

Effective way for determination of multicanonical weights

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The problem of calculating weight factors for simulations in a generalized ensemble is discussed. An approach for a fast and simple estimation of such weights is proposed and tested in the case of the simple peptide Met-enkephalin. [S1063-651X(97)12211-5]

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In the last few years generalized ensemble algorithms have become popular as a way to overcome the exponentially slow convergence in numerical simulations of systems with a rough energy landscape. Prominent examples of such an approach are the multicanonical algorithm [1,2], $1/k$ sampling [3], and simulated tempering [4,5]. These algorithms explore larger parts of the phase space than canonical molecular dynamics or Monte Carlo, which at low temperatures are easily trapped in one of the huge number of local minimas. This is because in the canonical ensemble the probability to cross an energy barrier of heights ΔE is proportional to $e^{-\Delta E/T}$ at temperature T . On the other hand, in generalized ensembles the probability to cross an energy barrier is independent of temperature. For instance, in the multicanonical algorithm [1,2], configurations with energy E are updated with a weight:

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

where $n(E)$ is the density of states and $S(E) = \ln n(E)$ is the microcanonical entropy. The so-defined weights lead to a uniform distribution in energy,

$$P_{\text{mu}}(E) \propto n(E)w_{\text{mu}}(E) = \text{const}. \quad (2)$$

Hence a simulation with this weight factor generates a one-dimensional random walk in the energy space, allowing itself to escape from any energy barrier. Since large parts of the phase space are explored, the expectation value of any physical quantity O can be calculated accurately for a wide range of temperatures by the reweighting techniques [6].

Despite many successful applications, for instance to spin glasses [7] and the protein-folding problem [8,9], generalized-ensemble methods are not without problems. In contrast to the canonical ensemble, the weight factors are not *a priori* known. For example, for the multicanonical algorithm knowledge of the exact weight [see Eq. (1)] would be equivalent to obtaining the density of states $n(E)$, i.e., solving the system. Hence for a numerical simulation one needs estimators of the weights. Their determination can be non-trivial and tedious. In fact, the problem of finding good estimators of the weights is very often limiting the use of generalized ensemble techniques. It is therefore important to develop methods which allow for their fast and easy calcu-

lation. Our aim here is to present such an approach. We will restrict ourselves to the problem of calculating multicanonical weights, since it was shown in Ref. [10] that knowledge of weights for one of the generalized ensembles algorithms implies a knowledge of the weights for the other algorithms.

Following the pioneering work by Berg [2], estimators of the multicanonical weights are usually calculated by an iterative procedure. The improved estimator of the multicanonical weight for the i th iteration is calculated from the histogram of energy distribution $P_{\text{mu}}^{(i-1)}(E)$ and the weight $w_{\text{mu}}^{(i-1)}$ of the previous simulation as follows:

$$w_{\text{mu}}^{(i)}(E) = \frac{w_{\text{mu}}^{(i-1)}(E)}{P_{\text{mu}}^{(i-1)}(E)}. \quad (3)$$

The iteration starts with a canonical simulation at sufficiently high temperature T_0 : $w_{\text{mu}}^{(0)}(E) = w_B(T_0, E) = e^{-E/k_B T_0}$, with k_B the Boltzmann constant. For details, see Ref. [2]. While the method is quite general, it has the disadvantage that it requires iterations of short simulations, the number of which is not known *a priori*. For the calculations in Ref. [8], about 40% total CPU time was spent for this task. Several attempts were made to accelerate the above iterative procedure (see for instance Refs. [11–13]), but there is still need for further improvement.

