Replica-exchange multicanonical algorithm and multicanonical replica-exchange method for simulating systems with rough energy landscape

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We propose two efficient algorithms for configurational sampling of systems with rough energy landscape. The first one is a new method for the determination of the multicanonical weight factor. In this method a short replica-exchange simulation is performed and the multicanonical weight factor is obtained by the multiple-histogram reweighting techniques. The second one is a further extension of the first in which a replica-exchange multicanonical simulation is performed with a small number of replicas. These new algorithms are particularly useful for studying the protein folding problem.

I. INTRODUCTION

With the great advancement of computational science over the past decades, partly due to the rapid growth of computer technologies, scientists in many research fields are now attacking realistic problems with large degrees of freedom and complexity. When dealing with systems with rough energy landscape, simulations by conventional molecular dynamics (MD) or Monte Carlo (MC) methods are of little use, because at low temperatures they tend to get trapped in local-minimum energy states and sample only a very limited region of the configurational space. The development of new powerful simulation algorithms that can alleviate this difficulty is thus particularly important.

Multicanonical algorithm (MUCA)\(^1\) may be one of the most popular methods that can sample a wide phase space (for a review, see, e.g., Ref. \(^2\)). A simulation in multicanonical ensemble is based on a non-Boltzmann weight factor, which we refer to as the multicanonical weight factor, and a free random walk in potential energy space is realized. The random walk can overcome any energy barrier and allows the simulation to escape from local-minimum states. Monitoring the potential energy throughout a MUCA simulation, one can obtain not only the global-minimum energy state but also canonical-ensemble averages of any physical quantity as a function of temperature. The latter is accomplished by the single-histogram reweighting techniques\(^3\). The multicanonical weight factor is usually determined by iterations of short trial simulations (the details of this process are described, for instance, in Refs. \(^4\)\(^-\)\(^5\)). This iterative process can be very difficult and tedious for complex systems, and there have been attempts to accelerate the convergence of the iterative process\(^6\). Despite these efforts, the determination of the multicanonical weight factor still remains to be non-trivial\(^7\).

Another powerful algorithm is the replica-exchange method (REM)\(^1\)\(^8\)\(^9\)\(^10\). (A similar method was independently developed earlier in Ref. \(^11\). REM is also referred to as multiple Markov chain method\(^12\) and parallel tempering\(^15\).) In this method, a number of non-interacting copies of the original system (or replicas) at different temperatures are simulated independently and simultaneously by the conventional MD or MC methods. Every few steps, pairs of replicas are exchanged with a specified transition probability. This exchange process realizes a random walk in temperature space, which in turn induces a random walk in the energy space so that a wide configurational space can be sampled during the simulation. The multiple-histogram reweighting techniques\(^16\)\(^17\) (an extension of which is also referred to as WHAM\(^17\)) are used to calculate various canonical-ensemble averages as a function of temperature. In the replica-exchange method the weight factor is just the product of Boltzmann factors, and so it is essentially

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known. However, REM also has a weak point: It is difficult to study the first-order phase transitions, because the replica-exchange rates passing the first-order transition temperatures are greatly reduced.

In a previous work we have developed a molecular dynamics algorithm for REM [18] (see, also, Refs. [19][21]). We then developed a multidimensional REM [21] (see, also, Refs. [22][23]). In this Letter we try to combine the merits of multicanonical algorithm and replica-exchange method. In the first method, which we refer to as replica-exchange multicanonical algorithm (REMUCA), a short replica-exchange simulation is performed and the multicanonical weight factor is determined by the multiple-histogram reweighting techniques [6,17]. (We remark that the multiple-histogram reweighting techniques are also used during the regular iterations of multicanonical weight factor determination in Refs. [4,14]). We then present a further extension of the new method, which we refer to as multicanonical replica-exchange method (MUCAREM), where a replica-exchange multicanonical simulation is performed with a small number of replicas. The effectiveness of these methods is tested with a short peptide, Met-enkephalin, in gas phase.

