Estimating thermodynamic expectations and free energies in expanded ensemble simulations: systematic variance reduction through conditioning

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Markov chain Monte Carlo methods are primarily used for sampling from a given probability distribution and estimating multi-dimensional integrals based on the information contained in the generated samples. Whenever it is possible, more accurate estimates are obtained by combining Monte Carlo integration and integration by numerical quadrature along particular coordinates. We show that this variance reduction technique, referred to as conditioning in probability theory, can be advantageously implemented in *expanded ensemble* simulations aiming at estimating thermodynamic expectations as a function of an external parameter that is sampled like an additional coordinate. In this approach, conditioning entails integrating along the external coordinate by numerical quadrature. We prove variance reduction and demonstrate the practical efficiency of the technique by estimating free energies and characterizing a structural phase transition between two solid phases.

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I. INTRODUCTION

One important goal of molecular simulation is the estimation of equilibrium thermodynamic quantities. Any such quantity corresponds to the ensemble average of an observable over the space of accessible states $\mathcal{Q}$ of a multi-dimensional system. The contribution of any given state to the ensemble average is weighted by its occurrence probability in the considered thermodynamic ensemble (the Gibbs-Boltzmann probability). If one knows how to sample from this probability distribution, for instance by using a Markov chain Monte Carlo method or a molecular dynamics algorithm, then any thermodynamic quantity can be accurately estimated in practice by taking advantage of the ergodic theorem.

A major bottleneck facing molecular simulation is broken numerical ergodicity. A versatile and widespread solution to alleviate this problem consists of sampling an expanded ensemble[1,2] that is a mixture of canonical ensembles equipped with an auxiliary biasing potential $\boldsymbol{\alpha}(\theta)$ function of the subensemble indexes. The external parameter θ may correspond to extensive quantities (such as volume or the numbers of particles) or intensive quantities (thermodynamic forces such as pressure, chemical potentials or inverse temperature). The method of expanded ensembles[1,2] also includes simulated tempering,[3–5] simulated scaling[6] and Lagrangian metadynamics[7,8] methods. In all these implementations, the external parameter behaves like an additional coordinate of the system. Improved numerical ergodicity is usually achieved compared to direct Monte Carlo or molecular dynamics simulations by allowing the system to circumvent barriers between metastable basins or even to cross them when, for instance, the external parameter is associated with inverse temperature and takes small values. Because of its popularity and versatility, the expanded ensemble method has been the subject of numerous studies[9–15] over recent years. To evaluate the thermodynamic expectations, several estimators have been proposed, namely, the histogram binning estimator,[1] a reweighting estimator[2], a histogram reweighting estimator[11] and the adiabatic reweighting estimator.[14,15] They are primarily used for calculating free energy differences between the successive thermodynamic states. The last estimator is derived from Bayes formula[14] and is shown to be particularly efficient for rare event problems.[15]

It is worth noting that expanded ensemble methods relate to multicanonical sampling methods,[16–19] in which the biases are associated with a generalized internal coordinate rather than an external coordinate. In both approaches, adequate biasing factors are constructed adaptively during the course of the simulation in such a way that uniform sampling is achieved along the external or internal coordinate. In the latter approach, the biasing factors are then set equal to the inverse of the density of states with respect to the associated coordinate that can be a reaction coordinate[20] or an order parameter,[16] depending on whether one is interested in monitoring a reaction along its transition pathway or simply in discriminating distinct structures or configurations of the system. A typical order parameter is the internal energy.[17]

The biasing factors can be constructed using several techniques that can be classified into two categories: adaptive biasing potential (ABP) methods — along internal[17,21,22] or external[23,24] coordinates— and adaptive biasing force (ABF) methods — along internal[20,25–28] or external[5] coordinates—, depending on whether it is the auxiliary biasing potential that is updated or its gradient, respectively. A review can be found in Ref 29. A detailed proof of convergence is given in Ref 22 for the the ABP algorithm[17] proposed by Wang and Landau and in Ref 27 for the ABF algorithm of Darve and Pohorille.

The common limitation of all ABP algorithms involves the optimal choice of the updating rate of the biasing potential. If the rate rapidly converges to zero, then the adaptation amplitude will be very small. The biasing potential will subsequently converge slowly to the free energy. At variance, if the rate slowly converges to zero, then the biasing potential will fluctuate for a long period prior to stabilizing. Finding a good trade-off between these two adverse situations requires judiciously tuning the updating parameters, a difficult task in general. ABF methods are (almost) free of such updating parameters. However, the method is not always applicable as it requires differentiating the reaction coordinate twice. For instance, implementing ABF to compute the free energy along the widely used bond orientational order parameters of Steinhardt et al.[30] is problematic and has never been achieved to our knowledge. In this paper, we will show how to alleviate the problem by performing the simulations in an expanded ensemble while implementing the adiabatic reweighting estimator. The theoretical motivation behind the algorithmic development is to generalize the adiabatic reweighting technique so that it can be used to efficiently estimate any type of thermodynamic expectations. To do this, we show that adiabatic reweighting amounts to implementing a variance reduction procedure known as *conditioning* in probability theory.[31,32] Herein, this procedure consists of combining Monte Carlo integration over the internal coordinate space and integration by numerical quadrature along the external parameter.

The paper is organized as follows: in section II, we define the expanded ensemble and show that thermodynamic ensemble averages can be cast as conditional expectations of the observable given the value of the external coordinate and that free energies can be expressed as the logarithm of a total expectation. In Section III, the adiabatic reweighting estimator is constructed from the binning or reweighting estimators through the conditioning procedure and the systematic reduction of the asymptotic variances is proved using the law of total variance. We complete the study in subsection III C by deriving the adiabatic reweighting estimator from postprocessing estimators based on Bennett acceptance ratio method.[33] Section IV discusses the form of the optimal biasing potential. In section V, we assess the variance reduction on free energy and rare event simulations of a simple model. Section VI describes the ABF algorithm for expanded ensemble simulations and show how to estimate free energies along the order parameter and to determine a structural transition temperature between two solid phases in an atomic cluster.

II. THERMODYNAMIC EXPECTATIONS IN EXPANDED ENSEMBLE

A. Preliminary definitions

Let first define the thermodynamic expectations and free energies along θ in an expanded ensemble. Unless otherwise specified, we assume that the auxiliary biasing potential $\mathfrak{a}(\theta)$ is constant, i.e. that it does not vary in the course of the simulation. This allows defining the entropic potential of the expanded ensemble as a partition function logarithm

$$\Psi_{\mathfrak{a}}^{\Theta} = \ln \sum_{\vartheta \in \Theta} \int_{\mathcal{Q}} \exp\left[\mathfrak{a}(\vartheta) - \mathcal{U}(\vartheta, q)\right] dx,$$

where Θ is the external parameter space. The entropic potential depends on the biasing potential and acts as a normalizing constant in the probability density within the expanded ensemble

$$\mathrm{p}_{\mathfrak{a}}(\vartheta, q) = \exp\left[\mathfrak{a}(\vartheta) - \mathcal{U}(\vartheta, q) - \Psi_{\mathfrak{a}}^{\Theta}\right].$$

Herein, the observable $(\vartheta, q) \mapsto \mathcal{O}(\vartheta, q)$ will depend both on the external parameter and the internal coordinates $q \in \mathcal{Q}$. The total expectation associated with the observable is given by:

$$\mathbb{E}_{a}\left[\mathcal{O}(\vartheta,q)\right] = \sum_{\vartheta\in\Theta}\int_{\mathcal{Q}} \mathcal{O}(\vartheta,q)\mathrm{p}_{a}(\vartheta,dq).$$

This expectation in particular allows one to define the free energy $\mathcal{A}(\theta)$ along the external parameter, which, adopting Landau's definition, corresponds to minus the logarithm of the indicator function $\mathbb{1}_{\theta}(\vartheta)$:

$$\mathcal{A}(\theta) = -\ln \mathbb{E}\left[\mathbb{1}_{\theta}(\vartheta)\right], \tag{1}$$

where expectation $\mathbb{E}$ corresponds to $\mathbb{E}_{a}$ with $\boldsymbol{a}$ set to 0 (unbiased ensemble). The free energy allows to formally define the conditional probability of q given that ϑ is equal to θ

$$\pi(q|\theta) = \frac{\mathrm{p}_0(\theta,q)}{\mathbb{E}\left[\mathbb{1}_{\theta}(\vartheta)\right]} = \exp\left[\mathcal{A}(\theta) - \mathcal{U}(\theta,q) - \Psi_0^{\Theta}\right],$$

as well as the conditional probability

$$\mathbb{E}\big[\mathcal{O}(\theta,q)|\theta\big] = \int_{\mathcal{Q}} \mathcal{O}(\theta,q)\pi(dq|\theta). \tag{2}$$

The fact that the relation $\pi(q|\theta) = \mathrm{p}_{a}(\theta,q)\big/\mathbb{E}_{a}\left[\mathbb{1}_{\theta}(\vartheta)\right]$ is valid whatever the value of the biasing potential entails the useful relation between total and conditional expectations

$$\mathbb{E}\big[\mathcal{O}(\theta,q)|\theta\big] = \frac{\mathbb{E}_{a}\left[\mathbb{1}_{\theta}(\vartheta)\mathcal{O}(\theta,q)\right]}{\mathbb{E}_{a}\left[\mathbb{1}_{\theta}(\vartheta)\right]}. \tag{3}$$

The denominator of the fraction corresponds to the marginal probability of θ

$$\mathscr{p}_{a}(\theta) = \int_{\mathcal{Q}} \mathrm{p}_{a}(\theta,dq). \tag{4}$$

B. Estimating conditional expectations

We show how to estimate conditional expectations of the observable $\mathcal{O}(\theta,q)$ using the histogram binning estimator[1] and the reweighting estimator.[2] As the forthcoming derivations involving the two estimators are similar, we will refer to both of them at the same time. We therefore introduce the following generic function

$$\phi_{a}^{\theta}(\vartheta,q) = \begin{cases} \mathbb{1}_{\theta}(\vartheta) & \text{if histogram binning,} \\ \rho_{a}^{\theta}(\vartheta,q) & \text{if reweighting,} \end{cases} \tag{5}$$

where

$$\rho_{a}^{\theta}(\vartheta,q) = \frac{1}{\|\Theta\|}\frac{\exp\left[\boldsymbol{a}(\theta) - \mathcal{U}(\theta,q)\right]}{\exp\left[\boldsymbol{a}(\vartheta) - \mathcal{U}(\vartheta,q)\right]}.$$

The quantity $\|\Theta\| = \sum_{\vartheta\in\Theta} 1$ corresponds to the cardinal of Θ. It scales the reweighting factor in Eq. (5) so that the expectation of ϕ_a^θ is equal to the marginal probability of the external parameter in both cases:

$$\mathbb{E}_a\big(\phi_a^\theta(\vartheta,q)\big) = \sum_{\vartheta\in\Theta}\int_{\mathcal{Q}} \phi_a^\theta(\vartheta,q)\mathrm{p}_a(\vartheta,dq) = \mathsf{p}_a(\theta). \tag{6}$$

Similarly, the following relation holds for both forms of the generic function:

$$\begin{aligned}\mathbb{E}_a\big(\phi_a^\theta(\vartheta,q)\mathcal{O}(\theta,q)\big) &= \int_{\mathcal{Q}} \mathcal{O}(\theta,q)\mathrm{p}_a(\theta,dq) \\ &= \mathbb{E}\big[\mathcal{O}(\theta,q)\big|\theta\big] \times \mathsf{p}_a(\theta).\end{aligned}$$

This relation together with Eq. (6) allows to express the conditional expectation of $\mathcal{O}$ given θ as a function of ϕ_a^θ

$$\mathbb{E}\big[\mathcal{O}(\theta,q)\big|\theta\big] = \frac{\mathbb{E}_a\left[\phi_a^\theta(\vartheta,q)\mathcal{O}(\theta,q)\right]}{\mathbb{E}_a\left[\phi_a^\theta(\vartheta,q)\right]}, \tag{7}$$

and to obtain the generic form of the binning and reweighting estimators by application of the ergodic theorem

$${}^{M}_{a}(\mathcal{O}|\theta) = \frac{\frac{1}{M}\sum_{m=1}^{M}\phi_a^\theta(\vartheta_m,q_m)\mathcal{O}(\theta,q_m)}{\frac{1}{M}\sum_{m=1}^{M}\phi_a^\theta(\vartheta_m,q_m)}, \tag{8}$$

where we used a Markov chain $\{\vartheta_m, q_m\}_{1\leq m\leq M}$ distributed according to $\mathrm{p}_a(\vartheta,q)$ probability.

Within the expanded ensemble, the external parameter usually couples either linearly to a potential energy of the internal coordinates or harmonically to a reaction coordinate $\xi(q)$.

With linear coupling, the extended system will evolve between a reference system S_0 and a target system S_1. In practice, it is convenient to write the extended potential as

$$\mathcal{U}(\vartheta,q) = (1-\vartheta)\,\mathcal{U}_0(q) + \vartheta\,\mathcal{U}_1(q), \tag{9}$$

where ϑ values range in the interval $[0,1]$. In Eq. (9), $\mathcal{U}_0(q)$ and $\mathcal{U}_1(q)$ are the potentials of the reference and target systems, respectively. This parameterization is usual and covers, in particular, situations where the external parameter is associated with temperature or pressure. For instance, when the reference and target systems correspond to a system of same potential energy $\mathcal{V}(q)$ held at two distinct temperatures $\beta_{\min}$ and $\beta_{\max}$, we simply set $\mathcal{U}_0 = \beta_{\min}\mathcal{V}$ and $\mathcal{U}_1 = \beta_{\max}\mathcal{V}$. This setup is also employed for calculating difference of free energies for instance. In this last case, the total expectation of an indicator function (see Eq. (1)) must be estimated. Another important task is to estimate conditional expectations given some values of the external parameter θ [see Eq. (7)] using an estimator described in subsection III B.

With harmonic coupling of the external parameter to a reaction coordinate, the extended potential exhibits the following form

$$\mathcal{U}(\vartheta, q) = \mathcal{U}_0(q) + \mathcal{R}^{\xi}\big(\vartheta, \xi(q)\big), \tag{10}$$

with $\mathcal{U}_0(q) = \beta_{\mathrm{ref}}\mathcal{V}(q)$ wherein $\mathcal{V}(q)$ and β_{ref} are the potential and the inverse temperature of the reference system. The restraining potential $\mathcal{R}^{\xi}\big(\vartheta, \xi(q)\big)$ is often harmonic below a cut-off r_c, infinite above and centered on the value of a reaction coordinate $q \mapsto \xi(q)$. If κ is the spring stiffness, the harmonic restraining potential can be written as ($\xi^\star \in \Xi$)

$$\mathcal{R}^{\xi}\big(\theta, \xi^\star\big) = \begin{cases} \frac{1}{2}\beta_{\mathrm{ref}}\kappa\|\vartheta - \xi^\star\|^2 + \epsilon & \text{for} \quad \|\vartheta - \xi^\star\| \le r_{\mathrm{c}}, \\ +\infty & \text{otherwise.} \end{cases}$$

In anticipation of manipulations to come, it is convenient to define an effective restraining potential as

$$\bar{\mathcal{R}}^{\xi}_{a}(\xi^\star) = -\ln \sum_{\vartheta\in\Theta} \exp\big[a(\vartheta) - \mathcal{R}^{\xi}(\vartheta, \xi^\star)\big] \tag{11}$$

and to set the constant ϵ such that the identity $\bar{\mathcal{R}}^{\xi}_{0} \circ \xi(q) = 0$ for all $q \in \mathcal{Q}$. This condition is met if Θ is sufficiently large so that for all $q \in \mathcal{Q}$, $\xi(q) \in [\theta_{\min} + r_c\, ,\, \theta_{\max} - r_c]$.

Without biasing potential a, the restraining potential is not really useful since it does not affect thermodynamic average when the associated observable depends on the position only. Denoting the observable as $\bar{\mathcal{O}}(q)$, the expectation in the unbiased expanded ensemble is indeed identical to the expectation in the reference thermodynamic ensemble:

$$\mathbb{E}\big[\bar{\mathcal{O}}(q)\big] = \sum_{\vartheta\in\Theta} \int_{\mathcal{Q}} \bar{\mathcal{O}}(q)\mathrm{p}_0(\vartheta, dq) = \int_{\mathcal{Q}} \bar{\mathcal{O}}(q)\bar{\mathrm{p}}_0(dq)$$

where $\bar{\mathrm{p}}_0(q) = \exp\big[-\mathcal{U}_0(q) - \Psi^{\Theta}_0\big]$ is the unbiased marginal probability of q. Hence, we subtract the auxiliary biasing potential $a(\vartheta)$ in order to drive the external parameter that in turn will pull the system towards regions of interests. This setup is used when one wishes to mechanically restrain the average value of the reaction coordinate ξ owing to an auxiliary biasing potential $a(\vartheta)$. As a result, the biased probability density $\mathrm{p}_a(\vartheta, q)$ is sampled, but expectations should be evaluated with respect to the unbiased probability density $\mathrm{p}_0(\vartheta, q)$.

To cover both the linear and harmonic couplings, and possibly any other type of coupling, we adopt a unified description and consider that the potential energy has the form

$$\mathcal{U}(\vartheta, q) = \mathcal{U}_0(q) + \mathcal{R}(\vartheta, q),$$

where $\mathcal{R}(\vartheta, q)$ can be set to $\vartheta[\mathcal{U}_1(q) - \mathcal{U}_0(q)]$ for linear coupling with $\vartheta \in [0, 1]$ or to $\frac{\beta\kappa}{2}|\vartheta - \xi(q)|^2 + \epsilon$ for harmonic coupling coupling with $|\vartheta - \xi(q)| < r_c$. With the auxiliary biasing potential $\boldsymbol{a}(\vartheta)$ switched on, the marginal probability of q is

$$\bar{\mathrm{p}}_a(q) \propto \exp\left[-\mathcal{U}_0(q) - \bar{\mathcal{R}}_a(q)\right],$$

$$\bar{\mathcal{R}}_a(q) = -\ln\left\{\sum_{\vartheta\in\Theta} \exp[\boldsymbol{a}(\vartheta) - \mathcal{R}(\vartheta, q)]\right\}.$$

We also define expectation with respect to the marginal probability of q

$$\bar{\mathbb{E}}_a\left[\bar{\mathcal{O}}(q)\right] \triangleq \int_{q\in\mathcal{Q}} \bar{\mathcal{O}}(q)\bar{\mathrm{p}}_a(dq). \tag{12}$$

III. CONDITIONING AND VARIANCE REDUCTION

Prior to showing how *conditioning* is done within the aforementioned binning and reweighting estimators, let first describe a simple conditioning scheme for which the reduction of variance compared to standard estimators can easily be proved.

