Well-Tempered Metadynamics: A Smoothly Converging and Tunable Free-Energy Method

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We present a method for determining the free-energy dependence on a selected number of collective variables using an adaptive bias. The formalism provides a unified description which has metadynamics and canonical sampling as limiting cases. Convergence and errors can be rigorously and easily controlled. The parameters of the simulation can be tuned so as to focus the computational effort only on the physically relevant regions of the order parameter space. The algorithm is tested on the reconstruction of an alanine dipeptide free-energy landscape.

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Computing free-energy differences is of crucial importance in molecular dynamics (MD) and Monte Carlo (MC) simulations. Whenever it is possible to define a few collective variables (CVs) that provide a coarse-grained description of the slow modes [1,2], it is also of great relevance to compute the associated free-energy surface (FES). In order to draw such a surface, a straightforward approach is often not possible due to high barriers or other sampling bottlenecks. A standard strategy for overcoming this problem is to introduce an external biasing potential that forces the system to explore regions of high free energy [3]. A major progress has been the recent introduction of adaptive nonequilibrium methods [4–7]. In all these methods, the simulation history is used to enhance the sampling speed. In a MC run, this can be done by varying the MC acceptance probability every time a new configuration is visited [4], while in MD, a time-dependent bias can be added either to the force [5] or to the potential [6,7].

We shall focus here on metadynamics [6], which has proven its effectiveness in a variety of contexts [8–18]. In metadynamics, the system evolution is biased by a history-dependent potential that is constructed as the sum of Gaussian functions [19] deposited along the trajectory in the CVs space. After a transient, the bias potential compensates the underlying FES and provides an estimate of its dependence on the CVs. A formal justification of this procedure has been given in Ref. [20]. In spite of its success, there is a need to improve metadynamics in several respects. First of all, it is often difficult to decide when to terminate a metadynamics run. In fact, in a single run, the free energy does not converge to a definite value but fluctuates around the correct result, leading to an average error which is proportional to the square root of the bias potential deposition rate [20,21]. Reducing this rate implies increasing the time required to fill the FES. Furthermore, in practical application, continuing a run carries the risk that the system is irreversibly pushed in regions of configurational space which are not physically relevant. These issues have already been recognized, and different ad-hoc solutions have been proposed to alleviate these problems [8–10,22–24].

In this Letter, inspired by the self-healing umbrella sampling method [7], we substantially improve metadynamics such that we obtain an estimate of the FES that converges to the exact result in the long time limit. Contrary to ordinary metadynamics, our approach offers the possibility of controlling the regions of FES that are physically meaningful to explore. Besides being highly effective and controllable, this new method provides a unified framework whose limiting cases are standard metadynamics and nonbiased standard sampling. We dub this new scheme well-tempered metadynamics.

Let us consider a system described by a set of microscopic coordinates q and a potential energy $U(q)$, evolving under the action of a dynamics (e.g., MD or MC) whose equilibrium distribution is canonical at the temperature T. We want to determine the free-energy dependence on a set of collective variable $s(q)$. The FES can be written within an immaterial constant as

$$F(s) = -T \lim_{t\to\infty} \ln N(s,t), \tag{1}$$

where $N(s,t) = \int_0^t \delta_{s,s(t')} dt'$ is the histogram of the variable s obtained from an unbiased simulation. By construction, $N(s,0) = 0$ and its time derivative $\dot{N}(s,t) = \delta_{s,s(t)}$. To accelerate sampling, we bias the dynamics by adding the history-dependent potential

$$V(s,t) = \Delta T \ln\left(1 + \frac{\omega N(s,t)}{\Delta T}\right), \tag{2}$$

where ω has the dimension of an energy rate, ΔT is a temperature, and $N(s,t)$ comes from the biased simulation. Since V is a monotonic function of N, such a bias potential disfavors the more frequently visited configurations. A crucial quantity is the rate at which the potential is modified. In particular, slower variation rates lead to a dynamics of the microscopic variables q which is closer to thermodynamic equilibrium. From Eq. (2), it follows that the rate with which $V(s, t)$ changes is

$$\dot{V}(s, t) = \frac{\omega \Delta T \delta_{s,s(t)}}{\Delta T + \omega N(s, t)} = \omega e^{-[V(s,t)/\Delta T]} \delta_{s,s(t)}. \quad (3)$$

The connection with metadynamics is evident if we examine Eq. (3) and replace $\delta_{s,s(t)}$ with a finite width Gaussian. Therefore, our scheme can easily be implemented in any metadynamics code by rescaling the height of the Gaussians according to Eq. (3). Using the notation in Ref. [21], the height of each Gaussian is determined by $w = \omega e^{-[V(s,t)/\Delta T]} \tau_G$, where τ_G is the time interval at which Gaussians are deposited. Thus, ω represents the initial bias deposition rate.

