Enhanced Sampling in the Well-Tempered Ensemble

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We introduce the well-tempered ensemble (WTE) which is the biased ensemble sampled by well-tempered metadynamics when the energy is used as collective variable. WTE can be designed so as to have approximately the same average energy as the canonical ensemble but much larger fluctuations. These two properties lead to an extremely fast exploration of phase space. An even greater efficiency is obtained when WTE is combined with parallel tempering. Unbiased Boltzmann averages are computed on the fly by a recently developed reweighting method [M. Bonomi *et al.*, J. Comput. Chem. **30**, 1615 (2009)]. We apply WTE and its parallel tempering variant to the $2d$ Ising model and to a Gō model of HIV protease, demonstrating in these two representative cases that convergence is accelerated by orders of magnitude.

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Monte Carlo (MC) or molecular dynamics (MD) simulations are routinely applied in all areas of science. However, severe difficulties are encountered when multiple metastable states separated by large free-energy barriers are present. Nucleation from one phase to another, chemical reactions, and protein folding are important examples. Accessing the low probability regions separating one state from another can overcome this difficulty. In standard MC or MD simulations this is not possible and the system remains confined to its initial basin hindering a proper phase space exploration. Sampling low probability regions would also be of great help in free-energy differences calculation [1]. Hence, many enhanced sampling methods have been suggested [2–12].

Recently, we have developed metadynamics [13] where few difficult to sample degrees of freedom or collective variables (CV) are selected [14,15]. If the CV are well chosen, large free-energy barriers can be overcome and the associated free-energy surface (FES) reconstructed [16]. Well-tempered metadynamics [17] is a nontrivial evolution of the method which lends itself to reweighting, thus allowing the calculation of unbiased canonical averages [18]. We show here that when the potential energy is used as CV, a well-defined distribution dubbed well-tempered ensemble (WTE) is sampled. Using WTE it is possible to observe transitions between states that otherwise would have been impossible to study in standard MC or MD simulations.

Many approaches have already been suggested in which the energy distribution is altered artificially [19–24]. However, all these methods can evaluate only the density of states from which thermal properties can be determined. If information on other variables is needed for each new variable, a separate calculation is required [20,25]. Here, instead, full information on all the variable distributions can be obtained from a single run. Furthermore, in an appropriate combination with parallel tempering (PT) [26], we show that orders of magnitude sampling efficiency can be gained.

Let us use as CV the potential energy $U = U(\boldsymbol{R})$ where $\boldsymbol{R}$ is the full set of atomic coordinates. In well-tempered metadynamics Newton's equations are altered by the addition of a bias potential $V(U(\boldsymbol{R}), t)$:

$$\boldsymbol{m}\,\ddot{\boldsymbol{R}} = -\frac{\partial U(\boldsymbol{R})}{\partial \boldsymbol{R}} - \frac{\partial V(U(\boldsymbol{R}), t)}{\partial \boldsymbol{R}}, \tag{1}$$

whose time evolution is governed by

$$\dot{V}(U, t) = \omega e^{-V(U,t)/k_B \Delta T} \delta_{U,U(t)}, \tag{2}$$

where $\boldsymbol{m}$ are the atomic masses, while ω and ΔT are parameters which have the dimension of an energy rate and a temperature, respectively. Asymptotically, $V(U, t)$:

$$V(U, t \to \infty) = -(1 - \gamma^{-1})F(U), \tag{3}$$

with $\gamma = (T + \Delta T)/T \geq 1$ and $F(U) = -\frac{1}{\beta} \ln[\int d\boldsymbol{R}\delta(U - U(\boldsymbol{R}))e^{-\beta U(\boldsymbol{R})} / \int d\boldsymbol{R} e^{-\beta U(\boldsymbol{R})}]$. Within an irrelevant constant,

$$F(U) = U - \beta^{-1} \ln N(U) \tag{4}$$

where $N(U) = \int d\boldsymbol{R}\delta(U - U(\boldsymbol{R}))$ is the number of states of energy U, which is a T independent property [6,19,20]. $V(U, t)$ quickly converges to its $t \to \infty$ limit and the configurations are distributed according to

