Replica-exchange simulated tempering method for simulations of frustrated systems

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We propose a new method for the determination of the weight factor for the simulated tempering method. In this method a short replica-exchange simulation is performed and the simulated tempering weight factor is obtained by the multiple-histogram reweighting techniques. The new algorithm is particularly useful for studying frustrated systems with rough energy landscape where the determination of the simulated tempering weight factor by the usual iterative process becomes very difficult. The effectiveness of the method is illustrated by taking an example for protein folding.

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I. INTRODUCTION

In complex systems such as spin glasses and biopolymers, it is very difficult to obtain accurate canonical distributions at low temperatures by conventional Monte Carlo (MC) and molecular dynamics (MD) simulation methods. This is because simulations at low temperatures tend to get trapped in one of huge number of local-minimum-energy states. One way to overcome this multiple-minima problem is to perform a simulation in a generalized ensemble where each state is weighted by a non-Boltzmann probability weight factor so that a random walk in potential energy space may be realized. (For a review of generalized-ensemble approach in the protein folding problem, see, e.g., Ref. [1].) The random walk allows the simulation to escape from any energy barrier and to sample much wider phase space than by conventional methods. Monitoring the energy in a single simulation run, one can obtain not only the global-minimum-energy state but also canonical ensemble averages as functions of temperature by the single-histogram and/or multiple-histogram reweighting techniques.

Two of the most well-known generalized-ensemble algorithms are perhaps multicanonical algorithm (MUCA) [3] and simulated tempering (ST) [6,7] (the latter method is also referred to as the method of expanded ensemble [6]). (For reviews, see, e.g., Refs. [8,9].) A simulation in MUCA performs a free 1D random walk in potential energy space. This method and its generalizations have already been used in many applications in protein systems (see, for instance, Refs. [10–20]). A simulation in ST performs a free 1D random walk in temperature space, which in turn induces a random walk in potential energy space and allows the simulation to escape from states of energy local minima again. ST has also been applied to protein folding problem [21–24].

The generalized-ensemble algorithms are powerful, but in the above two methods the probability weight factors are not a priori known and have to be determined by iterations of short trial simulations [5–7]. This process can be non-trivial and very tedious for complex systems with many local-minimum-energy states.

The replica-exchange method (REM) [25,26] alleviates this difficulty. (A similar method was independently developed earlier in Ref. [27]. REM is also referred to as multiple Markov chain method [28] and parallel tempering [29].) 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 MC or 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. We have developed a molecular dynamics algorithm for REM [28] (see, also, Ref. [30]). We then developed a multidimensional REM [31].

However, REM also has a computational difficulty: As the number of degrees of freedom of the system increases, the required number of replicas also increases, and so does the required computation time. This is why we want to combine the merits of MUCA and ST and those of REM so that we can determine the weight factors for MUCA and ST with ease and save the computation time greatly. We have presented such an example; we developed a new method for the determination of the multicanonical weight factor [32,33]. The method was referred to as the replica-exchange multicanonical algorithm (REMUCA). In REMUCA, a short replica-exchange simulation is performed, and the multicanonical weight factor is determined by the multiple-histogram reweighting techniques [34].

In this Letter we present another example of such a combination. In the new method, which we refer to as the replica-exchange simulated tempering (REST), a short replica-exchange simulation is performed, and the simulated tempering weight factor is determined by the multiple-histogram reweighting techniques [34]. The effectiveness of the method is tested with a penta peptide, Met-enkephalin, in gas phase.

