Replica-exchange multicanonical and multicanonical replica-exchange Monte Carlo simulations of peptides. I. Formulation and benchmark test

Ayori Mitsutake, Yuji Sugita, and Yuko Okamoto

Citation: J. Chem. Phys. **118**, 6664 (2003); doi: 10.1063/1.1555847
View online: https://doi.org/10.1063/1.1555847
View Table of Contents: http://aip.scitation.org/toc/jcp/118/14
Published by the American Institute of Physics

Replica-exchange multicanonical and multicanonical replica-exchange Monte Carlo simulations of peptides. I. Formulation and benchmark test

Ayori Mitsutake[a)]
Department of Physics, Faculty of Science and Technology, Keio University, Yokohama, Kanagawa 223-8522, Japan

Yuji Sugita[b)] and Yuko Okamoto[c)]
Department of Theoretical Studies, Institute for Molecular Science, Okazaki, Aichi 444-8585, Japan and Department of Functional Molecular Science, The Graduate University for Advanced Studies, Okazaki, Aichi 444-8585, Japan

(Received 22 November 2002; accepted 6 January 2003)

The replica-exchange multicanonical algorithm and the multicanonical replica-exchange method for molecular dynamics simulations have recently been developed. In the former method the multicanonical weight factor is determined from a short replica-exchange simulation with the multiple-histogram reweighting techniques. A long multicanonical production run with high statistics is then performed with this weight factor. In this method, the process of determining the multicanonical weight factor is faster and simpler than that in the usual iterative determination. The multicanonical replica-exchange method is a further extension of the first in which a replica-exchange multicanonical simulation is performed with a small number of replicas. In this paper, we give the formulations of these two methods for Monte Carlo simulations and demonstrate the effectiveness of these algorithms for a penta peptide in the gas phase. © *2003 American Institute of Physics.* [DOI: 10.1063/1.1555847]

I. INTRODUCTION

For simulations of complex systems such as proteins, the configurational space sampling is very important. One of the most powerful configurational space sampling methods is the generalized-ensemble algorithm (for reviews, see Refs. 1–3). This method is based on non-Boltzmann probability weight factors so that a random walk in potential energy space may be realized. The random walk allows the simulation to escape from any energy barrier and to sample much wider configurational space than by conventional methods.

One of the most well-known generalized-ensemble algorithms in the molecular simulation field is perhaps the multicanonical algorithm (MUCA)[4,5] (for a review, see Ref. 6). (The method is also referred to as entropic sampling[7,8] and adaptive umbrella sampling of the potential energy.[9]) MUCA was first applied to spin systems[5,10] and then also introduced to the protein folding simulations.[11] MUCA is powerful and has already been used in many applications in protein systems (see the above review[2] and references therein). In MUCA the weight factor is defined so that the probability distribution of potential energy is uniform. Each potential energy value enters with equal probability, and a free one-dimensional random walk in potential energy space is realized. This means that the multicanonical weight factor is inversely proportional to the density of states of the system. In MUCA simulations, however, the probability weight factors are not *a priori* known and have to be determined by iterations of short trial simulations. This process can be nontrivial and very tedious for complex systems.

Another powerful configurational space sampling method is the replica-exchange method (REM).[12–14] (REM is also referred to as the multiple Markov chain method[15] and parallel tempering.[16] Details of literature about REM and related algorithms can be found in recent reviews.[2,17]) In this method the difficulty of weight factor determination is greatly alleviated. REM was also introduced to the protein systems.[18] The details of molecular dynamics algorithm have been worked out for REM.[19] A multidimensional REM, which is particularly useful in free energy calculations, was also developed.[20] REM has already been used in many applications in protein systems (see the review in Ref. 2 and references therein). In REM a number of noninteracting copies (or replicas) of the original system at different temperatures are simulated independently and simultaneously by the conventional canonical Monte Carlo (MC) or molecular dynamics (MD) methods. Every few steps, pairs of replicas are exchanged with a specified transition probability. The weight factor is just the product of Boltzmann factors, and so it is essentially known unlike a multicanonical algorithm. However, REM also has a computational difficulty. As the number of degrees of freedom of the system increases, the required number of replicas also greatly increases whereas only a single replica is simulated in a MUCA simulation. This demands a lot of computer power for complex systems.

Therefore, new algorithms, which combine the merits of MUCA and REM, have been developed for molecular dynamics simulations.[21] These methods are referred to as a replica-exchange multicanonical algorithm (REMUCA) and

[a)]Electronic mail: ayori@rk.phys.keio.ac.jp
[b)]Present address: Department of Structural Biology, Institute of Molecular and Cellular Biosciences, University of Tokyo, Yayoi, Bunkyo-ku, Tokyo 113-0032, Japan; Electronic mail: sugita@iam.u-tokyo.ac.jp
[c)]Electronic mail: okamotoy@ims.ac.jp

multicanonical replica-exchange method (MUCAREM).[21] (The combination of simulated tempering[16] and REM has also been introduced and is referred to as replica-exchange simulated tempering.[22]) In REMUCA, a short replica-exchange simulation is performed, and the multicanonical weight factor is determined by the multiple-histogram reweighting techniques[23,24] [an extension of which is also referred to as the weighted histogram analysis method (WHAM)[24]]. This process is much simpler than previous iterative methods of multicanonical weight determinations. Finally, a long MUCA production run is performed with this weight factor. In MUCAREM, the multicanonical weight factor is first determined as in REMUCA (or by any other methods), and then a replica-exchange multicanonical production simulation is performed with a small number of replicas.

MC versions of these methods have also been worked out and preliminary results have been reported.[2] In this article, the details of the formulation are presented. They are tested with the system of a penta peptide, Met-enkephalin, in the gas phase. In the following article (which we refer to as Paper II) we give detailed comparisons of performance of REMUCA and MUCAREM, taking a more complex system of a 17-residue helical peptide as an example.

II. METHODS

Before we explain the formulation of REMUCA and MUCAREM for the MC version in detail, let us briefly review MUCA and REM.

A. Multicanonical algorithm

The multicanonical ensemble is based on the following non-Boltzmann weight factor so that the probability distribution of potential energy $P_{mu}(E)$ is uniform:[4,5]

$$P_{mu}(E) \propto n(E) W_{mu}(E) = \text{const}, \tag{1}$$

where $n(E)$ is the density of states and $W_{mu}(E)$ is the multicanonical weight factor. We then have

$$W_{mu}(E) \propto n^{-1}(E) = \exp(-\ln n(E)). \tag{2}$$

All potential energies have equal weight, and a one-dimensional random walk in potential energy space is realized, which ensures that the system can overcome any energy barrier. Monitoring the energy in this simulation, one will see that a random walk between high-energy states and the ground state is realized. In this way information is collected over the whole energy range.

Once the exact multicanonical weight factor $W_{mu}(E)$ is known, one can calculate the ensemble averages of any physical quantity A at any inverse temperature $\beta = 1/k_B T$ as follows:

$$\langle A \rangle_T = \frac{\sum_E A(E) n(E) \exp(-\beta E)}{\sum_E n(E) \exp(-\beta E)}, \tag{3}$$

where the density of states is given by [see Eq. (2)]

$$n(E) = W_{mu}^{-1}(E). \tag{4}$$

Here, the explicit form of the physical quantity A should be known as a function of potential energy E. For instance, $A(E) = E$ gives the average potential energy $\langle E \rangle_T$ as a function of temperature, and $A(E) = (E - \langle E \rangle_T)^2$ gives specific heat.

