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Metadynamics convergence law in a multidimensional system

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Metadynamics is a powerful sampling technique that uses a nonequilibrium history-dependent process to reconstruct the free-energy surface as a function of the relevant collective variables **s**. In Bussi *et al.* [Phys. Rev. Lett. **96**, 090601 (2006)] it is proved that, in a Langevin process, metadynamics provides an unbiased estimate of the free energy $F(\mathbf{s})$. We here study the convergence properties of this approach in a multidimensional system, with a Hamiltonian depending on several variables. Specifically, we show that in a Monte Carlo metadynamics simulation of an Ising model the time average of the history-dependent potential converge to $F(\mathbf{s})$ with the same law of an umbrella sampling performed *in optimal conditions* (i.e., with a bias exactly equal to the negative of the free energy). Remarkably, after a short transient, the error becomes approximately independent on the filling speed, showing that even in out-of-equilibrium conditions metadynamics allows recovering an accurate estimate of $F(\mathbf{s})$. These results have been obtained introducing a functional form of the history-dependent potential that avoids the onset of systematic errors near the boundaries of the free-energy landscape.

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In the last few years the use of non-Markovian sampling techniques has emerged as a paradigm in computational science. Prominent examples are the Wang-Landau [1] and metadynamics [2] approaches that have, respectively, become popular in the statistical physics [3] and in the computational chemistry and biophysics community [4,5]. These methods, although different, are based on similar ideas. Wang-Landau is formulated in a Monte Carlo (MC) framework and aims at calculating the density of states $g(E)$ by iteratively flattening the energy histogram $n(E)$. This is achieved by making the acceptance of the move depend on the reconstructed $1/g(E)$ up to that moment. Each time a certain move is proposed $g(E)$ is multiplied by a factor $f>1$. Once $n(E)$ is "flat," f is reduced and $n(E)$ is reset to zero. This process is repeated until f becomes smaller than some predefined value. Metadynamics is normally formulated in a molecular-dynamics framework and aims at calculating the free energy F as a function of collective variables (CVs) **s** that are explicit functions of the system coordinates. Like in Wang-Landau, this is achieved by flattening the histogram as a function of these CVs: the normal molecular-dynamics forces are combined with forces derived from a history-dependent potential $V_G(\mathbf{s})$ defined as a sum of Gaussians of height w centered along the trajectory in CVs space.

These two methods, Wang-Landau and metadynamics, have in common the idea of using an history-dependent (non-Markovian) process for forcing the system to flatten the probability distribution as a function of the relevant variables. However, in order to recover the correct (*equilibrium*) thermodynamic properties the two algorithms adopt a different strategy. In metadynamics, the history-dependent potential is assumed to be an estimator of the free energy also if the history-dependent potential is upgraded with Gaussians of finite w. This assumption is justified by the proof given in Ref. [6] that the history-dependent potential is an estimator of the F whenever the dynamics along the variable biased by metadynamics is much slower than the dynamics along all the other degrees of freedom ("adiabatic separation"). Additional fictitious coordinates [7] or a suitable discretization procedure [2] can be employed to enforce, in generic many-body systems, this time-scale separation. However, in practical applications adiabatic separation can be achieved only approximately. In Wang-Landau equilibrium properties are recovered in a different manner. At the end of the simulation, the modification factor f converge to a number close to one, and the bias becomes approximately time independent. Thus, the final analysis is performed on a histogram constructed in a quasiequilibrium process. A similar strategy has been successfully adopted also in a metadynamics-based scheme [8].

In this Rapid Communication we numerically show that neither adiabatic separation nor an iterative reduction in w is necessary to obtain a reliable estimate of F in non-Markovian sampling. We consider a two-dimensional Ising model with ferromagnetic nearest-neighbor interaction and periodic boundaries conditions [9]. For this system we apply a history-dependent MC scheme using ideas from both Wang-Landau and metadynamics [10] with a collective variable, the magnetization per spin, that is not adiabatically separated from the other coordinates. Despite of this, the average among history-dependent potential profiles at different times converge to an accurate estimate of the free energy. Remarkably, the convergence law of the error decays to zero like the one of an umbrella sampling [11] performed in *optimal conditions*, namely, with a bias equal to the negative of the free energy. This behavior turns out to be approximately independent on the details of the procedure, e.g., the value of w.

