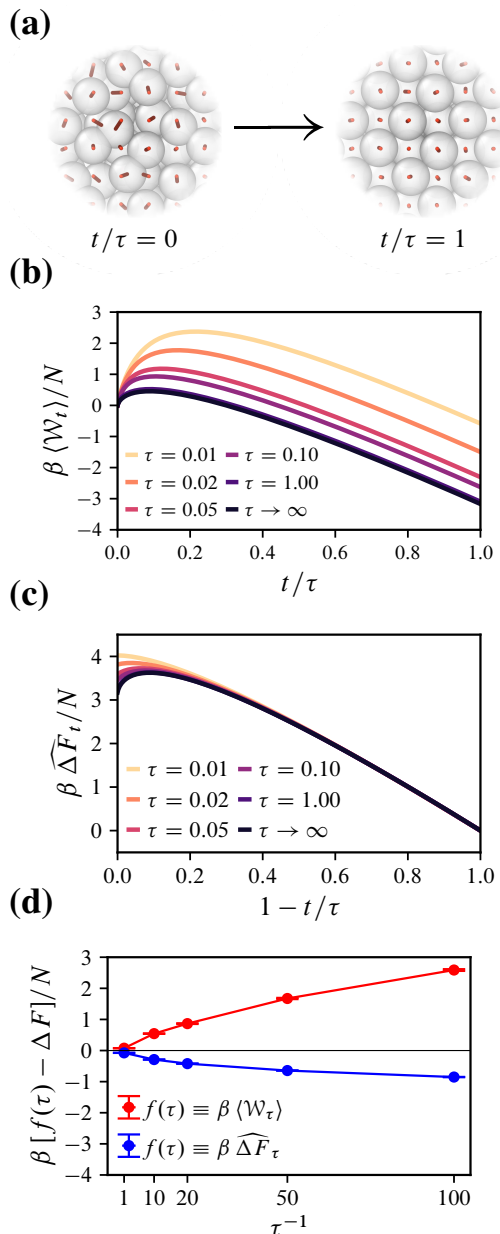


FIG. 4. Estimates of the free energy to form an LJ solid. (a) Configuration snapshots along the Frenkel–Ladd alchemical path, wherein a harmonic FCC lattice is driven toward an LJ solid. (b) The cumulative work per site at lattice relaxation rates τ^{-1} spanning two orders of magnitude. (c) Backward estimates of the formation free-energy difference per site are accurate across a range of relaxation rates τ^{-1} . (d) The bias in the formation free-energy difference per site at alchemical switching rates τ^{-1} .

applications of the variational free-energy bound in Eq. (20), we use computationally inexpensive ansätze for the nonadiabatic force to resolve its fluctuations along dominant dissipation pathways while ignoring higher-order interaction channels that contribute negligibly to the overall dissipation. In doing so, we illustrate the benefits of using system-adapted neural ansätze to more efficiently evaluate alchemical tran-

sitions. All numerical results presented in this work, along with generating code, are available in the GitHub repository [jrosaraices/nonadiabatic-force-matching](https://github.com/jrosaraices/nonadiabatic-force-matching).

The current work adds to a rapidly growing collection of free-energy estimation schemes that leverage controlled diffusions. Of note are Máté *et al.*'s work on *Neural TI* [22, 50], and He *et al.*'s work on free-energy difference estimation via adaptive transport [23, 51]. In these works, a counterdiabatic potential is sought to advect a molecular system along a set of equilibrium states connecting A and B, in the spirit of the *escorted work* framework introduced by Vaikuntanathan and Jarzynski [21, 52]. In contrast, our approach to free-energy estimation evolves from Hummer's *fast growth* framework [53], to which we add flow matching to mitigate biases associated with estimating the moment-generating function in Jarzynski's equality. Leaving an explicit performance comparison for the future, we believe that the fast-growth approach exhibits a computational advantage over the escorted approach in settings where training-adapted data generation would be too expensive or done *ex silico*, or where simulation-free training would bypass insurmountable cost bottlenecks [54].

SUPPORTING INFORMATION

Mathematical derivation of the free-energy difference along a nonadiabatic alchemical transformation [Eq. (9)]; development of the entropy balance along a diffusive process [Eq. (11)]; justification of the loss function to train the nonadiabatic force [Eq. (14)]; derivation of the relative path density between backward and forward diffusive processes [Eq. (18)]; derivation of the backward and forward bounds on the free-energy difference [Eqs. (20) and (21)]; and proof that the free-energy bounds are saturated by the optimal nonadiabatic potential

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- [1] Alberi, K. et al. The 2019 materials by design roadmap. *Journal of Physics D: Applied Physics* **2019**, 52, 013001, DOI: <https://doi.org/10.1088/1361-6463/aad926>.
- [2] Sadybekov, A. V.; Katritch, V. Computational approaches streamlining drug discovery. *Nature* **2023**, 616, 673–685, DOI: <https://doi.org/10.1038/s41586-023-05905-z>.
- [3] York, D. M. Modern alchemical free energy methods for drug discovery explained. *ACS Physical Chemistry Au* **2023**, 3, 478–491, DOI: <https://doi.org/10.1021/acspyschemau.3c00033>.
- [4] Kirkwood, J. G. Statistical mechanics of fluid mixtures. *The Journal of Chemical Physics* **1935**, 3, 300–353, DOI: <https://doi.org/10.1063/1.1749657>.
- [5] Gobbo, G.; Ciccotti, G.; Trout, B. L. On computing the solubility of molecular systems subject to constraints using the extended Einstein crystal method. *The Journal of Chemical Physics* **2019**, 150, 201104, DOI: <https://doi.org/10.1063/1.5099378>.
- [6] Cournia, Z.; Allen, B.; Sherman, W. Relative binding free energy calculations in drug discovery: Recent advances and practical considerations. *Journal of Chemical Information and Modeling* **2017**, 57, 2911–2937, DOI: <https://doi.org/10.1021/acs.jcim.7b00564>.
- [7] Mey, A. S. J. S.; Allen, B. K.; Bruce McDonald, H. E.; Chodera, J. D.; Hahn, D. F.; Kuhn, M.; Michel, J.; Mobley, D. L.; Naden, L. N.; Prasad, S.; Rizzi, A.; Scheen, J.; Shirts, M. R.; Tresadern, G.; Xu, H. Best practices for alchemical free energy calculations [Article v1.0]. *Living Journal of Computational Molecular Science* **2020**, 2, 18378, DOI: <https://doi.org/10.33011/livecoms.2.1.18378>.
- [8] Jarzynski, C. Nonequilibrium Equality for Free Energy Differences. *Physical Review Letters* **1997**, 78, 2690–2693, DOI: <https://doi.org/10.1103/PhysRevLett.78.2690>.
- [9] Oberhofer, H.; Dellago, C.; Geissler, P. L. Biased sampling of nonequilibrium trajectories: Can fast switching simulations outperform conventional free energy calculation methods? *The Journal of Physical Chemistry B* **2005**, 109, 6902–6915, DOI: <https://doi.org/10.1021/jp044556a>.
- [10] Shirts, M. R.; Mobley, D. L.; Chodera, J. D. In *Alchemical free energy calculations: Ready for prime time?*; Spellmeyer, D., Wheeler, R., Eds.; Annual Reports in Computational Chemistry; Elsevier, 2007; Vol. 3; pp 41–59, DOI: [https://doi.org/10.1016/S1574-1400\(07\)03004-6](https://doi.org/10.1016/S1574-1400(07)03004-6).
- [11] Dellago, C.; Hummer, G. Computing Equilibrium Free Energies Using Non-Equilibrium Molecular Dynamics. *Entropy* **2014**, 16, 41–61, DOI: <https://doi.org/10.3390/e16010041>.
- [12] Wan, S.; Bhati, A. P.; Coveney, P. V. Comparison of equilibrium and nonequilibrium approaches for relative binding free energy predictions. *Journal of Chemical Theory and Computation* **2023**, 19, 7846–7860, DOI: <https://doi.org/10.1021/acs.jctc.3c00842>.
- [13] Jarzynski, C. Rare events and the convergence of exponentially averaged work values. *Physical Review E* **2006**, 73, 046105, DOI: <https://doi.org/10.1103/PhysRevE.73.046105>.
- [14] Ho, J.; Jain, A.; Abbeel, P. Denoising diffusion probabilistic models. Proceedings of the 34th International Conference on Neural Information Processing Systems. Red Hook, NY, 2020; pp 6840–6851, URL: <https://dl.acm.org/doi/abs/10.5555/3495724.3496298>.
- [15] Papamakarios, G.; Nalisnick, E.; Rezende, D. J.; Mohamed, S.; Lakshminarayanan, B. Normalizing flows for probabilistic modeling and inference. *Journal of Machine Learning Research* **2021**, 22, 2617–2680, URL: <https://dl.acm.org/doi/10.1103/PhysRevLett.78.2690>.

