PHYSICAL REVIEW E VOLUME 54, NUMBER 5 NOVEMBER 1996

Monte Carlo simulations in generalized ensemble: Multicanonical algorithm versus simulated tempering

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(Received 3 July 1996)

It is shown that two Monte Carlo methods in generalized ensemble, multicanonical algorithm and simulated tempering, are closely related. The equivalence and effectiveness of the two methods are illustrated by taking an energy function for the protein folding problem as an example. [S1063-651X(96)11311-8]

PACS number(s): 02.70.Lq, 02.50.Ng, 02.60.Pn

The energy landscape of many important physical systems such as spin glasses or biological macromolecules is characterized by a multitude of local minima separated by high-energy barriers. For this class of systems low-temperature simulations by conventional methods (such as canonical molecular dynamics and Monte Carlo with local updates) will necessarily get trapped in configurations corresponding to one of these local minima. This is because the probability to cross an energy barrier of height ΔE is proportional to $e^{-\Delta E/T}$ (we set the Boltzmann constant k_B to unity hereafter). Hence, only small parts of the entire phase space are explored (in finite time) and physical quantities cannot be calculated accurately. One effective way to overcome this difficulty is to perform a simulation in a so-called *generalized ensemble* where the probability to cross an energy barrier is independent of temperature. Multicanonical algorithm [1,2] and simulated tempering [3,4] are two prominent examples of such an approach. The multicanonical algorithm was originally developed to overcome the supercritical slowing down of first-order phase transitions [1], and it was then proposed to be used for systems that suffer from the above-mentioned multiple-minima problem such as spin glasses [5] and the protein folding problem [6]. Simulated tempering, which is also called a method of ''expanded ensembles,'' was originally introduced as a method for calculating a free energy from a single simulation run in a model of electrolyte [3] and as an algorithm for overcoming a multiple-minima problem in a random-field Ising model [4]. Subsequent works in condensed matter physics and theoretical chemistry followed [7–9]. In this paper we examine the relation between multicanonical algorithm and simulated tempering and numerically compare their performances by taking an energy function for the protein folding problem as an example.

In the multicanonical approach [1,2] configurations with energy E are updated with a weight

$$w_{mu}(E) \propto n^{-1}(E) = e^{-S(E)}, \tag{1}$$

where $n(E)$ is the density of states and

$$S(E) = \ln n(E) \tag{2}$$

is the microcanonical entropy. A uniform distribution of energy is obtained with this weight factor:

$$P_{mu}(E) \propto n(E) w_{mu}(E) = \text{const.} \tag{3}$$

Hence, a simulation with this weight factor, which has no temperature dependence, generates a one-dimensional (1D) random walk in the energy space, allowing itself to escape from any energy barrier.

Unlike in a simulation of the canonical ensemble, the weight $w_{mu}(E)$ is not *a priori* known, and it should be determined by an iterative procedure (see Refs. [2] and [10] for the details). Once the multicanonical weight factor $w_{mu}(E)$ is obtained, one performs with this weight factor a multicanonical simulation with high statistics. From this single simulation one cannot only locate the energy global minimum but can also obtain the canonical distribution at any inverse temperature $\beta = 1/T$ for a wide range of temperatures by reweighting techniques [11]:

$$P_B(T,E) \propto P_{mu}(E) w_{mu}^{-1}(E) e^{-\beta E}, \tag{4}$$

where $P_{mu}(E)$ is the distribution of energy obtained from this production run. One can then calculate the expectation value of any physical quantity O at temperature T by

$$\langle O \rangle_T = \frac{\int dE\; O(E) P_B(T,E)}{\int dE\; P_B(T,E)}. \tag{5}$$

While in the multicanonical ensemble there is no temperature dependence, temperature itself becomes a dynamical variable in simulated tempering. Temperature and configuration are both updated with a weight

$$w_{ST}(T,E) = e^{-E/T - g(T)}, \tag{6}$$

where the function $g(T)$ is chosen so that the probability distribution of temperature is given by

$$P_{ST}(T) = \int dE\; n(E) e^{-E/T - g(T)} = \text{const.} \tag{7}$$

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Hence, in simulated tempering *temperature* is sampled uniformly, while simulations in multicanonical ensemble sample energy uniformly. A random walk in temperature space is realized. This in turn leads to a (weighted) random walk in energy space, allowing the simulation to escape from any energy barrier. Again, the weight $w_{ST}(T,E)$ is not *a priori* known and should be obtained iteratively (see, for instance, Ref. [9] for details). Once the weight factor $w_{ST}(T,E)$ is obtained, we make a single production run with high statistics. A physical quantity O has to be sampled for each temperature point separately. Its expectation value at temperature T is then calculated by

$$\langle O\rangle_T=\frac{\int dx\ O(x)e^{-E(x)/T}}{\int dx\ e^{-E(x)/T}}, \tag{8}$$

where x labels configurations, and only those configurations that were obtained at temperature T are included in the integral.

