Abstract
In complex systems with many degrees of freedom such as spin glass and biomolecular systems, conventional simulations in canonical ensemble suffer from the quasi-ergodicity problem. A simulation in generalized ensemble performs a random walk in potential energy space and overcomes this difficulty. From only one simulation run, one can obtain canonical ensemble averages of physical quantities as functions of temperature by the single-histogram and/or multiple-histogram reweighting techniques. In this article we review the generalized ensemble algorithms. Three well-known methods, namely, multicanonical algorithm (MUCA), simulated tempering (ST), and replica-exchange method (REM), are described first. Both Monte Carlo (MC) and molecular dynamics (MD) versions of the algorithms are given. We then present five new generalized-ensemble algorithms which are extensions of the above methods.

1. Introduction
Since the pioneering work of Metropolis et al. [1] half a century ago, computer simulations have been indispensable means of research in many fields of physical science. In the field of molecular science, for instance, a number of powerful simulation algorithms have been developed (for reviews see, e.g., Refs. [2–4]).Canonical fixed temperature simulations of complex systems such as spin glasses and biopolymers are greatly hampered by the multiple-minima problem, or the quasi-ergodicity problem. Because simulations at low temperatures tend to get trapped in one of huge number of local-minimum-energy states, it is very difficult to obtain accurate canonical distributions at low temperatures by conventional Monte Carlo (MC) and molecular dynamics (MD) methods. One way to overcome this multiple-minima problem is to perform a simulation in a generalized ensemble where each state is weighted by an artificial, non-Boltzmann probability weight factor so that a random walk in potential energy space may be realized (for reviews see, e.g., Refs. [5–8]). The random walk allows the simulation to escape from any energy barrier and to sample much wider configurational 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 [9] and/or multiple-histogram [10,11] reweighting techniques (an extension of the multiple-histogram method is also referred to as weighted histogram analysis method (WHAM) [11]). Besides generalized-ensemble algorithms, which are usually based on local updates, methods based on non-local updates such as cluster algorithms and their generalizations have also been widely used [12–14]. In this article, we focus our discussion on generalized-ensemble algorithms.

One of the most well-known generalized-ensemble methods is perhaps multicanonical algorithm (MUCA) [15,16] (for a review see, e.g., Ref. [17]). (The method is also referred to as entropic sampling [18], adaptive umbrella sampling [19] of the potential energy [20], random walk algorithm [21,22], and density of states Monte Carlo [23]. MUCA can also be considered as a sophisticated, ideal realization of a class of algorithms called umbrella sampling [24]. Also closely related methods are transition matrix methods reviewed in Refs. [8,25].) MUCA and its generalizations have been applied to spin systems (see, e.g., Refs. [26–30]). MUCA was also introduced to the molecular simulation field [31]. Since then MUCA and its generalizations have been extensively used in many applications in protein and related systems [32–60]. Molecular dynamics version of
MUCA has also been developed [38,41,20] (see also Refs. [38,61] for Langevin dynamics version). MUCA has been extended so that flat distributions in other parameters instead of potential energy may be obtained [27,28,37,44,45,59]. Moreover, multidimensional (or multicomponent) extensions of MUCA can be found in Refs. [37,42,43,60].

While a simulation in multicanonical ensemble performs a free 1D random walk in potential energy space, that in simulated tempering (ST) [62,63] (the method is also referred to as the method of expanded ensemble [62]) performs a free random walk in temperature space (for a review, see, e.g., Ref. [64]). This random walk, in turn, induces a random walk in potential energy space and allows the simulation to escape from states of energy local minima. ST has also been applied to protein folding problem [65,39,40,66].

The generalized-ensemble algorithm is 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. This process can be non-trivial and very tedious for complex systems with many degrees of freedom. Therefore, there have been attempts to accelerate the convergence of the iterative process for MUCA weight factor determination [20,26,37,44,59] (see also Refs. [17,70]).

The weight factor is just the product of Boltzmann factors, and so it is essentially known. REM has already been used in many applications in protein systems [79,80,66,81–91]. Other molecular simulation fields have also been studied by this method in various ensembles [92–97]. Moreover, REM was applied to cluster studies in quantum chemistry field [98]. The details of molecular dynamics algorithm have been worked out in REM in Ref. [80] (see also Refs. [79,95]). This led to a wide application of replica-exchange molecular dynamics method. 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.

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In the replica-exchange method (REM) [71–73], the difficulty of weight factor determination is greatly alleviated. (A closely related method was independently developed in Ref. [74].) Similar methods in which the same equations are used are the multicanonical-ensemble method of expanded ensemble (MUCAREM) [83,88] (see also Refs. [107,108]) and simulated tempering replica-exchange method (STREM) [109]. In MUCAREM, a replica-exchange simulation is performed with a small number of replicas each in multicanonical ensemble of different energy ranges. In STREM, on the other hand, a replica-exchange simulation is performed with a small number of replicas in “simulated tempering” ensemble of different temperature ranges.

Finally, one is naturally led to a multidimensional (or, multivariable) extension of REM, which we refer to as multicanonical replica-exchange method (MREM) [82] (see also Refs. [93,106,110,111]). Special realizations of MREM are replica-exchange free energy perturbation (REEFEP) [82] and replica-exchange umbrella sampling (REUUS) [82] and they are particularly useful in free energy calculations.

In this article, we describe the eight generalized-ensemble algorithms mentioned above. Namely, we first review three familiar methods: MUCA, ST, and REM. We then present the five new algorithms: REMUCA, REST, MUCAREM, STREM, and MREM (and REEFEP and REUUS).