II. METHODS

We first briefly review the original simulated tempering (ST) method [6,7]. In this method temperature itself becomes a dynamical variable, and both the configuration and the temperature are updated during the simulation with a weight:

$$W_{ST}(E; T) = e^{-\beta E + a(T)} ,$$  \hspace{1cm} (1)

where $\beta = 1/k_B T$ ($k_B$ is the Boltzmann constant), $E$ is the potential energy, and the function $a(T)$ is chosen so that the probability distribution of temperature is given by

$$P_{ST}(T) = \int dE \ n(E) \ W_{ST}(E; T) = \int dE \ n(E) \ e^{-\beta E + a(T)} = \text{const} ,$$  \hspace{1cm} (2)

where $n(E)$ is the density of states. Hence, in ST the temperature is sampled uniformly. A free random walk in temperature space is realized, which in turn induces a random walk in potential energy space and allows the simulation to escape from states of energy local minima.
In the numerical work we discretize the temperature in $M$ different values, $T_m$ ($m = 1, \cdots, M$); we can order the temperature so that $T_1 < T_2 < \cdots < T_M$. The lowest temperature $T_1$ should be sufficiently low so that the simulation can explore the global-minimum-energy region, and the highest temperature $T_M$ should be sufficiently high so that no trapping in a local-minimum-energy state occurs. The probability weight factor in Eq. (1) is then given by

$$W_{ST}(E; T_m) = e^{-\beta_m E + a_m},$$

where $a_m = a(T_m)$ ($m = 1, \cdots, M$). The parameters $a_m$ are not a priori known and have to be determined by iterations of short simulations (see, e.g., Refs. [29] for details). This process can be non-trivial and very difficult for complex systems. Note that from Eqs. (2) and (3) we have

$$e^{-a_m} \propto \int dE \, n(E) \, e^{-\beta_m E}.$$  

(4)

The parameters $a_m$ are therefore “dimensionless” Helmholtz free energy at temperature $T_m$ (i.e., the inverse temperature $\beta_m$ multiplied by the Helmholtz free energy).

Once the simulated tempering parameters $a_m$ are determined and the initial configuration and the initial temperature $T_m$ are chosen, a ST simulation is realized by alternately performing the following two steps [4,5]:

1. A canonical MC or MD simulation at the fixed temperature $T_m$ is carried out for a certain MC or MD steps.

2. The temperature $T_m$ is updated to the neighboring values $T_{m\pm 1}$ with the configuration fixed. The transition probability of this temperature-updating process is given by the Metropolis criterion (see Eq. (3)):

$$w(T_m \rightarrow T_{m\pm 1}) = \begin{cases} 1, & \text{for } \Delta \leq 0, \\ \exp(-\Delta), & \text{for } \Delta > 0, \end{cases}$$

(5)

where

$$\Delta = (\beta_{m\pm 1} - \beta_m) E - (a_{m\pm 1} - a_m).$$

(6)

In the present work, we employ Monte Carlo algorithm for Step 1. After a long ST production run, one can obtain canonical ensemble averages as functions of temperature by the multiple-histogram reweighting techniques [3,4] as described in detail below.

The replica-exchange method (REM) was developed as an extension of simulated tempering [25] (thus it is also referred to as parallel tempering [3]) (see, e.g., Ref. [29] for a detailed description of the algorithm). 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 $p[i]$) of the atoms in replica $i$ at temperature $T_m$ ($i, m = 1, \cdots, M$):

$$x_m[i] = \{q_m[i], p_m[i]\} \in \mathbb{R}^{3N}.$$  

(7)

In Monte Carlo algorithm we need to take into account only $q[i]$.

A REM simulation is then realized by alternately performing the following two steps [25-27].

1. Each replica in canonical ensemble of the fixed temperature is simulated simultaneously and independently for a certain MC or MD steps.

2. A pair of replicas, say $i$ and $j$, which are at neighboring temperatures, $T_m$ and $T_{m\pm 1}$, respectively, are exchanged: $X = \{\cdots, x_m[i], \cdots, x_m[j], \cdots\} \rightarrow X' = \{\cdots, x_{m\pm 1}[i], \cdots, x_m[j], \cdots\}$. The transition probability of this replica-exchange process is given by the Metropolis criterion:

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

(8)

where

$$\Delta = (\beta_{m\pm 1} - \beta_m) \left( E(q[i]) - E(q[j]) \right).$$

(9)

Here, $E(q[i])$ and $E(q[j])$ are the potential energy of the $i$-th replica and the $j$-th replica, respectively.
In the present work we employ Monte Carlo algorithm for Step 1. 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.