In general, the multicanonical weight factor $W_{mu}(E)$ is not *a priori* known, and one needs its estimator for a numerical simulation. This estimator is usually calculated from iterations of short trial multicanonical simulations (see, for instance, Refs. 2, 6, and 25). In practice, it is impossible to obtain the ideal multicanonical weight factor with a completely uniform potential energy distribution. The question is when to stop the iteration for the weight factor determination. Our criterion for a satisfactory weight factor is that as long as we do get a random walk in potential energy space, the probability distribution $P_{mu}(E)$ does not have to be completely flat with a tolerance of, say, an order of magnitude deviation. In such a case, we usually perform with this weight factor a multicanonical simulation with high statistics (production run) in order to get an even better estimate of the density of states. Let $N_{mu}(E)$ be the histogram of the potential energy distribution $P_{mu}(E)$ obtained by the production run. The best estimate of the density of states can then be given by the single-histogram reweighting techniques[26] as follows [see Eq. (1)]:

$$n(E) = \frac{N_{mu}(E)}{W_{mu}(E)}. \tag{5}$$

By substituting this quantity into Eq. (3), one can calculate ensemble averages of physical quantity $A(E)$ as a function of temperature. Moreover, ensemble averages of any physical quantity A (including those that cannot be expressed as functions of potential energy) can now be obtained as long as one stores the "trajectory" A_k from the production run. Namely, we have

$$\langle A \rangle_T = \frac{\sum_{x_k} A(x_k) W_{mu}^{-1}(E(x_k)) \exp(-\beta E(x_k))}{\sum_{x_k} W_{mu}^{-1}(E(x_k)) \exp(-\beta E(x_k))}, \tag{6}$$

where x_k is the configuration at the kth MC (or MD) step. Note that when A is a function of E, Eq. (6) reduces to Eq. (3).

The multicanonical weight factor is often parametrized by two functions, $\alpha(E)$ and $\beta(E)$, as follows:

$$W_{mu}(E) = \exp(-S(E)) = \exp(-\beta(E)E - \alpha(E)), \tag{7}$$

where $S(E) \equiv \ln n(E)$ is the microcanonical entropy (in units of Boltzmann constant k_B). Here, $\beta(E)$ can be interpreted as the inverse microcanonical temperature corresponding to the energy E, and we have

$$\beta(E) = \frac{\partial S(E)}{\partial E} = \frac{1}{k_B T_{\text{eff}}}, \tag{8}$$

which implies

$$\frac{\partial \beta(E)}{\partial E} E + \frac{\partial \alpha(E)}{\partial E} = 0. \tag{9}$$

Note also that the function $\alpha(E)$ is determined up to an additive constant.

We discretize the potential energy E with step size ϵ ($E=E_i$; $i=1,2,...$) and rewrite Eq. (8) as

$$\beta(E_i)=\frac{S(E_i+\epsilon)-S(E_i)}{\epsilon}. \tag{10}$$

Because $S(E)$ is a continuous function at $E=E_i+\epsilon$, we have from Eq. (7) [see also Eq. (9)],

$$\beta(E_i)(E_i+\epsilon)+\alpha(E_i)=\beta(E_i+\epsilon)(E_i+\epsilon)+\alpha(E_i+\epsilon). \tag{11}$$

We then get

$$\alpha(E_i)=\alpha(E_i+\epsilon)+[\beta(E_i+\epsilon)-\beta(E_i)](E_i+\epsilon). \tag{12}$$

In practice, we define the multicanonical weight factor in an energy range (E_L,E_H) and use Boltzmann weight factors outside this range. Namely, we have

$$\beta(E)\equiv\begin{cases}\beta(E_H), & \text{for } E>E_H,\\ \dfrac{S(E+\epsilon)-S(E)}{\epsilon}, & \text{for } E_L\leqslant E\leqslant E_H,\\ \beta(E_L), & \text{for } E<E_L,\end{cases} \tag{13}$$

and

$$\alpha(E)\equiv\begin{cases}\alpha(E_H), & \text{for } E>E_H,\\ \alpha(E+\epsilon)+[\beta(E+\epsilon)-\beta(E)](E+\epsilon), & \\ \quad \text{for } E_L\leqslant E\leqslant E_H,\\ \alpha(E_L), & \text{for } E<E_L,\end{cases} \tag{14}$$

where the constant $\alpha(E_H)$ is usually taken to be zero. Here, E_H is an arbitrarily chosen energy value that is sufficiently large so that simulations in this energy region can avoid getting trapped in states of energy local minima. Likewise, E_L is the lowest energy value that was obtained during the multicanonical weight factor determination process. The above multicanonical parameters $\alpha(E)$ and $\beta(E)$ are usually determined by iterations of short multicanonical simulations. However, the iterative process can be nontrivial and very tedius for complex systems.

Note that Eqs. (13) and (14) imply that $\beta(E)$ and $\alpha(E)$ are constants outside the energy range (E_L,E_H) and that this weight factor [see Eq. (7)] results in a canonical simulation at $T=1/k_B\beta(E_L)$ for $E<E_L$, a multicanonical simulation for $E_L\leqslant E\leqslant E_H$, and a canonical simulation at $T=1/k_B\beta(E_H)$ for $E>E_H$.

The transition probability from state X to state X' for multicanonical Monte Carlo simulations is given by the following Metropolis criterion:[27]

$$w(X\rightarrow X')=\begin{cases}1, & \text{for } \Delta\leqslant 0,\\ \exp(-\Delta), & \text{for } \Delta>0,\end{cases} \tag{15}$$

where

$$\begin{aligned}\Delta&=S(E')-S(E),\\ &=\beta(E')E'+\alpha(E')-\beta(E)E-\alpha(E).\end{aligned} \tag{16}$$

Here, E and E' are the potential energy of state X and state X', respectively.

B. Replica-exchange method

The generalized ensemble for REM consists of M noninteracting copies of the original system in the canonical ensemble at M different temperatures T_m ($m=1,...,M$). In Ref. 19 the replica-exchange method for MD was explained in detail. In this paper, we outline this method for the MC version. We arrange the replicas so that there is always exactly one replica at each temperature. Then there is a one-to-one correspondence between replicas and temperatures; the label i ($i=1,...,M$) for replicas is a permutation of the label m ($m=1,...,M$) for temperatures, and *vice versa*:

$$i=i(m)\equiv f(m),\quad m=m(i)\equiv f^{-1}(i), \tag{17}$$

where $f(m)$ is a permutation function of m and $f^{-1}(i)$ is its inverse.

Let $X=\{x_1^{[i(1)]},\ldots,x_M^{[i(M)]}\}=\{x_{m(1)}^{[1]},\ldots,x_{m(M)}^{[M]}\}$ stand for a "state" in this generalized ensemble. The state X is specified by the M sets of coordinates $x_m^{[i]}$ in replica i at temperature T_m. Since the replicas do not interact with one another, the weight factor for the state $X=\{\ldots,x_m^{[i(m)]},\ldots\}$ is given by the product of Boltzmann factors for each replica:

$$\begin{aligned}W_{REM}(X)&=\prod_{i=1}^{M}\exp(-\beta_{m(i)}E(x_{m(i)}^{[i]})),\\ &=\prod_{m=1}^{M}\exp(-\beta_m E(x_m^{[i(m)]})),\end{aligned} \tag{18}$$

where $i(m)$ and $m(i)$ are the permutation functions in Eq. (17). Without loss of generality we can assume $T_1<T_2<\cdots<T_M$. A simulation of the replica-exchange MC method is then realized by alternately performing the following two steps:

(1) Each replica in a canonical ensemble of the fixed temperature is simulated *simultaneously* and *independently* for certain MC steps. The transition probability of these MC steps in the canonical ensemble at T_m is given by the Metropolis criterion:

$$w(X\rightarrow X')=\begin{cases}1, & \text{for } \Delta\leqslant 0,\\ \exp(-\Delta), & \text{for } \Delta>0,\end{cases} \tag{19}$$

where

$$\Delta=\beta_m(E(x_m')-E(x_m)). \tag{20}$$

Here, $E(x_m')$ and $E(x_m)$ are the potential energy of the state X' and the state X at temperature T_m, respectively.

(2) A pair of replicas, say i and j, which are at neighboring temperatures T_m and $T_{m\pm1}$, respectively, are exchanged: $X=\{\ldots,x_m^{[i]},\ldots,x_{m\pm1}^{[j]},\ldots\}\rightarrow X'=\{\ldots,x_m^{[j]},\ldots,x_{m\pm1}^{[i]},\ldots\}$. The transition probability of this replica-exchange process is given by the Metropolis criterion:

$$w(X\rightarrow X')=\begin{cases}1, & \text{for } \Delta\leqslant 0,\\ \exp(-\Delta), & \text{for } \Delta>0,\end{cases} \tag{21}$$

where

$$\Delta=(\beta_m-\beta_{m\pm1})(E(q^{[j]})-E(q^{[i]})). \tag{22}$$

Here, $E(q^{[i]})$ and $E(q^{[j]})$ are the potential energy of the ith replica and the jth replica, respectively.