$$\mathcal{Z}_\gamma = \int d\boldsymbol{R} e^{-\beta U_\gamma(\boldsymbol{R})}, \tag{5}$$

with

$$U_\gamma(\boldsymbol{R}) = U(\boldsymbol{R}) - (1 - \gamma^{-1})[U(\boldsymbol{R}) - \beta^{-1} \ln N(U(\boldsymbol{R}))], \tag{6}$$

which defines WTE. It is then easy to rewrite the partition

function $\mathcal{Z}_\gamma$ as

$$\mathcal{Z}_\gamma = \int dU P(U)^{1/\gamma}, \tag{7}$$

where $P(U) = e^{-\beta U} N(U)$ is proportional to the energy probability distribution in the canonical ensemble. Varying γ one goes from the canonical partition function ($\gamma = 1$) to the multicanonical one ($\gamma = \infty$) [27]. In order to gain insight into the $\mathcal{Z}_\gamma$ properties, we make the assumption that $P(U)$ is strictly Gaussian, $P(U) \propto e^{-(U-\langle U\rangle)^2/2\Delta U^2}$, where $\langle U\rangle$ is the average energy in the canonical ensemble and ΔU^2 is the corresponding fluctuation [28]. Thus, $P(U)^{1/\gamma} \propto e^{-(U-\langle U\rangle)^2/2\gamma\Delta U^2}$, implying the same average energy as in the canonical case $\langle U\rangle_\gamma = \langle U\rangle$ but γ times larger fluctuations. The Gaussian assumption is not always justified, for instance, when $\langle U\rangle$ is close to the ground state energy or to a critical point. Still, for reasonably large γ one finds $\langle U\rangle_\gamma$ close to $\langle U\rangle$ with fluctuations which grow approximately linearly with γ. In a rather loose sense it is as if a quasicritical behavior is induced at all temperatures. This similitude is further increased by the fact that dynamical correlations are slowed down. However, when γ increases even further, the non-Gaussian tails in $P(U)$ are amplified until for $\gamma \rightarrow \infty$ one reaches the multicanonical limit.

We now combine WTE with PT (PT-WTE). In PT, n replicas of the system at the temperatures β_i, $i = 1, n$, are introduced and a MC procedure is used to attempt exchanging configurations between replicas. Colder replicas are prevented from being trapped in local minima by the exchange with the higher temperature ones. A figure of merit is the ability of a replica to diffuse across all range of β_i and methods that speed up this diffusion have been suggested (see Ref. [29] and references within). Given the special properties of WTE, it is tempting to explore its performance when combined with PT since one expects that the enhanced energy fluctuations will greatly facilitate exchange processes. In addition, if one uses the same γ factor for all the β_i, the swapping probability in PT-WTE is determined by

$$\Delta_{i,j} = \gamma^{-1}(\beta_i - \beta_j)[U(\boldsymbol{R}_i) - U(\boldsymbol{R}_j)], \tag{8}$$

implying a factor γ reduction relative to conventional PT ($\gamma = 1$). This is possibly the main result of this Letter and shows why PT-WTE leads to fast diffusion across the β_i.