Two important properties need to be underlined. The first is that since the histogram $N(s, t)$ grows linearly with simulation time, the rate $\dot{V}(s, t)$ tends to zero as $\propto 1/t$. This is the simplest, if possibly not the optimal [25], way to have a rate decrease fast enough for the bias eventually to converge, yet slow enough for the final result not to depend on the initial condition $V(s, 0)$. Similar arguments have been used in the field of stochastic optimization [26,27]. The second property is that $\dot{V}$ is not uniform in the s space since at a given point, the rate is inversely proportional to the time already spent there. This latter feature distinguishes our approach from others in which $1/t$ strategy has also been suggested either explicitly [28] or implicitly [7].

For large times, $V(s, t)$ varies so slowly that one can assume that the q's reach equilibrium, the probability distribution becomes $P(s, t)ds \propto \exp(\frac{-F(s)-V(s,t)}{T})ds$ and one has

$$\dot{V}(s, t) = \omega e^{-[V(s,t)/\Delta T]} P(s, t)$$
$$= \omega e^{-[V(s,t)/\Delta T]} \frac{e^{-[F(s)+V(s,t)]/T}}{\int ds e^{-[F(s)+V(s,t)]/T}}. \quad (4)$$

This implies that $V(s, t \to \infty) = -\frac{\Delta T}{\Delta T + T} F(s)$, modulo a constant. Thus, at variance with metadynamics and other methods, the bias does not fully compensate $F(s)$; rather, one has that $F(s) + V(s) = \frac{T}{T+\Delta T} F(s)$ leading to the following distribution of s:

$$P(s, t \to \infty)ds \propto e^{-[F(s)/(T+\Delta T)]} ds. \quad (5)$$

In practice, using Eq. (2), the FES can be estimated as

$$\tilde{F}(s, t) = -\frac{T + \Delta T}{\Delta T} V(s, t)$$
$$= -(T + \Delta T) \ln\left(1 + \frac{\omega N(s, t)}{\Delta T}\right). \quad (6)$$

Let us examine the two limiting cases, $\Delta T = 0$ and $\Delta T \to \infty$. For $\Delta T = 0$, the bias is equal to zero and Eq. (6) reduces to Eq. (1). More interesting is the $\Delta T \to \infty$ limit. In this case, the deposition rate is constant, and from Eq. (6), one finds that $\tilde{F}(s, t) = -V(s, t)$ and the standard metadynamics algorithm is recovered. Note however that the limit $\Delta T \to \infty$ is singular: if we first let $\Delta T \to \infty$, the convergence of $V(s, t)$ for $t \to \infty$ cannot be demonstrated by means of Eq. (4). This is a reflection of the already noted drawback of metadynamics that in a single simulation, the bias does not converge but oscillates around the correct $F(s)$ value. In intermediate cases, the calculated FES is the one corresponding to the target temperature T, with the transverse degrees of freedom correctly sampled. However, the s probability distribution is altered and corresponds to an enhanced temperature $T + \Delta T$. It must be stressed that this result has been obtained without having to assume adiabatic separation between s and the other variables as in Refs. [29–31].

Much is to be gained computationally by well-tempered metadynamics. By tuning ΔT, one can increase barrier crossing and facilitate the exploration in the CVs space. Furthermore, using a finite value of ΔT, one automatically limits the exploration of the FES region to an energy range of the order $T + \Delta T$. Hence, the exploration of the FES can be limited to the physically interesting regions of s. Longer simulation time results in improved statistical accuracy in the relevant regions. The risk of overfilling is avoided, and optimal use is made of the computer time. Deciding when to stop the run is now simple, and post-processing [8,22] is not necessary.