- abs/10.5555/3546258.3546315.
- [16] Albergo, M. S.; Boffi, N. M.; Vanden-Eijnden, E. Stochastic Interpolants: A unifying framework for flows and diffusions. arXiv (Computer Science), November 6, 2023; version 3, DOI: <https://doi.org/10.48550/arXiv.2303.08797>.
- [17] Vargas, F.; Padhy, S.; Blessing, D.; Nüsken, N. Transport meets variational inference: Controlled Monte Carlo diffusions. International Conference on Representation Learning. 2024; pp 55236–55278, URL: https://proceedings.iclr.cc/paper_files/paper/2024/file/f3716db40060004d0629d4051b2c57ab-Paper-Conference.pdf.
- [18] Noé, F.; Olsson, S.; Köhler, J.; Wu, H. Boltzmann generators: Sampling equilibrium states of many-body systems with deep learning. *Science* **2019**, *365*, eaaw1147, DOI: <https://doi.org/10.1126/science.aaw1147>.
- [19] Wirnsberger, P.; Ballard, A. J.; Papamakarios, G.; Abercrombie, S.; Racanière, S.; Pritzel, A.; Jimenez Rezende, D.; Blundell, C. Targeted free energy estimation via learned mappings. *The Journal of Chemical Physics* **2020**, *153*, 144112, DOI: <https://doi.org/10.1063/5.0018903>.
- [20] Zhao, L.; Wang, L. Bounding free energy difference with flow matching. *Chinese Physics Letters* **2023**, *40*, 120201, DOI: <https://doi.org/10.1088/0256-307X/40/12/120201>.
- [21] Zhong, A.; Kuznets-Speck, B.; DeWeese, M. R. Time-asymmetric fluctuation theorem and efficient free-energy estimation. *Physical Review E* **2024**, *110*, 034121, DOI: <https://doi.org/10.1103/PhysRevE.110.034121>.
- [22] Máté, B.; Fleuret, F.; Bereau, T. Neural thermodynamic integration: Free energies from energy-based diffusion models. *The Journal of Physical Chemistry Letters* **2024**, *15*, 11395–11404, DOI: <https://doi.org/10.1021/acs.jpcllett.4c01958>.
- [23] He, J.; Du, Y.; Vargas, F.; Wang, Y.; Gomes, C. P.; Hernández-Lobato, J. M.; Vanden-Eijnden, E. FEAT: Free energy estimators with adaptive transport. arXiv (Statistics), April 15, 2025; version 1, DOI: <https://doi.org/10.48550/arXiv.2504.11516>.
- [24] Liu, T.; Kaplan, A.; Alexander, L.; Yan, S.; Wen, J.-D.; Lancaster, L.; Wickersham, C. E.; Fredrick, K.; Noller, H.; Tinoco, J.; Ignacio; Bustamante, C. J. Direct measurement of the mechanical work during translocation by the ribosome. *eLife* **2014**, *3*, e03406, DOI: <https://doi.org/10.7554/eLife.03406.001>.
- [25] Ciliberto, S. Experiments in Stochastic Thermodynamics: Short History and Perspectives. *Physical Review X* **2017**, *7*, 021051, DOI: <https://doi.org/10.1103/PhysRevX.7.021051>.
- [26] Ross, D.; Strychalski, E. A.; Jarzynski, C.; Stavis, S. M. Equilibrium free energies from non-equilibrium trajectories with relaxation fluctuation spectroscopy. *Nature Physics* **2018**, *14*, 842–847, DOI: <https://doi.org/10.1038/s41567-018-0153-5>.
- [27] Bechhoefer, J.; Ciliberto, S.; Pigolotti, S.; Roldán, E. Stochastic thermodynamics: Experiment and theory. *Journal of Statistical Mechanics: Theory and Experiment* **2020**, *2020*, 064001, DOI: <https://doi.org/10.1088/1742-5468/ab7f35>.
- [28] Barker, D.; Scandi, M.; Lehmann, S.; Thelander, C.; Dick, K. A.; Perarnau-Llobet, M.; Maisi, V. F. Experimental verification of the work fluctuation-dissipation relation for information-to-work conversion. *Physical Review Letters* **2022**, *128*, 040602, DOI: <https://doi.org/10.1103/PhysRevLett.128.040602>.
- [29] Rosa-Raíces, J. L.; Limmer, D. T. Variational time reversal for free-energy estimation in nonequilibrium steady states. *Physical Review E* **2024**, *110*, 024120, DOI: <https://doi.org/10.1103/PhysRevE.110.024120>.
- [30] Song, Y.; Sohl-Dickstein, J.; Kingma, D. P.; Kumar, A.; Ermon, S.; Poole, B. Score-based generative modeling through stochastic differential equations. arXiv (Computer Science), February 10, 2021; Version 2, DOI: <https://doi.org/10.48550/arXiv.2011.13456>.
- [31] Limmer, D. T. *Statistical mechanics and stochastic thermodynamics: A textbook on modern approaches in and out of equilibrium*, 1st ed.; Oxford University Press, 2024; DOI: <https://doi.org/10.1093/oso/9780198919858.001.0001>.
- [32] Seifert, U. *Stochastic Thermodynamics*, 1st ed.; Cambridge University Press, 2025; DOI: <https://doi.org/10.1017/9781009024358>.
- [33] Sivak, D. A.; Crooks, G. E. Near-equilibrium measurements of nonequilibrium free energy. *Physical Review Letters* **2012**, *108*, 150601, DOI: <https://doi.org/10.1103/PhysRevLett.108.150601>.
- [34] Esposito, M.; Van den Broeck, C. Second law and Landauer principle far from equilibrium. *Europhysics Letters* **2011**, *95*, 40004, DOI: <https://doi.org/10.1209/0295-5075/95/40004>.
- [35] Seifert, U. Entropy Production along a Stochastic Trajectory and an Integral Fluctuation Theorem. *Physical Review Letters* **2005**, *95*, 040602, DOI: <https://doi.org/10.1103/PhysRevLett.95.040602>.
- [36] Muratore-Ginanneschi, P.; Schwieger, K. An application of Pontryagin’s principle to Brownian particle engineered equilibration. *Entropy* **2017**, *19*, 1, DOI: <https://doi.org/10.3390/e19070379>.
- [37] Song, Y.; Durkan, C.; Murray, I.; Ermon, S. Maximum likelihood training of score-based diffusion models. Advances in Neural Information Processing Systems. 2021; pp 1415–1428, URL: https://proceedings.neurips.cc/paper_files/paper/2021/file/0a9fddb17feb6ccb7ec405cfb85222c4-Paper.pdf.
- [38] Hartmann, C.; Richter, L.; Schütte, C.; Zhang, W. Variational characterization of free energy: Theory and algorithms. *Entropy* **2017**, *19*, 626, DOI: <https://doi.org/10.3390/e19110626>.
- [39] Das, A.; Rose, D. C.; Garrahan, J. P.; Limmer, D. T. Reinforcement learning of rare diffusive dynamics. *The Journal of Chemical Physics* **2021**, *155*, 134105, DOI: <https://doi.org/10.1063/5.0057323>.
- [40] Kloeden, P. E.; Platen, E. *Numerical solution of stochastic differential equations*, 1st ed.; Springer Berlin, Heidelberg, 1992; DOI: <https://doi.org/10.1007/978-3-662-12616-5>.
- [41] Widom, B. Some topics in the theory of fluids. *The Journal of Chemical Physics* **1963**, *39*, 2808–2812, DOI: <https://doi.org/10.1063/1.1734110>.
- [42] Crooks, G. E.; Chandler, D. Gaussian statistics of the hard-sphere fluid. *Physical Review E* **1997**, *56*, 4217–4221, DOI: <https://doi.org/10.1103/PhysRevE.56.4217>.
- [43] Behler, J.; Parrinello, M. Generalized neural-network representation of high-dimensional potential-energy surfaces. *Physical Review Letters* **2007**, *98*, 146401, DOI: <https://doi.org/10.1103/PhysRevLett.98.146401>.
- [44] Behler, J. Atom-centered symmetry functions for constructing high-dimensional neural network potentials. *The Journal of Chemical Physics* **2011**, *134*, 074106, DOI: <https://doi.org/10.1063/1.3553717>.
- [45] Clevert, D.-A.; Unterthiner, T.; Hochreiter, S. Fast and accurate deep network learning by exponential linear units (ELUs). arXiv (Computer Science), February 22, 2016; Version 5, DOI: <https://doi.org/10.48550/arXiv.1511.07289>.