We now present two representative applications of WTE and of PT-WTE to substantiate our claim. First we consider the performance of WTE in the single replica mode. We simulate the two-dimensional ferromagnetic Ising model for which an exact solution exists [30] and on which a large number of methods have been tested [31,32]. The Hamiltonian for this model is $\mathcal{H} = -J\sum_{\langle i,j\rangle} S_i S_j$. We put $J = 1$ and $S_i = \pm 1$ are spins on a square lattice with side L. Periodic boundary conditions are applied and only first-neighbor interactions are included. In the ferromagnetic state standard MC simulation explores only one magnetization direction (Fig. 1). WTE instead is able to sample either spin orientations overcoming the large free-energy barrier ($\simeq 110 k_B T$) that separates these two equivalent states. It is also seen that while the average values of the magnetization is approximately correct ($|M| \approx 1$ in the ferromagnetic phase and $M \approx 0$ in the paramagnetic one), the energy fluctuations grow with γ (see Table I). For $T > T_c$ the Gaussian assumption is clearly justified since $\langle U\rangle_\gamma$ and $\Delta U_\gamma^2/\gamma$ are approximately constant up to $\gamma \sim 100$. For $T < T_c$ and up to $\gamma \sim 100$, $\langle U\rangle_\gamma$ is also little shifted. However, the nonlinear fluctuation growth signals deviations from Gaussian behavior due to the proximity to the energy lower bound. In both cases relaxation times grow linearly with γ and do not outweigh the benefit of increased fluctuations. We expect a useful γ to be of the order of $\gamma \simeq k_B T \Delta F/\Delta U^2$, where ΔF is the relevant barrier. As such, γ will be system and size dependent.

Despite the fact that we have not attempted to optimize the replica distribution [31], the use of WTE leads to a great improvement in efficiency when combined with PT (Figs. 2 and 3). This is measured in terms of round-trip time t_γ, which is the time needed for a configuration in the coldest replica to reach the hottest temperature and come back [31]. It can be seen in Fig. 2 that the speedup grows almost linearly with γ up to $\gamma \simeq 30$ for $L = 10$ and $\gamma \simeq 100$ for $L = 20$, and is much larger than what is reported by optimizing the β_i distribution [31]. Empirically, the ratio between the smallest energy difference between successive β_i and the largest energy fluctuation measured in the unbiased ensemble provides a good estimate for the optimal γ. Above this value the speedup ceases to be linear in γ and the increased fluctuations and the reduction in acceptance ratio do not compensate the dynamical slowing down.

As a further example of the power of PT-WTE, we show an application to the folding process of the monomer of

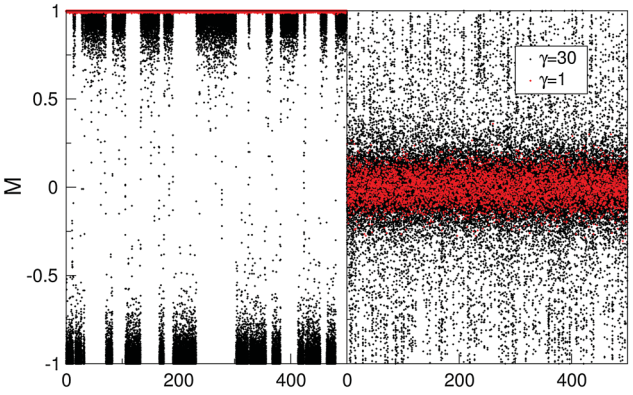

FIG. 1 (color). WTE (black) compared to standard ensemble sampling (red) at two temperatures, below ($T_1 = 1.0$) and above ($T_2 = 5.0$) the critical temperature $T_c = 2.269$. The unit on the x axis is 10^3 MC steps. Each MC move consists of a complete sweep of the $L = 20$ site lattice. Gaussians of 0.1 height and 5.0 width were deposited at each step.

TABLE I. Average value, fluctuation, and correlation time of the energy in WTE as a function of γ at the two representative temperatures, below and above T_c. The value of τ/γ at $\gamma = 1$, $T = T_1$ is smaller than a single sweep.

	$T_1 < T_c$			$T_2 > T_c$		
γ	$\langle U\rangle_\gamma$	$\Delta U^2_\gamma/\gamma$	τ/γ	$\langle U\rangle_\gamma$	$\Delta U^2_\gamma/\gamma$	τ/γ
1	−798.9	9.3	⋯	−170.8	974.7	1.5
5	−790.2	31.5	0.26	−174.8	999.4	1.67
10	−780.1	49.8	0.23	−180.2	1027.6	2.13
50	−710.4	154.2	0.45	−206.8	1079.5	2.58
100	−637.8	223.4	0.52	−192.5	923.2	2.09
1000	−193.6	180.2	0.26	−39.8	199.9	0.26