II. METHODS

A. Replica-exchange multicanonical algorithm

In the multicanonical ensemble each state is weighted by the multicanonical weight factor, $W_{\mu}(E)$, so that a flat potential energy distribution, $P_{\mu}(E)$, is obtained: $P_{\mu}(E) \propto n(E)W_{\mu}(E) = \text{const}$, where $E$ is the potential energy and $n(E)$ is the density of states. We can then write

$$W_{\mu}(E) \equiv e^{-\beta_0 E_{\mu}(E;T_0)} = \frac{1}{n(E)}, \quad (1)$$

where we have chosen an arbitrary reference temperature, $T_0 = 1/k_B \beta_0$ ($k_B$ is Boltzmann’s constant), and the “multicanonical potential energy” is defined by

$$E_{\mu}(E;T_0) = k_BT_0 \ln n(E). \quad (2)$$

Since the density of states of the system is usually unknown, the multicanonical weight factor has to be numerically determined by iterations of short preliminary runs [12].

Once the weight factor is given, multicanonical Monte Carlo simulation is performed, for instance, with the Metropolis criterion. The molecular dynamics algorithm in multicanonical ensemble also naturally follows from Eq. (1), in which the regular constant temperature molecular dynamics (with $T = T_0$) is performed by solving the following modified Newton equation: [24][25][13]

$$\dot{p}_i = -\frac{\partial E_{\mu}(E;T_0)}{\partial q_i} = \frac{\partial E_{\mu}(E;T_0)}{\partial E} f_i, \quad (3)$$

where $q_i$ and $p_i$ are the coordinate vector and momentum vector of the $i$-th atom, and $f_i$ is the regular force acting on the $i$-th atom. In this Letter the formulations of the new methods in terms of molecular dynamics algorithms are presented. The details of the Monte Carlo versions of the new algorithms have also been worked out and will be given elsewhere [24].

We now briefly review the original replica-exchange method (REM) [11]-[15] (see Ref. [18] for details). The system for REM consists of $M$ non-interacting copies (or, replicas) of the original system in the canonical ensemble at $M$ different temperatures $T_m$ ($m = 1, \cdots, M$). Let $X = \{ \cdots, x_m^{[i]}, \cdots \}$ stand for a state in this generalized ensemble. Here, the superscript $i$ and the subscript $m$ in $x_m^{[i]}$ label the replica and the temperature, respectively. The state $X$ is specified by the $M$ sets of coordinates $q^{[i]}$ (and momenta $p^{[i]}$).

A simulation of the replica-exchange method (REM) is then realized by alternately performing the following two steps [11]-[15]. Step 1: Each replica in canonical ensemble of the fixed temperature is simulated independently for a certain MC or MD steps. Step 2: A pair of replicas, say $i$ and $j$, which are at neighboring temperatures $T_m$ and $T_n$, respectively, are exchanged: $X = \{ \cdots, x_m^{[i]}, \cdots, x_n^{[j]}, \cdots \} \rightarrow X' = \{ \cdots, x_m^{[j]}, \cdots, x_n^{[i]}, \cdots \}$. The transition probability of this replica exchange is given by the Metropolis criterion:

$$w(X \rightarrow X') \equiv w(x_m^{[i]}, x_n^{[j]}) = \begin{cases} 1, & \text{for } \Delta \leq 0, \\ \exp(-\Delta), & \text{for } \Delta > 0, \end{cases} \quad (4)$$

where
\[ \Delta = (\beta_m - \beta_n) \left( E \left( q^{[i]} \right) - E \left( q^{[j]} \right) \right). \] (5)

Here, \( E \left( q^{[i]} \right) \) and \( E \left( q^{[j]} \right) \) are the potential energy of the \( i \)-th replica and the \( j \)-th replica, respectively. In the present work we employ molecular dynamics algorithm for Step 1. We remark that in molecular dynamics simulations we also have to deal with the momenta. It was shown that by rescaling the momenta uniformly by the square root of the ratio of \( T_m \) and \( T_n \), the kinetic energy terms in the Boltzmann factors are cancelled out and that the same criterion, Eqs. (4) and (5), which was originally derived for Monte Carlo algorithm [11]-[15] is recovered [18].

The major advantage of REM over other generalized-ensemble methods such as multicanonical algorithm [1] lies in the fact that the weight factor is essentially \textit{a priori} known, while in the latter algorithm the determination of the weight factor can be very tedious and time-consuming. A random walk in “temperature space” is realized for each replica, which in turn induces a random walk in potential energy space. This alleviates the problem of getting trapped in states of energy local minima.