- [46] Kingma, D. P.; Ba, J. Adam: A Method for Stochastic Optimization. arXiv (Computer Science), January 30, 2017; Version 9, DOI: <https://doi.org/10.48550/arXiv.1412.6980>.
- [47] Vega, C.; Noya, E. G. Revisiting the Frenkel–Ladd method to compute the free energy of solids: The Einstein molecule approach. *The Journal of Chemical Physics* **2007**, *127*, 154113, DOI: <https://doi.org/10.1063/1.2790426>.
- [48] Frenkel, D.; Ladd, A. J. C. New Monte Carlo method to compute the free energy of arbitrary solids: Application to the FCC and HCP phases of hard spheres. *The Journal of Chemical Physics* **1984**, *81*, 3188–3193, DOI: <https://doi.org/10.1063/1.448024>.
- [49] Frenkel, D.; Smit, B. *Understanding molecular simulation: From algorithms to applications*, 2nd ed.; Academic Press, Inc., 2002; DOI: <https://doi.org/10.1016/B978-0-12-267351-1.X5000-7>.
- [50] Máté, B.; Fleuret, F.; Bereau, T. Solvation free energies from neural thermodynamic integration. *The Journal of Chemical Physics* **2025**, *162*, 124107, DOI: <https://doi.org/10.1063/5.0251736>.
- [51] He, J.; Hernández-Lobato, J. M.; Du, Y.; Vargas, F. RNE: A plug-and-play framework for diffusion density estimation and inference-time control. arXiv (Computer Science), June 15, 2025; version 3, DOI: <https://doi.org/10.48550/arXiv.2506.05668>.
- [52] Vaikuntanathan, S.; Jarzynski, C. Escorted free energy simulations: Improving convergence by reducing dissipation. *Physical Review Letters* **2008**, *100*, 190601, DOI: <https://doi.org/10.1103/PhysRevLett.100.190601>.
- [53] Hummer, G. Fast-growth thermodynamic integration: Error and efficiency analysis. *The Journal of Chemical Physics* **2001**, *114*, 7330–7337, DOI: <https://doi.org/10.1063/1.1363668>.
- [54] He, J.; Du, Y.; Vargas, F.; Zhang, D.; Padhy, S.; OuYang, R.; Gomes, C.; Hernández-Lobato, J. M. No trick, no treat: Pursuits and challenges towards simulation-free training of neural samplers. arXiv (Computer Science), April 9, 2025; version 2, DOI: <https://doi.org/10.48550/arXiv.2502.06685>.

Supporting Information: *Nonadiabatic force matching*
for alchemical free-energy estimation

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This document supplements the Main Text with mathematical derivations of results presented therein. Reference to the following sections are placed at the relevant locations in the Main Text.

I. FREE-ENERGY DIFFERENCE ALONG A NONADIABATIC ALCHEMICAL TRANSFORMATION

Here, we provide a detailed derivation of Eq. (9) of the main text, which corresponds to the Helmholtz free-energy difference accrued along a nonadiabatic alchemical transformation. Starting from the first law of thermodynamics as stated in Eq. (7) of the main text, we compute:

$$\begin{aligned} \Delta U &\equiv \langle U(\mathbf{x}_\tau, \lambda(\tau)) - U(\mathbf{x}_0, \lambda(0)) \rangle \\ &= F(\lambda(\tau)) - F(\lambda(0)) - \beta^{-1} \langle \ln \pi(\mathbf{x}_0, \lambda(0)) - \ln \pi(\mathbf{x}_\tau, \lambda(\tau)) \rangle \end{aligned} \quad (\text{S1a})$$

$$\equiv \Delta F - \beta^{-1} \langle \ln \pi(\mathbf{x}_0, \lambda_A) - \ln \pi(\mathbf{x}_\tau, \lambda_B) \rangle \quad (\text{S1b})$$

$$\begin{aligned} &= \Delta F - \beta^{-1} \left[\langle \ln \rho(\mathbf{x}_0, 0) - \ln \rho(\mathbf{x}_\tau, \tau) \rangle + \left\langle \ln \frac{\rho(\mathbf{x}_\tau, \tau)}{\pi(\mathbf{x}_\tau, \lambda(\tau))} \right\rangle \right] \\ &\equiv \Delta F - \beta^{-1} [\Delta S + D_{\text{KL}}(\tau)] \end{aligned} \quad (\text{S1c})$$

where we rearranged the equilibrium density $\pi(\mathbf{x}, \lambda)$ introduced in Eq. (1) of the main text to obtain the second equality [Eq. (S1a)]; the definition $\Delta F \equiv F(\lambda(\tau)) - F(\lambda(0))$ along with the protocol boundary values $\lambda(t=0) \equiv \lambda_A$ and $\lambda(t=\tau) \equiv \lambda_B$ to obtain the third equality [Eq. (S1b)]; and the definitions of ΔS and $D_{\text{KL}}(\tau)$ stated in the main text, namely

$$\Delta S \equiv \left\langle -\ln \frac{\rho(\mathbf{x}_\tau, \tau)}{\rho(\mathbf{x}_0, 0)} \right\rangle \quad \text{and} \quad D_{\text{KL}}(\tau) \equiv \left\langle \ln \frac{\rho(\mathbf{x}_\tau, \tau)}{\pi(\mathbf{x}_\tau, \lambda(\tau))} \right\rangle \quad (\text{S2})$$

to finally obtain Eq. (S1c), which is the Helmholtz free-energy difference in Eq. (9) of the main text.

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II. ENTROPY BALANCE ALONG A DIFFUSIVE PROCESS

Here we derive Eq. (11) of the main text, which clarifies the dynamics of entropy production along a diffusive process that is driven by an implicit bath at constant temperature. To begin, we note that the entropy change ΔS defined in Eq. (S2) can be expanded into

$$\Delta S = \left\langle - \int_0^\tau d \ln \rho(\mathbf{x}_t, t) \right\rangle = \left\langle - \int_0^\tau dt \partial_t \ln \rho(\mathbf{x}, t) \right\rangle + \left\langle - \int_0^\tau d\mathbf{x}_t \circ \nabla \ln \rho(\mathbf{x}_t, t) \right\rangle \quad (\text{S3})$$

where we used the *Stratonovich chain rule* (see, e.g., Proposition 3.4 in Ref. 1) to expand an integral along the total differential $d \ln \rho(\mathbf{x}_t, t)$ into a deterministic and a (Stratonovich) stochastic integral. The deterministic integral vanishes upon an application of Leibniz's integral rule,

$$\begin{aligned} \left\langle \int_0^\tau dt \partial_t \ln \rho(\mathbf{x}_t, t) \right\rangle &= \int_0^\tau dt \langle \partial_t \ln \rho(\mathbf{x}_t, t) \rangle = \int_0^\tau dt \int d\mathbf{x} \rho(\mathbf{x}, t) \partial_t \ln \rho(\mathbf{x}, t) \\ &= \int_0^\tau dt \int d\mathbf{x} \partial_t \rho(\mathbf{x}, t) = \int_0^\tau dt \left[\frac{d}{dt} \int d\mathbf{x} \rho(\mathbf{x}, t) \right] \\ &= \int_0^\tau dt \left[\frac{d}{dt} \text{const.} \right] = 0 \end{aligned} \quad (\text{S4})$$

where the third equality follows from our assumption that the probability density $\rho(\mathbf{x}, t)$ is positive for all \mathbf{x} at each time $t \in [0, \tau]$, and the penultimate equality follows from the fact that probability is conserved along the diffusive process. The stochastic integral in Eq. (S3) is rendered deterministic by the equality

$$\left\langle \int_0^\tau d\mathbf{x}_t \circ \mathbf{f}(\mathbf{x}_t, t) \right\rangle = \left\langle \int_0^\tau dt D \nabla V(\mathbf{x}_t, t) \cdot \mathbf{f}(\mathbf{x}_t, t) \right\rangle \quad (\text{S5})$$

with $V(\mathbf{x}, t)$ the *nonadiabatic potential* defined in Eq. (6) of the main text. This equality is valid for any sufficiently smooth vector-valued function \mathbf{f} , and is derived in Sec. III of this document. Using Eq. (S5), we rewrite the second term on the right-hand side of Eq. (S3) as

$$\left\langle - \int_0^\tau d\mathbf{x}_t \circ \nabla \ln \rho(\mathbf{x}_t, t) \right\rangle = \left\langle - \int_0^\tau dt D \nabla V(\mathbf{x}_t, t) \cdot \nabla \ln \rho(\mathbf{x}_t, t) \right\rangle \quad (\text{S6a})$$

$$\begin{aligned} &= \left\langle \int_0^\tau dt D \nabla V(\mathbf{x}_t, t) \cdot [\nabla V(\mathbf{x}_t, t) - \nabla \ln \pi(\mathbf{x}_t, \lambda(t))] \right\rangle \\ &= \left\langle \int_0^\tau dt D |\nabla V(\mathbf{x}_t, t)|^2 \right\rangle + \beta \left\langle \int_0^\tau dt D \nabla V(\mathbf{x}_t, t) \cdot \nabla U(\mathbf{x}_t, t) \right\rangle \\ &= \left\langle \int_0^\tau dt D |\nabla V(\mathbf{x}_t, t)|^2 \right\rangle - \beta \left\langle - \int_0^\tau d\mathbf{x}_t \circ \nabla U(\mathbf{x}_t, t) \right\rangle \end{aligned} \quad (\text{S6b})$$

$$\equiv \left\langle \int_0^\tau dt D |\nabla V(\mathbf{x}_t, t)|^2 \right\rangle - \beta \langle \mathcal{Q}_\tau \rangle \quad (\text{S6c})$$

where we used Eq. (S5) in the first equality [Eq. (S6a)] and again in the third equality [Eq. (S6b)], and where we inserted the definition of the *heat*, introduced in Eq. (8b) of the main text, into the last equality [Eq. (S6c)]. Summing the results in Eqs. (S4) and (S6) finally yields Eq. (11) of the main text.