HIV-1 protease. For this we use a Gō model [33] which has a transition at $T_f \simeq 80$ K. For this reason, simulations using straightforward PT give poor results unless the distribution of temperatures across T_f is optimized [31]. In this example, we do not use the potential energy as CV, but the variable on which the energy uniquely depends, namely, the total number of native contacts between C_α atoms. It is easy to show that in this case an expression equivalent to Eq. (8) holds. Simulations have been carried out using GROMACS [34] and PLUMED [35]. In this case $t_1/t_\gamma \simeq 66$. We also measure the speedup in terms of MD steps needed to converge the free-energy difference between folded and unfolded state. In Fig. 4 we see that PT-WTE converges in less than 2.5×10^7 steps, while standard PT is still not converged after 2.4×10^8 steps. We also show that allowing for replicas to exchange is crucial since WTE alone fails to converge in the simulation time. As a further check we reconstruct the thermodynamics of three relevant subunits of HIV-1 protease (Fig. 5). Comparing our results with an umbrella sampling calculation that uses *a posteriori* the PT-WTE bias, we find an excellent agreement.

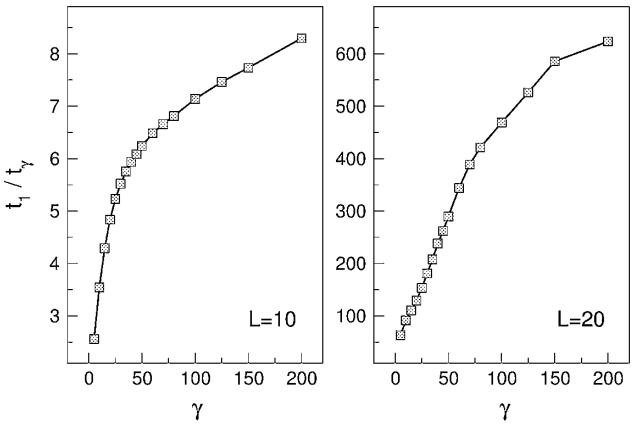

FIG. 2. Speedup of PT-WTE compared to standard PT as a function of γ in the Ising model with $L = 10$ (left-hand panel) and $L = 20$ (right-hand panel). Twenty-one replicas were distributed in a geometric progression in the interval $0.1 \leq T \leq 10.0$ as in Ref. [31]. Exchange moves were attempted after every lattice sweep. Gaussian parameters as in Fig. 1.

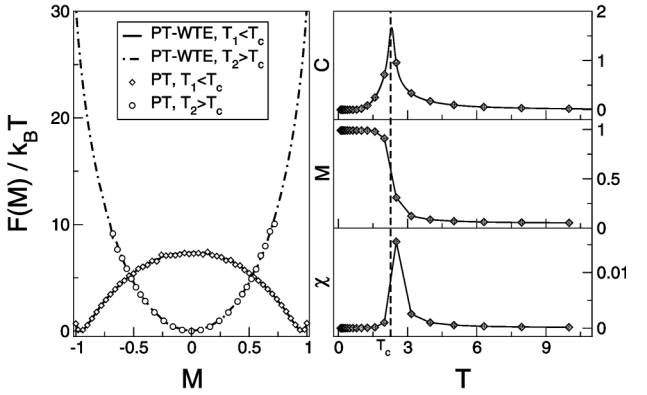

FIG. 3. Left-hand panel: FES as a function of the magnetization $F(M)$ of the $L = 10$ next neighbor ferromagnetic Ising model below and above the critical temperature, compared with an extensive PT calculation. The statistical error for the PT-WTE calculations is smaller than 2%. We have computed a similar curve for $L = 20$, but we do not show it here because the PT calculation to compare with could not be converged. It is remarkable that both magnetizations could be explored in spite of a barrier of the order of $110k_BT$. Right-hand panels: Specific heat per spin (top), modulus of the magnetization (middle), and magnetic susceptibility (bottom) as a function of temperature ($L = 20$). The continuos line in the top panel is the finite size exact solution [30]. In the middle and bottom panels the line is just a guide to the eye. The statistical error found is at worst 1% in all cases.