To achieve stationary fluctuations of the history-dependent potential around the correct F it was necessary to solve a technical problem. In metadynamics for reducing the

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computational cost it is customary to use finite width Gaussians that "fill" the free-energy surface very quickly. On the other hand, finite-width Gaussians can induce systematics errors at the boundaries ($\partial\Omega$) of the CVs space [4]. These errors are due to the fact that a sum of Gaussians cannot accurately reproduce discontinuities on the free-energy profile. The presence of discontinuities is common for several types of CVs that are intrinsically limited, e.g., atom coordination numbers, etc. [4]. At the beginning of the simulation these errors are small and are usually overlooked, but at long times they can become important, preventing the system from reaching a stationary state. In Ref. [6] it was shown that if the component of the free-energy gradient in the direction normal to $\partial\Omega$ vanishes at the boundaries $[\nabla_n F(\partial\Omega)=0]$, the systematic errors can be eliminated by choosing a functional form for the history-dependent potential that satisfies the same condition $[\nabla_n V_G(\partial\Omega)=0]$. In this Rapid Communication we introduce a more general procedure that eliminates systematic errors even if $\nabla_n F(\partial\Omega)\neq 0$, like in the case of the Ising model.

The algorithm is implemented as follows. A history-dependent potential V_G is included in the Boltzmann factor of the Metropolis algorithm. At the beginning of the simulation V_G is set to zero. Then a random move $\mathbf{x}\rightarrow\mathbf{x}'$ is proposed. The acceptance probability of the move is

$$P(\mathbf{x}\rightarrow\mathbf{x}',t)\equiv\min\{1,\exp(-\beta[E(\mathbf{x}')+V_G(\mathbf{s}(\mathbf{x}'),t) - E(\mathbf{x})-V_G(\mathbf{s}(\mathbf{x}),t)]\}, \quad (1)$$

where $E(\mathbf{x})$ is the energy of the system and β is the inverse temperature [10]. At each step the history-dependent potential is updated as

$$V_G(\mathbf{s},t+1)=V_G(\mathbf{s},t)+w\exp\left[-\frac{|\mathbf{s}-\mathbf{s}(\mathbf{x})|^2}{2\delta s^2}\right], \quad (2)$$

where w is the height of the added Gaussian and δs is its width. After a sufficient time, hereafter call the "filling time" t_F, V_G relaxes to its "equilibrium" shape approximately compensating the underlying free energy. After t_F the system diffuses freely in $\mathbf{s}$ [4]. In this scheme, like in Wang-Landau sampling, the history-dependent potential iteratively reduces the probability of the system to remain in the same state. At the same time, the Boltzmann factor keeps the system in regions of relevance at the temperature of interest.

Systematic errors in the free-energy reconstruction close to $\partial\Omega$ are eliminated in the following manner. To simplify the notation, we here assume the CV space is one-dimensional and defined by the equation $s\geq 0$, with the boundary at $s=0$. The procedure can be straightforwardly generalized to multidimensional CVs space, etc. If the system is in s, one extra Gaussian is added in $-s$ with the scope of iteratively imposing that, in a suitably chosen interval around $s=0$,

$$V_G(-s,t)\approx 2V_G(0,t)-V_G(s,t). \quad (3)$$

This property ensures that, at stationary conditions, the history-dependent potential is approximately linear close to the boundary, but it does not impose the value of its derivative that is iteratively determined by the thermodynamic bias.

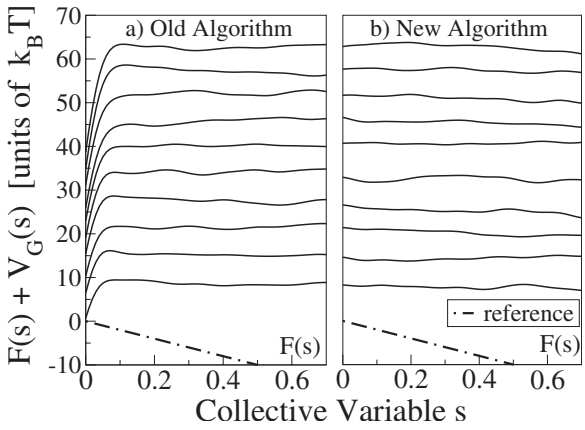

FIG. 1. Sum of the reference free energy and the history-dependent potential $[F(s)+V_G(s)]$ as a function of s. For a one-dimensional overdamped Langevin model, with a reflective wall at $s=0$ and a linear free energy $F(s)=\frac{1}{\beta}\frac{b}{\delta s}s$ (dot-dashed line). The following parameters were used $\delta s=0.05$, $w=0.3$, $\beta=1.0$, $b=-1.0$, and a diffusion coefficient of $D=2.0$. The results are shown for different simulations times (solid lines), (a) normal metadynamics ("Old algorithm") and (b) metadynamics including the proposed boundary correction ("New algorithm") with $\chi=2\delta s$.