III. LOSS FUNCTION FOR THE NONADIABATIC FORCE

In this section, we show that the loss function $\ell(\theta)$, introduced in Eq. (14) of the main text to train the nonadiabatic force ansatz ∇V_θ , is equivalent to the mean-squared-error (MSE) loss function

$$\begin{aligned}\ell_{\text{MSE}}(\theta) &\equiv \left\langle \int_0^\tau dt D |\nabla V_\theta(\mathbf{x}_t, t) - \nabla V(\mathbf{x}_t, t)|^2 \right\rangle \\ &= \left\langle \int_0^\tau dt D |\nabla V_\theta(\mathbf{x}_t, t)|^2 - 2D \nabla V(\mathbf{x}_t, t) \cdot \nabla V_\theta(\mathbf{x}_t, t) \right\rangle + \text{const.}\end{aligned}\quad (\text{S7})$$

where ∇V is the exact nonadiabatic force introduced in Eq. (5) of the main text. To demonstrate equivalence between $\ell(\theta)$ and $\ell_{\text{MSE}}(\theta)$, it is sufficient to show that the cross-terms in both losses are identical; this amounts to proving the equality in Eq. (S5). We apply the *Stratonovich-to-Itô conversion* (a corollary of *Itô's lemma*; see, e.g., Lemma 3.2 from Ref. 1) to the integrand in the left-hand side of Eq. (S5), obtaining

$$\int_0^\tau d\mathbf{x}_t \circ \mathbf{f}(\mathbf{x}_t, t) = \int_0^\tau d\mathbf{x}_t \cdot \mathbf{f}(\mathbf{x}_t, t) + \int_0^\tau dt \nabla \cdot [D \mathbf{f}(\mathbf{x}_t, t)] \quad (\text{S8})$$

where the first term on the right-hand side is an Itô stochastic integral against the process specified by Eq. (4) of the main text. Using this equation, we rewrite the right-hand side of Eq. (S5) as

$$\begin{aligned}\left\langle \int_0^\tau d\mathbf{x}_t \cdot \mathbf{f}(\mathbf{x}_t, t) \right\rangle &= \left\langle - \int_0^\tau dt D \beta \nabla U(\mathbf{x}_t, t) \cdot \mathbf{f}(\mathbf{x}_t, t) \right\rangle + \left\langle \int_0^\tau \sqrt{2D} d\mathbf{w}_t \cdot \mathbf{f}(\mathbf{x}_t, t) \right\rangle \\ &\equiv \left\langle \int_0^\tau dt D \nabla \ln \pi(\mathbf{x}_t, \lambda(t)) \cdot \mathbf{f}(\mathbf{x}_t, t) \right\rangle\end{aligned}\quad (\text{S9})$$

Here, the second term in the right-hand side of the first equality vanishes due to the non-anticipative property of $\{\mathbf{x}_t\}_{t=0}^\tau$ and the zero-mean property of the Wiener process $\{\mathbf{w}_t\}_{t=0}^\tau$. The second term on the right-hand side of Eq. (S8) can be brought to a similar form,

$$\begin{aligned}\left\langle \int_0^\tau dt \nabla \cdot [D \mathbf{f}(\mathbf{x}_t, t)] \right\rangle &= \int_0^\tau dt \int d\mathbf{x} \rho(\mathbf{x}, t) \nabla \cdot [D \mathbf{f}(\mathbf{x}, t)] \\ &= \int_0^\tau dt \left[- \int d\mathbf{x} D \nabla \rho(\mathbf{x}, t) \cdot \mathbf{f}(\mathbf{x}, t) \right] \\ &= \left\langle - \int_0^\tau dt D \nabla \ln \rho(\mathbf{x}_t, t) \cdot \mathbf{f}(\mathbf{x}_t, t) \right\rangle\end{aligned}\quad (\text{S10})$$

where the second equality is obtained upon integrating by parts in the configurational variable while assuming vanishing surface terms. Substituting Eqs. (S9) and (S10) into Eq. (S8) finally yields

$$\begin{aligned}\left\langle \int_0^\tau d\mathbf{x}_t \circ \mathbf{f}(\mathbf{x}_t, t) \right\rangle &= \left\langle - \int_0^\tau dt D \nabla \ln \frac{\rho(\mathbf{x}_t, t)}{\pi(\mathbf{x}_t, \lambda(t))} \cdot \mathbf{f}(\mathbf{x}_t, t) \right\rangle \\ &\equiv \left\langle \int_0^\tau dt D \nabla V(\mathbf{x}_t, t) \cdot \mathbf{f}(\mathbf{x}_t, t) \right\rangle\end{aligned}\quad (\text{S11})$$

where Eq. (S5) is recovered in the second equality per the definition of the nonadiabatic potential.

IV. RELATION BETWEEN THE FORWARD AND BACKWARD PROCESSES

In this section, we derive the likelihood ratio in Eq. (18) between the forward and backward processes specified by Eq. (4) and Eq. (16) of the main text. We split our work into three subsections. In Sec. IV A, we identify the time-reversed process that the backward process seeks to approximate. In Sec. IV B, we provide a detailed derivation of the likelihood ratio for a backward process with a general nonadiabatic potential ansatz. In Sec. IV C, we show that the likelihood ratio reduces to unity for almost all configurational trajectories when the backward process is endowed with an optimal nonadiabatic potential.

A. The forward process and its time-reversal

In this subsection, we re-introduce the forward process alongside its time-reversal, and we derive relations between the two that clarify the role of the backward process as established in later subsections. At times $t \in [0, \tau]$, the forward process and its time-reversal respectively obey

$$d\mathbf{x}_t = -\beta D \nabla U(\mathbf{x}_t, \lambda(t)) dt + \sqrt{2D} d\mathbf{w}_t \quad \text{and} \quad d\mathbf{x}_t = \beta D \nabla U(\mathbf{x}_t, \lambda(\tau-t)) dt + \sqrt{2D} \odot d\bar{\mathbf{w}}_t \quad (\text{S12})$$

with initial configurations \mathbf{x}_0 respectively drawn from the distributions with densities $\pi(\cdot, \lambda(0))$ and $\rho(\cdot, \tau)$. The symbol \odot indicates that the backward process should be interpreted in the *anti-Itô* sense [2, Section 2.7], and $\{\bar{\mathbf{w}}_t\}_{t=0}^\tau \equiv \{\mathbf{w}_t - \mathbf{w}_\tau\}_{t=0}^\tau$ is a time-reversed Wiener process. The forward process and its time-reversal each induce a probability measure, respectively denoted by $\mathbb{P}_\tau^\rightarrow$ and $\mathbb{P}_\tau^\leftarrow$, on the space of configurational trajectories.