In the \textit{replica-exchange multicanonical algorithm} (REMUCA) we first perform a short REM simulation (with \( M \) replicas) to determine the multicanonical weight factor and then perform with this weight factor a regular multicanonical simulation with high statistics. The first step is accomplished by the multiple-histogram reweighting techniques [16,17]. Let \( N_m(E) \) and \( n_m \) be respectively the potential-energy histogram and the total number of samples obtained at temperature \( T_m = 1/k_B \beta_m \) of the REM run. The density of states, \( n(E) \), is then given by [16,17]

\[ n(E) = \frac{\sum_{m=1}^{M} g_m^{-1} N_m(E)}{\sum_{m=1}^{M} n_m g_m^{-1} e^{f_m - \beta_m E}}, \] (6)

and

\[ e^{-f_m} = \sum_{E} n(E)e^{-\beta_mE}. \] (7)

Here, \( g_m = 1 + 2\tau_m \), and \( \tau_m \) is the integrated autocorrelation time at temperature \( T_m \). Note that the density of states \( n(E) \) and the “dimensionless” Helmholtz free energy \( f_m \) in Eqs. (6) and (7) are solved self-consistently by iteration [16,17].

Once the estimate of the density of states is obtained, the multicanonical weight factor can be directly determined by using Eq. (6) (see also Eq. (2)). Actually, the multicanonical potential energy, \( E_{mu}(E;T_0) \), thus determined is only reliable in the following range:

\[ E_1 \leq E \leq E_M, \] (8)

where \( T_1 \) and \( T_M \) are respectively the lowest and the highest temperatures used in the REM run and

\[ \begin{align*}
E_1 &= < E >_{T_1}, \\
E_M &= < E >_{T_M}.
\end{align*} \] (9)

Here, \( < E >_T \) stands for the canonical expectation value of \( E \) at temperature \( T \). Outside this range we extrapolate the multicanonical potential energy linearly as follows:

\[ E_{mu}^{(0)}(E) \equiv \begin{cases} \\
\frac{\partial E_{mu}(E;T_0)}{\partial E} \bigg|_{E=E_1} (E - E_1) + E_{mu}(E_1;T_0), & \text{for } E < E_1, \\
E_{mu}(E;T_0), & \text{for } E_1 \leq E \leq E_M, \\
\frac{\partial E_{mu}(E;T_0)}{\partial E} \bigg|_{E=E_M} (E - E_M) + E_{mu}(E_M;T_0), & \text{for } E > E_M.
\end{cases} \] (10)

In the present work the multicanonical potential energy function, \( E_{mu}(E;T_0) \), and its derivative, \( \frac{\partial E_{mu}(E;T_0)}{\partial E} \), were obtained by fitting the logarithm of the density of states, \( \ln n(E) \), (which was determined by the multiple-histogram reweighting techniques) by the cubic spline functions in the energy range of Eq. (8). A long multicanonical MD run is then performed by solving the Newton equations in Eq. (3) into which we substitute \( E_{mu}^{(0)}(E) \) of Eq. (10).

Let \( N_{mu}(E) \) be the histogram of the potential energy distribution, \( P_{mu}(E) \), that is obtained from this multicanonical production run. The expectation value of a physical quantity \( A \) at any temperature \( T \) is then calculated from
of the value of $T$ detailed discussion on this point will be given elsewhere \[2 7\]). Note also that the above arguments are independent of REMUCA and refer the new method as exchange method for the determination of the multicanonical weight factor. Here, we present a further modification the present method with the previous iterative methods \[6\]- \[10\]. such a case we can still greatly simplify the process of the multicanonical weight factor determination by combining not be able to give an accurate estimate of the density of states (like in the case of a first-order phase transition). In $E < E_1$ where \[E < E_1\], a multicanonical simulation for $E_1 \leq E \leq E_{M}$, and a canonical simulation at $T = T_M$ for $E > E_M$ (a detailed discussion on this point will be given elsewhere \[27\]). Note also that the above arguments are independent of the value of $T_0$, and we will get the same results, regardless of its value.

Finally, although we did not find any difficulty in the case of protein systems, a single REM run in general may not be able to give an accurate estimate of the density of states (like in the case of a first-order phase transition). In such a case we can still greatly simplify the process of the multicanonical weight factor determination by combining the present method with the previous iterative methods \[6\]- \[10\].