2. Generalized-ensemble algorithms

2.1. Multicanonical algorithm and simulated tempering

Let us consider a system of $N$ atoms of mass $m_k$ ($k = 1, \ldots, N$) with their coordinate vectors and momentum vectors denoted by $q \equiv \{q_1, \ldots, q_N\}$ and $p \equiv \{p_1, \ldots, p_N\}$, respectively. The Hamiltonian $H(q, p)$ of the system is the sum of the kinetic energy $K(p)$ and the potential energy $E(q)$:

$$H(q, p) = K(p) + E(q),$$

where

$$K(p) = \sum_{k=1}^{N} \frac{p_k^2}{2m_k}. \quad (2)$$

In the canonical ensemble at temperature $T$ each state $s \equiv (q, p)$ with the Hamiltonian $H(q, p)$ is weighted by the Boltzmann factor:

$$\mathcal{W}_s(x; T) = \exp(-\beta H(q, p),$$

where the inverse temperature $\beta$ is defined by $\beta = 1/k_BT$ ($k_B$ is the Boltzmann constant). The average kinetic energy
at temperature $T$ is then given by

$$\langle K(p) \rangle_{T} = \sum_{i=1}^{N} \frac{p_{i}^{2}}{2m_{i}} T = \frac{3}{2} W_{0} T .$$  

(4)

Because the coordinates $q$ and momenta $p$ are decoupled in Eq. (1), we can suppress the kinetic energy part and can write the Boltzmann factor as

$$W_{0}(x; T) = W_{0}(E; T) = \exp(-\beta E) .$$

(5)

The canonical probability distribution of potential energy $P_{k}(E; T)$ is then given by the product of the density of states $n(E)$ and the Boltzmann weight factor $W_{0}(E; T)$:

$$P_{k}(E; T) \propto n(E) W_{0}(E; T) .$$

(6)

Since $n(E)$ is a rapidly increasing function and the Boltzmann factor decreases exponentially, the canonical ensemble yields a bell-shaped distribution which has a maximum around the average energy at temperature $T$. The conventional MC or MD simulations at constant temperature are expected to yield $P_{k}(E; T)$. A MC simulation based on the Metropolis algorithm [1] is performed with the following transition probability from a state $x$ of potential energy $E$ to a state $x'$ of potential energy $E'$:

$$w(x \rightarrow x') = \min \left(1, \frac{W_{0}(E'; T)}{W_{0}(E; T)} \right) = \min \left(1, \exp(-\beta (E' - E)) \right) .$$

(7)

A MD simulation, on the other hand, is based on the following Newton equation:

$$p_{k} = -\frac{\partial E_{k}}{\partial q_{k}} = f_{k} ,$$

(8)

where $f_{k}$ is the force acting on the k-th atom ($k = 1, \ldots, N$). This equation actually yields the microcanonical ensemble, and we have to add a thermostat such as Nosé–Hoover algorithm [112,113] and the constraint method [114,115] in order to obtain the canonical ensemble. However, in practice, it is very difficult to obtain accurate canonical distributions of complex systems at low temperatures by conventional MC or MD simulation methods. This is because simulations at low temperatures tend to get trapped in one or a few of local-minimum-energy states.

In the multicanonical ensemble [15,16], on the other hand, each state is weighted by a Boltzmann weight factor $W_{0}(E)$ (which we refer to as the multicanonical weight factor) so that a uniform potential energy distribution $P_{\text{mult}}(E)$ is obtained:

$$P_{\text{mult}}(E) \propto n(E) W_{0}(E) \equiv \text{constant}. $$

(9)

The flat distribution implies that a free random walk in the potential energy space is realized in this ensemble. This allows the simulation to escape from any local minimum-energy states and to sample the configurational space much more widely than the conventional canonical MC or MD methods.

The definition in Eq. (9) implies that the multicanonical weight factor is inversely proportional to the density of states, and we can write it as follows:

$$W_{\text{mult}}(E) = \exp[-\beta_{0} E_{\text{mult}}(E; T_{0})] = \frac{1}{n(E)} .$$

(10)

where we have chosen an arbitrary reference temperature, $T_{0} = 1/k_{B} \beta_{0}$, and the "multicanonical potential energy" is defined by

$$E_{\text{mult}}(E; T_{0}) = k_{B} T_{0} \ln n(E) = T_{0} S(E) .$$

(11)

Here, $S(E)$ is the entropy in the microcanonical ensemble. Since the density of states of the system is usually unknown, the multicanonical weight factor has to be determined numerically by iterations of short preliminary runs [15,16].

A multicanonical Monte Carlo simulation is performed, for instance, with the usual Metropolis criterion [1]. The transition probability of state $x$ with potential energy $E$ to state $x'$ with potential energy $E'$ is given by

$$w(x \rightarrow x') = \min \left(1, \frac{W_{\text{mult}}(E')}{{W_{\text{mult}}(E)}} \right) = \min \left(1, \exp(-\beta_{0} \Delta E_{\text{mult}}) \right) .$$

(12)

where

$$\Delta E_{\text{mult}} = E_{\text{mult}}(E'; T_{0}) - E_{\text{mult}}(E; T_{0}) .$$

(13)

The molecular dynamics algorithm in multicanonical ensemble also naturally follows from Eq. (10), in which the regular constant temperature molecular dynamics simulation (with $T = T_{0}$) is performed by solving the following modified Newton equation instead of Eq. (8): [38,41]

$$p_{k} = -\frac{\partial E_{\text{mult}}(E; T_{0})}{\partial q_{k}} + \frac{\partial E_{\text{mult}}(E; T_{0})}{\partial E} f_{k} .$$

(14)

From Eq. (11) this equation can be rewritten as

$$p_{k} = \frac{T_{0}}{T(E)} f_{k} ,$$

(15)

where the following thermodynamic relation gives the definition of the “effective temperature” $T(E)$:

$$\frac{\partial S(E)}{\partial E} \bigg|_{E=E_{k}} = \frac{1}{T(E)} .$$

(16)

with $E_{k} = \langle E \rangle_{N=1}$.