By the Girsanov theorem [3, Theorem 8.6.6], the forward process and its time-reversal each have a relative density with respect to a corresponding *driftless* process (i.e., a process with $U \equiv 0$) endowed with the same initial condition. Along a trajectory $X \equiv \{\mathbf{x}_t\}_{t=0}^\tau$, the density of the forward process relative to its driftless counterpart is

$$\frac{d\mathbb{P}_\tau^\rightarrow[X]}{d\mathbb{P}_{\tau,0}^\rightarrow[X]} = \exp \left[-\frac{1}{4} \int_0^\tau D |\beta \nabla U(\mathbf{x}_t, \lambda(t))|^2 dt + 2\beta \nabla U(\mathbf{x}_t, \lambda(t)) \cdot d\mathbf{x}_t \right] \quad (\text{S13})$$

and, for the time-reversed process, we have

$$\frac{d\mathbb{P}_\tau^\leftarrow[X]}{d\mathbb{P}_{\tau,0}^\leftarrow[X]} = \exp \left[-\frac{1}{4} \int_0^\tau D |\beta \nabla U(\mathbf{x}_t, \lambda(\tau-t))|^2 dt - 2\beta \nabla U(\mathbf{x}_t, \lambda(\tau-t)) \odot d\mathbf{x}_t \right] \quad (\text{S14})$$

where $\mathbb{P}_{\tau,0}^\rightarrow$ and $\mathbb{P}_{\tau,0}^\leftarrow$ denote the probability measures induced by the respective driftless processes. Furthermore, the driftless processes are reversible with respect to one another, in the sense that the average of a test observable $\mathcal{O}_\tau[X]$ satisfies

$$\langle \mathcal{O}_\tau[X] \rangle_{\mathbb{P}_{\tau,0}^\rightarrow} \equiv \left\langle \mathcal{O}_\tau[RX] \frac{d\mathbb{P}_{\tau,0}^\rightarrow[RX]}{d\mathbb{P}_{\tau,0}^\leftarrow[X]} \right\rangle_{\mathbb{P}_{\tau,0}^\leftarrow} \quad \text{and} \quad \langle \mathcal{O}_\tau[X] \rangle_{\mathbb{P}_{\tau,0}^\leftarrow} \equiv \left\langle \mathcal{O}_\tau[RX] \frac{d\mathbb{P}_{\tau,0}^\leftarrow[RX]}{d\mathbb{P}_{\tau,0}^\rightarrow[X]} \right\rangle_{\mathbb{P}_{\tau,0}^\rightarrow} \quad (\text{S15})$$

where the subscript of each angled bracket indicates the process under which the average is taken, R is an involution that reverses a trajectory in time as $R\mathbf{X} \equiv \{\mathbf{x}_{\tau-t}\}_{t=0}^\tau$, and we introduced the likelihood ratios

$$\frac{d\mathbb{P}_{\tau,0}^{\rightarrow}[\mathbf{RX}]}{d\mathbb{P}_{\tau,0}^{\leftarrow}[\mathbf{X}]} \equiv \frac{\pi(\mathbf{x}_\tau, \lambda(0))}{\rho(\mathbf{x}_0, \tau)} \quad \text{and} \quad \frac{d\mathbb{P}_{\tau,0}^{\leftarrow}[\mathbf{RX}]}{d\mathbb{P}_{\tau,0}^{\rightarrow}[\mathbf{X}]} \equiv \frac{\rho(\mathbf{x}_\tau, \tau)}{\pi(\mathbf{x}_0, \lambda(0))} \quad (\text{S16})$$

of a trajectory and its time-reversal along the driftless processes.

The time-reversal equivalence between driftless processes in Eq. (S15) extends to the processes in Eq. (S12) due to a time-reversal symmetry of their respective densities. To introduce it, note that for almost every trajectory $\{\mathbf{x}_t\}_{t=0}^\tau$, the Itô integral of the vector-valued map $t \mapsto \mathbf{f}(\mathbf{x}_t, t)$ transforms under time-reversal of the trajectory according to the rule

$$\int_0^\tau d\mathbf{x}_t \cdot \mathbf{f}(\mathbf{x}_t, t) \xrightarrow{\{\mathbf{x}_t\}_{t=0}^\tau \rightarrow \{\mathbf{x}_{\tau-t}\}_{t=0}^\tau} - \int_0^\tau d\mathbf{x}_t \odot \mathbf{f}(\mathbf{x}_t, \tau-t) \quad (\text{S17})$$

Applying this rule to Eqs. (S13) and (S14) reveals the time-reversal symmetries

$$\frac{d\mathbb{P}_{\tau}^{\leftarrow}[\mathbf{RX}]}{d\mathbb{P}_{\tau,0}^{\leftarrow}[\mathbf{RX}]} = \frac{d\mathbb{P}_{\tau}^{\rightarrow}[\mathbf{X}]}{d\mathbb{P}_{\tau,0}^{\rightarrow}[\mathbf{X}]} \quad \text{and} \quad \frac{d\mathbb{P}_{\tau}^{\rightarrow}[\mathbf{RX}]}{d\mathbb{P}_{\tau,0}^{\rightarrow}[\mathbf{RX}]} = \frac{d\mathbb{P}_{\tau}^{\leftarrow}[\mathbf{X}]}{d\mathbb{P}_{\tau,0}^{\leftarrow}[\mathbf{X}]} \quad (\text{S18})$$

which allow converting between forward and time-reversed processes when evaluating expectation values. Indeed, the expectation value of a test observable $\mathcal{O}_\tau[\mathbf{X}]$ along the forward process is

$$\begin{aligned} \langle \mathcal{O}_\tau[\mathbf{X}] \rangle_{\mathbb{P}_{\tau}^{\rightarrow}} &= \left\langle \mathcal{O}_\tau[\mathbf{X}] \frac{d\mathbb{P}_{\tau}^{\rightarrow}[\mathbf{X}]}{d\mathbb{P}_{\tau,0}^{\rightarrow}[\mathbf{X}]} \right\rangle_{\mathbb{P}_{\tau,0}^{\rightarrow}} \\ &\equiv \left\langle \mathcal{O}_\tau[\mathbf{RX}] \frac{d\mathbb{P}_{\tau}^{\rightarrow}[\mathbf{RX}]}{d\mathbb{P}_{\tau,0}^{\rightarrow}[\mathbf{RX}]} \frac{d\mathbb{P}_{\tau,0}^{\leftarrow}[\mathbf{RX}]}{d\mathbb{P}_{\tau,0}^{\rightarrow}[\mathbf{X}]} \right\rangle_{\mathbb{P}_{\tau,0}^{\leftarrow}} \end{aligned} \quad (\text{S19a})$$

$$\begin{aligned} &= \left\langle \mathcal{O}_\tau[\mathbf{RX}] \frac{d\mathbb{P}_{\tau}^{\rightarrow}[\mathbf{RX}]}{d\mathbb{P}_{\tau,0}^{\rightarrow}[\mathbf{RX}]} \frac{d\mathbb{P}_{\tau,0}^{\leftarrow}[\mathbf{RX}]}{d\mathbb{P}_{\tau,0}^{\rightarrow}[\mathbf{X}]} \frac{d\mathbb{P}_{\tau,0}^{\leftarrow}[\mathbf{X}]}{d\mathbb{P}_{\tau}^{\leftarrow}[\mathbf{X}]} \right\rangle_{\mathbb{P}_{\tau}^{\leftarrow}} \\ &\equiv \left\langle \mathcal{O}_\tau[\mathbf{RX}] \frac{d\mathbb{P}_{\tau}^{\rightarrow}[\mathbf{RX}]}{d\mathbb{P}_{\tau}^{\leftarrow}[\mathbf{X}]} \right\rangle_{\mathbb{P}_{\tau}^{\leftarrow}} \end{aligned} \quad (\text{S19b})$$

where the second equality [Eq. (S19a)] uses Eq. (S15) and the last equality [Eq. (S19b)] defines the time-reversal likelihood ratio

$$\frac{d\mathbb{P}_{\tau}^{\rightarrow}[\mathbf{RX}]}{d\mathbb{P}_{\tau}^{\leftarrow}[\mathbf{X}]} \equiv \frac{d\mathbb{P}_{\tau}^{\rightarrow}[\mathbf{RX}]}{d\mathbb{P}_{\tau,0}^{\rightarrow}[\mathbf{RX}]} \frac{d\mathbb{P}_{\tau,0}^{\rightarrow}[\mathbf{RX}]}{d\mathbb{P}_{\tau,0}^{\leftarrow}[\mathbf{X}]} \frac{d\mathbb{P}_{\tau,0}^{\leftarrow}[\mathbf{X}]}{d\mathbb{P}_{\tau}^{\leftarrow}[\mathbf{X}]} = \frac{\pi(\mathbf{x}_\tau, \lambda(0))}{\rho(\mathbf{x}_0, \tau)} \quad (\text{S20})$$

with \mathbf{X} a realization of the time-reversed process. A similar derivation obtains

$$\frac{d\mathbb{P}_{\tau}^{\leftarrow}[\mathbf{RX}]}{d\mathbb{P}_{\tau}^{\rightarrow}[\mathbf{X}]} \equiv \frac{d\mathbb{P}_{\tau}^{\leftarrow}[\mathbf{RX}]}{d\mathbb{P}_{\tau,0}^{\leftarrow}[\mathbf{RX}]} \frac{d\mathbb{P}_{\tau,0}^{\leftarrow}[\mathbf{RX}]}{d\mathbb{P}_{\tau,0}^{\rightarrow}[\mathbf{X}]} \frac{d\mathbb{P}_{\tau,0}^{\rightarrow}[\mathbf{X}]}{d\mathbb{P}_{\tau}^{\rightarrow}[\mathbf{X}]} = \frac{\rho(\mathbf{x}_\tau, \tau)}{\pi(\mathbf{x}_0, \lambda(0))} \quad (\text{S21})$$

with \mathbf{X} a realization of the forward process.