B. Multicanonical replica-exchange method

In the previous subsection we presented a new generalized-ensemble algorithm, REMUCA, that uses the replica-exchange method for the determination of the multicanonical weight factor. Here, we present a further modification of REMUCA and refer the new method as multicanonical replica-exchange method (MUCAREM). In MUCAREM the final production run is not a regular multicanonical simulation (as in REMUCA) but a replica-exchange simulation with a few replicas, say $M$ replicas, in the multicanonical ensemble. We expect that this enhances the sampling further because a replica-exchange process can be considered to be a global update, while multicanonical simulations are usually based on local updates. We remark that replica-exchange simulations based on another generalized ensemble are introduced in Ref. \[19\].

We now give the details of MUCAREM. As in REMUCA, we first perform a short REM simulation with $M$ replicas with $M$ different temperatures (we order them as $T_1 < T_2 < \cdots < T_M$) and obtain the best estimate of the density of states $n(E)$ in the whole energy range of interest (see Eq. \[8\]). We then choose a number $M$ ($M \ll M$) and assign $M$ pairs of temperatures $(T_{L}^{(m)}, T_{H}^{(m)})$ ($m = 1, \cdots, M$). 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. We also set $T_{L}^{(1)} = T_1$ and $T_{H}^{(M)} = T_M$. We choose $M$ (arbitrary) temperatures $T_m$ ($m = 1, \cdots, M$). We then define the following quantities:

$$
\begin{align*}
E_{L}^{(m)} &= < E >_{T_L^{(m)}}, \\
E_{H}^{(m)} &= < E >_{T_H^{(m)}}, \quad (m = 1, \cdots, M)
\end{align*}
$$

(13)

and assign the following multicanonical potential energies (see Eq. \[10\]):

$$
\mathcal{E}_{mu}^{(m)}(E) = \begin{cases} \\
\frac{\partial E_{mu}(E; T_m)}{\partial E} \bigg|_{E=E_{L}^{(m)}} (E - E_{L}^{(m)}) + E_{mu}(E_{L}^{(m)}; T_m), \quad \text{for } E < E_{L}^{(m)}, \\
\frac{\partial E_{mu}(E; T_m)}{\partial E} \bigg|_{E=E_{H}^{(m)}} (E - E_{H}^{(m)}) + E_{mu}(E_{H}^{(m)}; T_m), \quad \text{for } E > E_{H}^{(m)}, \\
\end{cases}
$$

(14)

where $E_{mu}(E; T)$ is the multicanonical potential energy that was determined for the whole energy range of Eq. \[8\]. The Newton equation in Eq. \[3\] again implies that our choice of $\mathcal{E}_{mu}^{(m)}(E)$ in Eq. \[14\] results in a canonical simulation at $T = T_L^{(m)}$ for $E < E_L^{(m)}$, a multicanonical simulation for $E_L^{(m)} \leq E \leq E_H^{(m)}$, and a canonical simulation at $T = T_H^{(m)}$ for $E > E_H^{(m)}$ \[27\].

The production run of MUCAREM is a replica-exchange simulation with $M$ replicas with $M$ different temperatures $T_m$ and multicanonical potential energies $\mathcal{E}_{mu}^{(m)}(E)$. By following the same derivation that led to the original REM,
one can show that the transition probability of replica exchange, $w \left( x_m^{[i]} \mid x_n^{[i]} \right)$, is given by Eq. (3), where we now have

$$\Delta = \beta_m \left( \mathcal{E}_m^{(m)} \left( E \left( q^{[j]} \right) \right) - \mathcal{E}_n^{(m)} \left( E \left( q^{[i]} \right) \right) \right) - \beta_n \left( \mathcal{E}_n^{(n)} \left( E \left( q^{[j]} \right) \right) - \mathcal{E}_n^{(n)} \left( E \left( q^{[i]} \right) \right) \right).$$

Note that we need to newly evaluate the multicanonical potential energy, $\mathcal{E}_m^{(m)}(E(q^{[j]}))$ and $\mathcal{E}_n^{(n)}(E(q^{[i]}))$, because $\mathcal{E}_m^{(m)}(E)$ and $\mathcal{E}_n^{(n)}(E)$ are, in general, different functions for $m \neq n$. We remark that the same additional evaluation of the potential energy is necessary for the multidimensional replica-exchange method [17].