The major advantage of REM over other generalized-ensemble methods such as MUCA \(^3\) and ST \(^3\) lies in the fact that the weight factor is essentially \textit{a priori} known (which is just a product of Boltzmann factors), whereas in the latter algorithms the determination of the weight factors can be very tedious and time-consuming. However, the number of required replicas (or temperatures) for REM increases like \(\sqrt{N}\) where \(N\) is the number of degrees of freedom of the system \(^22\). We will need a huge number of replicas and a large amount of computation time to simulate a complex system such as a real protein system, while in MUCA or ST only one replica (the original system itself) is simulated. This led us to combine the merits of REM and ST (the combination of REM and MUCA was also realized \(^3\)).

We finally present the new method which we refer to as the \textit{replica-exchange simulated tempering} (REST). In this method we first perform a short REM simulation (with \(M\) replicas) to determine the simulated tempering weight factor and then perform with this weight factor a regular ST simulation with high statistics. The first step is accomplished by the multiple-histogram reweighting techniques \(^3\) as follows. 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 \(^3\)

\[
 n(E) = \frac{\sum_{m=1}^{M} g_m^{-1} N_m(E)}{\sum_{m=1}^{M} n_m g_m^{-1} e^{f_m - \beta_m E}}, \tag{10}
\]

where

\[
e^{-f_m} = \sum_E n(E)e^{-\beta_m E}. \tag{11}
\]

Here, \(g_m = 1 + 2\tau_m\), and \(\tau_m\) is the integrated autocorrelation time at temperature \(T_m\). Note that Eqs. \((10)\) and \((11)\) are solved self-consistently by iteration to obtain the density of states \(n(E)\) and the dimensionless Helmholtz free energy \(f_m\).

Once the estimate of the dimensionless Helmholtz free energy \(f_m\) are obtained, the simulated tempering weight factor can be directly determined by using Eq. \((3)\) where we set \(a_m = f_m\) (compare Eqs. \((1)\) and \((3)\)). A long ST run is then performed with this weight factor. Let \(N_m(E)\) and \(n_m\) be respectively the potential-energy histogram and the total number of samples obtained at temperature \(T_m = 1/k_B\beta_m\) from this ST run. The multiple-histogram reweighting techniques of Eqs. \((10)\) and \((11)\) can be used again to obtain the best estimate of the density of states \(n(E)\). The expectation value of a physical quantity \(A\) at any temperature \(T \ (= 1/k_B\beta)\) is then calculated from

\[
 <A>_T = \frac{\sum_E A(E) n(E) e^{-\beta E}}{\sum_E n(E) e^{-\beta E}}. \tag{12}
\]

\[4\]
The remaining dihedral angles constitute the variables to be updated in the MC simulations: $\phi_k$ and $\psi_k$ in the main chain ($k = 1, \ldots, 5$) and $\chi^\alpha_k$ in the side chains (there are 3 $\chi$'s for Tyr, 2 $\chi$'s for Phe, and 4 $\chi$'s for Met). For Met-enkephalin the number of degrees of freedom is thus 19. One MC sweep consists of updating all these 19 angles once with Metropolis evaluation for each update. The simulations (of all replicas) were started from randomly generated conformations.

In Table I we summarize the parameters of the simulations that were performed in the present work. As described in the previous section, REST consists of two simulations: a short REM simulation (from which the dimensionless Helmholtz free energy, or the simulated tempering weight factor, is determined) and a subsequent ST production run. The former simulation is referred to as REM1 and the latter as ST1 in Table I. In REM1 there exist 8 replicas with 8 different temperatures ($M = 8$), ranging from 50 K to 1000 K as listed in Table I (i.e., $T_1 = 50$ K and $T_M = T_8 = 1000$ K). The same set of temperatures were also used in ST1. The temperatures were distributed exponentially between $T_1$ and $T_M$, following the optimal distribution found in the previous simulated annealing schedule [35], simulated tempering run [23], and replica-exchange simulation [29]. Before taking the data in REM1, we made a REM simulation of 10,000 MC sweeps for thermalization. We then performed a REM simulation of $5 \times 10^4$ MC sweeps to obtain the weight factor for simulated tempering. After estimating the weight factor, we made a ST production run of $10^6$ MC sweeps (ST1), which followed additional 1,000 MC sweeps for equilibration. In REM1 and ST1, a replica exchange and a temperature update, respectively, were tried every 10 MC sweeps. Data were collected at each MC sweep in both REM1 and ST1.