Note that the trajectory $x_m^{[i(m)]}$ (with m fixed) for temperature T_m gives the canonical distribution at this temperature, while the trajectory of the ith replica $x_{m(i)}^{[i]}$ (with i fixed) realizes random walks in the temperature and potential energy space corresponding to all temperatures ($T_1 \leqslant T \leqslant T_M$).

For the expectation value at any temperature, we use the multiple-histogram reweighting techniques[23,24] as follows. Suppose we have made M independent simulation runs at M different temperatures. Let $N_m(E)$ and n_m be the energy histogram and the total number of samples obtained in the mth run, respectively. The expectation value of a physical quantity A at any intermediate temperature T is given by Eq. (3), where the density of states $n(E)$ is obtained by solving the following WHAM equations:

$$n(E)=\frac{\sum_{m=1}^{M} g_m^{-1}N_m(E)}{\sum_{m=1}^{M} g_m^{-1}n_m \exp(f_m-\beta_m E)}, \tag{23}$$

and

$$\exp(-f_m)\equiv\sum_E n(E)\exp(-\beta_m E). \tag{24}$$

Here, $g_m=1+2\tau_m$, and τ_m is the integrated autocorrelation time at temperature T_m. For biomolecular systems the quantity g_m can safely be set to be a constant in the reweighting formulas,[24] and so we set $g_m=1$ throughout the analyses in the present work. Note that $n(E)$ and f_m are solved self-consistently by iteration.

Moreover, ensemble averages of any physical quantity A (including those that cannot be expressed as functions of potential energy) can now be obtained from the "trajectory" of configurations of the production run. Namely, we first obtain f_m ($m=1,...,M$) by solving Eqs. (23) and (24) self-consistently, and then we have

$$\langle A\rangle_T=\frac{\sum_{m=1}^{M}\sum_{x_m} A(x_m)\dfrac{g_m^{-1}}{\sum_{l=1}^{M} g_l^{-1}n_l\exp(f_l-\beta_l E(x_m))}\exp(-\beta E(x_m))}{\sum_{m=1}^{M}\sum_{x_m}\dfrac{g_m^{-1}}{\sum_{l=1}^{M} g_l^{-1}n_l\exp(f_l-\beta_l E(x_m))}\exp(-\beta E(x_m))}, \tag{25}$$

where x_m are the configurations at temperature T_m. Here, the trajectories x_m are taken for each temperature T_m separately.

C. Replica-exchange multicanonical Monte Carlo algorithm

We now explain REMUCA for the MC version in detail. In this method a short REM simulation is performed first. The density of states $n(E)$ is next calculated by solving the WHAM equations of Eqs. (23) and (24) based on the results of this short REM simulation. The multicanonical weight factor can then be directly determined by Eq. (2). Finally, we perform a production run with the thus obtained multicanonical weight factor.

In the actual simulation the multicanonical weight factor is determined as follows. Using the notation of Eq. (7), we write

$$W_{\mathrm{REMUCA}}(E)=\exp(-\beta_{RM}(E)E-\alpha_{RM}(E)). \tag{26}$$

The density of states $n(E)$ thus obtained from the short REM simulation by the WHAM equations is only reliable in the following energy range:

$$E_1 \leqslant E \leqslant E_M, \tag{27}$$

where

$$E_1=\langle E\rangle_{T_1},$$

$$E_M=\langle E\rangle_{T_M}. \tag{28}$$

Here, T_1 and T_M are, respectively, the lowest and the highest temperatures used in the REM run and $\langle E\rangle_T$ stands for the canonical expectation value of E at temperature T. Therefore, $\beta_{RM}(E)$ is given by Eq. (10) in the energy range $E_1 \leqslant E < E_M$ and set to be constant outside this range:

$$\beta_{RM}(E)\equiv\begin{cases}\beta_{RM}(E_M), & \text{for } E>E_M,\\ \beta(E)=\dfrac{S(E+\epsilon)-S(E)}{\epsilon}, & \text{for } E_1\leqslant E\leqslant E_M,\\ \beta_{RM}(E_1), & \text{for } E<E_1,\end{cases} \tag{29}$$

where $S(E)=\ln n(E)$ and ϵ is the bin size of energy discretization.

Likewise, $\alpha_{RM}(E)$ is determined by Eq. (12), where we set $\alpha_{RM}(E)=0$ for $E>E_M$:

$$\alpha_{RM}(E) \equiv \begin{cases} 0, & \text{for } E > E_M, \\ \alpha_{RM}(E+\epsilon) + [\beta_{RM}(E+\epsilon) - \beta_{RM}(E)](E+\epsilon), & \\ \quad \text{for } E_1 \leq E \leq E_M, & \\ \alpha_{RM}(E_1), & \text{for } E < E_1. \end{cases} \tag{30}$$

We remark that we can also use β_1 and β_M instead of $\beta_{RM}(E_1)$ and $\beta_{RM}(E_M)$, respectively, on the right-hand side of Eq. (29), where β_1 and β_M correspond to the lowest and the highest temperatures used in the REM run. This is because the following thermodynamic relation holds:

$$\beta_i = \left.\frac{\partial S(E)}{\partial E}\right|_{E=\langle E\rangle_{T_i}}. \tag{31}$$

From Eqs. (29) and (31), we have

$$\beta_1 = \left.\frac{\partial S(E)}{\partial E}\right|_{E=E_1} \approx \frac{S(E_1+\epsilon) - S(E_1)}{\epsilon} = \beta_{RM}(E_1), \tag{32}$$

$$\beta_M = \left.\frac{\partial S(E)}{\partial E}\right|_{E=E_M} \approx \frac{S(E_M+\epsilon) - S(E_M)}{\epsilon} = \beta_{RM}(E_M). \tag{33}$$

The equality holds in the limit that the number of sampling is infinity and the bin size ϵ goes to zero.

Note that as one can see from Eqs. (26), (29), and (30), this REMUCA simulation actually results in a canonical simulation at $T = 1/k_B\beta_{RM}(E_1)$ (or T_1) for $E < E_1$, a multicanonical simulation for $E_1 \leq E \leq E_M$, and a canonical simulation at $T = 1/k_B\beta_{RM}(E_M)$ (or T_M) for $E > E_M$.

D. Multicanonical replica-exchange Monte Carlo method

In the previous section we presented REMUCA for Monte Carlo algorithm, which uses a short REM run for the determination of the multicanonical weight factor. Here, we present a modification of REM and refer to the new method as the multicanonical replica-exchange method (MUCAREM).[21] In MUCAREM the production run is a REM simulation with a few replicas not in the canonical ensemble but in the multicanonical ensemble. While multicanonical simulations are usually based on local updates, a replica-exchange process can be considered to be a global update, and global updates enhance the sampling further.

Let $\mathcal{M}$ be the number of replicas. Here, each replica is in one-to-one correspondence not with temperature but with multicanonical weight factors of a different energy range. The weight factor for this generalized ensemble is now given by [see Eq. (18)]

$$W_{\mathrm{MUCAREM}}(X) = \prod_{i=1}^{\mathcal{M}} W_{MR}^{\{m(i)\}}(E(x_{m(i)}^{[i]})), = \prod_{m=1}^{\mathcal{M}} W_{MR}^{\{m\}}(E(x_m^{[i(m)]})), \tag{34}$$

where

TABLE I. Summary of parameters in REM, REMUCA, and MUCAREM simulations of Met-enkephalin in the gas phase.