(17)

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

$$\langle A \rangle_{T} = \frac{\sum_{E} A(E) P_{k}(E; T)}{\sum_{E} P_{k}(E; T)} = \frac{\sum_{E} A(E) n(E) \exp(-\beta E)}{\sum_{E} n(E) \exp(-\beta E)} ,$$

(18)
where the density of states is given by (see Eq. (10))

\[ n(E) = \frac{1}{\mathcal{W}_{\text{base}}(E)}. \]  

(19)

The summation instead of integration is used in Eq. (18), because we often discretize the potential energy \( E \) with step size \( E_i \) \( (E_i = E; \ i = 1, 2, \ldots) \). 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 \( \langle E \rangle \) as a function of temperature, and \( A(E) = \beta^2(E - \langle E \rangle)^2 \) gives specific heat.

In general, the multicanonical weight factor \( \mathcal{W}_{\text{base}}(E) \), or the density of states \( n(E) \), is not a priori known, and one needs its estimator for a numerical simulation. This estimator is usually obtained from iterations of short trial multicanonical simulations. The details of this process are described, for instance, in Refs. [26,34]. However, the iterative process can be non-trivial and very tedious for complex systems.

In practice, it is impossible to obtain the ideal multicanonical weight factor with 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 \( P \) for uniform potential energy distribution can be non-trivial and very tedious for complex systems.

Eqs. (18) and (21) or any other equations which involve summations of exponential functions often encounter with numerical difficulties such as overflows. These can be overcome by using, for instance, the following equation [116,117]. For \( C = A + B \) (with \( A > 0 \) and \( B > 0 \) we have

\[ \ln C = \ln \max(A, B) + \ln(1 + \exp[\ln(\min(A, B) + \max(A, B))]). \]  

(22)

We now briefly review the original simulated tempering (ST) method [62,63]. In this method temperature itself becomes a dynamical variable, and both the configuration and the temperature are updated during the simulation with a weight:

\[ W_{\text{ST}}(E; T) = \exp(-\beta E + a(T)), \]  

(23)

where the function \( a(T) \) is chosen so that the probability distribution of temperature is flat:

\[ P_{\text{ST}}(T) = \int dE n(E)W_{\text{ST}}(E; T) = \text{constant}. \]  

(24)

Hence, in simulated tempering 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, \( T_m (m = 1, \ldots, M) \). Without loss of generality we can order the temperature so that \( T_1 < T_2 < \ldots < T_M \). 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 an energy-local-minimum state occurs. The probability weight factor in Eq. (23) is now written as

\[ W_{\text{ST}}(E; T_m) = \exp(-\beta a_{T_m} E + a_{T_m}), \]  

(25)

where \( a_{T_m} = a(T_m) \) \( (m = 1, \ldots, M) \). Note that from Eqs. (24) and (25) we have

\[ \exp(-a_{T_m}) \propto \int dE n(E) \exp(-\beta a_{T_m} E). \]  

(26)

The parameters \( a_{T_m} \) are therefore “dimensionless” Helmholtz free energy at temperature \( T_m \) (i.e., the inverse temperature \( \beta_{T_m} \) multiplied by the Helmholtz free energy). We remark that the density of states \( n(E) \) (and hence, the multicanonical weight factor) and the simulated tempering weight parameters \( a_{T_m} \) are related by a Laplace transform [39]. The knowledge of one implies that of the other, although in numerical work the inverse Laplace transform of Eq. (26) is nontrivial.
Once the parameters \(a_m\) are determined and the initial configuration and the initial temperature \(T_m\) are chosen, a simulated tempering simulation is then realized by alternately performing the following two steps [62,63]:

1. A canonical MC or MD simulation at the fixed temperature \(T_m\) (based on Eqs. (7) or (8)) is carried out for a certain steps.
2. The temperature \(T_m\) is updated to the neighboring values \(T_{m+1}\), with the configuration fixed. The transition probability of this temperature-updating process is given by the Metropolis criterion (see Eq. (25)):

\[
\text{w}(T_m \to T_{m+1}) = \min\{1, \exp(-\Delta)\},
\]

where

\[
\Delta = (T_{m+1} - T_m)E - (a_{m+1} - a_m).
\]

Note that in Step 2 we exchange only pairs of neighboring temperatures in order to secure sufficiently large acceptance ratio of temperature updates.

As in multicanonical algorithm, the simulated tempering parameters \(a_m = a(T_m)\) \((m = 1, \ldots, M)\) are also determined by iterations of short trial simulations (see, e.g., Refs. [40,64,65] for details). This process can be non-trivial and very tedious for complex systems.

\[
\langle A \rangle_T = \frac{1}{\tau_m \rho_m} \sum_{n=1}^{N_m} A(x_n(k)) \left( \sum_{m=1}^{M} \rho_m^{-1} \exp(\frac{E(x_n(k)) - E(x_m(k))}{\beta_m}) \right) \left( \sum_{m=1}^{M} \rho_m^{-1} \exp(-\beta_m E(x_n(k))) \right) \left( \sum_{m=1}^{M} \rho_m^{-1} \exp(-\beta_m E(x_m(k))) \right)
\]

where the density of states is given by the multiple-histogram reweighting techniques [10,11] as follows. Let \(N_m(E)\) and \(n_m\) be respectively the potential-energy histogram and the total number of samples obtained at temperature \(T_m = 1/k_B T_m\) \((m = 1, \ldots, M)\). The best estimate of the density of states is then given by [10,11]:
where \( f(m) \) is a permutation function of \( m \) and \( f^{-1}(i) \) is its inverse.