A. Estimating the marginal probability of θ

Let consider the various ways of estimating the marginal probability of θ from a sample $\{\vartheta_m, q_m\}_{1\leq m\leq M}$ distributed according to probability $\mathrm{p}_a(d\vartheta, dq)$. The two standard approaches for estimating $\boldsymbol{p}_a(\theta)$ exploit the relation in Eq. (6) by resorting to the ergodic theorem. They consist of evaluating the arithmetic mean of ϕ_a, denoted by

$$\mathrm{I}^M\left(\phi_a^\theta\right) = \tfrac{1}{M}\sum_{m=1}^{M} \phi_a^\theta(\vartheta_m, q_m), \tag{13}$$

where the extended configurations $\{\vartheta_m, q_m\}_{1\leq m\leq M}$ are distributed according to $\mathrm{p}_a(\vartheta, q)$ probability. Let now denote the conditional probability of θ given q by $\pi_a^\theta(q)$. We have

$$\pi_a^\theta(q) = \frac{\exp\left[\boldsymbol{a}(\theta - \mathcal{U}(\theta, q)\right]}{\sum_{\vartheta\in\Theta}\exp\left[\boldsymbol{a}(\vartheta - \mathcal{U}(\vartheta, q)\right]}. \tag{14}$$

Obviously, the conditionally expected value of ϕ_a^θ given q is the conditional probability of θ given q

$$\mathbb{E}_a\left[\phi_a^\theta(\vartheta,q)\middle|q\right] = \pi_a^\theta(q) \tag{15}$$

Besides, the expected value of ϕ_a^θ is the expected value of π_a^θ (law of total expectation)

$$\begin{aligned}\mathbb{E}_a\left[\phi_a^\theta(\vartheta,q)\right] = \bar{\mathbb{E}}_a\Big[\mathbb{E}_a\left[\phi_a^\theta(\vartheta,q)\middle|q\right]\Big] \\ = \bar{\mathbb{E}}_a\left[\pi_a^\theta(q)\right] = \mathbb{E}_a\left[\pi_a^\theta(q)\right].\end{aligned}$$

where we first resorted to Eq. (12) with $\bar{\mathcal{O}}(q)$ set to $\mathbb{E}_a\left[\phi_a^\theta(\vartheta,q)\middle|q\right]$. Interestingly, the last term in the sequence of equalities above means that for estimating $\mathbb{E}_a\left[\phi_a^\theta(\vartheta,q)\right]$, it is possible to replace $\phi_a^\theta(\vartheta_m,q_m)$ in Eq. (13) by $\pi_a^\theta(q_m)$. It is precisely this replacement scheme that is referred to as *conditioning*. Estimating the marginal probability of θ with the conditioning scheme therefore consists of evaluating the following quantity

$$\mathrm{I}^M\left(\pi_a^\theta\right) = \tfrac{1}{M}\sum_{m=1}^{M}\pi_a^\theta(q_m).$$

The equality between the $\bar{\mathbb{E}}_a\left[\pi_a\theta\right]$ and $\mathbb{E}_a\left[\pi_a\theta\right]$ expectations indicates that the arithmetic estimator can still be employed using a configuration chain $\{q_m\}_{1\leq m\leq M}$ directly distributed according to $\bar{\mathrm{p}}_a(q)$ marginal probability.

Conditioning is based on the law of total expectation and entails variance reduction owing to the law of total variance. The latter law states that the (total) variance of ϕ_a^θ is equal to the sum of two terms: the expectation of the conditional variances of ϕ_a^θ given q and the variance of the conditional expectation of ϕ_a^θ given q

$$\begin{aligned}\mathrm{var}_a\left[\phi_a^\theta(\vartheta,q)\right] = \mathbb{E}_a\Big[\mathrm{var}\big(\phi_a^\theta(\vartheta,q)\big|q\big)\Big] + \\ \mathrm{var}_a\Big[\mathbb{E}_a\big(\phi_a^\theta(\vartheta,q)\big|q\big)\Big].\end{aligned} \tag{16}$$

This elementary identity of probability theory can be verified through expressing the three variances as functions of total expectations, resorting to the law of total expectation with respect to q and identifying

$$\begin{aligned}\mathrm{var}_a\left[\phi_a^\theta(\vartheta,q)\right] = \mathbb{E}_a\left[\mathbb{E}_a\left(\phi_a^\theta(\vartheta,q)^2\middle|q\right)\right] - \mathbb{E}_a\left[\pi_a^\theta(q)\right]^2 = \\ \mathbb{E}_a\Bigg[\underbrace{\mathbb{E}_a\left(\phi_a^\theta(\vartheta,q)^2\middle|q\right) - \pi_a^\theta(q)^2}_{\mathrm{var}\left[\phi_a^\theta(\vartheta,q)\middle|q\right]}\Bigg] + \underbrace{\mathbb{E}_a\left[\pi_a^\theta(q)^2\right] - \mathbb{E}_a\left[\pi_a^\theta(q)\right]^2}_{\mathrm{var}_a\left[\mathbb{E}_a\left(\phi_a^\theta(\vartheta,q)\middle|x\right)\right]}.\end{aligned}$$

wherein we plugged $\pi_a^\theta(q) = \mathbb{E}_a\left[\phi_a^\theta(\vartheta,q)\middle|q\right]$ to simplify. Note in particular that the left-hand side variance corresponds to the total variance of π_a^θ, i.e. $\mathrm{var}_a\left[\pi_a^\theta(q)\right]$. The fact that, whatever q, $\vartheta \mapsto \phi_a^\theta(\vartheta,q)$ is not a constant function implies the following sequence of strict inequalities

$$\begin{aligned}
& \mathbb{E}_a\left[\phi(\vartheta,q)^2\middle|q\right] > \mathbb{E}_a\left[\phi_a^\theta(\vartheta,q)\middle|q\right]^2 \\
\Longrightarrow\quad & \mathrm{var}\left[\phi_a^\theta(\vartheta,q)\middle|q\right] > 0 \\
\Longrightarrow\quad & \mathrm{var}_a\left(\phi_a^\theta(\vartheta,q)\right) > \mathrm{var}_a\left[\pi_a^\theta(\vartheta,q)\right].
\end{aligned}$$

The last inequality between the total variance of ϕ_a^θ and that of π_a^θ can also be written for samples containing statistically iid states since we have

$$M\mathrm{var}_a\left[\tfrac{1}{M}\sum\nolimits_{m=1}^{M}\phi_a^\theta(\vartheta_m,q_m)\right] \Big\rangle\ M\mathrm{var}_a\left(\tfrac{1}{M}\sum\nolimits_{m=1}^{M}\pi_a^\theta(q_m)\right).$$

Hence, the statistical variance associated with the arithmetic mean of the generic function is always larger than that associated with arithmetic mean of the conditional probabilities of θ. It is therefore always preferable to use an estimator obtained through conditioning, provided that the overhead associated with the evaluation of the conditional expectation given the sampled states is small enough. Note that the variance is reduced whatever the choice of the biasing potential, although the values of the asymptotic variances do depend on a. Besides, when the dimension of Θ exceeds two or three, the cost of conditioning becomes substantial in practice and may not be negligible anymore compared to the cost of evaluating the potential energy. In this situation, the reduction of the variance may not be important enough to justify implementing a conditioning scheme. In the following, we always assume that performing the numerical quadrature integration within the conditioning scheme has a negligible cost compared to the one of evaluating the potential energy and its gradient.

We now show that it is also preferable to resort to a conditioning scheme for estimating conditional expectations in the expanded ensemble.

B. Estimation of conditional expectations

As for conditional expectations, conditioning consists of replacing $\phi_a^\theta(\vartheta_m,q_m)$ by $\pi_a^\theta(q_m)$, the conditional expectation given $q = q^m$ in the denominator and the numerator of the generic estimator (Eq. (8)). Making this simple substitution yields adiabatic reweighting estimator

$$
{}^{M}_{a}(\mathcal{O}|\theta) = \frac{\frac{1}{M}\sum_{m=1}^{M}\pi_a^\theta(q_m)\mathcal{O}(\theta,q_m)}{\frac{1}{M}\sum_{m=1}^{M}\pi_a^\theta(q_m)} \tag{17}
$$

where we used a Markov chain $\{\vartheta_m, q_m\}_{1\leq m\leq M}$ distributed according to $\mathrm{p}_a(\vartheta,q)$ probability, or a configuration chain $\{q_m\}_{1\leq m\leq M}$ distributed according to $\bar{\mathrm{p}}_a(q)$ marginal probability. The substitution that is done amounts to plugging the law of total expectation both in the numerator and the denominator of Eq. (7),

$$
\begin{aligned}
\mathbb{E}\left[\mathcal{O}|\theta\right] = \frac{\bar{\mathbb{E}}_a\left[\mathbb{E}_a\left[\phi_a^\theta(\vartheta,q)\mathcal{O}(\theta,q)\middle|q\right]\right]}{\bar{\mathbb{E}}_a\left[\mathbb{E}_a\left[\phi_a^\theta(\vartheta,q)\middle|q\right]\right]}&\\
&= \frac{\mathbb{E}_a\left[\pi_a^\theta(q)\mathcal{O}(\theta,q)\right]}{\mathbb{E}_a\left[\pi_a^\theta(q)\right]}.
\end{aligned} \tag{18}
$$

The adiabatic reweighting estimator was derived previously in Ref 14,15 starting from Bayes formula, which may be obtained here from Eq. (18) by substituting $\delta(q^\dagger - q)$ for the observable:

$$
\pi(q^\dagger|\theta) = \frac{\bar{\pi}_a(\theta|q^\dagger)\bar{\mathrm{p}}_a(q^\dagger)}{\boldsymbol{p}_a(\theta)} \tag{19}
$$

where $\bar{\pi}_a(\theta|q^\dagger)$ stands for $\pi_a^\theta(q^\dagger)$.

The present conditioning scheme entails variance reduction in the asymptotic limit of large sample sizes. To prove this property, we will compare the asymptotic variance of the adiabatic reweighting estimator (Eq. (17)) to that of the generic estimator (Eq. (8)). The present situation differs from that of subsection III A wherein reduction was guaranteed for any sample size. The difficulty is due to the presence of a denominator in Eq. (8) and 17. Let us assume that the function $q \mapsto \mathcal{O}(\theta,q)$ is non-constant (otherwise sampling would not be necessary) and introduce the centered observable $\mathcal{O}^\theta(q) = \mathcal{O}(\theta,q) - \mathbb{E}_a(\mathcal{O}|\theta)$, a quantity centered on the value of the conditional expectation given θ. Then, the quantity $\mathcal{O}^\theta\phi_a^\theta$ is centered with respect to the total expectation we have

$$
\begin{aligned}
\mathbb{E}_a\big(\phi_a^\theta(\vartheta,q)\mathcal{O}^\theta(q)\big) = \bar{\mathbb{E}}_a\Big(\mathbb{E}_a\big(\phi_a^\theta\left(\vartheta,q\right)|q\big)\mathcal{O}^\theta(q)\Big)&\\
&= \bar{\mathbb{E}}_a\big(\pi_a^\theta(q)\mathcal{O}(\theta,q)\big) - \mathbb{E}(\mathcal{O}(\theta,q)|\theta)\boldsymbol{p}_a(\theta) = 0.
\end{aligned}
$$

Let us now assume that the generated Markov chains $\{\vartheta_m, q_m\}_{1\leq m\leq M}$ consist of a sequences of random variables that are iid according to $\mathrm{p}_a(\vartheta,q)$. Then, in the limit of large sample sizes, the variance of the $\sqrt{M}\ \ {}^{M}_{a}(\mathcal{O}|\theta)$ quantity becomes equivalent to the following variance

$$
M\mathrm{var}_a\left[\Phi_a^M\left(\mathcal{O}|\theta\right)\right] \underset{M\to+\infty}{\sim} M\mathrm{var}_a\left(\frac{\frac{1}{M}\sum_{m=1}^{M}\phi_a^\theta(\vartheta_m,q_m)\mathcal{O}^\theta(q_m)}{\mathbb{E}_a\big(\phi_a^\theta(\vartheta,q)\big)}\right). \tag{20}
$$

It is precisely the limit of the left-hand side term of Eq. (20) as M tends to infinity that is called the asymptotic variance of the $\ _a^M(\mathcal{O}|\theta)$ estimator. Since the sampled states are iid, the variance of the arithmetic mean of $\phi_a^\theta(\vartheta_m, q_m)\mathcal{O}^\theta(q_m)$ in Eq. (20) multiplied by M decomposes into an average involving M identical variances:

$$\tfrac{1}{M}\sum_{m=1}^{M} \mathrm{var}_a\left(\phi_a^\theta(\vartheta_m, q_m)\mathcal{O}^\theta(q_m)\right) = \mathrm{var}_a\big(\phi_a^\theta(\vartheta, q)\mathcal{O}^\theta(q)\big). \tag{21}$$

The square-root of the asymptotic variance corresponds to the asymptotic error and writes

$$\sigma\left[\ _a^{+\infty}(\mathcal{O}|\theta)\right] = \frac{1}{p_a(\theta)}\sqrt{\mathrm{var}_a\big(\phi_a^\theta(\vartheta, q)\mathcal{O}^\theta(q)\big)}, \tag{22}$$

where we have substituted $p_a(\theta)$ for $\mathbb{E}_a(\phi_a^\theta)$. The rigorous mathematical justification of this result is given in Appendix A. More precisely, the following convergence in law is proved

$$\frac{\frac{1}{M}\sum_{m=1}^{M}\phi_a^\theta(\vartheta_m, q_m)\mathcal{O}(q_m)}{\frac{1}{M}\sum_{m=1}^{M}\phi_a^\theta(\vartheta_m, q_m)} \underset{M\to+\infty}{\xrightarrow{\mathcal{L}}} \mathcal{N}\left(\mathbb{E}\left[\mathcal{O}|\theta\right], \sigma^2\left[\ _a^{+\infty}(\mathcal{O}|\theta)\right]\right)$$

where $\mathcal{N}(\mu, \nu)$ denotes the normal law of mean μ and variance ν.

Similarly, the asymptotic error of the adiabatic reweighting estimator is, with iid assumption again,

$$\sigma\left[\ _a^{+\infty}(\mathcal{O}|\theta)\right] = \frac{1}{p_a(\theta)}\sqrt{\mathrm{var}_a\big(\pi_a^\theta(q)\mathcal{O}^\theta(q)\big)}. \tag{23}$$

To compare the two asymptotic errors, we resort to the law of total variance as in subsection III A, but with respect to $\mathcal{O}^\theta\phi_a^\theta$ quantity in place of ϕ_a^θ. The law states that the total variance is equal to the sum of the expectation of the conditional variances given q and the variance of the conditional expected values given q:

$$\mathrm{var}_a\big(\phi_a^\theta(\vartheta, q)\mathcal{O}^\theta(q)\big) = \mathbb{E}_a\Big(\mathrm{var}\big(\phi_a^\theta(\vartheta, q)\mathcal{O}^\theta(q)|q\big)\Big) + \mathrm{var}_a\Big(\mathbb{E}_a\big(\phi_a^\theta(\vartheta, q)\mathcal{O}^\theta(q)|q\big)\Big)$$

Plugging Eq. (15) into the law of total variance leads to

$$\mathrm{var}_a\big(\pi_a^\theta(q)\mathcal{O}^\theta(q)\big) = \mathrm{var}_a\big(\phi_a^\theta(\vartheta, q)\mathcal{O}^\theta(q)\big) - \mathbb{E}_a\left[\mathrm{var}_a\big(\phi_a^\theta(\vartheta, q)|q\big)\mathcal{O}^\theta(q)^2\right].$$

The quantity $\mathcal{O}^\theta(q)$ being non-constant and the conditional variance of ϕ_a^θ being strictly positive for all q, the last expectation above is strictly positive. The law of total variance therefore entails the following strict inequality

$$\mathrm{var}_a\big(\pi_a^\theta(q)\mathcal{O}^\theta(q)\big) < \mathrm{var}_a\big(\phi_a^\theta(\vartheta, q)\mathcal{O}^\theta(q)\big). \tag{24}$$

From identities 22 and 23 and inequality 24, we deduce the following strict inequality between the asymptotic errors of the estimators

$$\sigma\left[\ {}^{+\infty}_{a}(\mathcal{O}|\theta)\right] < \sigma\left[\ {}^{+\infty}_{a}(\mathcal{O}|\theta)\right]. \tag{25}$$

It is therefore always preferable to use the adiabatic reweighting estimator rather than the reweighting or histogram binning estimators.

We now proceed the comparative study by investigating the relevance of implementing the MBAR approach in the expanded ensemble compared to the conditioning approach.