Run	No. of replicas, M	Temperature, T_m (K) ($m=1,...,M$)	MC sweeps
REM1	8	50, 77, 118, 181, 277, 425, 652, 1000	50 000
REM2	8	50, 77, 118, 181, 277, 425, 652, 1000	125 000
MUCA1	1		1 000 000
MUCAREM1	4		250 000

$$W_{MR}^{\{m\}}(E(x_m^{[i(m)]})) = \exp[-\beta_{MR}^{\{m\}}(E(x_m^{[i(m)]}))E(x_m^{[i(m)]}) - \alpha_{MR}^{\{m\}}(E(x_m^{[i(m)]}))]. \tag{35}$$

Each multicanonical weight factor $W_{MR}^{\{m\}}(E)$ is defined as follows: For each m ($m=1,...,\mathcal{M}$), we assign a pair of temperatures $(T_L^{\{m\}}, T_H^{\{m\}})$. Here, we assume that $T_L^{\{m\}} < T_H^{\{m\}}$ and arrange the temperatures so that the neighboring regions covered by the pairs have sufficient overlaps. Without loss of generality we can assume that $T_L^{\{1\}} < \cdots < T_L^{\{\mathcal{M}\}}$ and $T_H^{\{1\}} < \cdots < T_H^{\{\mathcal{M}\}}$. We define the following quantities:

$$E_L^{\{m\}} = \langle E\rangle_{T_L^{\{m\}}}, \quad E_H^{\{m\}} = \langle E\rangle_{T_H^{\{m\}}} \quad (m=1,...,\mathcal{M}). \tag{36}$$

Suppose that the multicanonical weight factor $W_{mu}(E)$ [or equivalently, the multicanonical parameters $\beta(E)$ and $\alpha(E)$ in Eq. (7)] has been obtained as in REMUCA or by any other methods in the entire energy range of interest $(E_L^{\{1\}} < E < E_H^{\{\mathcal{M}\}})$. We then have for each m ($m=1,...,\mathcal{M}$),

$$\beta_{MR}^{\{m\}}(E) \equiv \begin{cases} \beta_{MR}^{\{m\}}(E_H^{\{m\}}), & \text{for } E > E_H^{\{m\}}, \\ \beta(E) = \dfrac{S(E+\epsilon) - S(E)}{\epsilon}, & \\ \quad \text{for } E_L^{\{m\}} \leq E \leq E_H^{\{m\}}, & \\ \beta_{MR}^{\{m\}}(E_L^{\{m\}}), & \text{for } E < E_L^{\{m\}}, \end{cases} \tag{37}$$

and

$$\alpha_{MR}^{\{m\}}(E) \equiv \begin{cases} \alpha_{MR}^{\{m\}}(E_H^{\{m\}}), & \text{for } E > E_H^{\{m\}}, \\ \alpha_{MR}^{\{m\}}(E+\epsilon) + [\beta_{MR}^{\{m\}}(E+\epsilon) - \beta_{MR}^{\{m\}}(E)](E+\epsilon), & \\ \quad \text{for } E_1 \leq E \leq E_M, & \\ \alpha_{MR}^{\{m\}}(E_L^{\{m\}}), & \text{for } E < E_L^{\{m\}}. \end{cases} \tag{38}$$

Finally, a MUCAREM simulation is realized by alternately performing the following two steps:

(1) Each replica of the fixed multicanonical ensemble is simulated *simultaneously* and *independently* for certain MC steps.

(2) A pair of replicas, say i and j, which are in neighboring multicanonical ensembles, say mth and $(m\pm1)$th, respectively, are exchanged: $X = \{\ldots, x_m^{[i]}, \ldots, x_{m\pm1}^{[j]}, \ldots\} \rightarrow X' = \{\ldots, x_m^{[j]}, \ldots, x_{m\pm1}^{[i]}, \ldots\}$. The transition probability of this replica exchange is given by the Metropolis criterion:

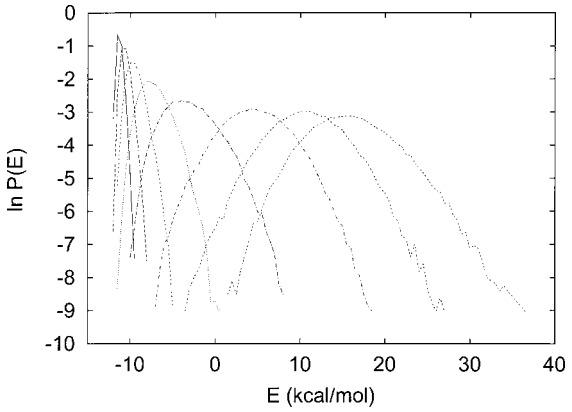

FIG. 1. Probability distribution of potential energy that was obtained from REM1 (see Table I for the parameters of the simulation).

$$w(X\to X')=\begin{cases}1, & \text{for } \Delta\leqslant 0,\\ \exp(-\Delta), & \text{for } \Delta>0,\end{cases} \tag{39}$$

where

$$\begin{aligned}\Delta=&\beta_{MR}^{\{m\}}(E(q^{[j]}))E(q^{[j]})+\alpha_{MR}^{\{m\}}(E(q^{[j]}))\\&+\beta_{MR}^{\{m\pm1\}}(E(q^{[i]}))E(q^{[i]})+\alpha_{MR}^{\{m\pm1\}}(E(q^{[i]}))\\&-\beta_{MR}^{\{m\}}(E(q^{[i]}))E(q^{[i]})-\alpha_{MR}^{\{m\}}(E(q^{[i]}))\\&-\beta_{MR}^{\{m\pm1\}}(E(q^{[j]}))E(q^{[j]})-\alpha_{MR}^{\{m\pm1\}}((q^{[j]})).\end{aligned} \tag{40}$$

Here $E(q^{[i]})$ and $E(q^{[j]})$ are the potential energy of the ith replica and the jth replica, respectively.

In this algorithm, the mth multicanonical ensemble actually results in a canonical simulation at $T=1/k_{\mathrm{B}}\beta$ ($E_L^{\{m\}}$) (or $T_L^{\{m\}}$) for $E<E_L^{\{m\}}$, a multicanonical simulation for $E_L^{\{m\}}\leqslant E\leqslant E_H^{\{m\}}$, and a canonical simulation at $T=1/k_{\mathrm{B}}\beta$ ($E_H^{\{m\}}$) (or $T_H^{\{m\}}$) for $E>E_H^{\{m\}}$, while the replica exchange process samples states of the whole energy range ($E_L^{\{1\}}\leqslant E\leqslant E_H^{\{\mathcal{M}\}}$).

TABLE II. Acceptance ratios of replica exchange in REM1.

Pair of temperature (K)	Acceptance ratio
50↔77	0.30
77↔118	0.27
118↔181	0.22
181↔277	0.17
277↔425	0.10
425↔652	0.27
652↔1000	0.40

As in REM, the expectation value of a physical quantity A at any intermediate temperature T is given by Eq. (3), where the density of states $n(E)$ is obtained by solving the following WHAM equations [see Eqs. (23) and (24)]:

$$n(E)=\frac{\sum_{m=1}^{M} g_m^{-1}N_m(E)}{\sum_{m=1}^{M} g_m^{-1}n_m\exp(f_m)W_{MR}^{\{m\}}(E)}, \tag{41}$$

and

$$\exp(-f_m)\equiv\sum_E n(E)W_{MR}^{\{m\}}(E). \tag{42}$$

Note that $W_{MR}^{\{m\}}(E)$ is used instead of the Boltzmann factor $\exp(-\beta_m E)$ in Eqs. (23) and (24).

Moreover, ensemble averages of any physical quantity A (including those that cannot be expressed as functions of potential energy) can now be obtained from the "trajectory" of configurations of the production run. Namely, we first obtain f_m ($m=1,\ldots,\mathcal{M}$) by solving Eqs. (41) and (42) self-consistently, and then we have

$$\langle A\rangle_T=\frac{\sum_{m=1}^{M}\sum_{x_m}A(x_m)\dfrac{g_m^{-1}}{\sum_{l=1}^{M} g_l^{-1}n_l\exp(f_l)W_{MR}^{\{m\}}(E(x_m))}\exp(-\beta E(x_m))}{\sum_{m=1}^{M}\sum_{x_m}\dfrac{g_m^{-1}}{\sum_{l=1}^{M} g_l^{-1}n_l\exp(f_l)W_{MR}^{\{m\}}(E(x_m))}\exp(-\beta E(x_m))}, \tag{43}$$

where the trajectories x_m are taken from each multicanonical simulation for the energy range of $E_L^{\{m\}}\leqslant E\leqslant E_H^{\{m\}}$ separately.