In practice, the extra Gaussian is added according to the following rules:

(i) An interval centered in 0 is chosen, whose width χ is of the order of δs.

(ii) If $s<\chi$ another Gaussian centered in $-s$ and with the same width and height is added.

(iii) If $s>\chi$ another Gaussian centered in $-s$ and with the same width is added. In this case, the height of the extra Gaussians depends on V_G and is given by

$$w=[2V_G(0,t)-V_G(-s,t)-V_G(s,t)]y(s), \quad (4)$$

where $y(s)=1/[1+(s/(4\chi))^l]$ with $l=10$.

The second factor in Eq. (4) is approximately one for $|s|<4\chi$ and goes to zero for $|s|>4\chi$. This ensures that V_G goes smoothly to zero in the unphysical region.

The proposed boundary correction scheme was tested by performing a metadynamics simulation on a one-dimensional overdamped Langevin model, with a reflective wall at $s=0$ and a linear free energy $F(s)=\frac{1}{\beta}\frac{b}{\delta s}s$ (see Fig. 1). b is a dimensionless parameter that defines the slope of the free energy, $\beta=1$ and $\delta s=0.05$. In Fig. 1, it is shown that, for $b=-1$ and $\chi=2\delta s$, the algorithm ("New algorithm" in figure) is capable of producing a V_G that compensates $F(s)$ almost exactly $[F(s)+V_G(s)\simeq\text{const}]$. Instead, if the extra Gaussians are not added ("Old algorithm"), large systematic errors are developed close to the boundary, and the system cannot reach a stationary state. It was verified that for values of $\chi\in[1.5\delta s,3\delta s]$, $l\in[4,20]$, and $b\in[-10,10]$ the error does not change significantly.

The algorithm described above was applied to a 16×16 two-dimensional classical Ising model. As a collective variable we used the magnetization per spin m. Clearly, the evolution of this system takes place in the 16^2 dimensional space of its spins variables, and it cannot be expressed as a one-

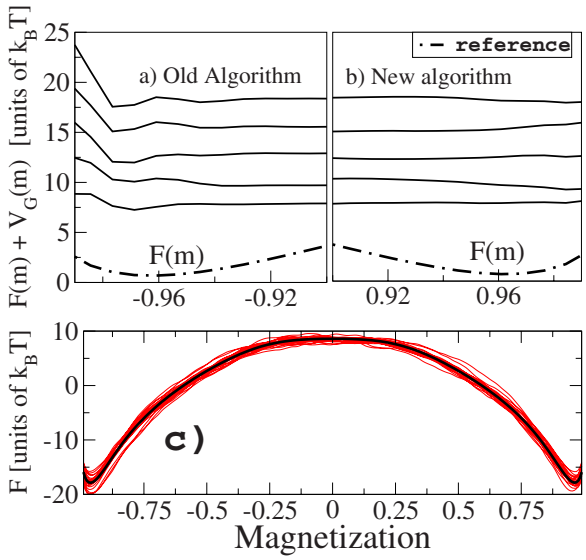

FIG. 2. (Color online) (a) and (b) Sum of the reference free energy (dot-dashed line) and the reconstructed history-dependent potential $[F(m)+V_G(m)]$ as a function of the magnetization per spin for $\beta=1./1.86$, $\delta s=1.4\times10^{-2}$, $w=1.0\times10^{-4}$ reconstructed profiles at different MC times (solid lines), (a) without and (b) with the boundaries correction using $\chi=2\delta s$. (c) V_G profiles reconstructed at different MC times, together with the reference profile $F(m)$ (thick line).