Here we propose another approach: calculating the multicanonical weights from simulated annealing [14] runs. This can be done in the following way. First, a simulated annealing run with small statistic is performed. While decreasing the temperature, the average potential energy $\langle E \rangle$ as a function of the inverse temperature $\beta = 1/k_B T$ is calculated and stored for further analyses. In general, simulated annealing cannot be used for the calculation of thermodynamic quantities, since only for the case of a logarithmic annealing of temperature (which is seldom feasible) is it guaranteed that the system will stay in thermodynamic equilibrium [15]. Hence, our estimates of $\langle E \rangle$ are hampered by a bias, but we expect this bias to be small enough that it can be neglected for our purpose. The stored values of our estimators for $\langle E \rangle$ should be a monotonic decreasing function of the inverse temperature β . Due to insufficient statistics, this may not always be the case, and it may be necessary to apply a smoothing algorithm to the stored energy values until a table of monotonically decreasing $\langle E \rangle(\beta)$ is obtained. From this final table it is easy to determine $\beta = \beta(\langle E \rangle)$ as a function of

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potential energy for an energy range $[E_{\min}, E_{\max}]$. Here, E_{\min} (E_{\max}) is the minimal (maximal) value of $\langle E \rangle(\beta)$. Using the thermodynamic relation

$$\beta(E) = \frac{dS(E)}{dE}, \quad (4)$$

the inverse function $\beta(E) \equiv \beta(\langle E \rangle)$ can be used now to calculate estimators for the microcanonical entropy $S(E)$ by evaluating

$$S(E) = \begin{cases} S(E_{\max}) + \beta(E_{\max})(E - E_{\max}), & E > E_{\max} \\ \int_{E_{\min}}^E dE \beta(\tilde{E}), & E_{\max} \geq E \geq E_{\min} \\ S(E_{\min}) - \beta(E_{\min})(E_{\min} - E), & E < E_{\min}. \end{cases} \quad (5)$$

Here, a linear extrapolation of the microcanonical entropy $S(E)$ is chosen outside of the energy interval $[E_{\min}, E_{\max}]$, for which data from the simulated annealing run are available. Knowledge of $S(E)$ is equivalent to that of the microcanonical weights since the latter were defined in Eq. (1) as $w_{\text{mu}}(E) = e^{-S(E)}$. With an estimate for the weights now given, one can perform a multicanonical simulation. It may sometimes be the case that the resulting distribution is not flat, and further improvements are necessary using Berg's iterative procedure [2], but we expect a fast convergence since the simulated annealing run has already collected information over a large temperature (and therefore energy) range. It also may sometimes be preferable to perform a set of simulated annealing runs, and average over these runs to obtain an improved estimate of the energies $\langle E \rangle(\beta)$.

We remark that the above-used relation $\beta(E) = \beta(\langle E \rangle)$ is not exact on finite systems. This implies that our method is not suitable for the case of first-order phase transitions. This is not a drawback as long as one is mainly interested in systems with rough energy landscapes, the kind of systems on which most generalized ensemble simulations focus. However, in the case that a first-order phase transition is suspected, another method should be employed.

The performance of our approach was tested by taking an energy function for the protein-folding problem. Here, Met-enkephalin, one of the simplest peptides, has become an often used model to examine new algorithms in the protein folding problem. Met-enkephalin has the amino acid sequence Tyr-Gly-Gly-Phe-Met. The potential energy function E_{tot} that we used is given by the sum of electrostatic term E_C , the 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 ECEPP/2 [16]. Fixing the peptide bond angles ω to 180° leaves us with 19 torsion angles as degree of freedom. The computer code SMC [17] was used. One Monte Carlo (MC) sweep updates every torsion angle of the peptide once.

To calculate the multicanonical parameters for Met-enkephalin, we performed a simulated annealing run of 20 000 MC sweeps following 100 MC sweeps at our start temperature $T_{\text{ST}} = 1000$ K for thermalization. We remark that a minimum of 40 000 MC sweeps (and often more) were needed to determine multicanonical parameters for this pep-