III. RESULTS AND DISCUSSION

We performed the REMUCA and MUCAREM simulations for the system of a penta peptide, Met-enkephalin, in the gas phase. The peptide has the amino-acid sequence Tyr-Gly-Gly-Phe-Met. Multicanonical MC simulations have already been performed for this peptide system.[11,28] Thus, it is a good benchmark system for testing the effectiveness of the new algorithms.

The backbone was terminated by a neutral NH_2 group and a neutral-COOH group at the N-terminus and at the C-terminus, respectively, as in the previous MC works of Met-enkephalin. The energy function that we used is the sum of the electrostatic term, Lennard-Jones term, hydrogen-bond term, and torsion term. The parameters in the energy function as well as the molecular geometry were taken from ECEPP/2.[29–31] The dielectric constant was set equal to 2 as

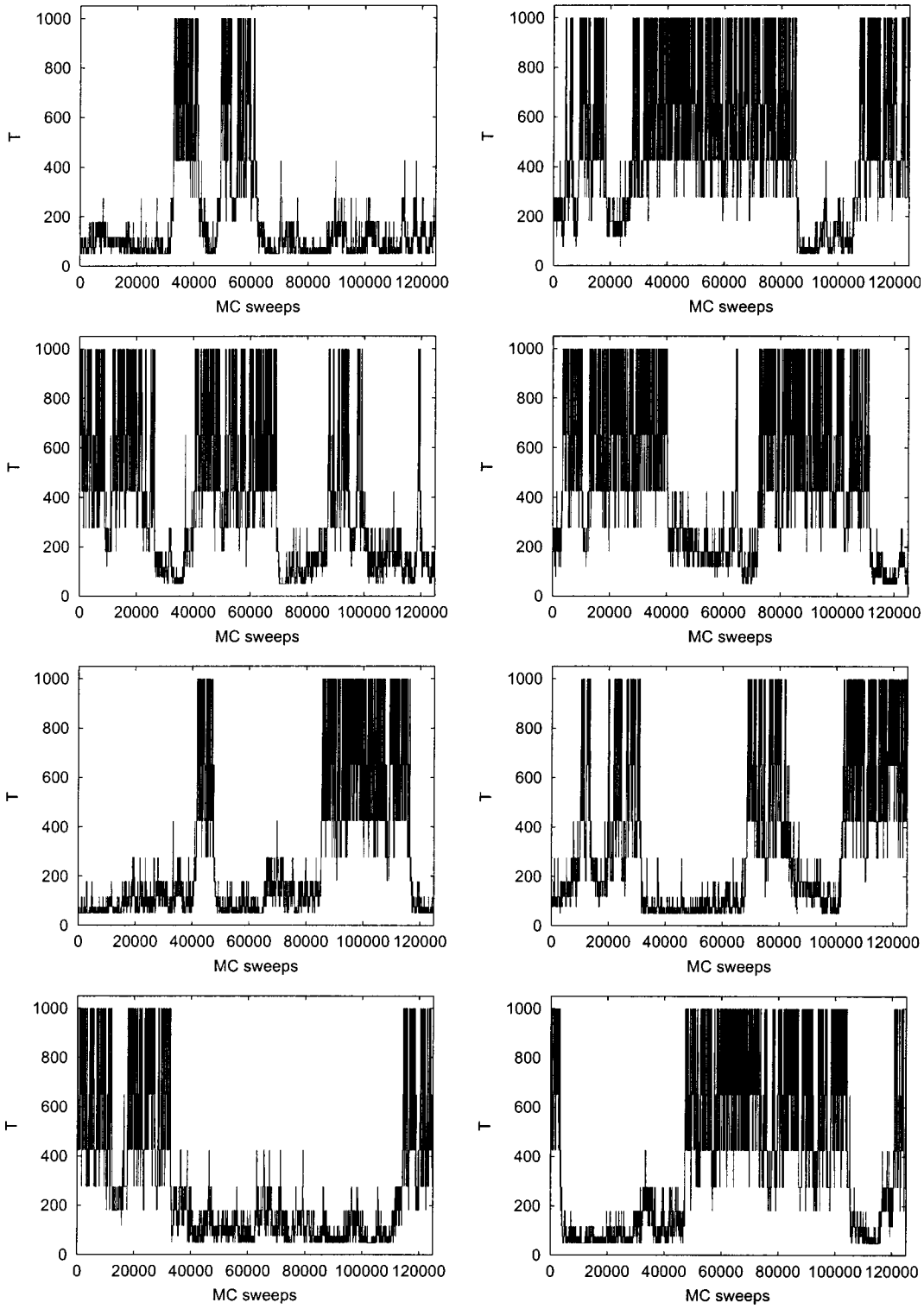

FIG. 2. Time series of temperature for each replica that was obtained from REM2 (see Table I for the parameters of the simulation).

in the previous works. For the potential energy histograms we took the bin size of $\epsilon = 1$ kcal/mol. The computer code KONF 90[32,33] was used, and MC simulations based on REM, REMUCA, and MUCAREM were performed.

The peptide-bond dihedral angles ω were set equal to 180° for simplicity. The remaining dihedral angles ϕ and ψ in the main chain and χ in the side chains constituted the variables to be updated in the simulations. For Met-enkephalin the number of degrees of freedom is 19. One MC sweep consists of updating all these angles once with a Metropolis evaluation[27] for each update. The simulations were started from randomly generated conformations.

We now present the results. In Table I we summarize the parameters of the simulations that were performed in the present work. As discussed in the previous section, REMUCA consists of two simulations: a short REM simula-

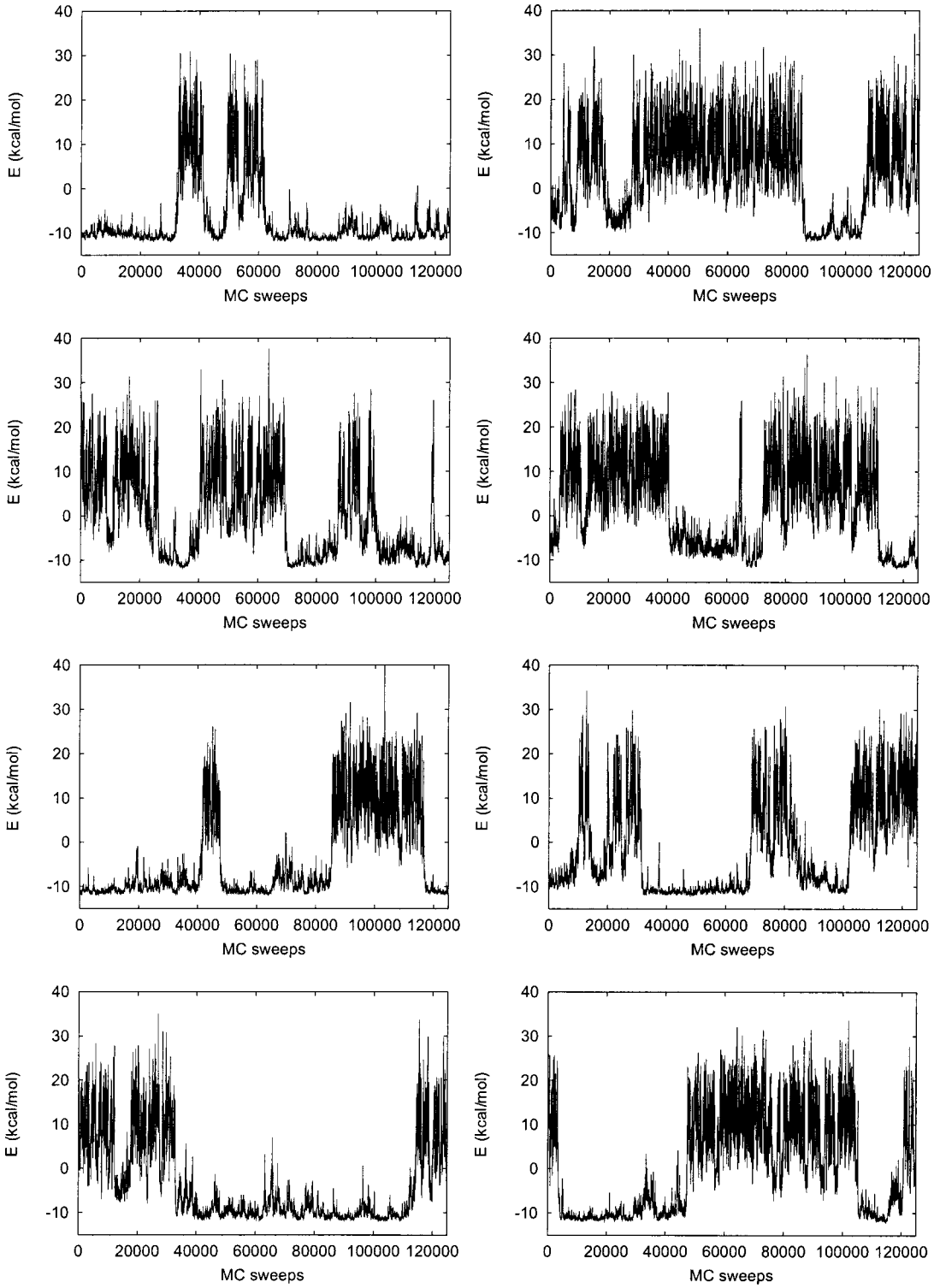

FIG. 3. Time series of potential energy for each replica that was obtained from REM2.