C. Well-conditioning rather than post-processing ?

To obtain the desired estimates with high accuracy, it has been suggested[11] to implement a histogram reweighting estimator[34] using a Markov chain generated from expanded ensemble simulations and taking the subsample sizes $M_i = \sum_{m=1}^{M} \mathbb{1}_{\theta^i}(\vartheta_m)$ as input values, where we assumed that Θ consists of $J+1$ points $\{\theta^i\}_{0\le i\le J}$. In this context, the collected data may equivalently be postprocessed using the MBAR solver.[35] Additionally, conditioning may be done to estimate the MBAR subsample sizes

$$\overline{M}_i = \sum_{m=1}^{M} \frac{\exp\left[\boldsymbol{a}(\theta^i) - \mathcal{U}(\theta^i, q_m)\right]}{\sum_{j=0}^{J} \exp\left[\boldsymbol{a}(\theta^j) - \mathcal{U}(\theta^j, q_m)\right]}. \tag{26}$$

Using $\overline{M}_i$ as input data, the MBAR estimator[35] writes

$$^{\overline{M}}(\mathcal{O}|\theta^i) = \sum_{m=1}^{M} \frac{\mathcal{O}(\theta^i, q_m)\exp[\widehat{\mathcal{A}}(\theta^i) - \mathcal{U}(\theta^i, q_m)]}{\sum_{j=0}^{J} \overline{M}_j \exp[\widehat{\mathcal{A}}(\theta^j) - \mathcal{U}(\theta^j, q_m)]}, \tag{27}$$

where the $\widehat{\mathcal{A}}(\theta^i)$ are the estimated free energies which, in MBAR, corresponds to the solutions to the following set of nonlinear equations:

$$^{\overline{M}}(1|\theta^i) = 1, \quad \text{for} \quad i \in [\![0\ ,\ J]\!]. \tag{28}$$

The solution can be given in closed form and writes (up to an additive constant)

$$\widehat{\mathcal{A}}(\theta^i) = \boldsymbol{a}(\theta^i) - \ln \overline{M}_i, \quad i \in [\![0\ ,\ J]\!]. \tag{29}$$

To check that this is a correct solution, let plug the conjectured free energies in Eq. (29) together with the conditioned subsample sizes in Eq. (26) into the MBAR estimator in

Eq. (27). We obtain

$$
\begin{aligned}
{}^{\overline{M}}(\mathcal{O}|\theta^i) &= \sum_{m=1}^{M} \frac{\mathcal{O}(\theta^i, q_m) \exp\left[\boldsymbol{a}(\theta^i) - \ln \overline{M}_i - \mathcal{U}(\theta^i, q_m)\right]}{\sum_{j=0}^{J} \overline{M}_j \exp\left[\boldsymbol{a}(\theta^j) - \ln \overline{M}_j - \mathcal{U}(\theta^j, q_m)\right]} \\
&= \frac{\frac{1}{M} \sum\limits_{m=1}^{M} \mathcal{O}(\theta^i, q_m) \dfrac{\exp\left[\boldsymbol{a}(\theta^i) - \mathcal{U}(\theta^i, q_m)\right]}{\sum_{j=0}^{J} \exp\left[\boldsymbol{a}(\theta^j) - \mathcal{U}(\theta^j, q_m)\right]}}{\frac{1}{M} \sum\limits_{m=1}^{M} \dfrac{\exp\left[\boldsymbol{a}(\theta^i) - \mathcal{U}(\theta^i, q_m)\right]}{\sum_{j=0}^{J} \exp\left[\boldsymbol{a}(\theta^j) - \mathcal{U}(\theta^j, q_m)\right]}} \\
&= \frac{\frac{1}{M} \sum_{m=1}^{M} \bar{\pi}_{\boldsymbol{a}}(\theta^i|q_m) \mathcal{O}(\theta^i, q_m)}{\frac{1}{M} \sum_{m=1}^{M} \bar{\pi}_{\boldsymbol{a}}(\theta^i|q_m)} = {}^{M}_{\boldsymbol{a}}(\mathcal{O}|\theta^i),
\end{aligned}
$$

where $\bar{\pi}_{\boldsymbol{a}}(\theta|q)$ stands for $\pi^{\theta}_{\boldsymbol{a}}(q)$. One recovers the adiabatic estimator 17 which obviously satisfies the set of nonlinear equations: ${}^{M}_{\boldsymbol{a}}(1|\theta^i) = 1$ for $i \in [\![0\ ,\ J]\!]$. This means that the MBAR estimator coincides with the adiabatic reweighting estimator when the subsample sizes used as input data in the former approach are conditioned. Hence, *conditioning* the expectations associated with the reweighting or binning estimators, as done in subsection III B, or the subsample sizes in MBAR, as presently, allows us to formulate the adiabatic reweighting estimator. Note that if the subsample sizes are estimated from the histogram bins (using M^i instead of $\overline{M}^i$), then a solver is to be implemented to evaluate the optimal free energy estimates $\widehat{\mathcal{A}}(\theta^i)$ of the MBAR estimor. To summarize, the use of the conditioned subsample sizes provides a reduction of the statistical variance associated with the input data in MBAR, and, concomitantly, the task of solving a large set of nonlinear equations is avoided. Nevertheless, an advantage of the histogram reweighting approach[11] proposed by Chodera *et al.* is that the statistical covariance of the samples is taken into account in the construction of the optimal estimator given the histogram bins (the sampled configurations are not iid in general), a feature that is overlooked in the present conditioning approach.

D. Estimation of total expectations

In addition to conditional expectations, expanded ensemble simulations also aim at estimating total expectations, for instance in order to compute free energies along internal or external coordinates. The questions then arise as to (i) how to transpose the binning and reweighting estimators, (ii) how to condition the transposed estimators and (iii) whether conditioning achieves variance reduction.

To answer question (i), we decompose the expectation of $\mathcal{O}(\vartheta, q)$ using the law of total expectation with respect to the external parameter

$$\mathbb{E}\left[\mathcal{O}(\vartheta, q)\right] = \sum_{\theta\in\Theta} \mathbb{E}\left[\mathcal{O}(\theta, q)|\theta\right] \boldsymbol{p}_0(\theta)$$

$$= \sum_{\theta\in\Theta} \frac{\mathbb{E}_a\left[\phi_a^\theta(\vartheta, q)\mathcal{O}(\theta, q)\right]}{\mathbb{E}_a\left[\phi_a^\theta(\vartheta, q)\right]} \boldsymbol{p}_0(\theta). \quad (30)$$

In the last term above, the conditional expectation given θ is expressed as a function of total expectations involving the observable and the generic function, using the expectation ratio of Eq. (7). The unbiased marginal probability of θ that appears in the rhs term is now expressed as a function of the marginal probability of θ with the biasing potential switched on

$$\boldsymbol{p}_0(\theta) = \frac{e^{-a(\theta)}\boldsymbol{p}_a(\theta)}{\sum_{\theta^\dagger\in\Theta} e^{-a(\theta^\dagger)}\boldsymbol{p}_a(\theta^\dagger)}$$

$$= \frac{e^{-a(\theta)}\mathbb{E}_a\left[\phi_a^\theta(\vartheta, q)\right]}{\mathbb{E}_a\left[\sum_{\theta^\dagger\in\Theta} e^{-a(\theta^\dagger)}\phi_a^{\theta^\dagger}(\vartheta, q)\right]}.$$

Inserting the last term above into the rhs term of 30 and eventually permuting the expectation $\mathbb{E}_a$ and the sum $\sum_{\vartheta\in\Theta}$ yields

$$\mathbb{E}\left[\mathcal{O}(\vartheta, q)\right] = \frac{\mathbb{E}_a\left[\sum_{\theta^\dagger\in\Theta} \mathcal{O}(\theta^\dagger, q) e^{-a(\theta^\dagger)}\phi_a^{\theta^\dagger}(\vartheta, q)\right]}{\mathbb{E}_a\left[\sum_{\theta^\dagger\in\Theta} e^{-a(\theta^\dagger)}\phi_a^{\theta^\dagger}(\vartheta, q)\right]}. \quad (31)$$

To manipulate such total expectations, it is more convenient to multiply the previously employed weighing functions ($\mathbb{1}_\theta$, ρ_a^θ, ϕ_a^θ and π_a^θ) by $\exp[-\boldsymbol{a}(\theta)]$. The modified weighing functions are denoted by $\mathbb{h}_a^\theta$, ϱ_a^θ, φ_a^θ and ϖ_a^θ, respectively. The employed notations with their definitions are compiled in Table I. Inserting the functions $\varphi_a^{\theta^\dagger}(\vartheta, q) = e^{-a(\theta^\dagger)}\phi_a^{\theta^\dagger}(\vartheta, q)$ and $\varphi_a(\vartheta, q) = \sum_{\theta^\dagger\in\Theta}\varphi_a^{\theta^\dagger}(\vartheta, q)$ into Eq. (31), we obtain

$$\mathbb{E}\left[\mathcal{O}(\vartheta, q)\right] = \frac{\mathbb{E}_a\left[\sum_{\theta^\dagger\in\Theta} \mathcal{O}(\theta^\dagger, q)\varphi_a^{\theta^\dagger}(\vartheta, q)\right]}{\mathbb{E}_a\left[\varphi_a(\vartheta, q)\right]}. \quad (32)$$

We are now in a position to formulate the estimator of the total expectation based on relation 31:

$${}^{M}_{a}(\mathcal{O}) = \frac{\frac{1}{M}\sum_{m=1}^{M}\sum_{\theta^\dagger\in\Theta}\mathcal{O}(\theta^\dagger, q_m)\varphi_a^{\theta^\dagger}(\vartheta_m, q_m)}{\frac{1}{M}\sum_{m=1}^{M}\varphi_a(\vartheta_m, q_m)} \quad (33)$$

where $\{\vartheta_m, q_m\}_{1\leq m\leq M}$ is a Markov chain generated according to $\mathrm{p}_a(\vartheta, q)$ probability distribution.

We have in particular for the binning estimator

$$\mathbb{H}_{a}^{M}(\mathcal{O})=\frac{\frac{1}{M}\sum_{m=1}^{M}\mathcal{O}(\vartheta_m,q_m)\exp[-\boldsymbol{a}(\vartheta_m)]}{\frac{1}{M}\sum_{m=1}^{M}\exp[-\boldsymbol{a}(\vartheta_m)]},$$

where we resorted to

$$\varphi_a(\vartheta,q)\equiv \mathbb{h}_a(\vartheta)=\exp\big[-\boldsymbol{a}(\vartheta)\big].$$

Similarly, the reweighting estimator writes

$$\mathbb{P}_{a}^{M}(\mathcal{O})=\frac{\frac{1}{M}\sum_{m=1}^{M}\sum_{\theta^\dagger\in\Theta}\mathcal{O}(\theta^\dagger,q_m)\ \varrho_a^{\theta^\dagger}\ (\vartheta_m,q_m)}{\frac{1}{M}\sum_{m=1}^{M}\ \varrho_a\ (\vartheta_m,q_m)},$$

where

$$\varrho_a^{\theta^\dagger}\ (\vartheta_m,q_m)=\|\Theta\|^{-1}\frac{\exp\left[-\mathcal{R}(\theta^\dagger,q_m)\right]}{\exp\left[\boldsymbol{a}(\vartheta_m)-\mathcal{R}(\vartheta_m,q_m)\right]}.$$

This relation often simplifies in practical applications. This is the case for instance when the observable is the indicator function $\mathbb{1}_\theta(\vartheta)$ as shown in Table III and illustrated in subsection III E.

With regards to question (ii), conditioning consists of replacing the $\varphi_a(\vartheta_m,q_m)$ and $\varphi_a^{\theta^\dagger}(\vartheta_m,q_m)$ terms by their expected values given q_m, which are respectively

$$\begin{aligned}\mathbb{E}_a\big(\varphi_a^{\theta^\dagger}(\vartheta,q)|q\big)&=\frac{\sum_{\vartheta\in\Theta}\varphi_a^{\theta^\dagger}(\vartheta,q)\exp\left[\boldsymbol{a}(\vartheta)-\mathcal{R}(\vartheta,q)\right]}{\sum_{\vartheta\in\Theta}\exp\left[\boldsymbol{a}(\vartheta)-\mathcal{R}(\vartheta,q)\right]}\\&=\frac{\exp\left[-\mathcal{R}(\theta^\dagger,q)\right]}{\exp\left[-\bar{\mathcal{R}}_a(q)\right]}=\varpi_a^{\theta^\dagger}(q),\end{aligned}$$

and

$$\begin{aligned}\mathbb{E}_a\big(\varphi_a(\vartheta,q)|q\big)&=\frac{\sum_{\vartheta\in\Theta}\varphi_a(\vartheta,q)\exp\left[\boldsymbol{a}(\vartheta)-\mathcal{R}(\vartheta,q)\right]}{\sum_{\vartheta\in\Theta}\exp\left[\boldsymbol{a}(\vartheta)-\mathcal{R}(\vartheta,q)\right]}\\&=\frac{\exp\left[-\mathcal{R}_0(q)\right]}{\exp\left[-\bar{\mathcal{R}}_a(q)\right]}=\varpi_a(q).\end{aligned}$$

Next, we write the law of total expectation in the rhs ratio of 31 and plug the expected value of $\varphi_a(\vartheta,q)$ given q

$$\begin{aligned}\mathbb{E}\left[\mathcal{O}(\vartheta,q)\right]&=\frac{\mathbb{E}_a\Big[\mathbb{E}_a\big[\varphi_a(\vartheta,q)\mathcal{O}(\vartheta,q)\big|q\big]\Big]}{\mathbb{E}_a\Big[\mathbb{E}_a\big[\varphi_a(\vartheta,q)\big|q\big]\Big]}\\&=\frac{\mathbb{E}_a\Big[\sum_{\vartheta\in\Theta}\varpi_a^{\theta^\dagger}(q)\mathcal{O}(\theta^\dagger,q)\Big]}{\mathbb{E}_a\Big[\varpi_a(q)\Big]}.\end{aligned}\tag{34}$$

From the rhs expectation ratio of 34 and by application of the ergodic theorem, the adiabatic reweighting estimator below is deduced:

$$
{}^{M}_{a}(\mathcal{O}) = \frac{\frac{1}{M}\sum_{m=1}^{M}\sum_{\theta^\dagger\in\Theta}\varpi_a^{\theta^\dagger}(q_m)\mathcal{O}(\theta^\dagger,q_m)}{\frac{1}{M}\sum_{m=1}^{M}\varpi_a(q_m)}, \tag{35}
$$

where $\{q_m\}_{1\le m\le M}$ is a Markov chain of states distributed according to probability distribution $\bar{\mathrm{p}}_a(q) = \exp\left[-\mathcal{U}_0(q) - \bar{\mathcal{R}}_a(q) - \Psi_a^\Theta\right]$ that can possibly be extracted from an expanded Markov chain $\{\vartheta_m, q_m\}_{1\le m\le M}$ generated according to $\mathrm{p}_a(\vartheta,q)$ probability density.

We answer question (iii) in the affirmative: conditioning for estimating total expectations achieves variance reduction. As for estimations of conditional expectations in section III, this property is a consequence of the law of total variance. The proof follows the same reasoning, but requires replacing the conditionally centered variable $\mathcal{O}^\theta(\theta,q^\dagger) = \mathcal{O}(\theta,q^\dagger) - \mathbb{E}\left(\mathcal{O}(\theta,q)|\theta\right)$ by the totally centered variable

$$
\mathcal{O}^\Theta(\theta^\dagger,q^\dagger) = \mathcal{O}(\theta^\dagger,q^\dagger) - \mathbb{E}\left(\mathcal{O}(\vartheta,q)\right)
$$

and the reweighting factor ϕ_a^θ by a sum over $\theta^\dagger\in\Theta$ involving the $\varphi_a^{\theta^\dagger}$ factors. The asymptotic variance of the ${}^{M}_{a}(\mathcal{O})$ estimator writes (see Appendix A)

$$
\sigma^2\left[\ {}^{\infty}_{a}(\mathcal{O})\right] = \mathrm{var}_a\left[\sum_{\theta^\dagger\in\Theta}\mathcal{O}^\Theta(\theta^\dagger,q)\frac{\varphi_a^{\theta^\dagger}(\vartheta,q)}{\mathbb{E}_a(\varphi_a)}\right], \tag{36}
$$

where the quantity inside the variance is obviously centered. The asymptotic variance of the ${}^{M}_{a}(\mathcal{O})$ estimator is obtained from the one of the ${}^{M}_{a}(\mathcal{O}|\theta)$ estimator by replacing the conditional probabilities $\pi_a^\theta(q)$ by sums involving $\varpi_a^{\theta^\dagger}(q)$ over $\theta^\dagger\in\Theta$. One obtains

$$
\begin{aligned}
\sigma^2\left[\ {}^{\infty}_{a}(\mathcal{O})\right] &= \mathrm{var}_a\left[\frac{\sum_{\theta^\dagger\in\Theta}\mathcal{O}^\Theta(\theta^\dagger,q)\varpi_a^{\theta^\dagger}(q)}{\mathbb{E}_a(\varpi_a)}\right] \\
&= \mathrm{var}_a\left[\mathbb{E}_a\left[\sum_{\theta^\dagger\in\Theta}\mathcal{O}^\Theta(\theta^\dagger,q)\frac{\varphi_a^{\theta^\dagger}(\vartheta,q)}{\mathbb{E}_a(\varphi_a)}\middle| q\right]\right],
\end{aligned}
$$

where $\varpi_a = \sum_{\theta^\dagger\in\Theta}\varpi_a^{\theta^\dagger}$. Plugging the law of total variance into the right-hand side variance enables one to conclude that the asymptotic variance of the ${}^{M}_{a}(\mathcal{O})$ estimator is smaller than that of the $\Phi_a^M(\mathcal{O})$ estimator

$$\sigma^2\left[\;{}^{\infty}_{a}(\mathcal{O})\right] = \mathrm{var}_a\left[\sum_{\theta^\dagger\in\Theta}\mathcal{O}^\Theta(\theta^\dagger,q)\frac{\varphi_a^{\theta^\dagger}(\vartheta,q)}{\mathbb{E}_a(\varphi_a)}\right] - \mathbb{E}_a\left[\mathrm{var}_a\left[\sum_{\theta^\dagger\in\Theta}\mathcal{O}^\Theta(\theta^\dagger,q)\frac{\varphi_a^{\theta^\dagger}(\vartheta,q)}{\mathbb{E}_a(\varphi_a)}\middle| q\right]\right]$$

$$< \sigma^2\left[\;{}^{\infty}_{a}(\mathcal{O})\right].$$

Observable dependence on internal coordinates exclusively

When the observable $\bar{\mathcal{O}}(q)$ does not depend on the external parameter, the generic and adiabatic reweighting (AR) estimators simplify into

$$\;{}^{M}_{a}(\bar{\mathcal{O}}) = \frac{\frac{1}{M}\sum_{m=1}^{M}\bar{\mathcal{O}}(q_m)\varphi_a(\vartheta_m,q_m)}{\frac{1}{M}\sum_{m=1}^{M}\varphi_a(\vartheta_m,q_m)},$$

$$\;{}^{M}_{a}(\bar{\mathcal{O}}) = \frac{\frac{1}{M}\sum_{m=1}^{M}\bar{\mathcal{O}}(q_m)\varpi_a(q_m)}{\frac{1}{M}\sum_{m=1}^{M}\varpi_a(q_m)}.$$