Let \( X = \{ x_1^{(i)}, \ldots, x_{N}^{(i)} \} = \{ x_1^{(j)}, \ldots, x_{N}^{(j)} \} \) stand for a “state” in this generalized ensemble. Each “substate” \( x_i^{(m)} \) is specified by the coordinates \( q^{(i)} \) and momenta \( p^{(i)} \) of \( N \) atoms in replica \( i \) at temperature \( T_m \):

\[
x_i^{(m)} = (q^{(i)}, p^{(i)}),
\]

(34)

Because the replicas are non-interacting, the weight factor for the state \( X \) in this generalized ensemble is given by the product of Boltzmann factors for each replica (or at each temperature):

\[
W_{\text{REM}}(X) = \prod_{i=1}^{M} \exp\{-\beta_{m(i)}[H(q^{(i)}, p^{(i)})]\}
\]

\[
= \prod_{i=1}^{M} \exp\{-\beta_{m(i)}[H(q^{(i)}, p^{(i)})]\}
= \exp\left\{-\sum_{i=1}^{M} \beta_{m(i)}[H(q^{(i)}, p^{(i)})]\right\}
= \exp\left\{-\sum_{i=1}^{M} \beta_{m(i)}[H(q^{(i)}, p^{(i)})]\right\},
\]

(35)

where \( \beta(m) \) and \( m(i) \) are the permutation functions in Eq. (33).

We now consider exchanging a pair of replicas in the generalized ensemble. Suppose we exchange replicas \( i \) and \( j \) which are at temperatures \( T_i \) and \( T_j \) respectively:

\[
X = \{ x_1^{(i)}, \ldots, x_{N}^{(i)}, \ldots \} \to
X' = \{ x_1^{(j)}, \ldots, x_{N}^{(j)}, \ldots \}.
\]

(36)

Here, \( i, j, m \), and \( n \) are related by the permutation functions in Eq. (33), and the exchange of replicas introduces a new permutation function \( f' \):

\[
\begin{align*}
  i &= f(m) \\
  j &= f(n)
\end{align*}
\]

(37)

The exchange of replicas can be written in more detail as

\[
\begin{align*}
  x_i^{(m)} &= (q^{(i)}, p^{(i)})_m \\
  x_j^{(n)} &= (q^{(j)}, p^{(j)})_n
\end{align*}
\]

\[
\begin{align*}
  x_i^{(f(m))} &= (q^{(i)}, p^{(i)})_{f(m)} \\
  x_j^{(f(n))} &= (q^{(j)}, p^{(j)})_{f(n)}
\end{align*}
\]

(38)

where the definitions for \( q^{(i)} \) and \( p^{(i)} \) will be given below. We remark that this process is equivalent to exchanging a pair of temperatures \( T_i \) and \( T_j \) for the corresponding replicas \( i \) and \( j \) as follows:

\[
\begin{align*}
  x_i^{(m)} &= (q^{(i)}, p^{(i)})_m \\
  x_j^{(n)} &= (q^{(j)}, p^{(j)})_n
\end{align*}
\]

\[
\begin{align*}
  x_i^{(f(m))} &= (q^{(i)}, p^{(i)})_{f(m)} \\
  x_j^{(f(n))} &= (q^{(j)}, p^{(j)})_{f(n)}
\end{align*}
\]

(39)

In the original implementation of the replica-exchange method [71–73], Monte Carlo algorithm was used, and only the coordinates \( q \) (and the potential energy function \( E(q) \)) had to be taken into account. In molecular dynamics algo-

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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 at neighboring temperatures, say \( x_i^0 \) and \( x_{i+1}^0 \), are exchanged with the probability \( w(x_i^0|x_{i+1}^0) \) in Eq. (46).

Note that in Step 2 we exchange only pairs of replicas corresponding to neighboring temperatures, because the acceptance ratio of the exchange process decreases exponentially with the difference of the two \( \beta \)'s (see Eqs. (44) and (46)).

Note also that whenever a replica exchange is accepted in Step 2, the permutation functions in Eq. (33) are updated.

The REM simulation is particularly suitable for parallel computers. Because one can minimize the amount of information exchanged among nodes, it is best to assign each replica to each node (exchanging pairs of temperature values among nodes is much faster than exchanging coordinates and momenta). This means that we keep track of the permutation exchanged among nodes, it is best to assign each computer. Because one can minimize the amount of information exchanged among nodes, it is best to assign each replica to each node (exchanging pairs of temperature values among nodes is much faster than exchanging coordinates and momenta).

The major advantage of REM over other generalized-ensemble methods such as multicanonical algorithm [15,16] and simulated tempering [62,63] lies in the fact that the weight factor is a priori known (see Eq. (35)), while in the latter algorithms the determination of the weight factors can be very tedious and time-consuming. A random walk in "temperature space" is realized for each replica, which in turn alleviates the problem of getting trapped in states of energy local minima. In REM, however, the number of required replicas increases as the system size \( N \) increases (according to \( \sqrt{N} \)) [71]. This demands a lot of computer power for complex systems.