tion (from which the density of states of the system, or the multicanonical weight factor, is determined), and a subsequent production run of the MUCA simulation. The former simulation is referred to as REM1 and the latter as MUCA1 in Table I. A production run of the MUCAREM simulation is referred to as MUCAREM1 in Table I, and it uses the same density of states that was obtained from REM1. Finally, a production run of the original REM simulation was also performed for a comparison of the performance with REMUCA and MUCAREM, and it is referred to as REM2 in Table I. The number of MC sweeps for REM1 was 50 000 for each replica. The total number of MC sweeps for the three production runs (REM2, MUCA1, and MUCAREM1) was all set equal (i.e., 1 000 000 MC sweeps). Before taking the data, we made thermalization simulations of 10 000 MC sweeps (for each replica). In REM1 and REM2 there exist eight replicas with eight different temperatures, ranging from 50 to 1000 K, as listed in Table I (i.e., $T_1 = 50$ K and $T_M = T_8$

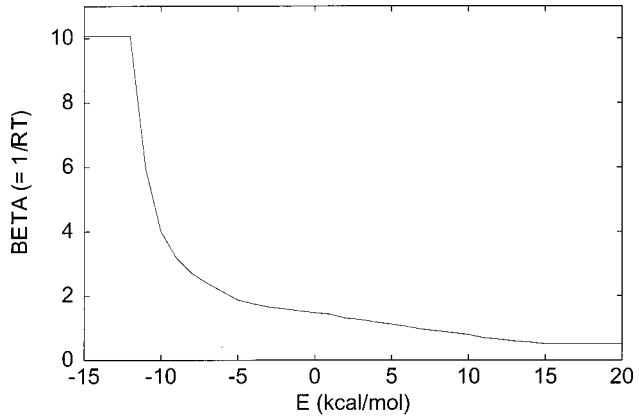

FIG. 4. The multicanonical parameter $\beta_{RM}(E)$ that was obtained from the results of REM1.

TABLE III. Summary of parameters and corresponding temperatures in MUCAREM1.

m	$T_L^{\{m\}}$	$T_H^{\{m\}}$	$E_L^{\{m\}}$ (kcal/mol)	$E_H^{\{m\}}$ (kcal/mol)
1	50	158	−20	−9.0
2	158	287	−9.0	−4.0
3	287	479	−4.0	6.0
4	479	1000	6.0	50.0

TABLE IV. Acceptance ratios of replica exchange in MUCAREM1.

Pair of multicanonical index	Acceptance ratio
1↔2	0.25
2↔3	0.35
3→4	0.32

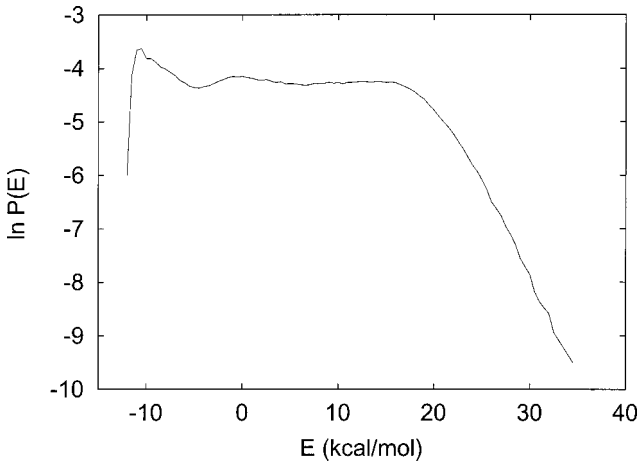

FIG. 5. Probability distribution of potential energy that was obtained from MUCA1 (see Table I for the parameters of the simulation).

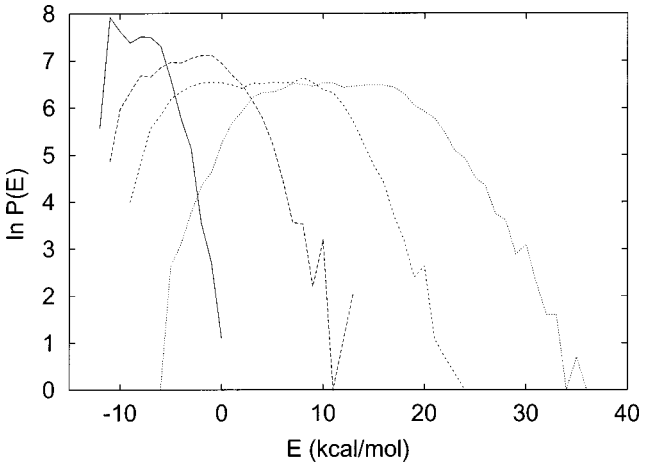

FIG. 7. Probability distribution of potential energy that was obtained from MUCAREM1 (see Tables I and III for the parameters of the simulation).

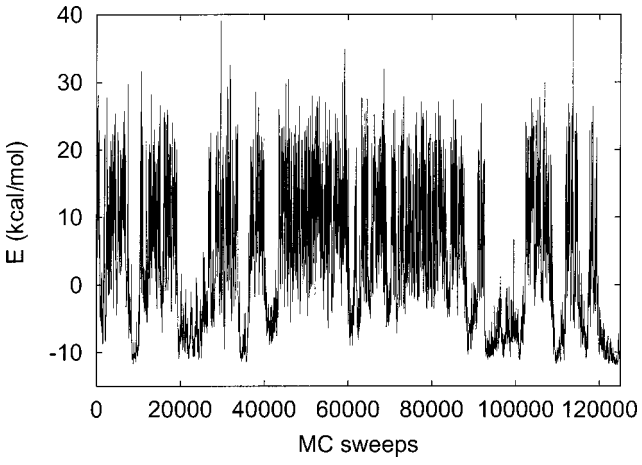

FIG. 6. Time series of potential energy that was obtained from MUCA1.

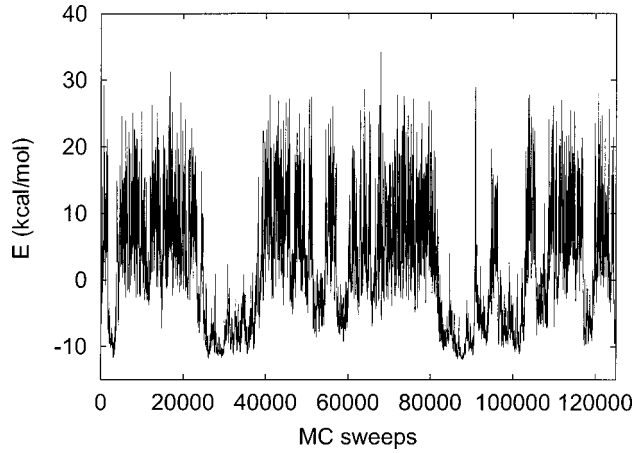

FIG. 8. Time series of potential energy for one of the replicas that was obtained from MUCAREM1.

TABLE V. The number of tunneling events and the average tunneling time during REM2, MUCA1, and MUCAREM1 (the number of total MC sweeps is 1 000 000 MC sweeps).