The corresponding asymptotic variances become (see Appendix A)

$$\sigma^2\left[\;{}^{\infty}_{a}(\bar{\mathcal{O}})\right] = \mathrm{var}_a\left[\bar{\mathcal{O}}^\Theta(q)\frac{\varphi_a(\vartheta,q)}{\mathbb{E}_a[\varphi_a]}\right],$$

$$\sigma^2\left[\;{}^{\infty}_{a}(\bar{\mathcal{O}})\right] = \mathrm{var}_a\left[\bar{\mathcal{O}}^\Theta(q)\frac{\varpi_a(q)}{\mathbb{E}_a[\varpi_a]}\right].$$

where $\bar{\mathcal{O}}^\Theta(q) = \bar{\mathcal{O}}(q) - \mathbb{E}[\bar{\mathcal{O}}]$. An example of application is given in Section VI in which the observable is the indicator function $\mathbb{1}_{\xi^\star}\circ\xi(q)$ with the external parameter harmonically coupled to the reaction coordinate $\xi(q)$. The measured thermodynamic quantity is the probability to observe the value $\xi^\star$ of the reaction coordinate. Note that with harmonic coupling, we have $\rho(\vartheta,q) = \exp\left[-\boldsymbol{a}(\vartheta) + \mathcal{R}^\xi\circ\xi(q)\right]$ and $\varpi_a(q) = \exp\left[\bar{\mathcal{R}}_a^\xi\circ\xi(q)\right]$ since $\bar{\mathcal{R}}_0 = 0$. Hence, the reweighting estimator and the adiabatic reweighting estimator respectively simplify into

$$\mathbb{P}_a^M(\bar{\mathcal{O}}) = \frac{\frac{1}{M}\sum_{m=1}^{M}\bar{\mathcal{O}}(q_m)\exp\left[-\boldsymbol{a}(\vartheta_m) + \mathcal{R}^\xi(\vartheta_m,\xi_m)\right]}{\frac{1}{M}\sum_{m=1}^{M}\exp[-\boldsymbol{a}(\vartheta_m) + \mathcal{R}^\xi(\vartheta_m,\xi_m)]}$$

and

$$\;{}^{M}_{a}(\bar{\mathcal{O}}) = \frac{\frac{1}{M}\sum_{m=1}^{M}\bar{\mathcal{O}}(q_m)\exp\bar{\mathcal{R}}_a^\xi(\xi_m)}{\frac{1}{M}\sum_{m=1}^{M}\exp\bar{\mathcal{R}}_a^\xi(\xi_m)}, \tag{37}$$

where $\xi_m = \xi(q_m)$. The correcting factors $\exp \bar{\mathcal{R}}_a^\xi(\xi_m)$ are proportional to the marginal probability ratios $\bar{\mathrm{p}}_0(q_m)/\bar{\mathrm{p}}_a(q_m)$. The proportionality factor is $\exp\left[\Psi_a^\Theta - \Psi_0^\Theta\right]$. The adiabatic reweighting estimator with $\bar{\mathcal{O}}$ set to $\mathbb{1}_{\xi^\star} \circ \xi$ is implemented in subsection VI C in particular.

Observable dependence on external parameter exclusively

Another example of application is given in Table I in which the observable to average is the indicator function $\mathbb{1}_\theta(\vartheta)$. The observable does not explicitly depend on the position q. Its average yields the probability to observe the value θ of the external parameter in the unbiased expanded ensemble, and the logarithm of this probability is the opposite of the free energy. We discuss in subsection III E various ways of estimating the free energy $\mathcal{A}(\theta)$. This task is the primary goal of expanded ensemble simulations.

E. Estimation of the free energy along an external parameter

The free energy $\mathcal{A}(\theta)$ for $\theta \in \Theta$ is minus the logarithm of the total expectation of the indicator function $\mathbb{1}_\theta$. Its derivative is $\mathbb{E}\left[\partial_\theta \mathcal{U}(\theta, q)|\theta\right]$, a conditional expectation given θ which can be estimated and then integrated. Table II illustrates the various ways allowing to estimate the corresponding total and conditional expectations using the generic weighing functions and a time-independent auxiliary biasing potential.

With the histogram binning, reweighting and conditioning estimators, denoted by $\mathbb{H}_a^M$, $\mathbb{P}_a^M$ and $\ _a^M$ respectively, that makes potentially 6 direct methods of computing the free energy, while direct such methods are usually classified into three *overlapping* categories in the literature: thermodynamic occupation[36–38] (TO), thermodynamic integration[39] (TI), free energy perturbation[40] (FEP). We next analyze the correspondence between estimators and free energy methods.

Estimating the free energy via the logarithm of the occupation probability of θ corresponds to the way of proceeding of methods belonging to the first category. The free energy

TABLE I. Notations and definitions of weighing functions and relations to conditional and total expectations.

Definitions

$$\mathbb{h}_a^\theta(\vartheta) = \exp\left[-\boldsymbol{a}(\theta)\right] \mathbb{1}_\theta(\vartheta), \qquad \mathbb{h}_a = \textstyle\sum_{\theta\in\Theta} \mathbb{h}_a^\theta,$$

$$\varrho_a^\theta(\vartheta, q) = \exp\left[-\boldsymbol{a}(\theta)\right] \rho_a^\theta(\vartheta, q) = \frac{1}{\|\Theta\|} \frac{\exp\left[-\mathcal{U}(\theta, q)\right]}{\exp\left[\boldsymbol{a}(\vartheta, q) - \mathcal{U}(\vartheta, q)\right]} \qquad \varrho_a = \textstyle\sum_{\theta\in\Theta} \varrho_a^\theta,$$

$$\varphi_a^\theta(\vartheta, q) = \exp[-\boldsymbol{a}(\theta)]\phi_a(\vartheta, q) = \begin{cases} \mathbb{h}_a^\theta(\vartheta) & \text{if histogram binning,} \\ \varrho_a^\theta(\vartheta, q) & \text{if reweighting,} \end{cases} \qquad \varphi_a = \textstyle\sum_{\theta\in\Theta} \varphi_a^\theta,$$

$$\varpi_a^\theta(q) = \exp\left[-\boldsymbol{a}(\theta)\right] \bar{\pi}_a(\theta|q) = \frac{\exp\left[-\mathcal{U}(\theta, q)\right]}{\sum_{\vartheta\in\Theta} \exp\left[\boldsymbol{a}(\vartheta, q) - \mathcal{U}(\vartheta, q)\right]}, \qquad \varpi_a = \textstyle\sum_{\theta\in\Theta} \varpi_a^\theta.$$

Expressions for total expectations

$$\mathbb{E}\left[\mathcal{O}(\vartheta, q)\right] = \frac{\mathbb{E}_a\left[\sum_{\theta^\dagger\in\Theta} \varphi_a^{\theta^\dagger}(\vartheta, q)\mathcal{O}(\theta^\dagger, q)\right]}{\mathbb{E}_a\left[\varphi_a(\vartheta, q)\right]} \implies \mathbb{E}\left[\mathbb{1}_\theta(\vartheta)\right] = \frac{\mathbb{E}_a\left[\varphi_a^\theta(\vartheta, q)\right]}{\mathbb{E}_a\left[\varphi_a(\vartheta, q)\right]}$$

$$\mathbb{E}\left[\mathcal{O}(\vartheta, q)\right] = \frac{\mathbb{E}_a\left[\sum_{\theta^\dagger\in\Theta} \varpi_a^{\theta^\dagger}(q)\mathcal{O}(\theta^\dagger, q)\right]}{\mathbb{E}_a\left[\varpi_a(q)\right]} \implies \mathbb{E}\left[\mathbb{1}_\theta(\vartheta)\right] = \frac{\mathbb{E}_a\left[\varpi_a^\theta(q)\right]}{\mathbb{E}_a\left[\varpi_a(q)\right]}$$

Expressions for conditional expectations

$$\mathbb{E}_a\left[\varphi_a^\theta(\vartheta, q)\middle|q\right] = \varpi_a^\theta(q) \quad \Longleftarrow \quad \mathbb{E}_a\left[\phi_a^\theta(\vartheta, q)\middle|q\right] = \pi_a^\theta(q),$$

$$\mathbb{E}\left[\partial_\theta\mathcal{U}(\theta, q)|\theta\right] = -\partial^\theta \ln \mathbb{E}_a\left[\varrho_a^\theta(\vartheta, q)\right] \quad \Longleftarrow \quad \partial^\theta \varrho_a^\theta(\vartheta, q) = -\partial_\theta\mathcal{U}(\theta, q)\, \varrho_a^\theta(\vartheta, q),$$

$$\mathbb{E}\left[\partial_\theta\mathcal{U}(\theta, q)|\theta\right] = -\partial^\theta \ln \mathbb{E}_a\left[\varpi_a^\theta(q)\right] \quad \Longleftarrow \quad \partial^\theta \varpi_a^\theta(q) = -\partial_\theta\mathcal{U}(\theta, q)\varpi_a^\theta(q).$$

estimate is related to the histogram binning estimator

$$\widehat{\mathcal{A}(\theta)}_{\mathrm{TO}}^M = -\ln\left[\frac{\frac{1}{M}\sum_{m=1}^M \mathbb{1}_\theta(\vartheta_m)\exp[-\boldsymbol{a}(\vartheta_m)]}{\frac{1}{M}\sum_{m=1}^M \exp[-\boldsymbol{a}(\vartheta_m)]}\right] = - \ln\left[\frac{\frac{1}{M}\sum_{m=1}^M \mathbb{h}_a^\theta(\vartheta_m)}{\frac{1}{M}\sum_{m=1}^M \mathbb{h}_a(\vartheta_m)}\right] = -\ln \mathbb{H}_a^M\left(\mathbb{1}_\theta\right).$$

TABLE II. Expectation ratios based on which the various free energy estimators of Table III are constructed. For simplicity, we omit the dependence of φ_a^θ and φ_a on their variables (ϑ, q) inside the expectations. For instance, $\mathbb{E}_a\left[\varphi_a^\theta \mathcal{U}(\theta,q)\right]$ reads $\mathbb{E}_a\left[\varphi_a^\theta(\vartheta,q)\mathcal{U}(\theta,q)\right]$, wherein θ is constant.

$$\mathcal{A}(\theta) \;=\; -\ln \mathbb{E}(\mathbb{1}_\theta) \;=\; \begin{cases} -\ln \dfrac{\mathbb{E}_a[\varphi_a^\theta]}{\mathbb{E}_a[\varphi_a]} & \text{for histogram binning or reweighting,} \\[2ex] -\ln \dfrac{\mathbb{E}_a\left[\mathbb{E}_a[\varphi_a^\theta]\middle|q\right]}{\mathbb{E}_a\left[\mathbb{E}_a\left[\varphi_a\right]\middle|q\right]} \;=\; -\ln \dfrac{\mathbb{E}_a\left[\varpi_a^\theta\right]}{\mathbb{E}_a\left[\varpi_a\right]} & \text{with conditioning,} \end{cases}$$

$$\mathcal{A}'(\theta) \;=\; \mathbb{E}(\partial_\theta \mathcal{U}|\theta) \;=\; \begin{cases} \dfrac{\mathbb{E}_a[\varphi_a^\theta \partial_\theta \mathcal{U}(\theta,q)]}{\mathbb{E}_a[\varphi_a^\theta]} & \text{for histogram binning or reweighting,} \\[2ex] \dfrac{\mathbb{E}_a\left[\partial_\theta \mathcal{U}(\theta,q)\mathbb{E}_a[\varphi_a^\theta]\middle|q\right]}{\mathbb{E}_a\left[\mathbb{E}_a\left[\varphi_a^\theta\right]\middle|q\right]} \;=\; -\dfrac{\mathbb{E}_a\left[\partial^\theta \varpi_a^\theta\right]}{\mathbb{E}_a\left[\varpi_a^\theta\right]} & \text{with conditioning.} \end{cases}$$

Methods of the second category consists of estimating the free energy derivative and evaluating the free energy through numerical integration. This is what is actually done in the ABF technique. From an expanded ensemble simulation, a simple way of obtaining an estimate $\widehat{\mathcal{A}}'(\theta)$ of the mean force involves the binning estimator $\mathbb{H}_a^M$

$$\widehat{\mathcal{A}'(\theta)}^M_{\mathrm{TI}} = \frac{\frac{1}{M}\sum_{m=1}^M \partial_\theta \mathcal{U}(\theta,q_m)\mathbb{h}_a^\theta(\vartheta_m)}{\frac{1}{M}\sum_{m=1}^M \mathbb{h}_a^\theta(\vartheta_m)} = \frac{\mathtt{I}^M(\partial_\theta \mathcal{U}\;\mathbb{h}_a^\theta)}{\mathtt{I}^M(\mathbb{h}_a^\theta)} = \mathbb{H}^M\left[\partial_\theta \mathcal{U}\middle|\theta\right].$$

It may be suggested to estimate the free energy derivative resorting instead to the reweighting estimator as it is done in umbrella sampling.[41] Using the reweighting function introduced in Table I together with the property $\partial_\theta\ \varrho_a^\theta\ (\vartheta,q) = -\partial_\theta \mathcal{U}(\theta,q)\ \varrho_a^\theta\ (\vartheta,q)$, we have

$$\widehat{\mathcal{A}'(\theta)}^M_{\mathrm{FEP}} = \mathbb{P}_a^M\big(\partial_\theta \mathcal{U}\big|\theta\big) = -\partial^\theta \ln\left[\frac{1}{M}\sum_{m=1}^M \varrho_a^\theta\ (\vartheta_m,q_m)\right].$$

The fact that the estimator can be written has a logarithmic derivative of another reweighing estimator indicates that it is not necessary to integrate the mean force to obtain the free energy. The reweighting approach pertains to the second category of free energy methods

(FEP), which aim at directly evaluating the free energy by estimating a partition function ratio and then taking minus its logarithm

$$\widehat{\mathcal{A}(\theta)}_{\mathrm{FEP}}^{M} = -\ln\left[\frac{\frac{1}{M}\sum_{m=1}^{M} \varrho_a^\theta\,(\vartheta_m, q_m)}{\frac{1}{M}\sum_{m=1}^{M} \varrho_a\,(\vartheta_m, q_m)}\right] = -\ln \mathbb{P}_a^M(\mathbb{1}_\theta).$$

To perform a conditioning with respect to the FEP and TO method above, one must replace the weighing factors $\mathbb{h}_a^\theta$ and ϱ_a^θ by their conditional expected values given q, which happens to be given by $\varpi_a^\theta(q)$. Similarly, $\mathbb{h}_a$ and ϱ_a must also be replaced by $\varpi_a(q)$. One thus obtains the following estimator

$$\widehat{\mathcal{A}(\theta)}_{\mathrm{AR}}^{M} = -\ln\left[\frac{\frac{1}{M}\sum_{m=1}^{M} \varpi_a^\theta(q_m)}{\frac{1}{M}\sum_{m=1}^{M} \varpi_a(q_m)}\right].$$

Differentiating the free energy estimate with respect to θ yields

$$\begin{aligned}
\frac{d\widehat{\mathcal{A}(\theta)}_{\mathrm{AR}}^{M}}{d\theta} &= -\partial^\theta \ln\left[\frac{\sum_{m=1}^{M} \varpi_a^\theta(q_m)}{\sum_{m=1}^{M} \varpi_a(q_m)}\right] \\
&= -\frac{\sum_{m=1}^{M} \partial^\theta \varpi_a^\theta(q_m)}{\sum_{m=1}^{M} \varpi_a^\theta(q_m)} \\
&= \;{}_a^M(\partial_\theta \mathcal{U}|\theta) = \widehat{\mathcal{A}'(\theta)}_{\mathrm{AR}}^{M},
\end{aligned}$$

where we substituted $-\partial_\theta \mathcal{U}(\theta, q_m)\varpi_a^\theta(q_m)$ for $\partial^\theta \varpi_a^\theta(q_m)$ in the second line and eventually identify with the AR estimate of $\partial_\theta \mathcal{U}$. The consistency between the estimated free energies and the estimated mean forces in the AR method is a property inherited from the FEP method. However, unlike FEP method, the adiabatic reweighting approach is directly related to thermodynamic integration, since the estimated mean force can also be constructed from the following conditioning scheme

$$\widehat{\mathcal{A}'(\theta)}_{\mathrm{AR}}^{M} = \frac{\frac{1}{M}\sum_{m=1}^{M} \partial_\theta \mathcal{U}(\theta, q_m)\mathbb{E}_a\left[\mathbb{h}_a^\theta(\vartheta)\middle| q_m\right]}{\frac{1}{M}\sum_{m=1}^{M} \mathbb{E}_a\left[\mathbb{h}_a^\theta(\vartheta)\middle| q_m\right]}.$$

This means in particular that each sampled point q_m with $1 \le m \le M$ contributes to the estimated mean force with an integrated weight over Θ that is equal to one. This property is inherited from the TI method and does not hold for the FEP method. This explains why the latter method may yield irrelevant results in some circumstances. This point is illustrated in Section V. The four ways of estimating the free energy and its derivative are summarized in Table III and are illustrated in Fig. 1.

Next, we compare the variances of the TI, FEP and TO methods to the one of the AR method. The asymptotic variance for the TO/FEP method can be cast in the following

TABLE III. Standard (TI, FEP, TO) and conditioning (AR) estimators for computing mean forces and free energies. Note that, unlike ϱ_a^θ and ϖ_a^θ weighing functions, the function $\mathbb{h}_a^\theta$ can not be differentiated with respect to θ. It results that two distinct methods (TO and TI) are based on histogram binning.