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 %). Moreover, in Fig. 1 the canonical probability distributions obtained at the chosen 8 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 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 dimensionless Helmholtz free energy at the eight temperatures, $f_m (m = 1, \ldots, 8)$, by the multiple-histogram reweighting techniques [4] (namely, by solving Eqs. (10) and (11) self-consistently). This gives the simulated tempering weight factor of Eq. (3) with $a_m = f_m$. We remark that for biomolecular systems the integrated autocorrelation times, $\tau_m$, in the reweighting formulae can safely be set to be a constant [4], and we do so throughout the analyses in this section.

After determining the simulated tempering weight factor, we carried out a long ST simulation for data collection (ST1 in Table I). In Fig. 2 the time series of temperature and potential energy from ST1 are plotted. In Fig. 2(a) we observe a random walk in the temperature space between the lowest and highest temperatures. In Fig. 2(b) the corresponding random walk of the total potential energy between low and high energies is observed. Note that there is a strong correlation between the behaviors in Figs. 2(a) and 2(b), as there should. It is known from our previous works that the global-minimum-energy conformation for Met-enkephalin has the potential energy value of $-12.2 \text{ kcal/mol}$ [4]. Hence, the random walk in Fig. 2(b) indeed visited the global-minimum region many times. It also visited high energy regions, judging from the fact that the average potential energy is around $15 \text{ kcal/mol}$ at $T = 1000 \text{ K}$ [4] (see Fig. 4 below).

For an optimal performance of ST, the acceptance ratios of temperature update should be sufficiently uniform and large. In Table III we list these quantities. It is clear that both points are met (the values vary between 26 % and 57 %); we find that the present ST run (ST1) indeed performed properly. We remark that the acceptance ratios in Table III are significantly larger and more uniform than those in Table II, suggesting that ST runs can sample the configurational space more effectively than REM runs, provided the optimal weight factor is obtained.

In the previous works of ST simulations of Met-enkephalin in gas phase [24], at least several iterations of trial simulations were required for the simulated tempering weight determination. We emphasize that in the present case of REST (REM1), only one simulation was necessary to determine the optimal simulated tempering weight factor that can cover the energy region corresponding to temperatures between 50 K and 1000 K.

In Fig. 3 we plot the simulated tempering parameters $f_m (m = 1, \ldots, 8)$ and the dimensionless Helmholtz free energy (inverse temperature multiplied by Helmholtz free energy) $f(T)$ as a function of temperature $T$. The former quantities, $f_m$, were estimated by the multiple-histogram reweighting techniques, using the results of the first REM run (REM1). The latter quantity, $f(T)$, was calculated by the multiple-histogram reweighting techniques, using the results of the final ST production run (ST1). Namely, the density of states, $n(E)$, was obtained by solving Eqs. (10) and (11) by iteration. The function $f(T)$ was then calculated by taking a summation of $n(E) \exp(-\beta E)$ over $E$ for each value of $T$ (i.e., replace $f_m$ and $\beta_m$ in Eq. (11) by $f(T)$ and $\beta$, respectively). The results agree very well with each other, implying that the simulated tempering parameters, $f_m$, that were obtained from a short REM run are already quite accurate.

To check the validity of the canonical-ensemble expectation values calculated by the new method, in Fig. 4 we
compare the average potential energy as a function of temperature obtained from ST1 with that obtained from the previous MUCA simulation [17]. The results for ST1 were obtained by the multiple-histogram method [3,4] (see Eqs. (10), (11), and (12)), whereas the single-histogram method [2] was used for the results of the MUCA simulation. We can see a perfect coincidence of the average values in Fig. 4.