	Number of tunneling events	Average tunneling
REM2	13	20 189
MUCA1	37	6 560
MUCAREM1	22	18 325

$=1000$ K). The temperatures are distributed exponentially between T_1 and T_M, following the optimal distribution found in Ref. 19. In REM1 and REM2 a replica exchange was tried every ten MC sweeps.

We first check whether the replica-exchange simulation of REM1 indeed performed properly. For an optimal performance of REM the acceptance ratios of replica exchange should be sufficiently uniform and large (say, $>10\%$). In Table II we list these quantities. It is clear that both points are met in the sense that they are of the same order (the values vary between 10% and 40%). In Fig. 1 the canonical probability distributions obtained at the eight chosen temperatures from REM1 are shown. We see that there are enough overlaps between all pairs of neighboring distributions, indicating that there will be sufficient numbers of replica exchange between all pairs of neighboring distributions (see Table II).

In Fig. 2 the time series of temperature for each replica in REM2 is shown (the results for REM1 essentially correspond to the first 50 000 MC sweeps of this figure). Each replica walks randomly in the temperature space. In Fig. 3 the time series of potential energy for each replica in REM2 are shown. Note that there is a strong correlation between Figs. 2 and 3. It is known from our previous works that the global-minimum-energy conformation for Met-enkephalin has the potential energy value of -12.2 kcal/mol and that the conformations with potential energy around 20 kcal/mol are almost random coils.[11,28] It is found that random walks in potential energy space between low energies and high energies were realized. Moreover, the random walk in Fig. 3 indeed visited the global-minimum region many times.

After REM1, we obtained the density of states, $n(E)$, by the multiple-histogram method [see Eqs. (23) and (24)]. We must estimate E_1 and E_M, that is the canonical expectation value of E at temperatures T_1 and T_M. We calculated the average energy as a function of temperature from the results of REM1 and found that it is -11.3 and 15.9 kcal/mol at temperature T_1 and T_M, respectively. Thus, we set

$$E_1=-11 \text{ kcal/mol}, \quad E_M=15 \text{ kcal/mol}. \tag{44}$$

The multicanonical weight factor was then determined for the three energy regions ($E<E_1$, $E_1\leqslant E\leqslant E_M$, and $E>E_M$) from Eqs. (29) and (30). In Fig. 4 we show $\beta_{RM}(E)$ as a function of energy. For $E<E_1$ and $E>E_M$, we set $\beta_{RM}(E)$ to 10.1 (corresponding to 50 K) and 0.50 (corresponding to 1000 K), respectively. This simulation will perform a canonical simulation at $T=50$ K for $E<E_1$, a multicanonical simulation for $E_1\leqslant E\leqslant E_M$, and a canonical simulation at $T=1000$ K for $E>E_M$. With this multicanonical weight factor, we carried out a MUCA simulation of 1 000 000 MC sweeps for data collection (MUCA1 in Table I). In Fig. 5 the probability distribution obtained by MUCA1 is plotted. It can be seen that a good flat distribution is obtained in the energy region $E_1\leqslant E\leqslant E_M$. In Fig. 6 we show the time series of the potential energy from this simulation. It is found that random walks in potential energy space between low energies and high energies are realized and the global-minimum-energy conformation is obtained by this simulation. In the previous works of multicanonical simulations of Met-enkephalin in the gas phase (see, for instance, Refs. 11 and 28) at least several iterations of trial simulations were required for the multicanonical weight determination. We emphasize that in the present case of REMUCA (REM1), only one simulation was necessary to determine the optimal multicanonical weight factor that can cover the energy region corresponding to temperatures between 50 and 1000 K.

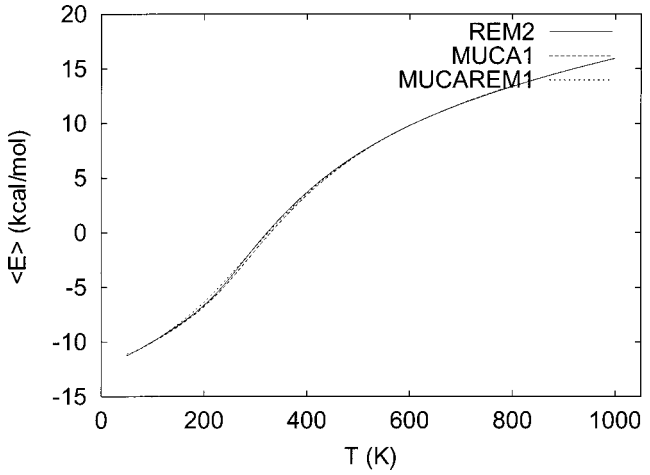

FIG. 9. Averages of potential energy as a function of temperature that were obtained from MUCA1, MUCAREM1, and REM2.

From the density of states obtained by REM1, we can prepare the multicanonical weight factors for the MUCAREM simulation by Eqs. (37) and (38). Here, we used four replicas to perform this simulation ($\mathcal{M}=4$). The parameters of MUCAREM1, such as temperature bounds $T_L^{\{m\}}$ and $T_H^{\{m\}}$ ($m=1,...,\mathcal{M}$) are listed in Table III. The choices of $T_L^{\{m\}}$ and $T_H^{\{m\}}$ are, in general, arbitrary, but significant overlaps between the probability distributions of adjacent replicas are necessary. In MUCAREM1 250 000 MC sweeps were performed for each replica, which followed additional 10 000 MC sweeps for equilibration. Replica exchange was tried every ten MC sweeps. The acceptance probabilities of this replica exchange are listed in Table IV. Relatively high probabilities of replica exchange in MUCAREM1 should be noted. In Fig. 7 the probability distributions of potential energy are shown. We observe that the probability distribution corresponding to the mth multicanonical ensemble is essentially flat for the energy region $E_L^{\{m\}}\leqslant E\leqslant E_H^{\{m\}}$, is of the canonical simulation at $T=T_L^{\{m\}}$ for $E<E_L^{\{m\}}$, and is of the canonical simulation at $T=T_H^{\{m\}}$ for $E>E_H^{\{m\}}$ ($m=1,...,\mathcal{M}$). As a result, each distribution in MUCAREM is much broader than in REM (compare Figs. 1 and 7). In Fig. 8 we

show the time series of potential energy for one of the replicas. We do observe a random walk between E_1 and E_M.

To study the efficiency of these algorithms, we calculated the number of tunneling events and the averages of tunneling times during REM2, MUCA1, and MUCAREM1. Here, the tunneling event is defined by a trajectory that goes from E_M to E_1 and back. The average tunneling time is defined by the average number of MC sweeps that are required for one tunneling event. We consider that the more tunneling events we observe during a fixed number of MC sweeps, the more efficient the method is as a generalized-ensemble algorithm. In Table V we summarize the results. In REM2 and MUCAREM1, we added the number of tunneling events of each replica to get the total number of tunneling events. Note that the total number of MC sweeps of REM2, MUCA1, and MUCAREM1 is set equal (i.e., 1 000 000 MC sweeps). The total number of tunneling events of REM2, MUCA1, and MUCAREM1 were 13, 37, and 22, respectively. The tunneling event of MUCA1 occurs most frequently among the three simulations. The number of tunneling events of REM2 is the lowest among the three. These results suggest that the REMUCA simulation is the most efficient algorithm among the three methods.

To check the validity of the canonical-ensemble expectation values calculated by the new algorithms, we compare the average potential energy as a function of temperature in Fig. 9. In REM2 and MUCAREM1 we used the multiple-histogram techniques, whereas the single-histogram method was used in MUCA1. We can see a good coincidence of the results in Fig. 9.

IV. CONCLUSIONS

Generalized-ensemble algorithms are very powerful simulation methods for configurational sampling of complex systems. In particular, two of the generalized-ensemble algorithms, namely, multicanonical algorithm and replica-exchange method, are now commonly used in the protein folding problem. In this article we have presented the details of the MC versions of two new generalized-ensemble algorithms, which combine the merits of multicanonical algorithm and replica-exchange method. In the first method, which we refer to as replica-exchange multicanonical algorithm (REMUCA), the multicanonical weight factor is determined from the results of a short replica-exchange simulation, and then a regular multicanonical production run is made with this weight. In the second method, which we refer to as multicanonical replica-exchange method (MUCAREM), a replica exchange of multicanonical ensembles is made. The number of required replicas in MUCAREM is much smaller than in the original replica exchange method. The new methods were tested with the system of a penta peptide in gas phase, which has often served as a benchmark system for testing new algorithms. The multicanonical weight factor was indeed obtained by a single, short replica-exchange simulation. Thus, REMUCA can determine the multicanonical weight factor faster than the usual iterative processes. In the following article (which we refer to as Paper II) we give detailed comparisons of the performance of REMUCA and MUCAREM, taking a more complex system of a 17-residue helical peptide as an example.