2.3. Replica-exchange multicanonical algorithm and replica-exchange simulated tempering

The replica-exchange multicanonical algorithm (RE-MUCA) [83,88] overcomes both the difficulties of MUCA (the multicanonical weight factor determination is non-trivial) and REM (a lot of replicas, or computation time, is required). In 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 [10,11]. Let \( N_0(E) \) and \( n_0 \) be respectively the potential-energy histogram and the total number of samples obtained at temperature \( T_0 = 1/\beta_0 \) of the REM run. The density of states \( n(E) \) is then given by solving Eqs. (30) and (31) self-consistently by iteration.

The results are analyzed by the single-histogram reweighting techniques as described in Eq. (20) (and Eq. (18)).
The Newton equation in Eq. (14) is then written as (see Eqs. (15)–(17)):

\[
p_k = \begin{cases} 
  \frac{T_0}{T(E)} f_k, & \text{for } E < E_1, \\
  \frac{T_0}{T(E)} f_1, & \text{for } E_1 \leq E \leq E_M, \\
  \frac{T_0}{T_0} f_1, & \text{for } E > E_M.
\end{cases}
\]

Because only the product of inverse temperature \(\beta\) and potential energy \(E\) enters in the Boltzmann factor (see Eq. (5)), a rescaling of the potential energy (or force) by a constant, say \(\alpha\), can be considered as the rescaling of the temperature by \(1/\alpha\) [38,95]. Hence, our choice of \(T_m(E)\) in Eq. (49) results in a canonical simulation at \(T = T_1\) for \(E < E_1\), a multicanonical simulation for \(E_1 \leq E \leq E_M\), and a canonical simulation at \(T = T_M\) for \(E > E_M\). 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.

For Monte Carlo method, the above statement follows directly from the following equation. Namely, our choice of the multicanonical potential energy in Eq. (49) gives (by substituting Eq. (50) into Eq. (10))

\[
W_{ac}(E) = \exp[-\beta f_{ac}(E)]
\]

\[
= \begin{cases} 
  \exp(-\beta E + \text{constant}), & \text{for } E < E_1, \\
  \frac{1}{n(E)}, & \text{for } E_1 \leq E \leq E_M, \\
  \exp(-\beta E + \text{constant}), & \text{for } E > E_M.
\end{cases}
\]

We now present another effective method of the multicanonical weight factor determination [7], which is closely related to REMUCA. We first perform a short REM simulation as in REMUCA and calculate \(\langle E \rangle_T\) as a function of \(T\) by the multiple-histogram reweighting techniques (see Eqs. (30) and (31)). Let us recall the Newton equation of Eq. (15) and the thermodynamic relation of Eqs. (16) and (17). The effective temperature \(T(E)\), or the derivative \((\partial E_{\text{can}}(E); T_0)/\partial E\), can be numerically obtained as the inverse function of Eq. (17), where the average \(\langle E \rangle_{T(E)}\) has been obtained from the results of the REM simulation by the multiple-histogram reweighting techniques. Given its derivative, the multicanonical potential energy can then be obtained by numerical integration (see Eqs. (11) and (16)) [7]:

\[
E_{\text{can}}(E); T_0 = T_0 \int_{E_1}^{E} \frac{\delta S(E)}{\delta E} dE = T_0 \int_{E_1}^{E} \frac{dE}{T(E)}
\]

We remark that the same equation was used to obtain the multicanonical weight factor in Ref. [68], where \(\langle E \rangle_T\) was estimated by simulated annealing instead of REM. Essentially the same formulation was also recently used in Ref. [58] to obtain the multicanonical potential energy, where \(\langle E \rangle_T\) was calculated by conventional canonical simulations.

We finally present the new method which we refer to as the multi-REM method [84]. In this method, just as in REMUCA, 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 [10,11], which give the dimensionless Helmholtz free energy \(f_0\) (see Eqs. (30) and (31)).

Once the estimate of the dimensionless Helmholtz free energy \(f_0\) are obtained, the simulated tempering weight factor can be directly determined by using Eq. (25) where we set \(\alpha_0 = f_0\) (compare Eq. (26) with Eq. (31)). A long simulated tempering run is then performed with this weight factor. Let \(N_{\mu}(E)\) and \(n_{\mu}\) be respectively the potential-energy histogram and the total number of samples obtained at temperature \(T_0(= 1/k_B T_0)\) from this simulated tempering run. The multiple-histogram reweighting techniques of Eqs. (30) and (31) 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 Eq. (18).

The formulations of REMUCA and REST are simple and straightforward, but the numerical improvement is great, because the weight factor determination for MUCA and ST becomes very difficult by the usual iterative processes for complex systems.

2.4. Multicanonical replica-exchange method and simulated tempering replica-exchange method

In the previous subsection we presented REMUCA, which uses a short REM run for the determination of the multicanonical weight factor. Here, we present two modifications of REM and refer to the new methods as multicanonical replica-exchange method (MUCAREM) [83,88] and simulated tempering replica-exchange method (STREM) [109].

In MUCAREM the production run is a REM simulation with a few replicas not in the canonical ensemble but in the multicanonical ensemble, i.e., different replicas perform MUCA simulations with different energy ranges. Likewise in STREM the production run is a REM simulation with a few replicas that performs REM simulations with different temperature ranges. While MUCA and ST 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.