IV. CONCLUSIONS

In this Letter we have proposed a new algorithm for configurational sampling of frustrated systems with rough energy landscape. In this method, which we refer to as replica-exchange simulated tempering (REST), the simulated tempering weight factor is determined from the results of a short replica-exchange simulation, and then a regular simulated tempering production run is made with this weight. The formulation of the method is simple and straightforward, but the numerical improvement is great, because the weight factor determination for simulated tempering becomes very difficult by the usual iterative process for complex systems. The new method was tested with the system of a small peptide in gas phase. The simulated tempering weight factor was indeed obtained by a single, short replica-exchange simulation.

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**TABLE I. Summary of parameters in REST simulations.**

| Run  | No. of replicas | Temperature, \(T_m\) (K)                  | MC sweeps   |
|------|-----------------|----------------------------------------|-------------|
| REM1 | 8               | 50, 77, 118, 181, 277, 425, 652, 1000   | \(5 \times 10^4\) |
| ST1  | 1               | 50, 77, 118, 181, 277, 425, 652, 1000   | \(1 \times 10^6\) |

**TABLE II. Acceptance ratios of replica exchange in REM1.**

| Pair of temperatures (K) | Acceptance ratio |
|--------------------------|------------------|
| 50 \(\leftrightarrow\) 77 | 0.30             |
| 77 \(\leftrightarrow\) 118 | 0.27             |
| 118 \(\leftrightarrow\) 181 | 0.22             |
| 181 \(\leftrightarrow\) 277 | 0.17             |
| 277 \(\leftrightarrow\) 425 | 0.10             |
| 425 \(\leftrightarrow\) 652 | 0.27             |
| 652 \(\leftrightarrow\) 1000 | 0.40             |

**TABLE III. Acceptance ratios of temperature update in ST1.**

| Pair of temperatures (K) | Acceptance ratio |
|--------------------------|------------------|
| 50 \(\rightarrow\) 77    | 0.47             |
| 77 \(\rightarrow\) 50    | 0.47             |
| 77 \(\rightarrow\) 118   | 0.43             |
| 118 \(\rightarrow\) 77   | 0.43             |
| 118 \(\rightarrow\) 181  | 0.37             |
| 181 \(\rightarrow\) 118  | 0.42             |
| 181 \(\rightarrow\) 277  | 0.29             |
| 277 \(\rightarrow\) 181  | 0.29             |
| 277 \(\rightarrow\) 425  | 0.30             |
| 425 \(\rightarrow\) 277  | 0.26             |
| 425 \(\rightarrow\) 652  | 0.43             |
| 652 \(\rightarrow\) 425  | 0.42             |
| 652 \(\rightarrow\) 1000 | 0.57             |
| 1000 \(\rightarrow\) 652 | 0.56             |
Figure Captions

• Fig. 1. Probability distribution of potential energy obtained at the eight temperatures from REM1 (see Table I for the parameters of the simulation). The left-most distribution corresponds to the lowest temperature ($T_1 = 50$ K), and the right-most to the highest one ($T_8 = 1000$ K).

• Fig. 2. Time series of temperature (a) and potential energy (b) in ST1 (see Table I for the parameters of the simulation).

• Fig. 3. Dimensionless Helmholtz free energy as a function of temperature $T$ (K). The dotted curve is the result from the simulated tempering production run (ST1). The crosses are the $f_m$ ($m = 1, \cdots, 8$) that were determined from the short preliminary replica-exchange run (REM1). Both results were normalized so that the values at $T = 50$ K agree with each other.

• Fig. 4. The average potential energy as a function of temperature. The solid curve was obtained by the multiple-histogram reweighting techniques from the results of ST1. The crosses were obtained by the single-histogram reweighting techniques from the results of the previous multicanonical MC simulation [17].