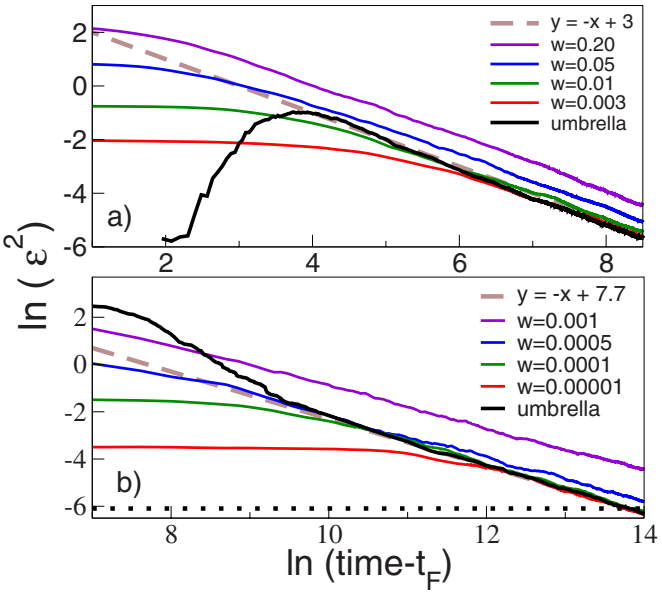

FIG. 3. (Color online) Square of the error in the reconstructed F as a function of simulation time after the filling time t_F, for two different cases: (a) a Langevin dynamics in a square well performed with $\beta=1$, $D=0.01$, $\delta s=0.025$, and $\chi=2\delta s$. The free energy is computed by umbrella sampling (black line) and metadynamics with four values of the Gaussian high $w=(0.20,0.05,0.01,0.003)$. (b) A 16×16 two-dimensional Ising model, calculated for $\beta=1/1.86$, $\delta s=1.4\times10^{-2}$, and $\chi=2\delta s$. The free energy is computed by umbrella sampling (black line) and metadynamics with four values of the Gaussian high $w=(1.0\times10^{-3},5.0\times10^{-4},1.0\times10^{-4},1.0\times10^{-5})$, taking as a reference an accurate umbrella sampling calculation. The dotted line is the estimated error in the reference F_{ref}, $\ln(\epsilon^2)\simeq-6.1$.

dimensional Markov process in m alone. This means that m is not adiabatically separated from the other degree of freedom as it would be required to apply the results of Ref. [6]. The height and the width of the Gaussians were $w=1.0\times10^{-4}$ and $\delta s=1.4\times10^{-2}$, respectively. For this system, the "exact" free energy $F(m)$ was calculated in a long umbrella sampling simulation [11].

In Figs. 2(a) and 2(b) we plot $F(m)+V_G(m)$ at different times for the "Old" and the "New" algorithm. Like in the test model of Fig. 1(a), the old algorithm generates systematic errors in the calculation of F close to the boundaries. Moreover, these errors increase as a function of MC time, and the simulation cannot reach a stationary state. In Fig. 2(b) we plot $F(m)+V_G(m)$ for the new algorithm using $\chi=2\delta s$, at the same MC times of panel a. The boundary corrections introduced in this work significantly reduce the systematics errors and allow the simulation to reach a stationary state where the history-dependent profiles are approximately parallel to each other. In Fig. 2(c) it is shown that the $V_G(m,t)$ at different MC times (thin lines) oscillates around the exact free-energy profile $F(m)$ (thick line). Thus the algorithm is able to reach a stationary condition in which the history-dependent potential is, at each time t, a reliable estimator of the equilibrium free energy.

In order to be more quantitative on this point, following Ref. [4] we considered the arithmetic average of all the profiles between the filling time t_F and the time $t>t_F$:

$$\overline{V_G}(s,t)=\frac{1}{t-t_F}\int_{t_F}^{t}dt'\,V_G(s,t'). \tag{5}$$

If $V_G(s,t)$ after t_F is an unbiased estimator of $-F$, $\lim_{t\to\infty}\overline{V_G}(s,t)=-F(s)$, modulus an irrelevant constant, that will be neglected in the following to simplify the notation. At finite simulation time, $\overline{V_G}(s,t)+F(s)$ will show deviations from zero that become smaller for large t. To study how the error depends on time, we first considered the case of a one-dimensional overdamped Langevin process in a square well. A flat free-energy profile $[F(s)=0]$ has been employed with reflecting boundaries at -1 and 1. The metadynamics algorithm has been used to reconstruct the free energy profile. For comparison, a trajectory was also generated without the metadynamics bias. In this case the free-energy profile $[F_u(s,t)]$ was estimated as

$$F_u(s,t)=-\beta^{-1}\ln[n(s,t)], \tag{6}$$

where $n(s,t)$ is the histogram of the visited positions up to time t. This corresponds to an *ideal* umbrella sampling simulation, in which the free energy is perfectly compensated by the bias. The error of the reconstructed free energy at a given simulation time t was calculated as

$$\varepsilon(t)^2=\left\langle\frac{1}{2}\int_{-1}^{1}[F_{rec}(s',t)-F_{ref}(s')]^2ds'\right\rangle, \tag{7}$$

where $F_{rec}=\overline{V_G}$ for the metadynamic case, $F_{rec}=F_u$ for umbrella sampling, and $F_{ref}(s)=0$ for both cases. The average was taken over 100 statistically independent runs.

