

## Equilibrium Free Energies from Nonequilibrium Metadynamics

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In this Letter we propose a new formalism to map history-dependent metadynamics in a Markovian process. We apply this formalism to model Langevin dynamics and determine the equilibrium distribution of a collection of simulations. We demonstrate that the reconstructed free energy is an unbiased estimate of the underlying free energy and analytically derive an expression for the error. The present results can be applied to other history-dependent stochastic processes, such as Wang-Landau sampling.

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In recent years increasing attention has been paid to the possibility of studying equilibrium thermodynamical processes by means of nonequilibrium processes [1–5]. A major breakthrough in this field is the work of Jarzynski [2], who has demonstrated that it is possible to estimate the free energy difference between two states as a suitable average of the work done on the system by forcing the transition in a finite time.

More recently, two of us have introduced, on a more empirical basis, the metadynamics method [6] in which the free energy as a function of one or more collective variables (CVs) is obtained from a nonequilibrium simulation. In this method, the dynamics of a system at finite temperature is biased by a history-dependent potential constructed as the sum of Gaussians centered on the trajectory of the CVs. After a transient period, the free energy dependence on the CVs can be estimated as the negative of the bias potential. This method is closely related to the local elevation method [7], to coarse molecular dynamics [8,9] and to the adaptive-force bias method [10]. Moreover, as described in Ref. [11], metadynamics can be viewed as a finite temperature extension of the Wang-Landau approach [12], where the density of states of a system is estimated by a Monte Carlo procedure in which the acceptance probability of a move is modified every time a configuration is explored. The practical validity of the metadynamics method has been demonstrated in a number of applications to real problems [6,11,13–20], and an empirical way to evaluate the error has been suggested in Ref. [21]. Attempts at a more formal approach have so far been frustrated by the lack of a formalism capable of handling a non-Markovian process [22].

The problem of working with history-dependent dynamics is that the forces (or the transition probabilities) on the system depend explicitly on its history. Hence it is not *a priori* clear if, and in which sense, the system can reach a stationary state under the action of these dynamics. In this Letter we introduce a formalism that allows us to demonstrate that this is indeed the case, at least when the evolution of the system is of the Langevin type. We introduce a novel mapping of the history-dependent evolution into a

Markovian process in the original variable and in an auxiliary field that keeps track of the configurations visited. Using this mapping we are able to validate rigorously the metadynamics method. In particular, we show that the average over several independent simulations of the metadynamics biasing potential is exactly equal to minus the free energy, and we obtain an explicit expression for the standard deviation of the single realization from this average. The same formalism can be extended to Monte Carlo-like samplings such as Wang-Landau and, more generally, to all stochastic processes augmented by a history-dependent term which is an explicit function of the system trajectory.

We will here consider the evolution of the CVs in the framework of stochastic differential equations. Dimensional reduction [23,24] leads in general to a process with a complex memory friction and an inertial term. However, we have extensively checked [21,25] that in real systems the *quantitative* behavior of metadynamics is perfectly reproduced by the Langevin equation in its strong friction limit. This is due to the fact that in real systems all the relaxation times are usually much smaller than the typical diffusion time in the CVs' space, and are therefore averaged out during a metadynamics reconstruction. Hence, we model the CVs' evolution as a Langevin-type dynamics. For this dynamics it is possible to solve analytically the equilibrium distribution of the system.

Under this assumption the metadynamics equation in the CVs  $s$  of a system with free energy  $F(s)$  becomes

$$ds = -D \frac{\partial}{\partial s} \left[ F(s) + \int_0^t dt' g(s, s(t')) \right] \Big|_{s=s(t)} dt + \sqrt{2D} dW, \quad (1)$$

where  $dW$  is a Wiener noise,  $D$  is the diffusion coefficient, and we measure the energies in units of temperature. The variable  $s$  is in general multidimensional, and  $\partial/\partial s$  indicates a vector derivative in the multidimensional space of the CVs. The integral in Eq. (1) is the history-dependent potential, generated through the kernel  $g(s, s')$ . So far  $g(s, s')$  has been taken to be a Gaussian [6,21] in the

distance  $|s - s'|$  with a prefactor related to the speed with which we wish to reconstruct  $F(s)$ , but different kernels can be considered. A stationary state can be reached if the system is confined in a region  $\Omega$ . The analysis is simplified by considering reflecting conditions at its boundaries  $\partial\Omega$  and assuming that the gradient of the free energy in the direction normal to  $\partial\Omega$  vanishes. Other boundary conditions could easily be introduced at the cost of algebraic complications. The kernel  $g(s, s')$  is required to satisfy the same boundary conditions as  $F(s)$  for any fixed value of  $s'$ , and to be such that the equation

$$\int ds' g(s, s') \varphi_0(s') + F(s) = 0 \quad (2)$$

has a solution for the function  $\varphi_0(s)$ .