Let $N_m(E)$ and $n_m$ be respectively the potential-energy histogram and the total number of samples obtained at $T_m$ ($m = 1, \ldots, M$). The expectation value of a physical quantity $A$ at any temperature $T = 1/k_B\beta$, is then given by Eq. (4), where the density of states is now obtained from the multiple-histogram reweighting formulæ [16,17] of Eqs. (3) and (7) with the replacements: $M \rightarrow \mathcal{M}$ and $\beta_m E \rightarrow \beta_m \mathcal{E}_m^{(m)}(E)$.

### III. RESULTS AND DISCUSSION

We tested the effectiveness of the new algorithms for the system of a penta-peptide, Met-enkephalin, in gas phase. This peptide has the amino-acid sequence, Tyr-Gly-Gly-Phe-Met. The N and C termini of the peptide were blocked with acetyl and N-methyl groups, respectively. The force-field parameters were taken from the all-atom version of AMBER developed by Cornell et al. [28], and the dielectric constant was set equal to 1.0.

We have performed MD simulations in the Cartesian coordinates based on the replica-exchange multicanonical algorithm (REMUCA) and multicanonical replica-exchange method (MUCAREM). As a thermostat for both MD simulations in the replica-exchange method (REM) and multicanonical algorithm (MUCA), we have adopted the constraint method [24,26] in which the total kinetic energy is constant, following Ref. [25], where the constraint method is recommended for MUCA simulations. The computer code developed in Refs. [23,24], which is based on PRESTO [33], was used. The unit time step was set to 0.5 fs. The simulations (of all replicas) were started from an extended conformation.

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 simulation (from which the density of states of the system, or the multicanonical weight factor, is determined) and a subsequent production run of MUCA simulation. The former simulation is referred to as REM1 and the latter as MUCA1 in Table I. A production run of 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 comparison and it is referred to as REM2 in Table I. The total simulation time for the three production runs (REM2, MUCA1, and MUCAREM1) was all set equal (i.e., 5 ns). Before taking the data, we made regular canonical MD simulations ranging from 200 K to 1000 K as listed in Table I (i.e., $T_1 = 200$ K and $T_M = T_{10} = 1000$ K). For the present purpose of the work, we believe that this range of temperature is sufficiently wide. The temperatures are distributed exponentially between $T_1$ and $T_M$, following the optimal distribution found in Ref. [18]. In REM1 and REM2 a replica exchange was tried every 20 time steps (or 10 fs) as in our previous work [18].

In REM1 each replica was simulated by a constant temperature MD of $2 \times 10^5$ steps (or 100 ps). 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 (the values vary only between 13 % and 16 %). Moreover, in Fig. 1 the canonical probability distributions obtained at the chosen 10 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 exchanges between pairs of replicas (see Table II). We did observe random walks in potential energy space between low energies and high energies.

After REM1, we obtained the density of states, $n(E)$, by the multiple-histogram method [16,17] (namely, by solving Eqs. (3) and (7) self-consistently). For biomolecular systems the integrated autocorrelation times, $\tau_m$, in the reweighting formulæ can safely be set to be a constant [17], and we do so throughout the analyses in this section. The density of states will give the average values of the potential energy from Eq. (11), and we found

$$\left\{ \begin{array}{l} E_1 = \langle E \rangle_{T_1} = -30 \text{ kcal/mol} , \\ E_M = \langle E \rangle_{T_M} = 195 \text{ kcal/mol} . \end{array} \right.$$  \hspace{1cm} (16)
Then our estimate of the density of states is reliable in the range $E_1 \leq E \leq E_M$. The multicanonical potential energy $E_{\text{mu}}(E)$ was thus determined for the three energy regions ($E < E_1$, $E_1 \leq E \leq E_M$, and $E > E_M$) from Eq. (10).

Namely, the multicanonical potential energy, $E_{\text{mu}}(E; T_0)$, in Eq. (2) and its derivative, $\frac{\partial E_{\text{mu}}(E; T_0)}{\partial E}$, were determined by fitting $\ln(n(E))$ by cubic spline functions in the energy region of ($-30 \leq E \leq 195$ kcal/mol). Here, we have set the arbitrary reference temperature to be $T_0 = 1000$ K. Outside this energy region, $E_{\text{mu}}(E; T_0)$ was linearly extrapolated as in Eq. (10).