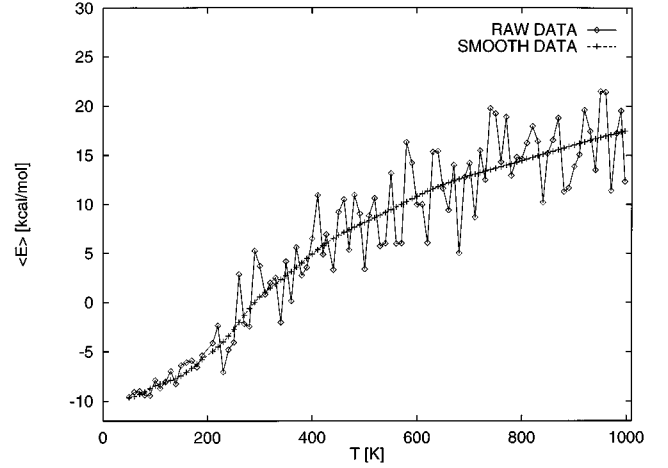


FIG. 1. Estimators of the average energy $\langle E \rangle$ (in kcal/mol) as a function of temperature T as obtained by a simulated annealing run of 20 000 sweeps with the annealing schedule described in the text. Both the raw data and our final (smooth) estimators shown.

ptide by the commonly used iterative procedure [8]. The temperature was lowered exponentially according to

$$T = T_{\text{ST}} \gamma^{i-1} \quad (6)$$

for the i th, sweep and

$$\gamma = \frac{T_{\text{FI}}^{1/1999}}{T_{\text{ST}}}, \quad (7)$$

where we chose a final temperature $T_{\text{FI}} = 50$ K. After each sweep we store the current inverse temperature β and $\bar{E} = \frac{1}{19} \sum_i^{19} E_i$, which is the average of the potential energy E taken over all 19 updates of angles within one sweep. Of course, \bar{E} is a poor estimator of the thermal average $\langle E \rangle(\beta)$ used in Eq. (5), and strongly fluctuating as a function

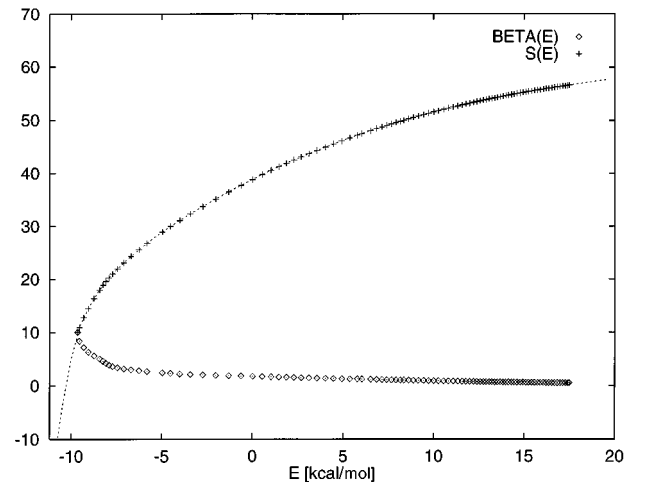


FIG. 2. Inverse temperature β (in 1/K) and our estimator for the microcanonical entropy $S(E)$ (in arbitrary units) as a function of energy E . The dotted line is our extrapolation of $S(E)$ outside of the range of energies for which we have data points from the simulated annealing run.

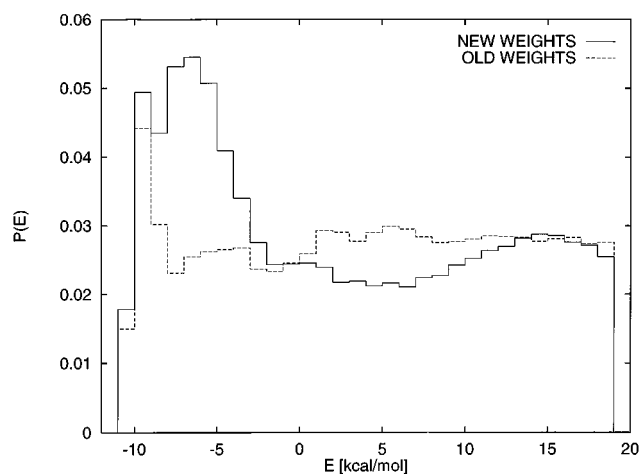


FIG. 3. Probability distribution of energy as obtained by a multicanonical simulation of 100 000 sweeps with weights calculated by our approach. For comparison we also show the distribution obtained with the weights of Ref. [18], which were calculated by the older iterative procedure.