In conclusion, we have shown that WTE can be profitably used as a biased ensemble to greatly enhance sampling speed especially when associated to parallel tempering. Properly designed WTE combines two proper-

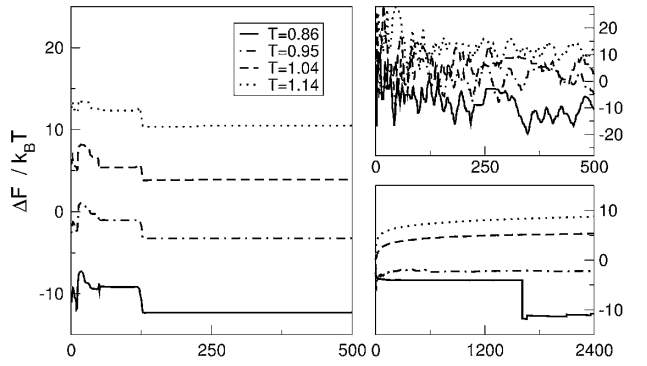

FIG. 4. Left-hand panel: Gō-model FES convergence in PT-WTE run measured as the free-energy difference between folded and unfolded state as a function of time in units of 10^5 MD steps. Sixteen replicas were distributed with a geometric progression in a temperature range between 0.625 and 1.25 in units of T_f. Exchanges between configurations were attempted every 200 MD steps. Gaussians of 1.0 kJ/mol height and 5.0 width were deposited every 1000 steps. A γ value of 80 was used for all replicas. Right-hand panels: Convergence of PT-WTE without exchanges (top) and of standard PT (bottom).

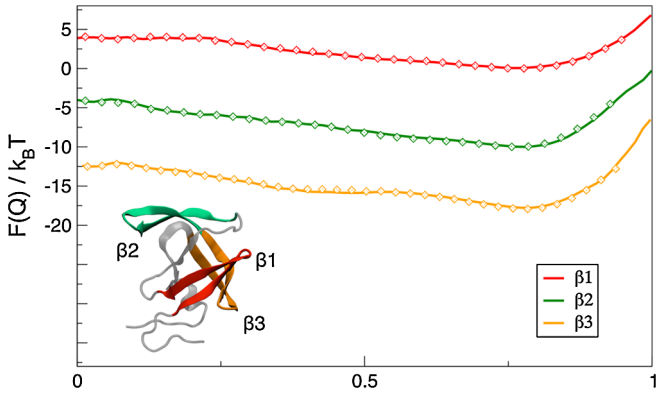

FIG. 5 (color online). Gō-model FES of three β-strand subunits of HIV-1 protease as a function of the native contacts at $T = 0.95$. The FES are obtained by reweighting the PT-WTE run (solid lines) and from an umbrella sampling calculation (points).

ties that are useful in this respect. The fact that average values are not changed ensures a significant overlap between the biased and unbiased ensemble facilitating the reconstruction of the latter. Yet the enhanced fluctuations favor exploring low probability regions and overcoming large barriers. Measuring the efficiency of this new method is a subtle question. We can claim on the basis of Ref. [19] that when it comes to reconstructing $N(U)$ we can obtain an efficiency at least comparable to Wang-Landau [6]. Furthermore, we have the additional bonus that we do not need extra calculations or expensive reconstruction of multidimensional histograms to evaluate quantities different from the energy or its fluctuations. In this respect the fair comparison is with PT where we gain relative to Ref. [31] as much as a factor of $\simeq$100 on the Ising model with $L = 20$. Much remains to be done to understand WTE properties and to optimize its performances. However, the very encouraging results obtained at these early stages suggest that a powerful method has been added to the literature and that exciting applications can be expected. Extension of the method in which additional CV are added to U is straightforward and will be explored in the near future.

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