After determining the multicanonical weight factor, we carried out a multicanonical MD simulation of $1 \times 10^7$ steps (or 5 ns) for data collection (MUCA1 in Table I). In Fig. 2 the probability distribution obtained by MUCA1 is plotted. It can be seen that a good flat distribution is obtained in the energy region $E_1 \leq E \leq E_M$. In Fig. 2 the canonical probability distributions that were obtained by the reweighting techniques at $T = T_i = 200$ K and $T = T_M = 1000$ K are also shown (these results are essentially identical to one another among MUCA1, MUCAREM1, and REM2, as discussed below). Comparing these curves with those of MUCA1 in the energy regions $E < E_1$ and $E > E_M$ in Fig. 2, we confirm our claim in the previous section that MUCA1 gives canonical distributions for $E_1 \leq E \leq E_M$.

In the previous works of multicanonical simulations of Met-enkephalin in gas phase (see, for instance, Refs. [24,25]), 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 200 K and 1000 K.

From the density of states obtained by REMUCA (i.e., REM1), we prepared the multicanonical weight factors (or the multicanonical potential energies) for the MUCAREM simulation (see Eq. (14)). The parameters of MUCAREM1, such as energy bounds $E_L^{(m)}$ and $E_H^{(m)}$ ($m = 1, \cdots, \mathcal{M}$) are listed in Table III. The choices of $T_L^{(m)}$ and $T_H^{(m)}$ are, in general, arbitrary, but significant overlaps among the probability distributions of adjacent replicas are necessary. The replica-exchange process in MUCAREM1 was tried every 200 time steps (or 100 fs). It is less frequent than in REM1 (or REM2). This is because we wanted to ensure a sufficient time for system relaxation.

In Fig. 3 the probability distributions of potential energy obtained by MUCAREM1 are shown. As expected, we observe that the probability distributions corresponding to the temperature $T_m$ are essentially flat for the energy region $E_L^{(m)} \leq E \leq E_H^{(m)}$, are of the canonical simulation at $T = T_L^{(m)}$ for $E < E_L^{(m)}$, and are of the canonical simulation at $T = T_H^{(m)}$ for $E > E_H^{(m)}$ $(m = 1, \cdots, \mathcal{M})$. As a result, each distribution in MUCAREM is much broader than those in the conventional REM (see Fig. 1) and a much smaller number of replicas are required in MUCAREM than in REM ($\mathcal{M} = 4$ in MUCAREM versus $M = 10$ in REM).

The acceptance probabilities of replica exchange in MUCAREM1 are listed in Table IV. Relatively high probabilities of replica exchange in MUCAREM1 should be noted. In MUCAREM1, the exchange probability is given by Eqs. (14) and (15). Suppose that a pair of replicas $i$ (at temperature $T_m$) and $j$ (at temperature $T_n$) are respectively in the energy ranges between $E_L^{(m)} \leq E \leq E_H^{(m)}$ and between $E_L^{(n)} \leq E \leq E_H^{(n)}$. Then Eq. (14) together with Eqs. (3) and (4) gives

$$\Delta = \beta_m \left(E_{\text{mu}} \left(E \left(q[i] \right); T_m \right) - E_{\text{mu}} \left(E \left(q[j] \right); T_m \right)\right) - \beta_n \left(E_{\text{mu}} \left(E \left(q[j] \right); T_n \right) - E_{\text{mu}} \left(E \left(q[i] \right); T_n \right)\right)$$

$$= \ln n \left(E \left(q[j] \right)\right) - \ln n \left(E \left(q[i] \right)\right) - \ln n \left(E \left(q[j] \right)\right) + \ln n \left(E \left(q[i] \right)\right)$$

$$= 0.$$  \hspace{1cm} (17)

Thus, in this case the replica exchange is always accepted. This is the main reason for the high acceptance ratio in MUCAREM simulations.

In Fig. 4 the time series of potential energy for the first 500 ps of REM2 (a), MUCA1 (b), and MUCAREM1 (c) are plotted. Note that in MUCA1 (Fig. 4(b)) some extra MD steps are required to escape from the lowest-energy region (from about 300 ps to 450 ps) and the transition from the highest to the lowest energy occurs only once during the first 500 ps in MUCA1. This is presumably due to the nature of local updates. In REM2 and MUCAREM1, such transitions occur twice or three times. This is because global updates by the replica-exchange process make the random walk more efficient (more quantitative comparisons of REM, MUCA, and MUCAREM will be given elsewhere [27]).