The defining equation, Eq. (7), for the distribution of temperatures in simulated tempering implies that

$$e^{g(T)}\propto\int dE\ n(E)e^{-E/T}. \tag{9}$$

Therefore, the density of states $n(E)$ [and hence, the multicanonical weight $w_{mu}(E)=n^{-1}(E)$] and the exponential of the function $g(T)$ [and hence the simulated tempering weight $w_{ST}(T,E)$] are related by a Laplace transform. Knowledge of one implies that of the other, although in numerical work, the inverse Laplace transform of Eq. (9) is nontrivial. The two methods are in this sense equivalent.

The performances of the two methods were compared by taking an energy function for the protein folding problem. To be specific, we studied the system of one of the simplest peptides, Met-enkephalin. The potential energy function E_{tot} that we used is given by the sum of electrostatic term E_C, Lennard-Jones term E_{LJ}, and hydrogen-bond term E_{hb} for all pairs of atoms in the peptide together with the torsion term E_{tors} for all torsion angles. The parameters for the energy function were adopted from the Empirical Conformational Energy Program for Peptides, version 2 (ECEPP/2) [12]. The computer code KONF90 [13] was used. One Monte Carlo (MC) sweep updates every torsion angle of the peptide once.

In the case of simulated tempering we chose 30 temperature points between $T_{\text{min}}=50$ K and $T_{\text{max}}=1000$ K. We found it convenient to choose the temperature points not equidistant, but so that the increment of adjacent temperature points decreases exponentially with decreasing temperature. We needed 150 000 MC sweeps to obtain the simulated tempering parameter $g(T)$. In our earlier work [6] we needed 40 000 MC sweeps to calculate the multicanonical weight for Met-enkephalin. Instead of attempting to optimize our method of calculating the simulated tempering weight, we tried to improve the multicanonical weight by further iterations until the total number of MC sweeps was also 150 000. After the determination of the weight factors, we made a single production run of 300 000 MC sweeps for each method. The simulations started from completely random initial configurations.

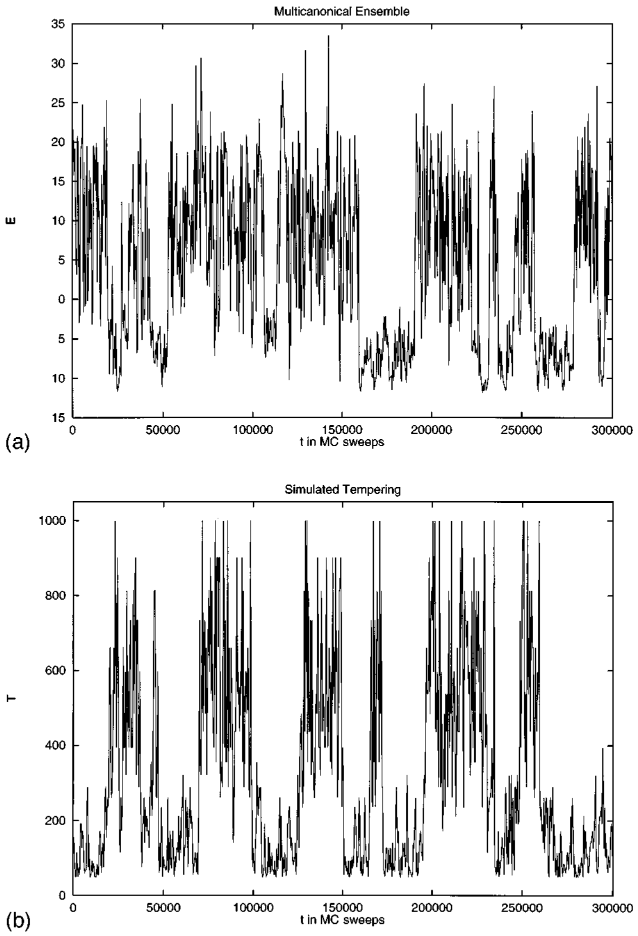

FIG. 1. (a) Time series of potential energy E (kcal/mol) from a multicanonical simulation of 300 000 MC sweeps. (b) Time series of temperature T (K) from a simulated tempering simulation of 300 000 MC sweeps.