It is notable that the above likelihood ratios are independent of most details of a trajectory, essentially amounting to a reweighing of its endpoints. The same property is shared by the likelihood of a trajectory along a given driftless process relative to its time-reversal along the same process, which takes the form

$$\frac{d\mathbb{P}_{\tau,0}^{\rightarrow}[\mathbf{RX}]}{d\mathbb{P}_{\tau,0}^{\rightarrow}[\mathbf{X}]} = \frac{\pi(\mathbf{x}_{\tau}, \lambda(0))}{\pi(\mathbf{x}_0, \lambda(0))} \quad \text{and} \quad \frac{d\mathbb{P}_{\tau,0}^{\leftarrow}[\mathbf{RX}]}{d\mathbb{P}_{\tau,0}^{\leftarrow}[\mathbf{X}]} = \frac{\rho(\mathbf{x}_{\tau}, \tau)}{\rho(\mathbf{x}_0, \tau)} \quad (\text{S22})$$

and will prove useful in the following subsections.

B. The forward-backward likelihood ratio

In this subsection, we re-introduce the backward process, originally introduced in Eq. (16) of the main text, as a parametric approximation of the reverse-time process from the previous subsection. Recall that the backward process obeys

$$d\mathbf{x}_t = -D[\beta\nabla U(\mathbf{x}_t, \lambda(\tau-t)) + 2\nabla V_{\theta}(\mathbf{x}_t, \tau-t)] dt + \sqrt{2D} dw_t \quad \text{for } t \in [0, \tau] \quad (\text{S23})$$

with initial configuration \mathbf{x}_0 drawn from the distribution with density $\rho(\cdot, \tau)$. Like the forward process and its time-reversal, the backward process induces a path measure $\mathbb{P}_{\tau,\theta}$ on the space of configurational trajectories. Given any such trajectory $\mathbf{X} \equiv \{\mathbf{x}_t\}_{t=0}^{\tau}$, we seek an expression for its likelihood along the backward process relative to that of its time-reversal $\mathbf{RX} \equiv \{\mathbf{x}_{\tau-t}\}_{t=0}^{\tau}$ along the forward process. This forward-backward likelihood ratio may be defined as

$$\frac{d\mathbb{P}_{\tau}[\{\mathbf{x}_{\tau-t}\}_{t=0}^{\tau}]}{d\mathbb{P}_{\tau,\theta}[\{\mathbf{x}_t\}_{t=0}^{\tau}]} \equiv \frac{d\mathbb{P}_{\tau}^{\rightarrow}[\mathbf{RX}]}{d\mathbb{P}_{\tau,0}^{\rightarrow}[\mathbf{X}]} \frac{d\mathbb{P}_{\tau,0}^{\rightarrow}[\mathbf{X}]}{d\mathbb{P}_{\tau,\theta}[\mathbf{X}]} \quad (\text{S24})$$

where the first factor on the right-hand side, which is the likelihood of the time-reversed trajectory \mathbf{RX} under the forward process, reduces to

$$\frac{d\mathbb{P}_{\tau}^{\rightarrow}[\mathbf{RX}]}{d\mathbb{P}_{\tau,0}^{\rightarrow}[\mathbf{X}]} \equiv \frac{d\mathbb{P}_{\tau,0}^{\rightarrow}[\mathbf{RX}]}{d\mathbb{P}_{\tau,0}^{\rightarrow}[\mathbf{X}]} \frac{d\mathbb{P}_{\tau}^{\rightarrow}[\mathbf{RX}]}{d\mathbb{P}_{\tau,0}^{\rightarrow}[\mathbf{RX}]} = \frac{\pi(\mathbf{x}_{\tau}, \lambda(0))}{\pi(\mathbf{x}_0, \lambda(0))} \frac{d\mathbb{P}_{\tau}^{\leftarrow}[\mathbf{X}]}{d\mathbb{P}_{\tau,0}^{\leftarrow}[\mathbf{X}]} \quad (\text{S25})$$

by using Eqs. (S15) and (S22). The second factor on the right-hand side of Eq. (S24), which corresponds to the likelihood of the trajectory \mathbf{X} along the backward process, is

$$\begin{aligned} \frac{d\mathbb{P}_{\tau,0}^{\rightarrow}[\mathbf{X}]}{d\mathbb{P}_{\tau,\theta}[\mathbf{X}]} &= \frac{\pi(\mathbf{x}_0, \lambda(0))}{\pi(\mathbf{x}_{\tau}, \lambda(0))} \frac{\pi(\mathbf{x}_{\tau}, \lambda(0))}{\rho(\mathbf{x}_0, \tau)} \\ &\times \exp \left[\int_0^{\tau} D [|\nabla V_{\theta}(\mathbf{x}_t, \tau-t)|^2 + \beta\nabla U(\mathbf{x}_t, \lambda(\tau-t)) \cdot \nabla V_{\theta}(\mathbf{x}_t, \tau-t)] dt + \nabla V_{\theta}(\mathbf{x}_t, \tau-t) \cdot d\mathbf{x}_t \right] \\ &\times \exp \left[\frac{1}{4} \int_0^{\tau} D |\beta\nabla U(\mathbf{x}_t, \lambda(\tau-t))|^2 dt + 2\beta\nabla U(\mathbf{x}_t, \lambda(\tau-t)) \cdot d\mathbf{x}_t \right] \end{aligned} \quad (\text{S26})$$

obtained by direct application of Girsanov's formula [3, Theorem 8.6.6]. The three factors on the right-hand side, one on each line, can be simplified with the following manipulations:

First factor— Rewrite the second term of the first factor in Eq. (S26) as

$$\begin{aligned} \frac{\pi(\mathbf{x}_\tau, \lambda(0))}{\rho(\mathbf{x}_0, \tau)} &= \frac{\pi(\mathbf{x}_0, \lambda(\tau))}{\rho(\mathbf{x}_0, \tau)} \frac{\pi(\mathbf{x}_\tau, \lambda(0))}{\pi(\mathbf{x}_0, \lambda(\tau))} \\ &= \exp\left[-\ln \frac{\rho(\mathbf{x}_0, \tau)}{\pi(\mathbf{x}_0, \lambda(\tau))} + \ln \frac{\pi(\mathbf{x}_\tau, \lambda(0))}{\pi(\mathbf{x}_0, \lambda(\tau))}\right] \\ &\equiv \exp\left[V(\mathbf{x}_0, \tau) + \int_0^\tau d \ln \pi(\mathbf{x}_t, \lambda(\tau-t))\right] \end{aligned} \quad (\text{S27a})$$

$$= \exp\left[V(\mathbf{x}_0, \tau) - \beta \Delta F - \beta \int_0^\tau \nabla U(\mathbf{x}_t, \lambda(\tau-t)) \circ d\mathbf{x}_t + \partial_t U(\mathbf{x}_t, \lambda(\tau-t)) dt\right] \quad (\text{S27b})$$

$$\equiv \exp[-\beta(\overline{W}_\tau + \Delta F) + V(\mathbf{x}_0, \tau) + \beta \overline{Q}_\tau] \quad (\text{S27c})$$

Here, Eq. (S27a) introduced the definition of the nonadiabatic potential, Eq. (S27b) used the Stratonovich chain rule to expand the differential $d \ln \pi(\mathbf{x}_t, \lambda(\tau-t))$ along the trajectory \mathbf{X} , and Eq. (S27c) introduced the reverse-time heat and work, which are

$$\overline{Q}_\tau \equiv - \int_0^\tau \nabla U(\mathbf{x}_t, \lambda(\tau-t)) \circ d\mathbf{x}_t \quad \text{and} \quad \overline{W}_\tau \equiv \int_0^\tau \partial_t U(\mathbf{x}_t, \lambda(\tau-t)) dt, \quad (\text{S28})$$

respectively.

Second factor— Using Eq. (S23), rewrite the second factor in Eq. (S26) as $\exp(-\overline{S}_{\tau, \theta})$, where

$$\overline{S}_{\tau, \theta} \equiv \int_0^\tau D |\nabla V_\theta(\mathbf{x}_t, \tau-t)|^2 dt - \sqrt{2D} \nabla V_\theta(\mathbf{x}_t, \tau-t) \cdot d\mathbf{w}_t \quad (\text{S29})$$

is the reverse-time surprisal defined in Eq. (19b) of the main text.