Estimation of free energy $\widehat{\mathcal{A}(\theta)}_{\mathrm{X}}^{M}$		Corresponding mean force $\widehat{\mathcal{A}'(\theta)}_{\mathrm{X}}^{M}$
$\widehat{\mathcal{A}(\theta)}_{\mathrm{TO}}^{M} = -\ln \mathbb{H}_a^M(\mathbb{1}_\theta) = -\ln \dfrac{\mathtt{I}^M(\mathbb{h}_a^\theta)}{\mathtt{I}^M(\mathbb{h}_a)}$	$\rightarrow$	finite differentiation of $\widehat{\mathcal{A}(\theta)}_{\mathrm{TO}}^{M}$ yields $\widehat{\mathcal{A}'(\theta)}_{\mathrm{TO}}^{M}$
$\widehat{\mathcal{A}(\theta)}_{\mathrm{TI}}^{M} \leftarrow$ numerical quadrature	$\leftarrow$	$\dfrac{\mathtt{I}^M(\mathbb{h}_a^\theta \partial_\theta \mathcal{U})}{\mathtt{I}^M(\mathbb{h}_a^\theta)} = \mathbb{H}_a^M(\partial_\theta \mathcal{U}\vert\theta)$
$\widehat{\mathcal{A}(\theta)}_{\mathrm{FEP}}^{M} = -\ln \mathbb{P}_a^M(\mathbb{1}_\theta) = -\ln \dfrac{\mathtt{I}^M(\varrho_a^\theta)}{\mathtt{I}^M(\varrho_a)}$	$\rightleftarrows$	$-\partial^\theta \ln \dfrac{\mathtt{I}^M(\varrho_a^\theta)}{\mathtt{I}^M(\varrho_a)} = \dfrac{\mathtt{I}^M(-\partial^\theta \varrho_a^\theta)}{\mathtt{I}^M(\varrho_a^\theta)} = \mathbb{P}_a^M(\partial_\theta \mathcal{U}\vert\theta)$
$\widehat{\mathcal{A}(\theta)}_{\mathrm{AR}}^{M} = -\ln \sqcap_a^M(\mathbb{1}_\theta) = -\ln \dfrac{\mathtt{I}^M(\varpi_a^\theta)}{\mathtt{I}^M(\varpi_a)}$	$\rightleftarrows$	$-\partial^\theta \ln \dfrac{\mathtt{I}^M(\varpi_a^\theta)}{\mathtt{I}^M(\varpi_a)} = \dfrac{\mathtt{I}^M(-\partial^\theta \varpi_a^\theta)}{\mathtt{I}^M(\varpi_a^\theta)} = \sqcap_a^M(\partial_\theta \mathcal{U}\vert\theta)$

form using the generic functions φ_a^θ and φ_a (see Appendix A, Eq. (A3))

$$\sigma^2\left[\widehat{\mathcal{A}(\theta)}_{\mathrm{FEP/TO}}^{\infty}\right] = \mathrm{var}_a\left[\frac{\varphi_a^\theta(\vartheta,q)}{\mathbb{E}_a[\varphi_a^\theta]} - \frac{\varphi_a(\vartheta,q)}{\mathbb{E}_a[\varphi_a]}\right]. \tag{38}$$

The asymptotic variance of the AR method can be cast in the similar form (see Appendix A, Eq. (A4))

$$\sigma^2\left[\widehat{\mathcal{A}(\theta)}_{\mathrm{AR}}^{\infty}\right] = \mathrm{var}_a\left[\mathbb{E}_a\left[\frac{\varphi_a^\theta(\vartheta,q)}{\mathbb{E}_a[\varphi_a^\theta]} - \frac{\varphi_a(\vartheta,q)}{\mathbb{E}_a[\varphi_a]}\middle| q\right]\right]$$
$$= \mathrm{var}_a\left[\frac{\varpi_a^\theta(q)}{\mathbb{E}_a[\varpi_a^\theta]} - \frac{\varpi_a(q)}{\mathbb{E}_a[\varpi_a]}\right].$$

The law of total variance then entails the following strict inequality

$$\mathrm{var}_a\left[\frac{\varphi_a^\theta}{\mathbb{E}_a[\varphi_a^\theta]} - \frac{\varphi_a}{\mathbb{E}_a[\varphi_a]}\right] - \mathrm{var}_a\left[\frac{\varpi_a^\theta}{\mathbb{E}_a[\varpi_a^\theta]} - \frac{\varpi_a}{\mathbb{E}_a[\varpi_a]}\right] =$$
$$\mathbb{E}_a\left\{\mathrm{var}_a\left[\frac{\varphi_a^\theta}{\mathbb{E}_a[\varphi_a^\theta]} - \frac{\varphi_a}{\mathbb{E}_a[\varphi_a]}\middle| q\right]\right\} > 0.$$

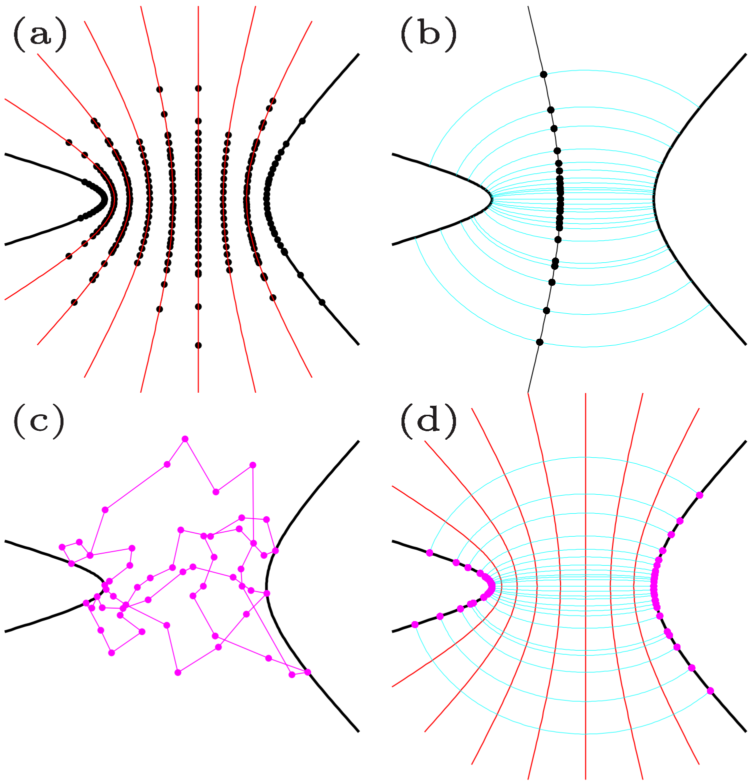

FIG. 1. Schematic illustration of the various methods of estimating the free energy difference between the two extremal θ values symbolized by the two black and thick hyperbolic curves: (a) the thermodynamic integration (TI) estimates the free energy derivative on a series of intermediate θ values (red curves) and then integrate; (b) free energy perturbation (FEP) estimates associated partition function ratios: the black filled circles represents the sampled states and the cyan elliptic curves symbolize the 2 reweighting processes; (c) thermodynamic occupation measures the occupation probabilities of the two extremal θ values and takes the logarithmic difference; (d) the use of a conditioning scheme unifies these three standard approaches.

It results the following strict inequality for the asymptotic variances

$$\sigma^2\left[\widehat{\mathcal{A}(\theta)}^{\infty}_{\mathrm{AR}}\right] < \min\left\{\sigma^2\left[\widehat{\mathcal{A}(\theta)}^{\infty}_{\mathrm{TO}}\right], \sigma^2\left[\widehat{\mathcal{A}(\theta)}^{\infty}_{\mathrm{FEP}}\right]\right\}.$$

With regards to the TI method, the efficiencies of the adiabatic reweighting and histogram binning estimators are more easily compared considering the derivative of the free energy. The asymptotic variances associated with the ${}^{M}_{a}(\partial_\theta \mathcal{U}|\theta)$ and $\mathbb{H}^M(\partial_\theta \mathcal{U}|\theta)$ estimators satisfy the relation $\sigma^2\left[\ {}^{M}_{a}(\partial_\theta \mathcal{U}|\theta)\right] < \sigma^2\left[\mathbb{H}^M(\partial_\theta \mathcal{U}|\theta)\right]$. It is therefore always preferable to estimate free energies in combination with a conditioning scheme when the auxiliary biasing potential is time-independent. Remarkably, whatever the standard free energy method (TO, FEP, TI) that is chosen, conditioning with respect to the external parameter provides the same AR estimator, as illustrated in Fig. 1.

Nevertheless, pre-processing is required instead to construct a relevant auxiliary biasing potential. Prior to showing how this can be done, we derive the form of the optimal biasing potential.

IV. OPTIMAL BIASING POTENTIAL WITH HISTOGRAM BINNING

A. Conditional expectations

When estimating conditional expectations of an observable $q \mapsto \mathcal{O}(\theta, q)$ given $\theta \in \Theta$, the biasing potential should ideally be chosen such that it minimizes the sum of the asymptotic variances over $\theta \in \Theta$, assuming all estimates to be equally important. It appears that an analytical form of the optimal biasing potential can be exhibited for the binning estimator $\mathtt{H}_a^M(\mathcal{O}|\theta)$. Let consider that θ takes values in a discrete set $\Theta = \{\theta^j\}_{0\leq j\leq J}$ with for instance $\theta^j = j/J$ or $\theta^j = \theta_{\min} + j\theta_{\max}/J$ depending on the set-up. Then, the sum of asymptotic variances to minimize is

$$
\begin{aligned}
\sigma^2_{\mathbb{H}}(\mathcal{O}) &= \sum_{\theta\in\Theta} \sigma^2 \left[\mathbb{H}_a^{+\infty}(\mathcal{O}|\theta)\right] \\
&= \sum_{\theta\in\Theta} \frac{\mathbb{E}_a\left[\mathbb{1}_\theta(\vartheta)\left(\mathcal{O}(\theta,q) - \mathbb{E}\left[\mathcal{O}(\theta,q)|\theta\right]\right)^2\right]}{p_a(\theta)^2} \\
&= \sum_{\theta\in\Theta} \frac{\mathbb{E}\left[\mathcal{O}(\theta,q)^2\middle|\theta\right] - \mathbb{E}\left[\mathcal{O}(\theta,q)|\theta\right]^2}{p_a(\theta)} \\
&= \sum_{j=0}^{J} \frac{\mathrm{var}(\mathcal{O}(\theta^j,q)|\theta^j)}{p_a(\theta^j)},
\end{aligned}
$$

where we exploited the fact that $\mathbb{1}_\theta(\vartheta)^2 = \mathbb{1}_\theta(\vartheta)$. Expression 39 is obtained from Eq. (22) by substituting $\mathbb{1}_\theta(\vartheta)$ for $\phi_a^\theta(\vartheta, q)$, summing and simplifying. The nice feature is that the variances of the numerators do not depend on the biasing potential a as they are conditioned on θ. Given the conditional variances $v^j = \mathrm{var}(\mathcal{O}(\theta,q)|\theta^j)$, the auxiliary potential minimizing $\sigma^2_{\mathtt{H}}(\mathcal{O})$ subject to the equality constraint $\sum_{j=0}^J p_a(\theta^j) = 1$ can be obtained through the method of Lagrange's multipliers. The discretized biases $a^j = a(\theta^j)$ being determined up to a common additive constant, we can assume that

$$a^j = \ln \mathbf{p}_a(\theta^j) + \mathcal{A}(\theta^j). \tag{39}$$

Denoting by λ the multiplier associated with the constraint, the Lagrangian function to minimize is therefore

$$\mathcal{L}(\lambda, \mathbf{a})\, c = \lambda \left(-1 + \sum_{j=0}^{J} \exp\left[a^j - \mathcal{A}(\theta^j)\right] \right) + \sum_{j=0}^{J} \exp\left[-a^j + \mathcal{A}(\theta^j) + \ln v^j\right]$$

where $\mathbf{a} = \{a^j\}_{0 \le j \le J}$. The stationary points of the cost function $\mathcal{L}$ must satisfy the following conditions

$$\begin{cases} \dfrac{\partial \mathcal{L}}{\partial \lambda}(\lambda, \mathbf{a}) = 0, \\ \dfrac{\partial \mathcal{L}}{\partial a^j}(\lambda, \mathbf{a}) = 0, \quad j \in [\![0\ ,\ J]\!] \end{cases}$$

which are equivalent to

$$\begin{cases} \lambda = \left(\sum_{\imath=1}^{J} \sqrt{v^\imath} \right)^2 \\ a^j = \mathcal{A}(\theta^j) + \ln \sqrt{v^j} - \ln \left(\sum_{\imath=1}^{J} \sqrt{v^\imath} \right),\ j \in [\![0\ ,\ J]\!]. \end{cases}$$

The solution, denoted by $(\lambda_c, \mathbf{a}_c)$, corresponds to a minimum of the function $\mathbf{a} \mapsto \mathcal{L}(\lambda_c, \mathbf{a})$ because the associated Hessian matrix at $\mathbf{a}_c$ is diagonal and because its diagonal entries (the eigenvalues) are strictly positive

$$\frac{\partial^2 \mathcal{L}}{\partial a^i \partial a^j}(\lambda_c, \mathbf{a}_c) = \begin{cases} \left(\dfrac{1 + v^i}{\sqrt{v^i}} \right) \left(\sum\limits_{j=0}^{J} \sqrt{v^j} \right) & \text{if } j = i, \\ 0 & \text{if } j \neq i. \end{cases}$$

The marginal probability of θ associated with the optimal biasing potential $\boldsymbol{a}_c$ is such that

$$\mathbf{p}_{a_c}(\theta^i) = \exp\left[\boldsymbol{a}_c(\theta^i) - \mathcal{A}(\theta^i)\right] = \frac{\sqrt{\operatorname{var}\left[\mathcal{O}(\theta^i, q)|\theta\right]}}{\sum\limits_{j=0}^{J} \sqrt{\operatorname{var}\left[\mathcal{O}(\theta^j, q)|\theta^j\right]}}$$

Hence, assuming that the sampled states are iid, then the optimal biasing potential for estimating $\mathbb{E}[\mathcal{O}(\theta, q)|\theta]$ over Θ is equal to the sum of the free energy and of the half logarithm of the normalized variance of the observable. Biasing potentials that include this variance term have never been used to the best of our knowledge. They are traditionally adapted on the free energy only, probably because estimating this quantity is already a difficult task. One may then wonder what is the optimal biasing potential for estimating the free energy, since its knowledge is required. We exhibit the form of the optimal bias for the TO method which is based on histogram binning.

B. Thermodynamics occupation

We assume that the biasing potential still satisfies Eq. (39). This entails that $\mathcal{p}_a(\theta) = \exp\left[a(\theta) - \mathcal{A}(\theta)\right]$ and $\mathbb{E}_a[\varphi_a] = 1$. The asymptotic variance of this TO method is therefore

$$\begin{aligned}\sigma^2\left[\widehat{\mathcal{A}(\theta)}^{\infty}_{\mathrm{TO}}\right] &= \mathrm{var}_a\left[\frac{\mathbb{1}_\theta(\vartheta)}{\mathcal{p}_a(\theta)} - \sum_{\theta^\dagger\in\Theta}\mathbb{1}_{\theta^\dagger}(\vartheta)e^{-a(\theta^\dagger)}\right] \\ &= e^{-a(\theta)}\left[e^{\mathcal{A}(\theta)} - 2\right] + \sum_{\theta^\dagger\in\Theta} e^{-a(\theta^\dagger)-\mathcal{A}(\theta^\dagger)}\end{aligned}$$

where we developed the variance resorting to the equalities $\mathbb{E}_a\left[\mathbb{1}_\theta(\vartheta)^2\right] = \mathbb{E}_a\left[\mathbb{1}_\theta(\vartheta)\right] = \mathcal{p}_a(\theta)$. The summed variance of the TO method is therefore, assuming equal weight for all bins

$$\sigma^2_{\mathrm{TO}} = \sum_{\theta^\dagger\in\Theta} e^{-a(\theta^\dagger)}\left[e^{\mathcal{A}(\theta^\dagger)} - 2 + (1+J)e^{-\mathcal{A}(\theta^\dagger)}\right].$$

The summed variance can now be minimized using the method of Lagrange multipliers with the normalizing constraint given by Eq. (39), in a way analogous to what was done in subsection IV A for conditional expectations. The analysis provides us with the optimal biasing potential that follows

$$a_{\mathrm{opt}}(\theta) = \mathcal{A}(\theta) + \frac{1}{2}\ln\left[1 - 2e^{-\mathcal{A}(\theta)} + (1+J)e^{-2\mathcal{A}(\theta)}\right].$$

in which we omitted the additive constant

$$K_\Theta = -\ln\left[\sum_{\theta^\dagger\in\Theta}\sqrt{1 - 2e^{-\mathcal{A}(\theta^\dagger)} + (1+J)e^{-2\mathcal{A}(\theta^\dagger)}}\right]$$

used as normalizing factor in Eq. (39). The optimal bias compensates the free energy wherever this one is substantially larger than $\ln(1+J)$. The compensation becomes exact for all $\theta \in \Theta$ in the limit of large numbers of bins, because the quantity $\exp[-\mathcal{A}(\theta)]$ scales proportionally to J^{-1} with increasing J.