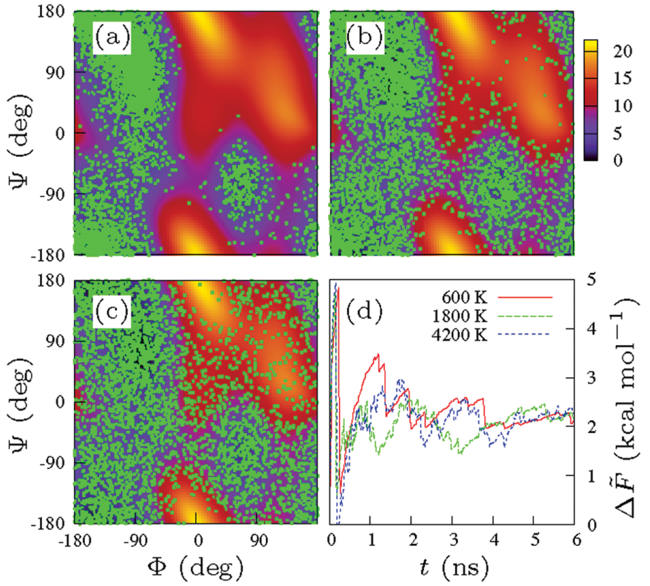

FIG. 1 (color). Panels (a–c) Green dots represent 6 ns long trajectories in the (Φ, Ψ) space for different choices of ΔT [600 K (a), 1800 K (b), and 4200 K (c)]. The underlying color map (kcal mol^{-1}) shows the reference free-energy landscape. Panel (d) Estimate of the free-energy difference between the two metastable minima $C_{7\mathrm{ax}}$ (70, −70) and $C_{7\mathrm{eq}}$ (− 83, 74) as a function of the simulation time, as obtained from the same trajectories.

As an illustration, we study the FES of alanine dipeptide in vacuum as a function of the backbone dihedral angles (Φ, Ψ). This surface has been well studied and is known to exhibit two minima $C_{7\mathrm{eq}}$ and $C_{7\mathrm{ax}}$ separated by a barrier of ≈ 9 kcal mol^{-1} [32,33]. Since such a barrier cannot be crossed with standard dynamics at room temperature, this system has provided a testing ground for many sampling schemes. The CHARMM27 [34] force field has been used in ORAC MD code [35], and canonical sampling at a temperature of 300 K was achieved by means of the stochastic thermostat in Ref. [36]. The Gaussian width was set to 20 degrees, and the deposition interval was 120 fs with a starting Gaussian height of 0.287 kcal mol^{-1}, which corresponds to a deposition rate $\omega = 2.4$ cal mol^{-1} fs^{-1}.

We calculated a reference $F(\Phi, \Psi)$ using standard umbrella sampling which is in good agreement with previous studies. On this surface, we superimpose three different trajectories (see Fig. 1) started from the same initial conditions [$C_{7\mathrm{eq}}$ $(-83, 74)$], but with three different choices of ΔT (600 K, 1800 K, and 4200 K). In all three cases, the secondary metastable state $C_{7\mathrm{ax}} = (70, -70)$ was frequently visited. It is worth noting that, as discussed earlier, by increasing ΔT, larger and larger regions were explored. In order to demonstrate how the method converges, for the three mentioned cases, in Fig. 1 we also show the time evolution of $\Delta\tilde{F}(t) = \tilde{F}(C_{7\mathrm{ax}}, t) - \tilde{F}(C_{7\mathrm{eq}}, t)$, i.e., the estimated free-energy difference between the two minima. $\Delta\tilde{F}(t)$ converges to the reference value ($\Delta F \approx 2.2$ kcal mol^{-1}) in all three trajectories. At variance with standard metadynamics, the time derivative of the bias potential tends to zero, and the fluctuations around the correct value are progressively damped. All three simulations provide an accurate estimate of the free-energy difference within a few nanoseconds, even in the lowest ΔT case where the lower number of barrier crossing events leads to a jumpier $\Delta\tilde{F}$ evolution.

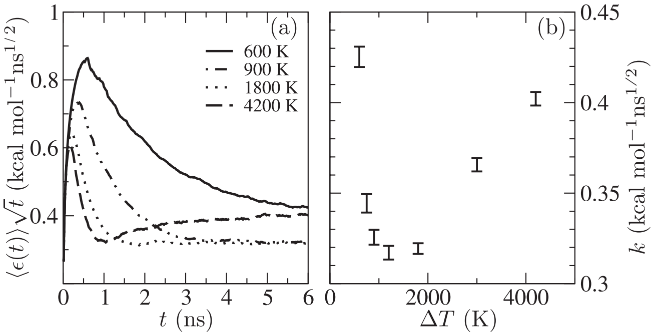

FIG. 2. Panel (a) Time evolution of $\langle\epsilon(t)\rangle\sqrt{t}$ for different choices of ΔT. $\langle\epsilon(t)\rangle$ is the error as defined in Eq. (7), averaged over an ensemble of 100 independent atomistic simulations starting from $C_{7\mathrm{eq}}$. Panel (b) Dependence of k (see text for definition) on ΔT, as estimated from 6 ns long trajectories.