Third factor— For almost every trajectory $\{\mathbf{x}_t\}_{t=0}^\tau$, a Stratonovich integral of the vector-valued map $t \mapsto \mathbf{f}(\mathbf{x}_t, t)$ along the trajectory can be expressed as a sum of Itô and anti-Itô integrals using the relation

$$\int_0^\tau \mathbf{f}(\mathbf{x}_t, t) \circ d\mathbf{x}_t = \frac{1}{2} \left[\int_0^\tau \mathbf{f}(\mathbf{x}_t, t) \cdot d\mathbf{x}_t + \int_0^\tau \mathbf{f}(\mathbf{x}_t, t) \odot d\mathbf{x}_t \right] \quad (\text{S30})$$

Applying this relation to the third factor in Eq. (S26) yields

$$\begin{aligned} &\exp\left[\frac{1}{4} \int_0^\tau D |\beta \nabla U(\mathbf{x}_t, \lambda(\tau-t))|^2 dt + 2\beta \nabla U(\mathbf{x}_t, \lambda(\tau-t)) \cdot d\mathbf{x}_t\right] \\ &= \exp\left[\frac{1}{4} \int_0^\tau D |\beta \nabla U(\mathbf{x}_t, \lambda(\tau-t))|^2 dt - 2\beta \nabla U(\mathbf{x}_t, \lambda(\tau-t)) \odot d\mathbf{x}_t\right] \\ &\quad \times \exp\left[\frac{\beta}{2} \int_0^\tau \nabla U(\mathbf{x}_t, \lambda(\tau-t)) \odot d\mathbf{x}_t + \nabla U(\mathbf{x}_t, \lambda(\tau-t)) \cdot d\mathbf{x}_t\right] \\ &= \frac{d\mathbb{P}_{\tau,0}^{\leftarrow}[\mathbf{X}]}{d\mathbb{P}_\tau^{\leftarrow}[\mathbf{X}]} \\ &\quad \times \exp(-\beta \overline{Q}_\tau) \end{aligned} \quad (\text{S31})$$

where the last equality uses Eq. (S14) and Eq. (S30) to introduce the reverse-time heat in Eq. (S28).

Substituting Eqs. (S27), (S29) and (S31) into Eq. (S26), we obtain

$$\begin{aligned} \frac{d\mathbb{P}_{\tau,0}^{\rightarrow}[\mathbf{X}]}{d\mathbb{P}_{\tau,\theta}[\mathbf{X}]} &= \exp[-\beta(\overline{\mathcal{W}}_{\tau} + \Delta F) + V(\mathbf{x}_0, \tau) - \overline{\mathcal{S}}_{\tau,\theta}] \\ &\times \frac{\pi(\mathbf{x}_0, \lambda(0))}{\pi(\mathbf{x}_{\tau}, \lambda(0))} \frac{d\mathbb{P}_{\tau,0}^{\leftarrow}[\mathbf{X}]}{d\mathbb{P}_{\tau}^{\leftarrow}[\mathbf{X}]} \end{aligned} \quad (\text{S32})$$

a simplified expression for the likelihood of a backward trajectory, which upon multiplying by Eq. (S25) finally becomes

$$\frac{d\mathbb{P}_{\tau}[\{\mathbf{x}_{\tau-t}\}_{t=0}^{\tau}]}{d\mathbb{P}_{\tau,\theta}[\{\mathbf{x}_t\}_{t=0}^{\tau}]} = \exp[-\beta(\overline{\mathcal{W}}_{\tau} + \Delta F) + V(\mathbf{x}_0, \tau) - \overline{\mathcal{S}}_{\tau,\theta}] \quad (\text{S33})$$

the expression in Eq. (18) of the main text.

The forward-backward likelihood ratio derived above must be understood in reference to the backward process. An analogous derivation, which we omit for brevity, obtains

$$\frac{d\mathbb{P}_{\tau,\theta}[\{\mathbf{x}_{\tau-t}\}_{t=0}^{\tau}]}{d\mathbb{P}_{\tau}[\{\mathbf{x}_t\}_{t=0}^{\tau}]} = \exp[-\beta(\mathcal{W}_{\tau} - \Delta F) - V(\mathbf{x}_{\tau}, \tau) + \mathcal{S}_{\tau,\theta}] \quad (\text{S34})$$

a backward-forward likelihood ratio that is defined in reference to the forward process, where

$$\mathcal{Q}_{\tau} \equiv -\int_0^{\tau} \nabla U(\mathbf{x}_t, \lambda(t)) \circ d\mathbf{x}_t \quad \text{and} \quad \mathcal{W}_{\tau} \equiv \int_0^{\tau} \partial_t U(\mathbf{x}_t, \lambda(t)) dt \quad (\text{S35})$$

are the heat dissipated by, and the work done on, a system evolving along the trajectory \mathbf{X} , and where

$$\mathcal{S}_{\tau,\theta} \equiv \int_0^{\tau} D|\nabla V_{\theta}(\mathbf{x}_t, t)|^2 dt - \sqrt{2D} \nabla V_{\theta}(\mathbf{x}_t, t) \cdot d\mathbf{w}_t \quad (\text{S36})$$

is the surprisal along the forward process. Though not introduced in the main text, Eq. (S34) is key to derive the forward free-energy bound in Eq. (21) of the main text, as seen in Sec. V of this document.

C. The forward-backward likelihood ratio given an optimal nonadiabatic potential

To see that the backward process can become an exact approximation of the time-reversed process, we evaluate the likelihood ratio derived in the previous subsection given an optimal nonadiabatic potential $V(\mathbf{x}, t) \equiv V_{\theta^*}(\mathbf{x}, t) - \ln\langle \exp[V_{\theta^*}(\mathbf{x}_t, t)] \rangle_{\mathbb{P}_{\tau}^{\rightarrow}}$ that satisfies Eq. (15) of the main text. Define

$$\overline{\mathcal{S}}_{\tau} \equiv -\int_0^{\tau} D[|\nabla V(\mathbf{x}_t, \tau-t)|^2 + \nabla U(\mathbf{x}_t, \lambda(\tau-t)) \cdot \nabla V(\mathbf{x}_t, \tau-t)] dt + \nabla V(\mathbf{x}_t, \tau-t) \cdot d\mathbf{x}_t \quad (\text{S37})$$

by substituting $V_{\theta}(\mathbf{x}, t) \rightsquigarrow V(\mathbf{x}, t)$ in the definition of $\overline{\mathcal{S}}_{\tau,\theta}$ in Eq. (S29), and by using Eq. (S23) to rewrite the integral against the Wiener process. We now show that, given (almost) any trajectory $\{\mathbf{x}_t\}_{t=0}^{\tau}$, the remaining terms in the forward-backward likelihood ratio [Eq. (S33)] reduce to Eq. (S37), rendering the likelihood ratio unity for almost every trajectory. Indeed,

$$V(\mathbf{x}_0, \tau) - \beta(\overline{\mathcal{W}}_{\tau} + \Delta F) = V(\mathbf{x}_0, \tau) - V(\mathbf{x}_{\tau}, 0) - \beta(\overline{\mathcal{W}}_{\tau} + \Delta F)$$

$$\begin{aligned}
&= -\int_0^\tau \partial_t V(\mathbf{x}_t, \tau-t) dt + \nabla V(\mathbf{x}_t, \tau-t) \circ d\mathbf{x}_t - \beta(\overline{W}_\tau + \Delta F) \\
&= -\int_0^\tau [-\partial_t \ln \rho(\mathbf{x}_t, \tau-t)] dt + \nabla V(\mathbf{x}_t, \tau-t) \circ d\mathbf{x}_t \tag{S38}
\end{aligned}$$

where the first equality uses the boundary condition $V(\cdot, t=0) \equiv 0$, the second equality uses the Stratonovich chain rule to expand the differential $dV(\mathbf{x}_t, \tau-t) = d \ln \pi(\mathbf{x}_t, \lambda(\tau-t)) - d \ln \rho(\mathbf{x}_t, \tau-t)$ along the trajectory, and the final equality uses the definition of the reverse-time work \overline{W}_τ in Eq. (S28). Now, note that the Fokker–Planck equation solved by $\rho(\mathbf{x}, t)$, stated in Eq. (5) of the main text, can be rewritten to describe the time evolution of the time-reversed log-density $\ln \rho(\mathbf{x}, \tau-t)$ as

$$-\partial_t \ln \rho(\mathbf{x}, \tau-t) = D[|\nabla V(\mathbf{x}, \tau-t)|^2 + \beta \nabla U(\mathbf{x}, \lambda(\tau-t)) \cdot \nabla V(\mathbf{x}, \tau-t)] - \nabla \cdot [D \nabla V(\mathbf{x}, \tau-t)] \tag{S39}$$

where substituting $t \rightsquigarrow \tau-t$ introduced the negative sign on the left-hand side. Inserting this equation into Eq. (S38), we get

$$\begin{aligned}
V(\mathbf{x}_0, \tau) - \beta(\overline{W}_\tau + \Delta F) &= -\int_0^\tau D[|\nabla V(\mathbf{x}_t, \tau-t)|^2 + \beta \nabla U(\mathbf{x}_t, \lambda(\tau-t)) \cdot \nabla V(\mathbf{x}_t, \tau-t)] dt \\
&\quad + \int_0^\tau \nabla V(\mathbf{x}_t, \tau-t) \circ d\mathbf{x}_t - \nabla \cdot [D \nabla V(\mathbf{x}_t, \tau-t)] dt \\
&= -\int_0^\tau D[|\nabla V(\mathbf{x}_t, \tau-t)|^2 + \beta \nabla U(\mathbf{x}_t, \lambda(\tau-t)) \cdot \nabla V(\mathbf{x}_t, \tau-t)] dt \\
&\quad + \int_0^\tau \nabla V(\mathbf{x}_t, \tau-t) \cdot d\mathbf{x}_t \\
&= \overline{S}_\tau \tag{S40}
\end{aligned}$$

where the second equality used Eq. (S8) to transform the Stratonovich integral into an Itô integral.