In order to study the average properties of an ensemble of independent metadynamics calculations, we have to transform the stochastic description of Eq. (1) in a probabilistic description. When the stochastic evolution is Markovian, this is done using the Fokker-Planck equation. However, Eq. (1) contains a history-dependent term (the bias potential) and is clearly non-Markovian. In order to circumvent this problem we define a time-dependent field  $\varphi(s; t)$ ,

$$\varphi(s; t) = \int_0^t dt \delta(s - s(t)) + \varphi_0(s), \quad (3)$$

which is made up of two terms: the histogram of the positions already visited by the system and a time-independent gauge term  $\varphi_0(s)$  defined by Eq. (2), introduced to simplify the resulting equations. With this choice of the gauge it is implicitly assumed that the initial conditions are  $\varphi(s; 0) = \varphi_0(s)$ . In terms of the variables  $s(t)$  and  $\varphi(s; t)$  the stochastic process in Eq. (1) can be rewritten in the simple form

$$ds(t) = -D \int ds' \frac{\partial g(s, s')}{\partial s} \varphi(s'; t) \Big|_{s=s(t)} dt + \sqrt{2D} dW, \quad (4a)$$

$$d\varphi(s; t) = \delta(s - s(t)) dt, \quad (4b)$$

as can be verified by direct substitution. This is the crucial step that allows the non-Markovian evolution of a single dynamic variable  $s(t)$  in Eq. (1) to be replaced with a Markovian evolution for the extended set of variables which includes  $s(t)$  and the field  $\varphi(s; t)$ . In fact, the state of the system at time  $t + dt$  [ $s(t + dt)$ ,  $\varphi(s; t + dt)$ ] depends only on the state of the system at time  $t$  [ $s(t)$ ,  $\varphi(s; t)$ ]. The information related to the underlying free energy  $F(s)$  has disappeared from the equation of motion but is still present through the initial condition for  $\varphi(s; t)$ ; see Eq. (3).

Using the Markovian property it is possible to analyze in a rigorous manner the behavior of Eq. (4). In particular, by using standard techniques [26], it is possible to write a generalized Fokker-Planck equation and study its asymptotic behavior for large  $t$ . We consider an ensemble of

independent metadynamics runs, and define an ensemble density. Since our dynamic variables are the position of the walker  $s$  and the field  $\varphi(s)$ , the probability density will be a function of  $s$  and a functional of  $\varphi$ . We denote this probability as  $P(\{\varphi\}, s; t)$ . The Fokker-Planck equation for  $P(\{\varphi\}, s; t)$  is

$$\begin{aligned} \frac{\partial P(\{\varphi\}, s; t)}{\partial t} = & - \frac{\delta P(\{\varphi\}, s; t)}{\delta \varphi(s)} \\ & + DP(\{\varphi\}, s; t) \int ds' \frac{\partial^2 g(s, s')}{\partial s'^2} \varphi(s') \\ & + D \frac{\partial P(\{\varphi\}, s; t)}{\partial s} \int ds' \frac{\partial g(s, s')}{\partial s} \varphi(s') \\ & + D \frac{\partial^2 P(\{\varphi\}, s; t)}{\partial s^2}. \end{aligned} \quad (5)$$

Here, if the dimensionality of the system is higher than 1, a trace is implied and the second derivative is in fact a Laplacian. The probabilistic description in Eq. (5) is completely equivalent to the coupled stochastic Eqs. (4a) and (4b).

Equation (5) is our main result and describes the evolution of an ensemble of metadynamics runs. We would like to stress that this result has far more general relevance than its application to the Langevin model in Eq. (1). In fact, our formalism would allow mapping the metadynamics equations into a Markovian form also before performing the dimensional reduction. For example, it could be applied to the Hamilton equations of motion in the canonical coordinates of the system,  $p$  and  $q$ , augmented with a Langevin thermostat in order to impose the temperature. This would lead to a set of Markovian equations in the original coordinates of the system and in the field  $\varphi(s; t)$ , and to a Fokker-Planck equation in a probability  $P(\{\varphi\}, p, q; t)$ .