In Fig. 3(a) $\varepsilon(t)^2$ is plotted as a function of simulation time in logarithmic scale. It can be seen from the figure that the error of metadynamics, after an initial transient that increases when w is reduced, decreases with the same law of an ideal umbrella sampling, namely, with the inverse square root of t:

$$\varepsilon \sim 1/\sqrt{t}. \tag{8}$$

Remarkably, for large t the errors depends weakly on w and for $w \lesssim 0.05$, it is practically indistinguishable from the ideal umbrella sampling case. This is not a trivial result since it was demonstrated that the error on a *single* profile V_G grows with $\sqrt{w}$ [6]. This corresponds to the error observed at $t=0$ (i.e., at filling time). The behavior observed in Fig. 3 can be rationalized assuming that profiles obtained with large w have large errors but decorrelate more quickly. The accuracy gained from fast decorrelation approximately compensates the accuracy lost due to large w. Indeed, for small w, taking the average between different profiles does not improve the accuracy, as the V_G profiles are strongly correlated. This is the origin of the plateau observed in the error curves for small time; consistently the plateau becomes longer for small w.

To investigate the effect of a violation of adiabatic separation on these results, we repeated all the analysis for the two-dimensional Ising model. In this case, as a reference, we performed umbrella sampling using as a bias the same $F_{ref} = F(m)$ of Fig. 2. The error as a function of simulation time is shown in Fig. 3(b). Clearly, also in this case the error decays to zero following the same law Eq. (8) of the ideal umbrella sampling. Moreover, like in the metadynamics simulation on the Langevin system, the decay law Eq. (8) depend weakly on the height w of the Gaussians.

In summary, we have shown that the history-dependent potential of metadynamics, after a transient, fluctuates around a well-defined average that, for the system considered in this work, is a good approximation of the negative of the free energy. Stationary conditions can be reached thanks to a procedure that eliminates the systematic errors at the boundaries generated by finite-width Gaussians. By applying this technique to a two-dimensional Ising model we showed that a stationary state is reached even for a system which lacks adiabatic separation between the biased CV and the remaining degrees of freedom. The error of the algorithm in reconstructing the equilibrium free energy, after a transient, decays like umbrella sampling performed in optimal conditions. Another important result is that this decay law on the error holds independently on the filling speed determined by w. The numerical evidence presented here does not allow excluding that systematic errors might appear when looking at very fine details of the free-energy surfaces, possibly due to the violation of adiabatic separation and/or to residual effects of the boundaries. However, these errors, if present, are so small $[\ln(\epsilon^2) \leq -6.1 \Rightarrow \epsilon < e^{-3} k_B T]$ that are not expected to affect the validity of the approach in most practical applications.

[1] F. Wang and D. P. Landau, Phys. Rev. Lett. **86**, 2050 (2001); Phys. Rev. E **64**, 056101 (2001).
[2] A. Laio and M. Parrinello, Proc. Natl. Acad. Sci. U.S.A. **99**, 12562 (2002).
[3] T. Wust, D. P. Landau, C. Gervais, and Y. Xu, Comput. Phys. Commun. **180**, 475 (2009).
[4] A. Laio and F. L. Gervasio, Rep. Prog. Phys. **71**, 126601 (2008).
[5] V. Leone, F. Marinelli, P. Carloni, and M. Parrinello, Curr. Opin. Struct. Biol. **20**, 148 (2010).
[6] G. Bussi, A. Laio, and M. Parrinello, Phys. Rev. Lett. **96**, 090601 (2006).
[7] M. Iannuzzi, A. Laio, and M. Parrinello, Phys. Rev. Lett. **90**, 238302 (2003).
[8] A. Barducci, G. Bussi, and M. Parrinello, Phys. Rev. Lett. **100**, 020603 (2008).
[9] A. E. Ferdinand and M. E. Fisher, Phys. Rev. **185**, 832 (1969).
[10] Y. Crespo, A. Laio, G. E. Santoro, and E. Tosatti, Phys. Rev. E **80**, 015702(R) (2009).
[11] G. M. Torrie and J. P. Valleau, J. Comput. Phys. **23**, 187 (1977).