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. 5. In REM2 and MUCAREM1 we used the multiple-histogram techniques [14,15] (see Eqs. (4) and (5) for REM2 and the corresponding variants for MUCAREM1), whereas the single-histogram method [3] (see Eq. (12)) was used in MUCA1. We can see a perfect coincidence of these quantities among REM2, MUCA1, and MUCAREM1 in Fig. 5.
IV. CONCLUSIONS

In this Letter we have proposed two new algorithms for configurational sampling of systems with rough energy landscape. 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), the multicanonical weight factor is determined as in REMUCA, and then a replica-exchange multicanonical production run 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 small peptide in gas phase. This is one of the smallest models of protein systems. The multicanonical weight factor was indeed obtained by a single, short replica-exchange simulation. It may occur, however, that this first step may not be as easy in more complicated systems such as a protein with explicit solvent molecules. In such a case one can still simplify the multicanonical weight factor determination by iteratively combining the present algorithms (and also the previous methods).

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TABLE I. Summary of parameters in REM, REMUCA, and MUCAREM simulations.

| Run     | No. of replicas, $M$ | Temperature, $T_m$ [K] ($m = 1, \cdots, M$) | MD steps |
|---------|---------------------|---------------------------------------------|----------|
| REM1    | 10                  | 200, 239, 286, 342, 409, 489, 585, 700, 836, 1000 | $2 \times 10^7$ |
| REM2    | 10                  | 200, 239, 286, 342, 409, 489, 585, 700, 836, 1000 | $1 \times 10^6$ |
| MUCA1   | 1                   | 1000                                        | $1 \times 10^7$ |
| MUCAREM1| 4                   | 375, 525, 725, 1000                         | $2.5 \times 10^6$ |

TABLE II. Acceptance ratios of replica exchange in REM1.

| Pair of temperatures [K] | Acceptance ratio |
|--------------------------|------------------|
| 200 ←→ 239              | 0.15             |
| 239 ←→ 286              | 0.16             |
| 286 ←→ 342              | 0.15             |
| 342 ←→ 409              | 0.14             |
| 409 ←→ 489              | 0.13             |
| 489 ←→ 585              | 0.13             |
| 585 ←→ 700              | 0.13             |
| 700 ←→ 836              | 0.14             |
| 836 ←→ 1000             | 0.15             |

TABLE III. Summary of parameters in MUCAREM1.

| $m$ | $T_{x}^{(m)}$ [K] | $T_{H}^{(m)}$ [K] | $E_{x}^{(m)}$ [kcal/mol] | $E_{H}^{(m)}$ [kcal/mol] |
|-----|------------------|------------------|--------------------------|--------------------------|
| 1   | 200              | 375              | -30                      | 20                       |
| 2   | 300              | 525              | -5                       | 65                       |
| 3   | 375              | 725              | 20                       | 120                      |
| 4   | 525              | 1000             | 65                       | 195                      |

TABLE IV. Acceptance ratios of replica exchange MUCAREM1.

| Pair of temperatures [K] | Acceptance ratio |
|--------------------------|------------------|
| 375 ←→ 525              | 0.25             |
| 525 ←→ 725              | 0.35             |
| 725 ←→ 1000             | 0.32             |
Figure Captions

- Fig. 1. Probability distribution of potential energy obtained from REM1 (see Table I for the parameters of the simulation).
- Fig. 2. Probability distribution of potential energy obtained from MUCA1 (see Table I). The dotted curves are the probability distributions of the reweighted canonical ensemble at $T = 200$ K (left) and 1000 K (right).
- Fig. 3. Probability distributions of potential energy obtained from MUCAREM1 (see Tables I and III).
- Fig. 4. Time series of potential energy for one of the replicas in (a) REM2, (b) MUCA1, and (c) MUCAREM1 (see Tables I and III for the parameters of the simulation).
- Fig. 5. The average potential energy as a function of temperature. The solid, dotted, and dashed curves are obtained from REM2, MUCA1, and MUCAREM1, respectively (see Tables I and III for the parameters of the simulations).
\[ \ln P(E) \]

E [kcal/mol]