ACKNOWLEDGMENTS

The simulations were performed on the HITACHI and other computers at the Research Center for Computational Science, Okazaki National Research Institutes. This work was supported, in part, by grants from the Research for the Future Program of the Japan Society for the Promotion of Science (JSPS-RFTF98P01101) and from the Japanese Ministry of Education, Culture, Sports, Science, and Technology.

APPENDIX: EQUIVALENCE OF FORMULAS FOR MONTE CARLO AND MOLECULAR DYNAMICS VERSIONS

In the previous work, the REMUCA and MUCAREM algorithms for molecular dynamics simulations were presented.[21] In REMUCA the formulas for the multicanonical weight factor that were given there appear to be rather different from the present ones [compare Eq. (10) of Ref. 21 and Eqs. (37) and (38) in this article]. In this Appendix we show that they are actually equivalent.

In Ref. 21 the multicanonical weight factor is expressed in terms of multicanonical potential energy as follows:

$$W_{mu}(E)=e^{-\beta_0 E_{mu}(E;T_0)}, \tag{A1}$$

where an arbitrary reference temperature, $T_0=1/k_B\beta_0$ is introduced and the multicanonical potential energy is defined by [see also Eq. (7)]

$$E_{mu}(E;T_0)=k_B T_0 S(E)=k_B T_0(\beta(E)E+\alpha(E)). \tag{A2}$$

In REMUCA the multicanonical weight factor, or $E_{mu}(E;T_0)$, can be obtained in the energy range $E_1<E<E_M$. Hence, we use the notation $\mathcal{E}_{mu}^{\{0\}}$ when we include energy regions outside this range. We have from Eq. (10) of Ref. 21

$$\mathcal{E}_{mu}^{\{0\}}(E)\equiv\begin{cases}\left.\dfrac{\partial E_{mu}(E;T_0)}{\partial E}\right|_{E=E_M}(E-E_M)+E_{mu}(E_M;T_0), & \text{for } E>E_M,\\ E_{mu}(E;T_0), & \text{for } E_1\leqslant E\leqslant E_M,\\ \left.\dfrac{\partial E_{mu}(E;T_0)}{\partial E}\right|_{E=E_1}(E-E_1)+E_{mu}(E_1;T_0), & \text{for } E<E_1.\end{cases} \tag{A3}$$

By Eq. (8) we have

$$\frac{\partial E_{mu}(E;T_0)}{\partial E}=k_{\mathrm{B}}T_0\frac{\partial S(E)}{\partial E}=k_{\mathrm{B}}T_0\beta(E). \tag{A4}$$

Equation (A3) then becomes

$$\mathcal{E}_{mu}^{\{0\}}(E)\equiv\begin{cases} k_{\mathrm{B}}T_0(\beta(E_M)E+\alpha(E_M)) & \text{for } E>E_M, \\ k_{\mathrm{B}}T_0(\beta(E)E+\alpha(E)), & \text{for } E_1\leqslant E\leqslant E_M, \\ k_{\mathrm{B}}T_0(\beta(E_1)E+\alpha(E_1)), & \text{for } E<E_1. \end{cases} \tag{A5}$$

This equation is equivalent to Eqs. (29) and (30). In the MUCAREM case also, we can show the equivalence between the formulas in Ref. 21 and those in the present article.

[1] U. H. E. Hansmann and Y. Okamoto, in *Annual Reviews of Computational Physics VI*, edited by D. Stauffer (World Scientific, Singapore, 1999), p. 129.
[2] A. Mitsutake, Y. Sugita, and Y. Okamoto, Biopolymers **60**, 96 (2001).
[3] Y. Sugita and Y. Okamoto, in *Lecture Notes in Computational Science and Engineering*, edited by T. Schlick and H. H. Gan (Springer-Verlag, Berlin, 2002), p. 304.
[4] B. A. Berg and T. Neuhaus, Phys. Lett. B **267**, 249 (1991).
[5] B. A. Berg and T. Neuhaus, Phys. Rev. Lett. **68**, 9 (1992).
[6] B. A. Berg, Fields Inst. Commun. **26**, 1 (2000); see also cond-mat/9909236.
[7] J. Lee, Phys. Rev. Lett. **71**, 211 (1993).
[8] M. H. Hao and H. A. Scheraga, J. Phys. Chem. **98**, 4940 (1994).
[9] C. Bartels and M. Karplus, J. Phys. Chem. B **102**, 865 (1998).
[10] B. A. Berg and T. Celik, Phys. Rev. Lett. **69**, 2292 (1992).
[11] U. H. E. Hansmann and Y. Okamoto, J. Comput. Chem. **14**, 1333 (1993).
[12] K. Hukushima and K. Nemoto, J. Phys. Soc. Jpn. **65**, 1604 (1996).
[13] K. Hukushima, H. Takayama, and K. Nemoto, Int. J. Mod. Phys. C **7**, 337 (1996).
[14] C. J. Geyer, in *Computing Science and Statistics, Proceedings of the 23rd Symposium on the Interface*, edited by E. M. Keramidas (Interface Foundation, Fairfax Station, 1991), p. 156.
[15] M. C. Tesi, E. J. J. van Rensburg, E. Orlandini, and S. G. Whittington, J. Stat. Phys. **82**, 155 (1996).
[16] E. Marinari, G. Parisi, and J. J. Ruiz-Lorenzo, *Spin Glasses and Random Fields*, edited by A. P. Young (World Scientific, Singapore, 1998), p. 59.
[17] Y. Iba, Int. J. Mod. Phys. C **12**, 623 (2001).
[18] U. H. E. Hansmann, Chem. Phys. Lett. **281**, 140 (1997).
[19] Y. Sugita and Y. Okamoto, Chem. Phys. Lett. **314**, 141 (1999).
[20] Y. Sugita, A. Kitao, and Y. Okamoto, J. Chem. Phys. **113**, 6042 (2000).
[21] Y. Sugita and Y. Okamoto, Chem. Phys. Lett. **329**, 261 (2000).
[22] A. Mitsutake and Y. Okamoto, Chem. Phys. Lett. **332**, 131 (2000).
[23] A. M. Ferrenberg and R. H. Swendsen, Phys. Rev. Lett. **63**, 1195 (1989).
[24] S. Kumar, D. Bouzida, R. H. Swendsen, P. A. Kollman, and J. M. Rosenberg, J. Comput. Chem. **13**, 1011 (1992).
[25] B. A. Berg, Nucl. Phys. B (Proc. Suppl.) **63A–C**, 982 (1998).
[26] A. M. Ferrenberg and R. H. Swendsen, Phys. Rev. Lett. **61**, 2635 (1988).
[27] N. Metropolis, A. W. Rosenbluth, M. N. Rosenbluth, A. H. Teller, and E. Teller, J. Chem. Phys. **21**, 1087 (1953).
[28] A. Mitsutake, U. H. E. Hansmann, and Y. Okamoto, J. Mol. Graphics Modell. **16**, 226 (1998).
[29] F. A. Momany, R. F. McGuire, A. W. Burgess, and H. A. Scheraga, J. Phys. Chem. **79**, 2361 (1975).
[30] G. Némethy, M. S. Pottle, and H. A. Scheraga, J. Phys. Chem. **87**, 1883 (1983).
[31] M. J. Sippl, G. Némethy, and H. A. Scheraga, J. Phys. Chem. **88**, 6231 (1984).
[32] H. Kawai, Y. Okamoto, M. Fukugita, T. Nakazawa, and T. Kikuchi, Chem. Lett. **1991**, 213.
[33] Y. Okamoto, M. Fukugita, T. Nakazawa, and H. Kawai, Protein Eng. **4**, 639 (1991).