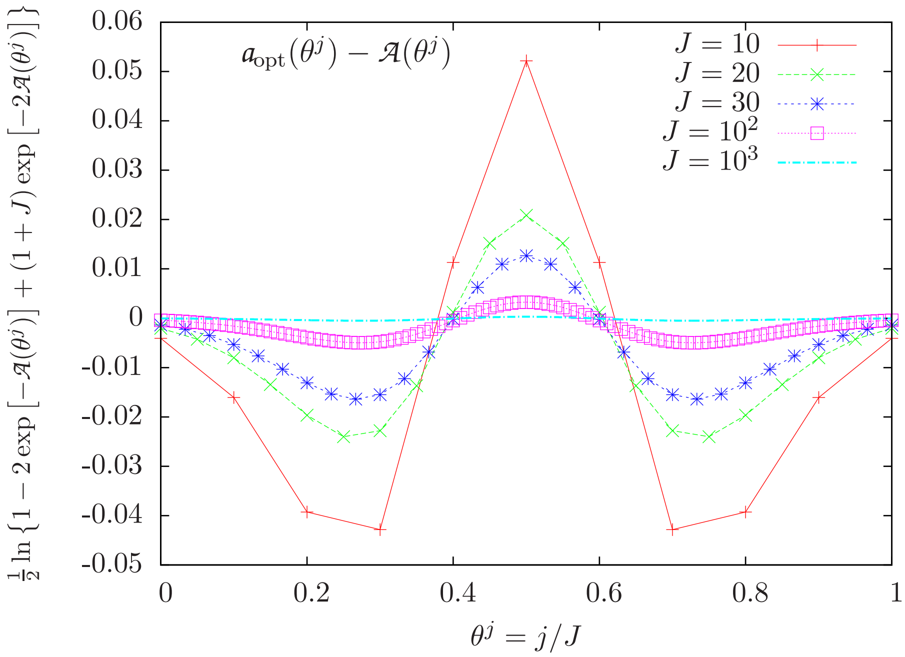

FIG. 2. Difference between the optimal biasing potential and the free energy as a function of $\theta^j = j/J$ with increasing the bin number J and with $\omega = 16$. Lines are guides to the eyes.

To illustrate the convergence of the optimal biasing potential towards the free energy, we consider a one-dimensional system with extended potential

$$\mathcal{U}(\vartheta, q) = \omega\left(q^2 - 2q\vartheta\right), \tag{40}$$

and set $\Theta = \{\theta^j\}_{0\leq j\leq J}$ with $\theta^j = j/J$. We then compute the difference $a_{\rm opt}(\theta) - \mathcal{A}(\theta)$ for various number of bins up to 10^3, a typical value that is used in simulations. The convergence of $a_{\rm opt}(\theta)$ towards $\mathcal{A}(\theta)$ with increasing J is shown in Fig. 2.

We now assess the numerical performance of the four methods of estimating the free energy on the simple toy system. We also justify the conditioning approach for estimating the probability of rare events in subsection V B.

V. ASSESSMENT OF VARIANCE REDUCTION

A. Free energy estimations

For the toy system whose extended potential is given in Eq. (40), the extended probability $\mathrm{p}_a(\vartheta, q)$ is proportional to $\exp\left[a(\vartheta) - \omega q^2 + 2\omega\vartheta q\right]$ and the conditional probability of q given

θ is

$$\pi(q|\theta) = \sqrt{\omega/\pi}\exp\left[-\omega(q-\theta)^2\right]. \tag{41}$$

For small values of ω, the various conditional probabilities substantially overlap with each other. The degree of overlap decreases with increasing ω value.

We set the biasing potential equal to the free energy and perform $K = 2\cdot 10^3$ simulations consisting of $M_{\max} = 10^5$ sampled states. We estimate the mean variance of the four estimators for $M < M_{\max}$ as follows

$$\bar{\mathrm{var}}^K\left(\widehat{\mathcal{A}}_{\mathrm{X}}^M\right) = \tfrac{1}{J+1}\sum_{j=0}^{J}\tfrac{1}{K}\sum_{k=1}^{K}\left(\frac{\widehat{\mathrm{P}}_{kj}^{M,\mathrm{X}}}{\frac{1}{K}\sum_{h=1}^{K}\widehat{\mathrm{P}}_{hj}^{M,\mathrm{X}}} - \frac{\sum_{\imath=0}^{J}\widehat{\mathrm{P}}_{k\imath}^{M,\mathrm{X}}}{\sum_{\imath=0}^{J}\frac{1}{K}\sum_{h=1}^{K}\widehat{\mathrm{P}}_{h\imath}^{M,\mathrm{X}}}\right)^2 \tag{42}$$

where $\widehat{\mathrm{P}}_{kj}^{M,\mathrm{X}}$ is the kth estimates of the quantity $\exp[-\alpha(\theta^j)]p_{\mathcal{A}}(\theta^j)$, as obtained using M sampled points and employing method X = TI, FEP, TO or AR. For thermodynamic integration, the estimated $\widehat{\mathrm{P}}_{kj}^{M,\mathrm{TI}}$ are reconstructed from the estimated free energy $\widehat{\mathcal{A}}(\theta)$. Note that the statistical variances in Eq. (42) is derived from the form of the asymptotic variance to avoid the singularity of the logarithm of $\widehat{\mathrm{P}}_{kj}^{M,\mathrm{TO}}$ at zero. It happens that this quantity takes value zero even for substantially large M.

We display in Fig. 3 the estimated variances multiplied by the sample size M as a function of M in order to observe the convergence towards the asymptotic limit for the given number K of independent simulations. We observe that a considerable variance reduction is achieved in practice owing to the conditioning scheme. Furthermore, the asymptotic regime is obtained faster and the estimated variances are also less fluctuating with conditioning.

While fluctuations decrease with increasing K, it is extremely costly to obtain accurate estimates of the asymptotic variance for large sample sizes M for the FEP method when ω is large. The observed inefficiency of the FEP method when the involved distributions do not overlap is responsible for the limitations of umbrella sampling,[41] a method that is based on a reweighting estimator.

B. Estimation of rare-event probabilities

Here, we recall the usefulness of conditioning for estimating probabilities of rare-events.[15] Let consider that the conditional distribution obtained by setting θ to 0 in Eq. (41) is our

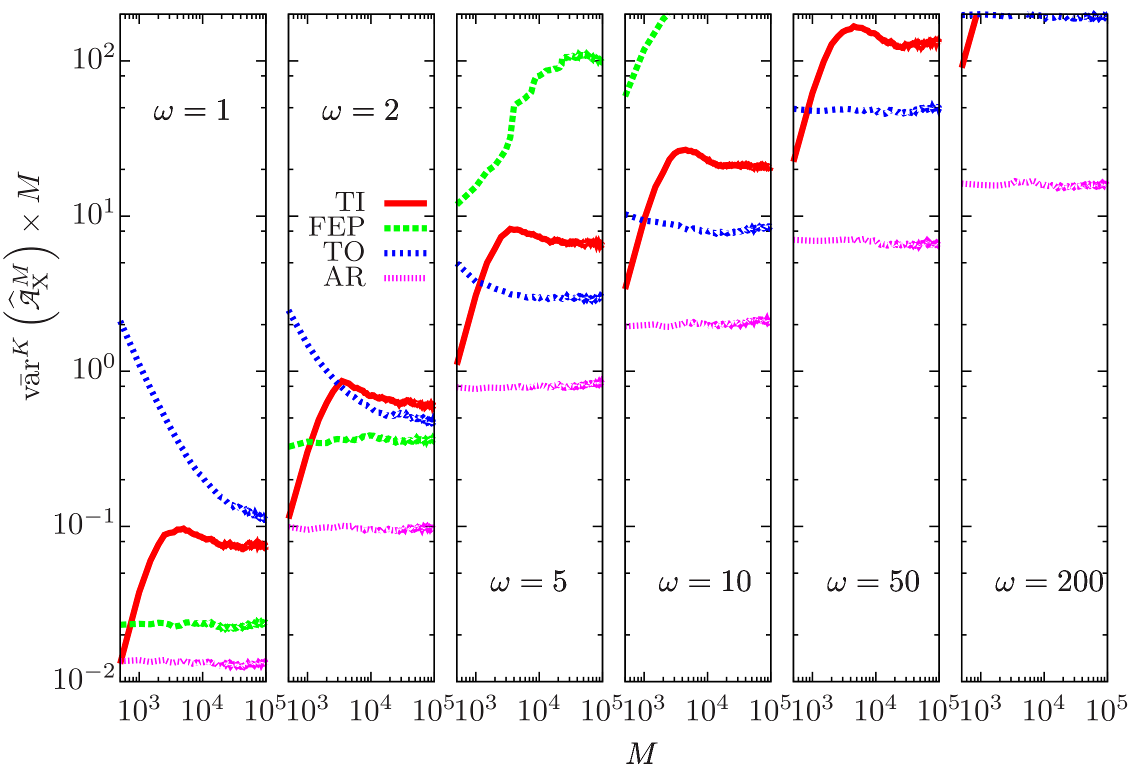

FIG. 3. Evolution of the estimated variances as a function of the sample size M for the four free energy method (X=TI,FEP,TO,AR) and using $K = 2000$ simulations.

physical distribution. It corresponds to the normal distribution $q \to \sqrt{\omega/\pi}\exp(-\omega q^2)$. The probability that a point sampled from the normal distribution is found at a position larger than 1 is $\mathcal{C} = \mathrm{erfc}(\sqrt{\omega})/2$ (the integral of the distribution from 1 to ∞). Here, we show that it is possible to compute $\mathcal{C}$ through the biased sampling of points, even for very narrow normal laws in which the value of ω is large and $\mathcal{C}$ is very small. We thus bias the simulation by adding the soft restraint $\mathcal{R}(\theta, q) = -2\theta\omega q$ to the potential energy $\mathcal{U}_0(q) = \omega q^2$, so as to gradually increase the fraction of points such that $q \geq 1$ with increasing θ value. This way of proceeding corresponds to the so-called tilting protocol that is used in path sampling simulations to sample rare trajectories from a path distribution.[15,42,43]

With the biasing potential set equal to the free energy, the probability C that point q is larger than one can easily be estimated using the adiabatic reweighting estimator. This probability is

$$\mathbb{E}\left[h_{\mathtt{B}}(q)\middle|\theta = 0\right],$$

where $\mathtt{B} = [1, +\infty[$ and $h_{\mathtt{B}}(q)$ denotes the indicator function equal to 1 if $q \in \mathtt{B}$ and to 0 otherwise. The conditional expectation is estimated using the adiabatic reweighting estimator and (standard) reweighting estimator respectively given by

$$ {}^{M}_{a}\left(h_{\mathrm{B}}\middle|0\right) = \frac{\frac{1}{M}\sum_{m=1}^{M} h_{\mathrm{B}}(q_m)\pi^{0}_{\mathscr{A}}(q_m)}{\frac{1}{M}\sum_{m=1}^{M} \pi^{0}_{\mathscr{A}}(q_m)} \tag{43} $$

$$ \mathrm{P}^{M}_{a}\left(h_{\mathrm{B}}\middle|0\right) = \frac{\frac{1}{M}\sum_{m=1}^{M} h_{\mathrm{B}}(q_m)\rho^{0}_{\mathscr{A}}(\vartheta_m, q_m)}{\frac{1}{M}\sum_{m=1}^{M} \rho^{0}_{\mathscr{A}}(\vartheta_m, q_m)}, \tag{44} $$

as obtained by replacing the observable $\mathcal{O}(0,q)$ by the indicator function. The goal is to retrieve information from the sampled configurations whose ϑ_m and q_m values are large. Here, we did not consider the histogram binning estimator as it is obviously not suited to the present rare event problem.

We observe in Fig. 4 that, with increasing ω parameter, only the AR estimator yields accurate estimates of $\mathcal{C}$. The computational speed-up of convergence that is achieved by conditioning the reweighting estimator can be assessed from their respective standard errors. As soon as ω becomes larger than 20, conditioning reduced the variance by more than four orders of magnitude. For rare-event problems, available alternatives to conditioning consists of post-processing the harvested information by implementing either the histogram reweighting estimator[11] or the MBAR estimator.[35]

VI. CHARACTERIZATION OF STRUCTURAL TRANSITION

A. The 38-atom Lennard-Jones cluster

We now turn to our application to the 38-atom Lennard-Jones (LJ) cluster. The LJ potential $\mathcal{V}_{\mathrm{LJ}}(q) = 4\epsilon\sum_{i>j}\left[r_{ij}^{-12} - r_{ij}^{-6}\right]$ where $r_{ij} = \|\mathrm{q}_j - \mathrm{q}_i\|/\sigma$ is the reduced distance separating atoms q_i and q_j. LJ reduced units of length, energy and mass ($\sigma = 1$, $\epsilon = 1$, $m = 1$) will be used in the following. LJ_{38} undergoes a two-stage phase change with increasing temperature.[44,45] A solid-solid transition between the truncated octahedral funnel and the icosahedral funnel occurs near $\mathrm{T_{ss}}$=0.12, melting follows near $\mathrm{T_{sl}}$= 0.17. As in other finite size systems,[38] the transitions are not sharp but gradual. The most stable octahedral and icosahedral structures of the 38-atom cluster are a truncated octahedron with energy $E_0 = -173.9284$ (global minimum) and an incomplete icosahedron with energy $E_1 = -173.2524$, respectively. The bond orientational order parameter Q_4 of Steinhardt et

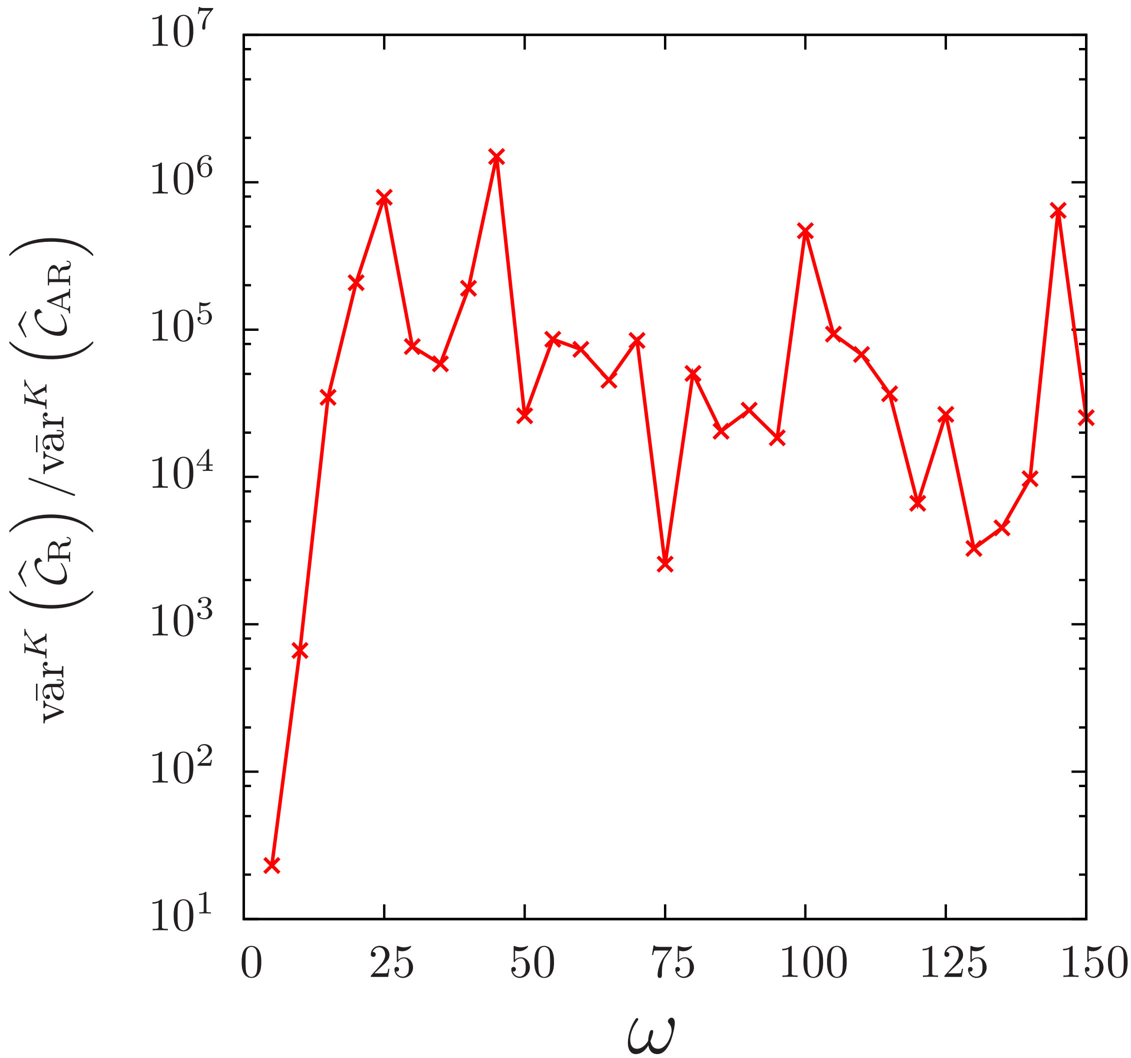

FIG. 4. Variance reduction factor obtained through conditioning when estimating the probability $\mathcal{C}$. The quantities $\widehat{\mathcal{C}}_{\mathrm{R}}$ and $\widehat{\mathcal{C}}_{\mathrm{AR}}$ denote the estimates obtained using $\mathbb{P}_a^M\left(h_{[1,+\infty[}|0\right)$ and $\Pi_a^M\left(h_{[1,+\infty[}|0\right)$ estimators, respectively. We use $M = 10^4$ points for each estimate and $K = 10^5$ estimates for both statistical variances $\bar{\mathrm{var}}^K$.

al.[30] is a convenient collective variable to distinguish between the cubic structure favored at low temperatures and the icosahedral isomers above T_{ss}. The values of Q_4 typically range from $0.002 - 0.06$ (icosahedral structures) to 0.19 (octahedral structures).

We wish to compute the free energy along the Q_4 order parameter. The standard ABF method[20,25,28] cannot be employed because the second derivatives of the Q_4 order parameter are not available. To circumvent this problem, ABF method will instead be implemented in an expanded ensemble and used to compute the free energy along Q_4 order parameter based on harvested histograms.

B. Algorithms

The ABF method in expanded ensemble is described in Algorithm 1. The description that is given is general and encompasses both the harmonic and linear couplings. The external parameter will couple either harmonically to the Q_4 coordinate or linearly to the potential energy $\mathcal{V}_{\mathrm{LJ}}(q)$ so as to scale the inverse temperature.