We have thus shown that, given an optimal nonadiabatic potential, the likelihood ratio in Eq. (S33) reduces to unity for almost all realizations of the backward process. Taking the likelihood ratio as a measure of alignment between the time-reversed process and the backward process, we deduce that the two processes are *probabilistically equal*, meaning that the expectation value of any observable may be written as an average of either process without reweighing.

V. VARIATIONAL BOUNDS ON THE FREE-ENERGY DIFFERENCE

In the following two subsections, we derive the lower and upper bounds on the free-energy difference introduced in Eq. (20) and Eq. (21) of the main text, which we respectively dub the *backward bound* and the *forward bound*.

A. The backward (lower) bound on ΔF

An argument to obtain Eq. (20) of the main text is outlined therein up to the appearance of the learned nonadiabatic potential, $V_\theta(\mathbf{x}, \tau) - \ln\langle \exp[V_\theta(\mathbf{x}_\tau, \tau)] \rangle$, in place of its exact counterpart, $V(\mathbf{x}, \tau)$. To justify this, notice that if the learned nonadiabatic potential $V_\theta(\mathbf{x}, \tau)$ is bounded from below, its cumulant-shifted exponential may be expressed as a ratio of two probability densities,

$$\frac{\exp[V_\theta(\mathbf{x}, \tau)]}{\langle \exp[V_\theta(\mathbf{x}_\tau, \tau)] \rangle} \equiv \frac{\pi(\mathbf{x}, \lambda(\tau))}{\rho_\theta(\mathbf{x}, \tau)}, \quad (\text{S41})$$

where both the equilibrium density $\pi(\mathbf{x}, \lambda(\tau))$ and the learned nonequilibrium density $\rho_\theta(\mathbf{x}, \tau)$ are positive. Taking logarithms and averaging with respect to the initial distribution of the backward process on both sides yields

$$\begin{aligned} \langle V_\theta(\mathbf{x}_\tau, \tau) \rangle - \ln\langle \exp[V_\theta(\mathbf{x}_\tau, \tau)] \rangle &\equiv \int d\mathbf{x} \rho(\mathbf{x}, \tau) \ln \frac{\pi(\mathbf{x}, \lambda(\tau))}{\rho_\theta(\mathbf{x}, \tau)} \\ &= \int d\mathbf{x} \rho(\mathbf{x}, \tau) \ln \frac{\rho(\mathbf{x}, \tau)}{\rho_\theta(\mathbf{x}, \tau)} + \int d\mathbf{x} \rho(\mathbf{x}, \tau) \ln \frac{\pi(\mathbf{x}, \lambda(\tau))}{\rho(\mathbf{x}, \tau)} \\ &\geq - \int d\mathbf{x} \rho(\mathbf{x}, \tau) \ln \frac{\rho(\mathbf{x}, \tau)}{\pi(\mathbf{x}, \lambda(\tau))} \\ &= \langle V(\mathbf{x}_\tau, \tau) \rangle \end{aligned} \quad (\text{S42})$$

an inequality between the learned and exact averaged nonadiabatic potentials that follows from the non-negativity of Kullback–Leibler divergence. After substituting Eq. (18) into Eq. (17), the inequality in Eq. (S42) may be invoked to finally obtain Eq. (20) of the main text.

B. The forward (upper) bound on ΔF

In this subsection, we derive Eq. (21) of the main text. Because the time-reversal operator R is a involution on the space of configurational trajectories, the pushforward of $\mathbb{P}_{\tau, \theta}$ by R , denoted $R\# \mathbb{P}_{\tau, \theta}$, remains a probability measure and thus satisfies $\langle 1 \rangle_{R\# \mathbb{P}_{\tau, \theta}} = 1$. Taking logarithms in this equality and using the likelihood ratio in Eq. (S34) to reweigh onto the forward process, we have

$$\begin{aligned} 0 = \ln \langle 1 \rangle_{R\# \mathbb{P}_{\tau, \theta}} &= \ln \left\langle \frac{d\mathbb{P}_{\tau, \theta}[RX]}{d\mathbb{P}_\tau^\rightarrow[X]} \right\rangle_{\mathbb{P}_\tau^\rightarrow} \\ &= \ln \left\langle \exp[-\beta(\mathcal{W}_\tau - \Delta F) - V(\mathbf{x}_\tau, \tau) + \mathcal{S}_{\tau, \theta}] \right\rangle_{\mathbb{P}_\tau^\rightarrow} \end{aligned} \quad (\text{S43a})$$

$$\geq \left\langle -\beta(\mathcal{W}_\tau - \Delta F) - V(\mathbf{x}_\tau, \tau) + \mathcal{S}_{\tau, \theta} \right\rangle_{\mathbb{P}_\tau^\rightarrow} \quad (\text{S43b})$$

$$= \left\langle -\beta(\mathcal{W}_\tau - \Delta F) \right\rangle_{\mathbb{P}_\tau^\rightarrow} + \left\langle \int_0^\tau dt D |\nabla V_\theta(\mathbf{x}_t, t)|^2 - V(\mathbf{x}_\tau, \tau) \right\rangle_{\mathbb{P}_\tau^\rightarrow} \quad (\text{S43c})$$

$$\begin{aligned}
&\geq \langle -\beta(\mathcal{W}_\tau - \Delta F) \rangle_{\mathbb{P}_\tau^\rightarrow} + \left\langle \int_0^\tau dt D|\nabla V_\theta(\mathbf{x}_t, t)|^2 \right\rangle_{\mathbb{P}_\tau^\rightarrow} \\
&\quad - [\langle V_\theta(\mathbf{x}_\tau, \tau) \rangle_{\mathbb{P}_\tau^\rightarrow} - \ln \langle \exp[V_\theta(\mathbf{x}_\tau, \tau)] \rangle_{\mathbb{P}_\tau^\rightarrow}]
\end{aligned} \tag{S43d}$$

Here, Eq. (S43a) uses Eq. (S21), Eq. (S43b) uses Jensen's inequality, Eq. (S43c) expands the forward surprisal $\mathcal{S}_{\tau, \theta}$ from Eq. (S36), and Eq. (S43d) applies the inequality in Eq. (S42) to introduce the nonadiabatic potential ansatz. Solving the last inequality for ΔF gives the forward free-energy bound in Eq. (21) of the main text.

VI. SATURATING THE VARIATIONAL FREE-ENERGY BOUNDS

To see that the forward free-energy bound in Eq. (21) of the main text is saturated upon substituting $V_\theta \rightsquigarrow V$, simply note that the substitution renders the right-hand side equal to that of Eq. (12), which is an equality in the main text. As for the backward free-energy bound in Eq. (20) of the main text, note that the forward-backward likelihood ratio in Eq. (18) reduces to unity for almost every trajectory as shown in Sec. IV of this document; consequently, the left-hand side of Eq. (17) is reduced to zero and must be equal to the nonnegative right-hand side.

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- [1] Pavliotis, G. A. *Stochastic processes and applications*, 1st ed.; Springer New York, NY, 2014; DOI: <https://doi.org/10.1007/978-1-4939-1323-7>.
- [2] Kunita, H. *Stochastic flows and jump diffusions*, 1st ed.; Springer Nature Singapore, 2019; DOI: <https://doi.org/10.1007/978-981-13-3801-4>.
- [3] Øksendal, B. *Stochastic differential equations: An introduction with applications*, 6th ed.; Springer Berlin, Heidelberg, 2010; DOI: <https://doi.org/10.1007/978-3-642-14394-6>.