We first describe MUCAREM. Let \(M\) be the number of replicas. Here, each replica is in one-to-one correspondence not with temperature but with multicanonical weight factors of different energy range. Note that because multicanonical simulations cover much wider energy ranges than regular canonical simulations, the number of required replicas for the production run of MUCAREM is much less than that for the regular REM (\(M \ll M\)).
Given by (see Eq. (35))

$$W_{\text{MUCAREM}}(X) = \prod_{i=1}^{n} W_{\text{mic}}^{(m(i))}(E_{\text{mic}}^{(m(i))})$$

$$= \prod_{i=1}^{n} W_{\text{mic}}^{(m(i))}(E_{\text{mic}}^{(m(i))})$$

(54)

where we prepare the multicanonical weight factor (and the density of states) separately for each equal quantum (see Eq. (10)):

$$W_{\text{mic}}^{(m(i))}(E_{\text{mic}}^{(m(i))}) = \exp[-\beta_{m}(E_{\text{mic}}^{(m(i))})] = \frac{1}{\mu_{m}(E_{\text{mic}}^{(m(i))})}$$

(55)

Here, we have introduced $M$ arbitrary reference temperatures $T_{m} = \frac{1}{k_{B}T} (m = 1, \ldots, M)$, but the final result will be independent of the values of $T_{m}$, as one can see from the second equality in Eq. (55) (these arbitrary temperatures are necessary only for MD simulations).

Each multicanonical weight factor $W_{\text{mic}}^{(m)}(E_{\text{mic}})$, or the density of states $\rho_{\text{mic}}^{(m)}(E_{\text{mic}})$, is defined as follows. For each $m$ ($m = 1, \ldots, M$), we assign a pair of temperatures ($T_{m}^{k_{m}}, T_{m}^{k_{m+1}}$). Here, we assume that $T_{m}^{k_{m}} \leq T_{m}^{k_{m+1}}$ and arrange the temperatures so that the neighboring regions covered by the pairs have sufficient overlaps. Without loss of generality, we can assume $T_{m}^{1} \leq \ldots \leq T_{m}^{k_{m}}$ and $T_{m}^{k_{m+1}} \leq \ldots \leq T_{m}^{N_{m}}$. We define the following quantities:

$$L_{m}^{k} = \{E_{\text{mic}} \leq E_{\text{mic}}^{(k)}(m)\},$$

$$L_{m}^{k} = \{E_{\text{mic}} \leq E_{\text{mic}}^{(k)}(m)\}, (m = 1, \ldots, \mu).$$

(56)

Suppose that the multicanonical weight factor $W_{\text{mic}}^{(m)}(E_{\text{mic}})$ is obtained as in REMUCA or by any other methods in the entire energy range of interest ($L_{m}^{k} \leq E < L_{m}^{k+1}$). We then have for each $m$ ($m = 1, \ldots, \mu$) the following multicanonical potential energies (see Eq. (49)) [83]

$$\epsilon_{\text{mic}}^{(m)}(E) = \frac{\partial E_{\text{mic}}(E, T_{m})}{\partial E} \bigg|_{E=E_{\text{mic}}^{(m)}, T_{m}} = E_{\text{mic}}^{(m)}(E) + E_{\text{mic}}^{(m)}(E_{\text{mic}}^{(m)}, T_{m}).$$

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 a certain MC or MD step.
2. A pair of replicas, say $i$ and $j$, which are in neighboring multicanonical ensembles, say $m$-th and $(m+1)$-th, respectively, are exchanged: $X = \{x_{m}, \ldots, x_{m+1}, \ldots\}$.

The transition probability of this replica exchange is given by the Metropolis criterion:

$$w(X \rightarrow X') = \min(1, \exp(-\Delta)),$$

(58)

where we now have (see Eq. (43)) [83]

$$\Delta = \beta_{m}(E_{\text{mic}}^{(q_{m}(i))}) - \beta_{m}(E_{\text{mic}}^{(q_{m}(j))}),$$

(59)

Here, $E_{\text{mic}}^{(q_{m}(i))}$ and $E_{\text{mic}}^{(q_{m}(j))}$ are the potential energy of the $i$-th replica and the $j$-th replica, respectively. Note that in Eq. (59) we need to evaluate the multicanonical potential energy, $\epsilon_{\text{mic}}^{(m)}(E_{\text{mic}}^{(q_{m}(i))})$ and $\epsilon_{\text{mic}}^{(m)}(E_{\text{mic}}^{(q_{m}(j))})$, because $\epsilon_{\text{mic}}^{(m)}(E)$ and $\epsilon_{\text{mic}}^{(m)}(E)$ are, in general, different functions for $m \neq n$.

In this algorithm, the $m$-th multicanonical ensemble actually results in a canonical simulation at $T = T_{m}^{k_{m}}$ for $E < E_{\text{mic}}^{(m)}$, a canonical simulation for $E_{\text{mic}}^{(m)} \leq E \leq E_{\text{mic}}^{(m)}$, and a canonical simulation at $T = T_{m}^{k_{m+1}}$ for $E > E_{\text{mic}}^{(m)}$, while the replica-exchange process samples states of the whole energy range ($E_{\text{mic}}^{(m)} \leq E \leq E_{\text{mic}}^{(m)}$).