As a measure of the error of $\tilde{F}(\Psi, \Phi)$ in the relevant regions, we define

$$\epsilon(t) = \left(\frac{1}{A}\int_{\Gamma}[F(\Psi, \Phi) - \tilde{F}(\Psi, \Phi, t) - C(t)]^2 d\Phi d\Psi\right)^{1/2} \tag{7}$$

where Γ is the region in dihedral space such that $F(\Psi, \Phi) - F(C_{7\mathrm{eq}}) < 10$ kcal, and A is its area. Γ is defined to include all the minima and all the transition states. The value of $C(t)$ is chosen so as to align the averages of F and $\tilde{F}$ over Γ. It is seen that after an initial transient period, $\langle\epsilon(t)\rangle$ converges to zero as $k/\sqrt{t}$. Such behavior is shown in Fig. 2(a) where $\langle\epsilon(t)\rangle\sqrt{t}$ is plotted against the simulation time for three values of ΔT. This is clearly at variance with standard metadynamics in which the error does not to converge to zero during a single simulation [20,21]. The behavior of the present scheme is consistent with an error analysis done on a simulation performed at a constant bias. In Fig. 2(b), we study the dependence of $k = \lim_{t\to\infty}\langle\epsilon(t)\rangle\sqrt{t}$ on ΔT as a way of optimizing the choice of ΔT. In this case, the optimal choice is close to $\Delta T = 1200$ K resulting in a sampling temperature for the collective variables of $T + \Delta T = 1500$ K, which is of the order of magnitude of the barrier height. Its actual value may depend on the s relaxation times and on the area one wishes to explore.

We discuss now the role of ω, the initial deposition rate which we relate to the time constant $\tau_B = \frac{\Delta T}{\omega}$ that sets the time scale for the bias evolution. While in the long time limit τ_B is irrelevant, it could affect the transient regime in a nontrivial way. At constant ΔT, a small τ_B implies a high initial deposition rate, thus leading to rapid filling of the wells. However, if τ_B is too small relative to the time necessary to properly average out the transverse degrees of freedom, the large fluctuations in the initial FES reconstruction need a longer time to be recovered.

This effect is conveniently investigated by introducing an artificial model based on the alanine dipeptide FES. We model the dynamics on the two-dimensional space (Φ, Ψ) with a high-friction Langevin equation driven by the free-energy surface $F(\Phi, \Psi)$ and the diffusion coefficients D_Φ, D_Ψ determined from the atomistic simulations. We shall apply our scheme to calculate the one-dimensional projection $F(\Phi)$, using a one-dimensional bias on Φ. In such a case, the relaxation speed of the transverse degree of freedom Ψ can be tuned by changing D_Ψ, thus mimicking a situation in which the transverse degrees of freedom are either fast or slow. As can be seen in Fig. 3, in the fast case, the orthogonal degree of freedom is rapidly averaged out, resulting in a Markovian dynamics on Φ, and a small τ_B is the best choice. In the slow case, the effective dynamics of Φ is strongly non-Markovian due to coupling with Ψ, and a small τ_B is not the best choice since it results in an increase of the transient time. However, it is worth noting that the method is robust and in the range of reported cases, which spans 2 orders of magnitude in τ_B and D_Ψ, the calculation converged to the same results on approximately the same time scale.

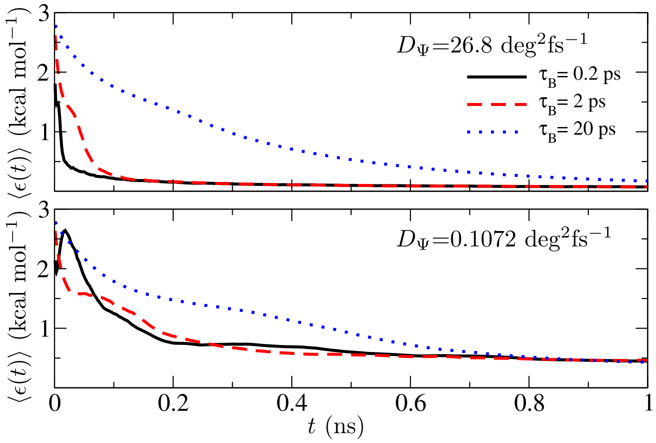

FIG. 3 (color online). Time evolution of the average error $\langle\epsilon(t)\rangle$ for different values of τ_B and D_Ψ, where $D_\Phi = 12.3\ \mathrm{deg}^2\,\mathrm{fs}^{-1}$ and $\Delta T = 1200$ K. The error is averaged over an ensemble of 1000 independent Langevin simulations starting from $C_{7\mathrm{eq}}$.

In conclusion, well-tempered metadynamics solves the convergence problems of metadynamics and allows the computational effort to be focused on the physically relevant regions of the conformational space. The latter property makes it possible to use adaptive-bias methods in higher dimensionality cases, thus paving the way for the study of complex systems where it is difficult to select *a priori* a very small number of relevant degrees of freedom. The proposed approach can easily be applied to generalizations of metadynamics based on multiple replicas [15,37,38], and can be extended to the Wang-Landau algorithm [4].

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