of β . To obtain a better estimator, we apply the following smoothing algorithm to the stored energies. We replace each value of $\bar{E}(\beta_i)$ by the average over its neighbors: $\bar{E}^{\text{new}}(\beta_i) = [\bar{E}(\beta_{i+1}) + \bar{E}(\beta_i) + \bar{E}(\beta_{i-1})]/3$, where β_{i+1} , β_i , and β_{i-1} follow on each other in the temperature annealing schedule. Here we require that the difference in temperature be small in simulated annealing between subsequent steps of the annealing procedure, and therefore that the expectation values of thermodynamic quantities should also change only slightly between subsequent temperatures. We repeat this smoothing procedure until we obtain new values of $\bar{E}(\beta)$, which are a monotonous decreasing function of the inverse temperature β , and set $\langle E \rangle(\beta) \equiv \bar{E}(\beta)$. In Fig. 1 we display both our original data and the new, smooth estimator of $\langle E \rangle$ as a function of temperature. Since the function $\langle E \rangle(\beta)$ is now given explicitly by a table, it can be easily inverted. Integrating $\beta(E)$ allows us to calculate estimators for the microcanonical entropy $S(E)$ and the multicanonical weights $w_{\text{mu}}(E) = e^{-S(E)}$ by Eq. (5). In Fig. 2 we show both $\beta(E)$ and our estimators for $S(E)$ as calculated by Eq. (5).

Using the so-obtained weights, we performed a multicanonical simulation of 100 000 sweeps for Met-enkephalin. In Fig. 3 we show the probability distribution of energy as obtained with these weights. The distribution is essentially flat over the whole energy range which covers both high- and low-temperature states. The entries differ only by factors of

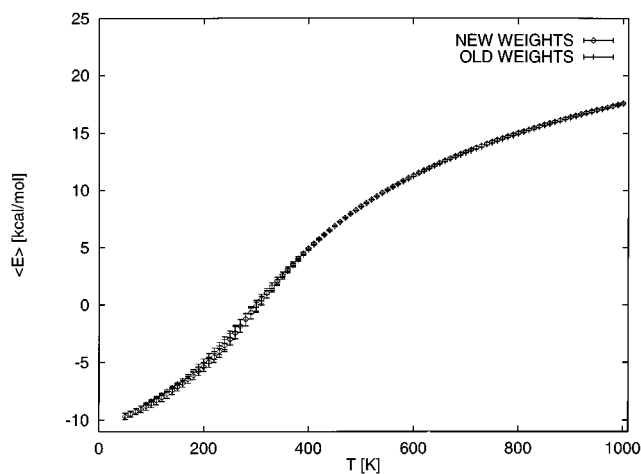


FIG. 4. Average energy $\langle E \rangle$ as calculated from multicanonical simulation of 100 000 sweeps with weights calculated by our approach. For comparison we also show the results from a multicanonical simulation with same statistic, but where the weights of Ref. [18] (calculated by the older iterative procedure) were used.

3. For comparison we also show the distribution we obtained with the weights of Ref. [18], which were calculated by the iterative procedure described in Ref. [8]. The differences between the two distributions are small, and when we calculate thermodynamic quantities from the two distributions their differences are within the errorbars. This can be seen in Fig. 4, where the average energy $\langle E \rangle$ is shown as a function of temperature T . Hence we conclude that our approach is well suited to calculate estimators for the multicanonical weights.

Let us summarize our results. We have proposed an approach to calculate multicanonical parameters for systems with conflicting constraints. For the simple peptide Met-enkephalin, we were able to obtain these weights from a single simulated annealing run of 20 000 sweeps, where, with the commonly used iterative procedure of Berg [2], we needed at least twice as many sweeps and often more. This shows that our ansatz indeed allows a faster and simpler calculation of the weights for generalized ensemble simulations. Since the need to find estimators for the weights is the main drawback of multicanonical and other generalized ensemble algorithms, we hope that our ansatz will help to apply these simulation techniques to a wider range of problems.

These simulations were performed on the computers at the Computer Center at the Institute for Molecular Science (IMS), Okazaki, Japan.

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