For obtaining the canonical distributions at any intermediate temperature $T$, the multiple-histogram reweighting techniques [10,11] are again used. Let $N_{m}(E)$ and $n_{m}$ be respectively the potential-energy histogram and the total number of samples obtained with the multicanonical weight factor $W_{\text{mic}}^{(m)}(E_{\text{mic}})$ ($m = 1, \ldots, M$). The expectation value of a physical quantity $A$ at any temperature $T = \frac{1}{k_{B}T}$ is then obtained from Eq. (18), where the best estimate of the density of states is obtained by solving the WHAM equations, which now read [83]

$$a(E) = \frac{\sum_{m=1}^{M} \sum_{i=1}^{N_{m}} n_{m} \epsilon_{\text{mic}}^{(m)}(E_{\text{mic}}^{(m)}) \exp(-f_{m}(E_{\text{mic}}^{(m)}))}{\sum_{m=1}^{M} \sum_{i=1}^{N_{m}} n_{m} \exp(f_{m} - \beta_{m}(E_{\text{mic}}^{(m)}))},$$

(60)

for $E < E_{\text{mic}}^{(m)}$,

$$\text{for } E_{\text{mic}}^{(m)} \leq E \leq E_{\text{mic}}^{(m)}$$

(57)

and for each $m = 1, \ldots, M$

$$\exp(-f_{m}) = \sum_{E} n(E) W_{\text{mic}}^{(m)}(E)$$

(61)

Note that $W_{\text{mic}}^{(m)}(E)$ is used instead of the Boltzmann factor $\exp(-\beta_{m}E)$ in Eqs. (50) and (31).
Moreover, ensemble averages of any physical quantity $A$ (including those that cannot be expressed as functions of potential energy) at any temperature $T = \text{Id}k_B\theta$ can now be obtained from the "trajectory" of configurations of the production run. Namely, we first obtain $f_m$ ($m = 1, \ldots, M$) by solving Eqs. (60) and (61) self-consistently, and then we have [88]

$$
\langle A \rangle_T = \frac{1}{\sum_{m=1}^{M} n_m} \left\{ \sum_{m=1}^{M} \frac{1}{n_m} \left( \sum_{\ell=1}^{N} \exp \left( \beta E(x_m(\ell)) \right) \right) \exp \left( -\beta E(x_m(\ell)) \right) \right\}^{1/n_m} \left( \sum_{\ell=1}^{N} \exp \left( \beta E(x_m(\ell)) \right) \right).
$$

where the trajectories $x_m(\ell)$ ($k = 1, \ldots, n_m$) are taken from each multicanonical simulation with the multicanonical weight factor $W_m(E)$ ($m = 1, \ldots, M$) separately.

As seen above, both REMUCA and MUCAREM can be used to obtain the multicanonical weight factor, or the density of states, for the entire potential energy range of interest. For complex systems, however, a single REMUCA or MUCAREM simulation is often insufficient. In such cases we can iterate MUCA (in REMUCA) and/or MUCAREM simulations in which the estimate of the multicanonical weight factor is updated by the single- and/or multiple-histogram reweighting techniques, respectively.

To be more specific, this iterative process can be summarized as follows [88]. The REMUCA production run corresponds to a MUCA simulation with the weight factor $W_m(E)$. The new estimate of the density of states can be obtained by the single-histogram reweighting techniques of Eqs. (20). On the other hand, from the MUCAREM production run, the improved density of states can be obtained by the multiple-histogram reweighting techniques of Eqs. (60) and (61).

The improved density of states thus obtained leads to a new multicanonical weight factor (see Eq. (10)). The next iteration can be either a MUCA production run (as in REMUCA) or MUCAREM production run. The results of this production run may yield an optimal multicanonical weight factor that yields a sufficiently flat energy distribution for the entire energy range of interest. If not, we can repeat the above process by obtaining the third estimate of the multicanonical weight factor either by a MUCA production run (as in REMUCA) or by a MUCAREM production run, and so on.

We remark that as the estimate of the multicanonical weight factor becomes more accurate, one is required to have a less number of replicas for a successful MUCAREM simulation, because each replica will have a flat energy distribution for a wider energy range. Hence, for a large, complex system, it is often more efficient to first try MUCAREM and iteratively reduce the number of replicas so that eventually one needs only one or a few replicas (instead of trying REMUCA directly from the beginning and iterating MUCA simulations).

We now describe the simulated tempering replica-exchange method (STREM) [109]. Suppose that the simulated tempering weight factor $W_m(E, T_\ell)$ (or equivalently, the dimensionless Helmholtz free energy $\mu_m$ in Eq. (25)) has been obtained as in REST or by any other methods in the entire temperature range of interest ($T_1 \leq T_\ell \leq T_M$). We divide the overlapping temperature ranges into $M$ regions ($M \ll M$). Suppose each temperature range $m$ has $N_m$ temperatures: $T_m(k) = kT_M$, for $m = 1, \ldots, M$. We assign each temperature range to a replica; each replica $i$ is in one-to-one correspondence with a different temperature range $m$ of ST run, where $T_{m_i} \leq T_{m_i} \leq T_{m_i}(k = 1, \ldots, N_m)$. We then introduce the replica-exchange process between neighboring temperature ranges. This works when we allow sufficient overlaps between the temperature regions.

A STREM simulation is then realized by alternately performing the following two steps [109].

1. Each replica performs a ST simulation within the fixed temperature range simultaneously and independently for a certain MC or MD steps.

2. A pair of replicas, say $i$ and $j$, which are at, say $T = T_m$ and $T = T_j$, in neighboring temperature ranges, say $m$-th and $(m+1)$-th, respectively, are exchanged:

$$
X = \{ \ldots, x_m^i, \ldots, x_{m+1}^j, \ldots, x_M \} \rightarrow X' = \{ \ldots, x_m^i, \ldots, x_{m+1}^j, \ldots, x_M \}.
$$

The transition probability of this replica-exchange is given by the Metropolis criterion:

$$
w(X \rightarrow X') = \min(1, \exp(-\Delta)),
$$

where

$$
\Delta = \left( \mu_m^{(i)} - \mu_{m+1}^{(i)} \right) \left( E(x_m^i) - E(x_{m+1}^j) \right).
$$

While in MUCAREM each replica performs a random walk in multicanonical ensemble of finite energy range, in STREM each replica performs a random walk by simulated tempering of finite temperature range. These “local” random walks are made “global” to cover the entire energy range of interest by the replica-exchange process.