Algorithm 1 ABF algorithm in expanded ensemble[14] with conditioning for $\theta \in \Theta$. The K replicas of the system share the same biasing force. Replicas are propagated using either a Metropolis sampling or Langevin dynamics.

for $\theta \in \Theta$ **do**

  $C(\theta) \leftarrow 0$, $D(\theta) \leftarrow 0$

end for

for $m = 1$ to M **do**

  for $k = 1$ to K **do**

    $\tilde{q}^k = q^k_{m-1} + \sqrt{2\tau} G^k_m$ with $G^k_m \sim \mathcal{N}(0,1)$ ▷ Generate trial configuration

    if Metropolis algorithm **then**

      $r \sim_{[0,1[}$ ▷ r is drawn uniformly in $[0,1[$

      if $r \leq \dfrac{\sum_{\theta\in\Theta} \exp\left[a_{m-1}(\theta) - \mathcal{U}(\theta, \tilde{q}^k)\right]}{\sum_{\theta\in\Theta} \exp\left[a_{m-1}(\theta) - \mathcal{U}(\theta, q^k_{m-1})\right]}$ **then**

        $q^k_m \leftarrow \tilde{q}^k$

      else

        $q^k_m \leftarrow q^k_{m-1}$

      end if

    else if Overdamped Langevin dynamics **then**

      $q^k_m = \tilde{q}^k + \tau \nabla_q \ln \sum_{\theta\in\Theta} \exp\left[a_{m-1}(\theta) - \mathcal{U}(\theta, \tilde{q}^k)\right]$

    end if

  end for

  for $\theta \in \Theta$ **do**

    $\bar{\pi}_{a_{m-1}}(\theta | q^k_m) = \dfrac{\exp\left[a_{m-1}(\theta) - \mathcal{U}(\theta, \tilde{q}^k)\right]}{\sum_{\vartheta\in\Theta} \exp\left[a_{m-1}(\vartheta) - \mathcal{U}(\vartheta, \tilde{q}^k)\right]}$

    $C(\theta) \leftarrow C(\theta) + \sum_{k=1}^K \partial_\theta \mathcal{U}(\theta, q^k_m) \bar{\pi}_{a_{m-1}}(\theta | q^k_m)$

    $D(\theta) \leftarrow D(\theta) + \sum_{k=1}^K \bar{\pi}_{a_{m-1}}(\theta | q^k_m)$

    $a'_m(\theta) = \dfrac{C(\theta)}{D(\theta)}$ ▷ biasing force update

    $a_m(\theta) \leftarrow \int_{\theta^0}^{\theta} a'_m(\vartheta) d\vartheta$ ▷ integration of biasing force performed by numerical quadrature based on trapezoidal rule

    $a_m(\theta) \leftarrow a_m(\theta) + \ln \sum_{\vartheta\in\Theta} \exp\left[-a_m(\vartheta)\right]$ ▷ normalization

  end for

end for

Once the biasing force has converged to the corresponding free energy using Algorithm 1, the expected value of any observable can be estimated using the adiabatic reweighting estimator described in Algorithm 2.

Algorithm 2 Conditioning scheme for sampling the expanded ensemble with time-homogeneous biasing potential $\widehat{\mathcal{A}}(\theta)$ and for estimating the conditional and total expectations of observable $\mathcal{O}(\vartheta, q)$.

$\tilde{C} \leftarrow 0,\ \tilde{D} \leftarrow 0$

for $\theta \in \Theta$ **do**

  $C(\theta) \leftarrow 0,\ D(\theta) \leftarrow 0$

end for

for $m = 1$ to M **do**

  for $k = 1$ to K **do**

    $\tilde{q}^k = q^k_{m-1} + \sqrt{2\tau} G^k_m$ with $G^k_m \sim \mathcal{N}(0,1)$

    if Metropolis algorithm **then**

      $r \sim \mathrm{U}_{[0,1[}$

      if $r \leq \dfrac{\sum_{\theta\in\Theta} \exp\left[\widehat{\mathcal{A}}(\theta) - \mathcal{U}(\theta, \tilde{q}^k)\right]}{\sum_{\theta\in\Theta} \Theta \exp\left[\widehat{\mathcal{A}}(\theta) - \mathcal{U}(\theta, q^k_{m-1})\right]}$ **then**

        $q^k_m \leftarrow \tilde{q}^k$

      else

        $q^k_m \leftarrow q^k_{m-1}$

      end if

    else if Overdamped Langevin dynamics **then**

      $q^k_m = \tilde{q}^k + \tau \nabla_q \ln \sum_{\theta\in\Theta} \exp\left[\widehat{\mathcal{A}}(\theta) - \mathcal{U}(\theta, \tilde{q}^k)\right]$

    end if

  end for

  for $\theta \in \Theta$ **do**

    $\bar{\pi}_{\widehat{\mathcal{A}}}\big(\theta | q^k_m\big) = \dfrac{\exp\left[\widehat{\mathcal{A}}(\theta) - \mathcal{U}(\theta, \tilde{q}^k)\right]}{\sum_{\vartheta\in\Theta} \exp\left[\widehat{\mathcal{A}}_{m-1}(\vartheta) - \mathcal{U}(\vartheta, \tilde{q}^k)\right]}$

    $C(\theta) \leftarrow C(\theta) + \sum_{k=1}^K \mathcal{O}\big(q^k_m\big) \bar{\pi}_{\widehat{\mathcal{A}}}\big(\theta | q^k_m\big)$

    $D(\theta) \leftarrow D(\theta) + \sum_{k=1}^K \bar{\pi}_{\widehat{\mathcal{A}}}\big(\theta | q^k_m\big)$

    $\varpi^\theta_{\widehat{\mathcal{A}}}(q^k_m) = \exp\left[-\widehat{\mathcal{A}}(\theta)\right] \bar{\pi}_{\widehat{\mathcal{A}}}\big(\theta | q^k_m\big)$

  end for

  $\tilde{C} \leftarrow \tilde{C} + \sum_{k=1}^K \sum_{\theta\in\Theta} \varpi^\theta_{\widehat{\mathcal{A}}}(q^k_m) \mathcal{O}\big(\theta, q^k_m\big)$

  $\varpi_{\widehat{\mathcal{A}}}(q^k_m) = \sum_{\theta\in\Theta} \varpi^\theta_{\widehat{\mathcal{A}}}(q^k_m) \mathcal{O}\big(\theta, q^k_m\big)$

  $\tilde{D} \leftarrow \tilde{D} + \sum_{k=1}^K \varpi_{\widehat{\mathcal{A}}}(q^k_m)$

end for

for $\theta \in \Theta$ **do**

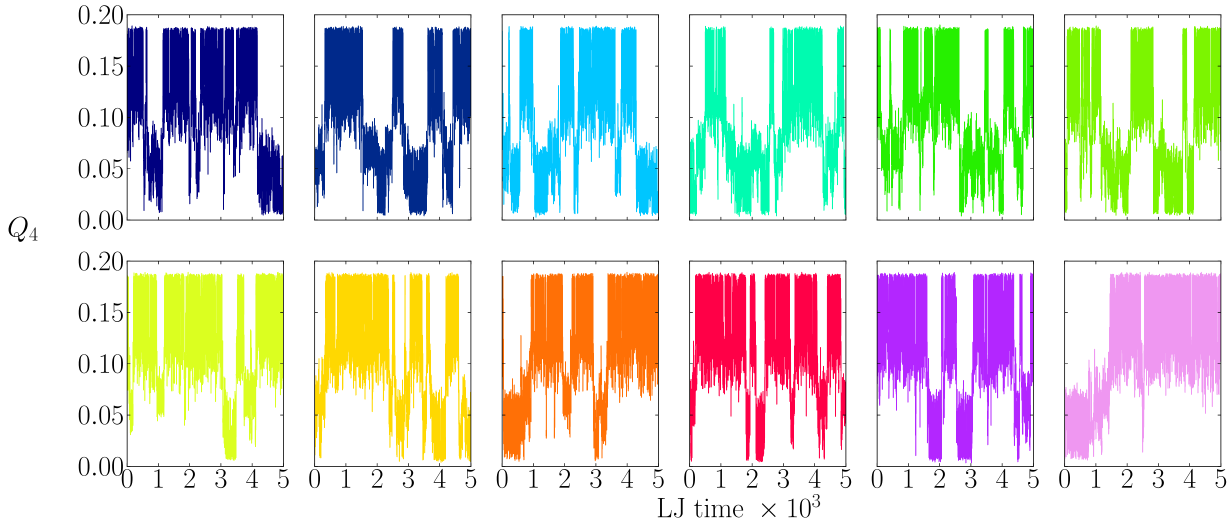

FIG. 5. Evolution of the Q_4 parameter during the adaptation/production run for each replica. Although the 12 replicas are allocated on 12 distinct processors, they share the same bias.

C. Free energy along Q_4

We implement the ABF method described in Algorithm 1 and harmonic coupling to the Q_4 order parameter to compute the free energy along θ . Twelve replicas of the system are propagated using Langevin dynamics (instead of the Metropolis sampling). The restraining potential is $\frac{\kappa}{2T_{\mathrm{ref}}}\|Q_4(q)-\theta\|^2$ and the extended potential exhibits the form given in Eq. (10), so that the free energy derivative $\mathcal{A}'(\theta)$ is constructed from the following identity

$$\mathbb{E}\left[\partial_\theta \mathcal{U}(\theta,q)|\theta\right] = \frac{\kappa}{T_{\mathrm{ref}}}\left[\theta - \frac{\bar{\mathbb{E}}_a\left[\bar{\pi}_a(\theta|q)Q_4(q)\right]}{\bar{\mathbb{E}}_a\left[\bar{\pi}_a(\theta|q)\right]}\right]. \tag{45}$$

We set $\kappa = 10^{-4}$ and $T_{\mathrm{ref}} = 0.15$. At this temperature, spontaneous structural transitions cannot be observed on the simulation timescale. The time-step $\tau = 5\cdot 10^{-5}$ (lju) is chosen very small so as to keep discretization errors negligible. The simulation length $M = 10^8$ and replica number $K = 12$ enable the auxiliary biasing force to converge and ensure that the sampling is homogeneous along Q_4 parameter, as shown in Fig. 5.

Using the estimated free energy $\widehat{\mathcal{A}}(\theta) = \boldsymbol{a}_M(\theta)$, we run Algorithm 2 to harvest biased histograms of Q_4, denoted by $\mathrm{P}_{\widehat{\mathcal{A}}}(Q_4)$. The unbiased histogram of $\xi^\star \equiv Q_4$ can be expressed as a ratio of two biased expectations

$$\mathbb{E}\left[\mathbb{1}_{\xi^\star}\circ\xi(q)\right] = \frac{\mathbb{E}_{\widehat{\mathcal{A}}}\left[\exp \mathcal{R}^{\xi}_{\widehat{\mathcal{A}}}\circ\xi(q)\mathbb{1}_{\xi^\star}(\xi(q))\right]}{\mathbb{E}_{\widehat{\mathcal{A}}}\left[\exp \mathcal{R}^{\xi}_{\widehat{\mathcal{A}}}\circ\xi(q)\right]}.$$

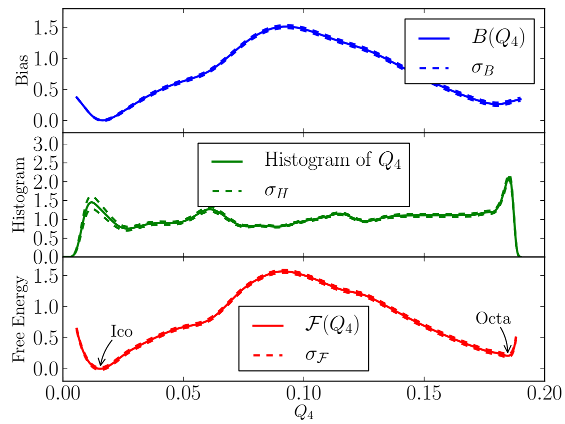

FIG. 6. Estimation of bias, histogram and free energy along Q_4.

The total expectation is estimated using the AR estimator given in Eq. (37) with $\bar{\mathcal{O}}(q)$ set to $\xi(q) \equiv Q_4(q)$ while taking advantage of the following factorization

$$\mathbb{E}\left[\mathbb{1}_{\xi^\star} \circ \xi(q)\right] = \frac{\overbrace{\exp \mathcal{R}^{\xi}_{\widehat{\mathfrak{A}}}(\xi^\star)}^{\exp[-\beta B(\xi^\star)]}\overbrace{\mathbb{E}_{\widehat{\mathfrak{A}}}\left[\mathbb{1}_{\xi^\star} \circ \xi(q)\right]}^{\mathrm{P}_{\widehat{\mathfrak{A}}}(\xi^\star)}}{\underbrace{\mathbb{E}_{\widehat{\mathfrak{A}}}\left[\exp \mathcal{R}^{\xi}_{\widehat{\mathfrak{A}}} \circ \xi(q)\right]}_{\exp[\beta C]}}.$$

Hence, the free energy is directly evaluated from an estimate of $\mathrm{P}_{\widehat{\mathfrak{A}}}(Q_4)$ histogram based on

$$\mathscr{F}(Q_4) = \beta B(Q_4) - \ln \mathrm{P}_{\widehat{\mathfrak{A}}}(Q_4) + \beta C.$$

The obtained results for the bias $B(Q_4)$, the histogram $\mathrm{P}_{\widehat{\mathfrak{A}}}(Q_4)$ and the scaled free energy $\mathcal{F}(Q_4) = \beta^{-1}\mathscr{F}(Q_4)$ are shown in the left panels of Fig. 6. The displayed error intervals σ_B, σ_H and $\sigma_{\mathcal{F}}$ are estimated from 40 simulations and correspond to a 95% confidence interval (approximately twice the standard error).

From the free energy profile along Q_4, the occurrence probabilities of the icosahedral and octahedral structures can be evaluated. For these two structures, the Landau free energies $\Lambda(\text{ico}|T_{\text{ref}}^{-1})$ and $\Lambda(\text{octa}|T_{\text{ref}}^{-1}))$, defined as minus the logarithm of their respective occurrence probabilities, can be directly evaluated. We now wish to compute the two Landau free energies at other temperatures so as to characterize the structural transition temperature for which $\Lambda(\text{ico}|T_{\text{ss}}^{-1}) = \Lambda(\text{octa}|T_{\text{ss}}^{-1})$. Unfortunately, ABF simulations along Q_4 do not converge at temperature lower than 0.13, meaning that Q_4 becomes a bad reaction coordinate and that T_{ss} can not be determined this way.

D. Free energy along inverse temperature

The problem is solved by evaluating $\Lambda(\mathtt{x}|T^{-1})$ as a function of inverse temperature separately for the two structures $\mathtt{x}$ of set $\mathtt{X} \triangleq \{\mathtt{ico}, \mathtt{octa}\}$ from the knowledge of $\mathcal{A}(T^{-1}|\mathtt{ico})$ and $\mathcal{A}(T^{-1}|\mathtt{octa})$, the free energies along the inverse temperature given the structure. The identity connecting the two kinds of free energies corresponds to Bayes formula expressed in log-space

$$\Lambda(\mathtt{x}|T^{-1}) = \mathcal{A}(T^{-1}|\mathtt{x}) + \Lambda(\mathtt{x}) + \underbrace{\ln \sum_{\tilde{\mathtt{x}} \in \mathtt{X}} \exp\left[-\mathcal{A}(T^{-1}|\tilde{\mathtt{x}}) - \Lambda(\tilde{\mathtt{x}})\right]}_{-\mathcal{A}(T^{-1})}, \quad (46)$$

where $\Lambda(\bar{\mathtt{x}})$ is minus the logarithm of the marginal probability of structure $\bar{\mathtt{x}}$ in the expanded ensemble ($\bar{\mathtt{x}} = \mathtt{x}$ or $\bar{\mathtt{x}} = \tilde{\mathtt{x}}$). The sum inside the logarithm acts as an appropriate normalizing factor for $\exp\left[-\lambda(\mathtt{x}|T_{\mathrm{ref}}^{-1})\right]$, the probability of structure $\mathtt{x}$ given T_{ref}^{-1}. It is a transcription of the law of total probability applied to the marginal probability of T_{ref}^{-1} with respect to the given set of structures $\mathtt{X}$ and marginal probabilities $\{\exp\left[-\Lambda(\bar{\mathtt{x}})\right]\}_{\mathtt{x} \in \mathtt{X}}$. The quantity $\Lambda(\bar{\mathtt{x}})$ is determined using the simulation data collected at the reference inverse temperature together with Bayes formula, again expressed in log-space

$$\Lambda(\bar{\mathtt{x}}) = -\mathcal{A}(T_{\mathrm{ref}}^{-1}|\bar{\mathtt{x}}) + \Lambda(\bar{\mathtt{x}}|T_{\mathrm{ref}}^{-1}) + \underbrace{\ln \sum_{\tilde{\mathtt{x}} \in \mathtt{X}} \exp\left[\mathcal{A}(T_{\mathrm{ref}}^{-1}|\tilde{\mathtt{x}}) - \Lambda(\tilde{\mathtt{x}}|T_{\mathrm{ref}}^{-1})\right]}_{+\mathcal{A}(T_{\mathrm{ref}}^{-1})}, \quad (47)$$

in which we developed the free energy $\mathcal{A}(T_{\mathrm{ref}}^{-1})$ to emphasize how this quantity can be calculated. Plugging Eq. (47) into Eq. (46) for $\bar{\mathtt{x}} = \mathtt{x}$ and $\bar{\mathtt{x}} = \tilde{\mathtt{x}}$ yields, after simplifying the logarithmic term, the desired Landau free energy

$$\Lambda\left(\mathtt{x}|T^{-1}\right) = \mathcal{A}\left(T^{-1}|\mathtt{x}\right) - \mathcal{A}\left(T_{\mathrm{ref}}^{-1}|\mathtt{x}\right) + \Lambda\left(\mathtt{x}|T_{\mathrm{ref}}^{-1}\right) + \underbrace{\ln \sum_{\tilde{\mathtt{x}} \in \mathtt{X}} \exp\left[-\mathcal{A}\left(T^{-1}|\tilde{\mathtt{x}}\right) + \mathcal{A}\left(T_{\mathrm{ref}}^{-1}|\tilde{\mathtt{x}}\right) - \Lambda\left(\tilde{\mathtt{x}}|T_{\mathrm{ref}}^{-1}\right)\right]}_{\mathcal{A}\left(T_{\mathrm{ref}}^{-1}\right) - \mathcal{A}(T^{-1})}.$$