We now look for the limiting distribution of Eq. (5) when  $t \rightarrow \infty$ , namely, the probability density  $\bar{P}$  which satisfies  $\frac{\partial \bar{P}(\{\varphi\}, s; t)}{\partial t} = 0$ . Remarkably, this solution is independent of  $s$  and is

$$\bar{P}(\{\varphi\}) = C \exp\left(\frac{D}{2} \int ds ds' \varphi(s) \frac{\partial^2 g(s, s')}{\partial s'^2} \varphi(s')\right), \quad (6)$$

as can be verified by direct substitution. Strictly speaking, not all initial conditions might flow to this solution. However, extensive numerical experimentation has shown this not to be the case in practical applications.  $C$  is a normalization constant, and the kernel  $\frac{\partial^2 g(s, s')}{\partial s'^2}$  is assumed to be symmetric and negative definite.

These kernel properties are better discussed through a change of basis. The most general form for  $g$  with the correct properties is

$$g(s, s') = \sum_k a_k(s) g_k a_k(s'), \quad \text{with } g_k > 0, \quad (7)$$

where the  $a_k(s)$  are the eigenfunctions of the Laplacian operator on  $\Omega$ . In the one-dimensional case the label  $k$  is a

positive or null integer and the basis functions are  $a_0(s) = \sqrt{1/S}$  and  $a_k(s) = \sqrt{2/S} \cos(\frac{\pi ks}{S})$  for  $k \neq 0$ . For a cubic  $d$  dimensional domain with side  $S$ , the eigenfunctions can be factorized and the label  $k$  is a  $d$ -dimensional vector of positive or null integers. For  $g_k$  in Eq. (7) we can chose the Fourier transform of a general radial function. If this is a Gaussian with standard deviation  $\delta s$ ,  $g_k \propto \exp(-\frac{\pi^2 k^2 \delta s^2}{2S^2})$ , where  $k^2$  is the square norm of the vector  $k$ . It is easily verified that the form in Eq. (7) for the kernel is equivalent to adding not only a Gaussian centered on the actual value of the CVs, but also reflected Gaussians that are positioned at an equal distance on the other side of the boundaries. This form of the kernel is slightly different from the one introduced in Refs. [6,21], but eliminates the systematic errors close to the boundaries that are observed using the simple Gaussians [11] and produces a reconstructed free energy that is reliable everywhere on  $\Omega$ . This has been extensively checked on a variety of model systems.

Equation (6) expresses the probability of obtaining a given field  $\varphi$  at the end of a metadynamics simulation. Since the negative of the biasing potential is used to estimate the free energy, we define the error  $\epsilon(s)$  as the sum of the exact underlying free energy and the biasing potential. Using Eqs. (2) and (3) we find that the error is linearly related to the field  $\varphi$  through

$$\epsilon(s) = \int ds' g(s, s') \varphi(s'). \quad (8)$$

Equation (6) implies that for a specific realization of a metadynamics process the probability of finding large errors in the estimation of the free energy is small. Using Eq. (6) we can explicitly calculate the expected average error of a series of runs. Since the distribution is a Gaussian with respect to  $\varphi$ , the expectation value of this field is vanishing. The error  $\epsilon(s)$  is linear in the field  $\varphi(s)$ , and consequently also its expectation value is vanishing:

$$\langle \epsilon(s) \rangle = 0. \quad (9)$$

Thus, we proved that the average of the biasing potential over a series of metadynamics runs provides an unbiased estimate for the underlying free energy.

Using Eq. (6) we can also address the problem of accuracy, determining the expected quadratic deviation  $\langle \epsilon^2(s) \rangle$  of a single metadynamics run from the average. This expectation value can be easily calculated on the basis of the eigenfunctions of the Laplacian:

$$\langle \epsilon^2(s) \rangle = \frac{S^2}{D} \sum_{k \neq 0} \frac{g_k a_k^2(s)}{\pi^2 k^2}. \quad (10)$$

The average value of the error in the domain  $\Omega$  is

$$\langle \epsilon^2 \rangle = \frac{1}{S^d} \int ds \langle \epsilon^2(s) \rangle = \frac{S^2}{DS^d} \sum_{k \neq 0} \frac{g_k}{\pi^2 k^2}. \quad (11)$$

A formal generalization of these expressions to domains of a different shape is straightforward.