As explained above, we expect to obtain a 1D random walk in energy (temperature) for multicanonical algorithm (simulated tempering). In Fig. 1 we show the time series of the potential energy E_{tot} (kcal/mol) [Fig. 1(a)] and temperature T (K) [Fig. 1(b)] for multicanonical and simulated tempering algorithms, respectively. They both exhibit a random walk between low-energy (temperature) states and high-energy (temperature) states. For simulated tempering, the time series of E_{tot} also produces a (weighted) random walk that is positively correlated with that of T in Fig. 1(b). In Ref. [14] it was shown that with the energy parameters of KONF90, states with energies less than -11 kcal/mol essentially have the same structure, ground-state structure. The random walks in Fig. 1 both reached this lowest-energy state many times. The number of independent such visits was 7 for both multicanonical and simulated tempering simulations. We conclude that both algorithms do not differ significantly in their numerical performance.

The independently obtained weight factors for the two methods should be related to each other by Eq. (9). Both sides of Eq. (9) are plotted in Fig. 2. The results are in complete agreement, as they should be. This shows that it is

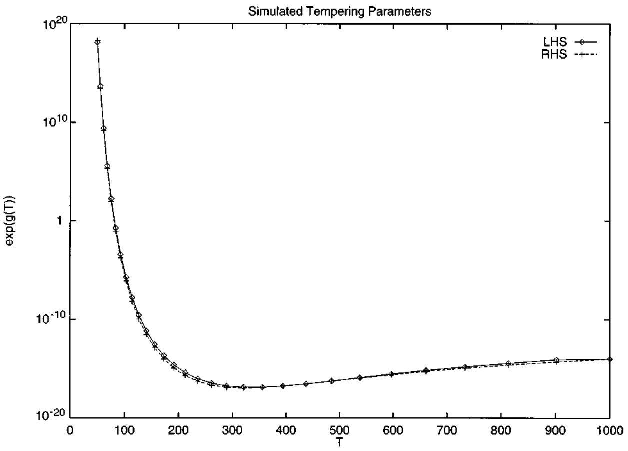

FIG. 2. Comparison of the weight factors obtained from the multicanonical simulation and from simulated tempering simulation. The left-hand side (LHS) and right-hand side (RHS) of Eq. (9) are plotted. The weights were obtained from iterations of simulations with a total of 150 000 MC sweeps.

not necessary to estimate the weight factors for each ensemble independently.

A major advantage of the two methods studied in this paper over conventional ones is that from just one simulation run one can not only obtain the lowest-energy state but also calculate thermodynamic quantities at any temperature [see Eqs. (5) and (8)]. As an example we show in Fig. 3 the average potential energy $\langle E \rangle_T$ as a function of temperature calculated from the production runs of the two algorithms. They are again in complete agreement. The agreement implies that our calculations are reliable (since they were obtained from independent data). Note that the average potential energy at the lowest-temperature region is about -12 kcal/mol, which is the global-minimum energy value for the energy function of KONF90 [14]. The value at a high temperature, say $T = 1000$ K, is as large as ≈ 16 kcal/mol. Thus, the random walk in Fig. 1(a) indeed covered a very wide range of the phase (energy) space.

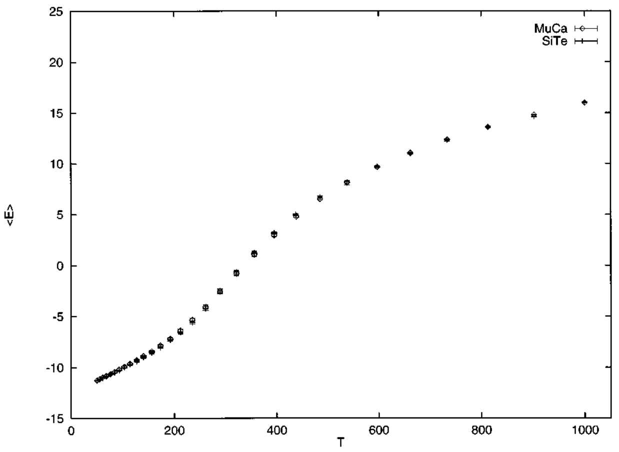

FIG. 3. Average potential energy $\langle E \rangle$ (kcal/mol) as a function of temperature T (K) calculated from the data of multicanonical and simulated tempering simulations. The number of MC sweeps was 300 000 for each method.

In summary, we have shown that the multicanonical algorithm and simulated tempering are closely related and that they are equally effective in the numerical work. Weight factors for the two algorithms can be calculated from each other. Hence, both methods can be easily used to cross-check results at low temperatures where otherwise no comparison is possible. We remark that uniform sampling in temperature or energy is by no means the only realization of *generalized ensembles* (see, for instance, Ref. [15]), nor is there any restriction to one variable.

Our simulations were performed on the computers at the Computer Center at the Institute for Molecular Science (IMS), Okazaki, Japan. This work was supported, in part, by the Grants-in-Aid for Scientific Research from the Japanese Ministry of Education, Science, Sports, and Culture and by the Schweizerische Nationalfonds (Grant No. 20-40'838.94).

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