The sum in the logarithmic contribution corresponds to the exponential of the free energy difference $\mathcal{A}(T_{\mathrm{ref}}^{-1}) - \mathcal{A}(T^{-1})$. This common contribution to all structures does not affect

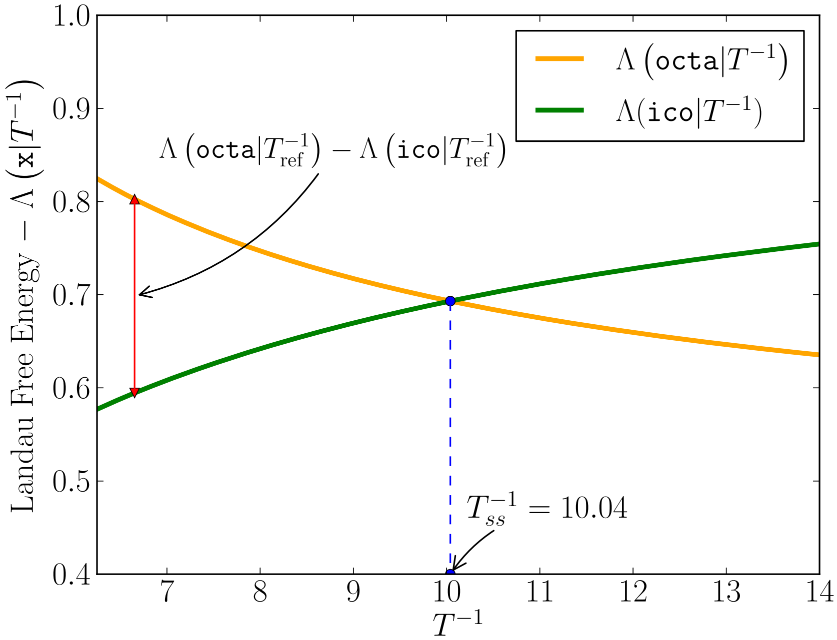

FIG. 7. Estimation of the free energies of the icosahedral and octahedral structures as a function of inverse temperature.

phase equilibrium properties and merely serves as a normalizing factor. In our case study, phase equilibrium is reached when the two structures are equi-probable:

$$\Lambda\left(\texttt{ico}|T_{\text{ss}}^{-1}\right) = \Lambda\left(\texttt{octa}|T_{\text{ss}}^{-1}\right).$$

This condition is equivalent to, resorting to the 6 quantities that are actually calculated,

$$\begin{aligned}\mathcal{A}\left(T_{\text{ss}}^{-1}|\texttt{ico}\right) + \Lambda\left(\texttt{ico}|T_{\text{ref}}^{-1}\right) + \mathcal{A}(T_{\text{ref}}^{-1}|\texttt{octa}) &= \\ &\mathcal{A}\left(T_{\text{ss}}^{-1}|\texttt{octa}\right) + \Lambda\left(\texttt{octa}|T_{\text{ref}}^{-1}\right) + \mathcal{A}\left(T_{\text{ref}}^{-1}|\texttt{ico}\right).\end{aligned}$$

We proceed as follows: after setting the external parameter to the inverse temperature $\theta = T^{-1}$, we perform two supplementary simulations to compute $\mathcal{A}(T^{-1}|\texttt{ico})$ and $\mathcal{A}(T^{-1}|\texttt{octa})$ with the AR estimator and the external parameter ranging from $\theta_{\text{min}} = 6.25$ to $\theta_{\text{max}} = 14$, taking advantage of the fact that structural transitions do not occur spontaneously in the range of involved temperatures. The transition temperature is characterized by the intersection point of our two Landau free energies as a function of inverse temperature, as shown in Fig. 7.

VII. SUMMARY AND CONCLUSION

Molecular simulations methods usually requires to vary the value of an external parameter θ within a specified range Θ. In such problems, enhanced ergodicity is achieved if simulations are performed in an expanded ensemble wherein the external parameter behaves like an additional coordinate subject to an auxiliary biasing force. The various standard methods of computing thermodynamic expectations and free energies in particular which are currently used in the literature can be straightforwardly transposed into the expanded ensemble framework. They are reviewed below

(a) *Thermodynamic integration* to estimate the derivative of the free energy and then to obtain the free energy through integration by numerical quadrature. Combination with adaptive biasing force method allows to construct an adequate biasing potential that converges towards the free energy.

(b) *Thermodynamic occupation* to directly extract the free energy from occupation probabilities. Combination with the adaptive biasing potential method is also possible.

(c) *Free energy perturbation* to extract the free energies from partition function ratios.

(d) Post-processing and reweighting schemes based on *Bennett acceptance ratio* method and its extension to multiple thermodynamic states. The goal is to obtain the optimal estimate of any thermodynamic property given the harvested histograms and data.

Remarkably, the expanded framework makes it possible to straightforwardly implement a conditioning scheme with respect to the external parameter. This allows to systematically reduce the statistical variance of the estimates of any thermodynamic quantity evaluated with method (a-d). Besides, as a result of conditioning, the free energy estimators associated with the various free energy techniques become equivalent. In addition, combination of *umbrella sampling* and conditioning allows to enhance the occurrence of rare events and to accurately estimate the free energies that are required to remove the simulation biases correctly. Finally, we practically showed how to perform simulations in the expanded ensemble in order to compute the free energy along a complex order parameter and to characterize a structural transition temperature.

In conclusion, the advocated conditioning strategy is well positioned to further extend the range of applicability of molecular dynamics and Monte Carlo techniques to the calculation of free energies and thermodynamic properties in condensed matter systems. From a general perspective, it would be highly desirable to learn how to perform expanded ensemble simulations using a biasing potential that is optimal with respect to conditioning (rather than histogram binning as presently) and to account for the statistical covariance (correlations) within the sampled data, inspiring from what is actually done in popular postprocessing approaches[11,35] based on Bennett acceptance ratio method.

ACKNOWLEDGMENTS

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Appendix A: Asymptotic variances of estimators

Delta method

Since expectations are considered with respect to the expanded ensemble, we write the dependence on the biasing potential $a(\theta)$ explicitly when needed and use the notation var_a adopted throughout the article for the variance. The lemma below establishes a general and useful property of covariance matrices

Lemma A.1. *Let Γ be the covariance matrix of a random vector Y taking its values in $\mathbb{R}^d$ and $u \in \mathbb{R}^d$ be a constant vector. Then, we have*

$$u^T \Gamma u = \mathrm{var}_a \left[u^T Y \right]. \tag{A1}$$

Proof. Let write $Y = (Y^\imath)_{1 \leq \imath \leq d}$ and $u = (u^\imath)_{1 \leq \imath \leq d}$. By definition, element Γ_{ij} of covariance matrix Γ is equal to $\mathrm{cov}_a\left(Y^i, Y^j\right)$ the covariance of the one-dimensional random variables Y^i and Y^j, defined by

$$\mathrm{cov}_a[Y^i, Y^j] = \mathbb{E}_a\left[Y^i Y^j\right] - \mathbb{E}_a\left[Y^i\right] \mathbb{E}_a\left[Y^j\right].$$

Since the covariance has scalar product properties, we have the following sequence of equalities

$$u^T \Gamma u = \sum_{i=1}^{d} \sum_{j=1}^{d} u^i \mathrm{cov}_a(Y^i, Y^j) u^j =$$

$$= \mathrm{cov}_a(u^T Y, u^T Y) = \mathrm{var}_a(u^T Y).$$

□

The delta method will allow us to characterize the asymptotic variance of all aforementioned estimators. It consists of applying the generalized central limit theorem that follows:

Theorem A.2. *Let $\{Y_m\}_{m\geq 1}$ be a sequence of independent, identically distributed and square integrable random vectors taking their values in $\mathbb{R}^d$. Let μ and Γ respectively denote the expected vector and the covariance matrix of the Y_m and $\bar{Y}_M = \frac{1}{M}\sum_{m=1}^{M} Y_m$. Let $g : \mathbb{R}^d \mapsto \mathbb{R}$ be a function that is differentiable at μ. Then, we have the following convergence in law*

$$\sqrt{M}\left(g(\bar{Y}_M) - g(\mu)\right) \underset{M\to+\infty}{\xrightarrow{\mathcal{L}}} \mathcal{N}\left(0, \nabla g(\mu)^T \Gamma \nabla g(\mu)\right).$$

We refer the reader to Ref 31 for a proof of this classical result. The variance of the gaussian variable above is called the asymptotic variance of random variable $g(Y)$.

Theorem A.2 is applied together with Eq. (A1) to express the asymptotic variance of the estimators below as a variance of random variable $\nabla g(\mu)^T Y$:

$$\nabla g(\mu)^T \Gamma \nabla g(\mu) = \mathrm{var}_a\left(\nabla g(\mu)^T Y\right). \tag{A2}$$

Estimation of conditional expectations

For the $\Phi_a^M(\mathcal{O}|\theta)$ estimator given in Eq. (8) and conditioned in subsection III B), we set $Y_m = \left(\phi_a^\theta(\vartheta_m, q_m)\mathcal{O}(\theta, q_m), \phi_a^\theta(\vartheta_m, q_m)\right)^T \in \mathbb{R}^2$, $g(r,s) = r/s$. We thus have $\mu = \left(\mathbb{E}_a\left[\phi_a^\theta(\vartheta, q)\mathcal{O}(\theta, q)\right], \mathbb{E}_a\left[\phi_a^\theta(\vartheta, q)\right]\right)^T$ and

$$\nabla g(\mu) = \begin{pmatrix} 1/\mathbb{E}_a\left[\phi_a^\theta\right] \\ -\mathbb{E}_a\left[\phi_a^\theta(\vartheta, q)\mathcal{O}(\theta, q)\right] \Big/ \mathbb{E}_a\left[\phi_a^\theta\right]^2 \end{pmatrix}$$

$$= \frac{1}{\mathbb{E}_a\left[\phi_a^\theta\right]} \begin{pmatrix} 1 \\ -\mathbb{E}\left[\mathcal{O}|\theta\right] \end{pmatrix}.$$

Resorting to Eq. (A2), the asymptotic variance $\nabla g(\mu)^T \Gamma \nabla g(\mu)$ is therefore

$$\frac{1}{\mathbb{E}_a\left[\phi_a^\theta\right]^2}\mathrm{var}_a\left[\begin{pmatrix}1\\ -\mathbb{E}\left[\mathcal{O}|\theta\right]\end{pmatrix}^T\begin{pmatrix}\phi_a^\theta(\vartheta,q)\mathcal{O}(\theta,q)\\ \phi_a^\theta(\vartheta,q)\end{pmatrix}\right]$$

$$= \frac{\mathrm{var}_a\left[\phi_a^\theta \mathcal{O}^\theta\right]}{p_a(\theta)^2},$$

recalling that $\mathcal{O}^\theta(\theta,q^\dagger) = \mathcal{O}(\theta,q^\dagger) - \mathbb{E}_a\left[\mathcal{O}(\vartheta,q)|\theta\right]$ and that $\mathbb{E}_a\left[\phi_a^\theta\right] = p_a(\theta)$. One recovered the asymptotic variance of the $\Phi_a^M(\mathcal{O}|\theta)$ estimator whose square root is given in Eq. (22). Along the same line of reasoning, the asymptotic variance of adiabatic reweighting estimator ${}_a^M(\mathcal{O}|\theta)$ can be deduced after substituting π_a^θ for ϕ_a^θ.

Estimation of total expectations

For the ${}_a^M(\bar{\mathcal{O}})$ generic estimator associated with observable $\bar{\mathcal{O}}(q)$ considered in subsection III D, we set $g(r,s) = r/s$ and

$$Y_m = \begin{pmatrix}\varphi_a(\vartheta_m,q_m)\bar{\mathcal{O}}(q_m)\\ \varphi_a(\vartheta_m,q_m)\end{pmatrix} \Longrightarrow \mu = \begin{pmatrix}\mathbb{E}_a\left[\varphi_a\bar{\mathcal{O}}\right]\\ \mathbb{E}_a\left[\varphi_a\right]\end{pmatrix}.$$

We thus have

$$\nabla g(\mu) = \begin{pmatrix}1/\mathbb{E}_a\left[\varphi_a\right]\\ -\left(\mathbb{E}_a\left[\varphi_a\bar{\mathcal{O}}\right]/\mathbb{E}_a\left[\varphi_a\right]\right)/\mathbb{E}_a\left[\varphi_a\right]\end{pmatrix}$$

$$= \frac{1}{\mathbb{E}_a\left[\varphi_a\right]}\begin{pmatrix}1\\ -\mathbb{E}\left[\bar{\mathcal{O}}\right]\end{pmatrix}.$$

The asymptotic variance 36 directly follows

$$\sigma^2\left[{}_a^{+\infty}(\bar{\mathcal{O}})\right] = \mathrm{var}_a\left[\frac{1}{\mathbb{E}_a\left[\varphi_a\right]}\begin{pmatrix}1\\ -\mathbb{E}\left[\bar{\mathcal{O}}\right]\end{pmatrix}^T\begin{pmatrix}\varphi_a\bar{\mathcal{O}}\\ \varphi_a\end{pmatrix}\right]$$
$$= \mathrm{var}_a\left[\bar{\mathcal{O}}^\Theta\frac{\varphi_a}{\mathbb{E}_a[\varphi_a]}\right],$$

recalling that $\bar{\mathcal{O}}^\Theta(q) = \bar{\mathcal{O}}(q) - \mathbb{E}\left[\bar{\mathcal{O}}\right]$. The asymptotic variance of adiabatic reweighting estimator ${}_a^M(\mathcal{O})$ can be deduced by substituting $\varpi_a = \mathbb{E}_a[\varphi_a|q]$ for φ_a and following the same line of reasoning.

Observable dependence on θ

For the generic estimator $\,{}_a^M(\mathcal{O})$ given in Eq. (33) and associated with total expectations of observables of the general form $\mathcal{O}(\vartheta, q)$, we set $g(r,s) = r/s$ together with

$$Y = \begin{pmatrix} \sum_{\theta^\dagger \in \Theta} \mathcal{O}(\theta^\dagger, q)\varphi_a^{\theta^\dagger}(\vartheta, q) \\ \varphi_a(\vartheta, q) \end{pmatrix},$$

$$\nabla g\left(\mathbb{E}[Y]\right) = \frac{1}{\mathbb{E}_a[\varphi_a]} \begin{pmatrix} 1 \\ -\mathbb{E}[\mathcal{O}] \end{pmatrix},$$

where $\varphi^{\theta^\dagger}(\vartheta, q) = \exp[-\boldsymbol{a}(\theta^\dagger)]\phi_a^{\theta^\dagger}(\vartheta, q)$ and $\varphi_a = \sum_{\theta^\dagger \in \Theta} \varphi_a^{\theta^\dagger}$. This enables one to obtain the asymptotic variance of the estimator by application of Theorem A.2

$$\sigma^2\left[\,{}_a^{+\infty}(\mathcal{O})\right] = \\ \mathrm{var}_a\left[\frac{\sum_{\theta^\dagger \in \Theta} \mathcal{O}(\theta^\dagger, q)\varphi_a^{\theta^\dagger}(\vartheta, q) - \mathbb{E}[\mathcal{O}]\varphi_a(\vartheta, q)}{\mathbb{E}_a[\varphi_a]}\right].$$

The generalization of estimator $\,{}_a^M$ to observables that depend on the sampled ϑ is useful in the free energy context below.

Estimation of free energies along θ

As for the generic estimator of the free energy $\mathcal{A}(\theta^j)$ considered in subsection III E, the asymptotic variance can be obtained by noticing that the free energy corresponds to minus the logarithm of the total expectation of observable $\mathbb{1}_\theta$. Here, one applies theorem A.2 with g set to minus the logarithm function and $\bar{Y}_M$ set to $\,{}_a^M(\mathbb{1}_\theta)$, which yields the following expression for the asymptotic variance of the FEP/TO method

$$\sigma^2\left[\widehat{\mathcal{A}(\theta)}^{\infty}_{\mathrm{FEP/TO}}\right] = \frac{\sigma^2\left[\,{}_a^{+\infty}(\mathbb{1}_\theta)\right]}{\boldsymbol{p}_0(\theta)^2} \\ = \mathrm{var}_a\left[\frac{\varphi_a^\theta(\vartheta, q)}{\boldsymbol{p}_0(\theta)\mathbb{E}_a\left[\varphi_a\right]} - \frac{\mathbb{E}[\mathbb{1}_\theta]}{\boldsymbol{p}_0(\theta)}\frac{\varphi_a(\vartheta, q)}{\mathbb{E}_a[\varphi_a]}\right].$$

Noticing that $\mathbb{E}[\mathbb{1}_\theta]$ is $\boldsymbol{p}_0(\theta)$ and that $\boldsymbol{p}_0(\theta)\mathbb{E}_a\left[\varphi_a\right]$ is $\mathbb{E}_a\left[\varphi_a^\theta\right]$, one eventually obtain the desired asymptotic variance in a more compact form

$$\sigma^2\left[\widehat{\mathcal{A}(\theta)}^{\infty}_{\mathrm{FEP/TO}}\right] = \mathrm{var}_a\left[\frac{\varphi_a^\theta}{\mathbb{E}_a\left[\varphi_a^\theta\right]} - \frac{\varphi_a}{\mathbb{E}_a\left[\varphi_a\right]}\right]. \tag{A3}$$

The asymptotic variance of the AR method similarly writes

$$\sigma^2\left[\widehat{\mathcal{A}(\theta)}^{\infty}_{\mathrm{AR}}\right] = \mathrm{var}_a\left[\frac{\mathbb{E}_a\left[\varphi_a^\theta|q\right]}{\mathbb{E}_a\left[\varphi_a^\theta\right]} - \frac{\mathbb{E}_a\left[\varphi_a|q\right]}{\mathbb{E}_a\left[\varphi_a\right]}\right]$$

$$= \mathrm{var}_a\left[\frac{\varpi_a^\theta}{\mathbb{E}_a\left[\varpi_a^\theta\right]} - \frac{\bar{\varpi}_a}{\mathbb{E}_a\left[\bar{\varpi}_a\right]}\right]. \quad \text{(A4)}$$

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