So far the results are quite general and can be used to optimize the simulation parameters. Since all the metadynamics simulations carried out so far are based on a Gaussian kernel, it is useful to specialize our results to this case and compare the error estimate in Eq. (11) with the empirical expression given in Ref. [21]. In order to facilitate the comparison we shall use the same conventions as in Ref. [21]; that is to say, reintroducing standard energy units we write in  $k$  space  $g_k = \frac{w(\sqrt{2\pi}\delta s)^d}{\tau_G} \times \exp(-\frac{\pi^2 k^2 \delta s^2}{2S^2})$ , where the energy  $w$  is the Gaussian strength and  $1/\tau_G$  is the frequency at which the Gaussians are added to the bias. In this case Eq. (11) gives

$$\langle \epsilon^2 \rangle = \frac{S^2 w}{\beta D \tau_g} \left( \frac{\delta s \sqrt{2\pi}}{S} \right)^d \sum_{k \neq 0} \frac{\exp(-\frac{\pi^2 k^2 \delta s^2}{2S^2})}{\pi^2 k^2}. \quad (12)$$

This is to be compared with the empirical expression  $\epsilon_{\text{fit}} = C(d) \sqrt{\frac{S^2 w}{\beta D \tau_g} \frac{\delta s}{S}}$ , where  $C(d)$  is a constant depending on the dimensionality, namely, 0.5 for  $d = 1$  and 0.3 for  $d = 2$ . Since the dependence on  $\beta$ ,  $D$ ,  $S$ ,  $w$ , and  $\tau_G$  is identical, we compare here the error as a function of  $\delta s/S$ . In Fig. 1(a) it can be seen that the empirical expression works quite well, in spite of the fact that it was fitted on a very small range of Gaussian widths, namely,  $\delta s/S \in [0.003, 0.05]$ , and that the total error was averaged discarding the region near the boundaries.

In Ref. [21] we also noticed that the total simulation time required to fill the entire domain is proportional to  $\frac{\tau_g}{w} (\frac{S}{\delta s})^d$ . Therefore the sum in Eq. (12) is proportional to the square error at fixed simulation time, and is a function of the dimensionless ratio  $\delta s/S$  and of the dimensionality  $d$ . As can be observed in Fig. 1(b), this quantity is a decreasing function of the Gaussian width. Thus, to optimize the accuracy of a metadynamics calculation, the width has to be chosen to be as large as possible, the only limit being the

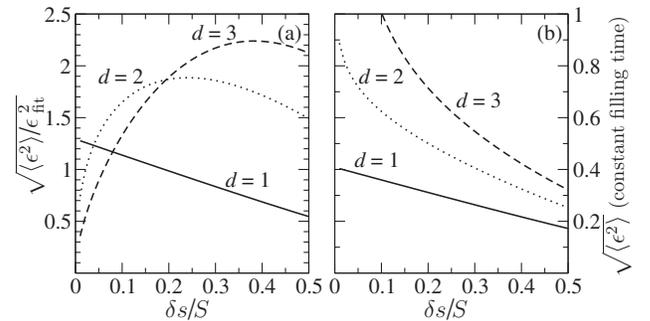


FIG. 1. (a) Ratio between the present expression for the error and the formula obtained by fitting results for  $d = 1$  and  $2$  in Ref. [21]. Since in the  $d = 3$  case the constant  $C(d)$  was not estimated, we assume here  $C(3) = C(2)$ . (b) Plot of the square root of the sum in Eq. (12), indicating the dependence of the error on  $\delta s/S$  for a fixed filling time (see text for details).

resolution needed to describe the underlying free energy. The Wang-Landau sampling as formulated in Ref. [12] can be viewed as a history-dependent stochastic sampling in which the kernel is a Kronecker delta. The present analysis suggests that the use of a smoother kernel might be advantageous.

As a final remark, we notice that a similar analysis can be carried out also in the multiple-walkers extension of metadynamics [25], in which  $N_w$  independent processes contribute to the reconstructed free energy. Equation (4b) is generalized as

$$d\varphi(s; t) = \sum_{i=1}^{N_w} \delta(s - s_i(t)) dt, \quad (13)$$

where  $s_i(t)$  is the trajectory of the walker  $i$ . It is straightforward to show that the asymptotic probability distribution of the system is also in this case independent of  $s_i$  and given by Eq. (6). This confirms the empirical result discussed in Ref. [25] that the error does not depend on the number of walkers.

In conclusion, the approach introduced in this Letter allows history-dependent dynamics such as metadynamics to be mapped in a Markovian process where the estimated free energy is treated as a dynamical variable. We have applied this formalism to a Langevin model system. When the proper collective variables of a reaction are used, this model is representative of a large class of realistic systems. Our approach allows this stochastic dynamics to be treated in a probabilistic manner and to search for its equilibrium distribution. We were able to demonstrate analytically the correctness of metadynamics, and we obtained an explicit expression for the error in the estimated free energy at the end of a metadynamics simulation. The present work is a step towards the understanding of all the sampling methods based on adaptive biases.

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