2.5 Multidimensional replica-exchange method

We now present our multidimensional extension of REM, which we refer to as multidimensional replica-exchange method (MREM) [82]. The crucial observation that led to the new algorithm is: As long as we have $M$ non-interacting
replicas of the original system, the Hamiltonian $H(q, p)$ of the system does not have to be identical among the replicas and it can depend on a parameter with different parameter values for different replicas. 

Namely, we can write the Hamiltonian for the $i$-th replica at temperature $T_m$ as

$$H_m(q^{(i)}, p^{(i)}) = K(q^{(i)}) + E_m(q^{(i)})$$

(65)

where the potential energy $E_m$ depends on a parameter $\lambda_m$ and can be written as

$$E_m(q^{(i)}) = E_0(q^{(i)}) + \lambda_m V(q^{(i)})$$

(66)

This expression for the potential energy is often used in simulations. For instance, in umbrella sampling [24], $E_m(q)$ and $V(q)$ can be respectively taken as the original potential energy and the “biasing” potential energy with the coupling parameter $\lambda_m$. In simulations of spin systems, on the other hand, $E_m(q)$ and $V(q)$ (here, $q$ stands for spins) can be respectively considered as the zero-field term and the magnetization term coupled with the external field $\lambda_m$.

While replica $i$ and temperature $T_m$ are in one-to-one correspondence in the original REM, replica $i$ and “parameter set” $\Lambda_m \equiv (T_m, \lambda_m)$ are in one-to-one correspondence in the new algorithm. Hence, the present algorithm can be considered as a multidimensional extension of the original replica-exchange method where the “parameter space” is one-dimensional (i.e., $\Lambda_m \equiv T_m$). Because the replicas are non-interacting, the weight factor for the state $X$ in this new generalized ensemble is again given by the product of Boltzmann factors for each replica (see Eq. (35))

$$W_{\text{REM}}(X) = \exp \left[-\sum_{i=1}^{M} \beta_m H_m(q^{(i)}, p^{(i)}) \right]$$

$$= \exp \left[-\sum_{i=1}^{M} \beta_m (E_m(q^{(i)}) + \lambda_m V(q^{(i)})) \right]$$

(67)

where $\beta_m$ and $m(i)$ are the permutation functions in Eq. (33). Then the same derivation that led to the original replica-exchange criterion follows, and the transition probability of replica exchange is given by Eq. (46), where we now have (see Eq. (43)) [82]

$$\Delta = \beta_m (E_m(q^{(i)}) - E_m(q^{(j)}))$$

$$\beta_m (E_m(q^{(i)}) - E_m(q^{(j)}))$$

(68)

Here, $E_m$ and $E_{m(i)}$ are the total potential energies (see Eq. (66)). Note that we need to newly evaluate the potential energy for exchanged coordinates, $E_{m(i)}(q^{(j)})$ and $E_{m(i)}(q^{(j)})$, because $E_m$ and $E_{m(i)}$ are in general different functions.

For obtaining the canonical distributions, the multiple-histogram reweighting techniques [10,11] are particularly suitable. Suppose we have made a single run of the present replica-exchange simulation with $M$ replicas that correspond to $M$ different parameter sets $\Lambda_m \equiv (T_m, \lambda_m)$ ($m = 1, \ldots, M$). Let $N_m(E_0, V)$ and $n_m$ be respectively the potential-energy histogram and the total number of samples obtained for the $m$-th parameter set $\Lambda_m$. The WHAM equations that yield the canonical probability distribution $P_{\text{WHAM}}(E_0, V) = n(E_0, V) \exp(-\beta E_0)$ with any potential-energy parameter value $\lambda$ at any temperature $T = 1/\beta$ are then given by [82]

$$n(E_0, V) = \sum_{m=1}^{M} \frac{N_m(E_0, V)}{\sum_{m=1}^{M} \exp(-\beta E_m)}$$

(69)

and for each $m = 1, \ldots, M$

$$\exp(-f_m) = \sum_{E_0} n(E_0, V) \exp(-\beta E_m)$$

(70)

Here, $m(E_0, V)$ is the generalized density of states. Note that $m(E_0, V)$ is independent of the parameter sets $\Lambda_m \equiv (T_m, \lambda_m)$ ($m = 1, \ldots, M$). The density of states $m(E_0, V)$ and the “dimensionless” Helmholtz free energy $f_m$ in Eqs. (69) and (70) are solved self-consistently by iteration.

Incidentally, these formulations of MREM give multidimensional extensions of REMUCA [83,88] and REST [84]. In the former, we obtain uniform distributions both in $E_0$ and $V$, whereas in the latter, the parameter sets $\Lambda_m$ become dynamical variables and a uniform distribution in those parameters will be obtained. Namely, after a short MREM simulation, we can use the multiple-histogram reweighting techniques of Eqs. (69) and (70) to obtain $m(E_0, V)$ and $f_m$. Hence, we can determine the multidimensional canonic weight factor $W_{\text{REM}}(E_0, V)$ and the multidimensional simulated tempering weight factor $W_{\text{ST}}(E_0, V, \Lambda_m)$. The former is given by

$$W_{\text{REM}}(E_0, V) = \frac{1}{n(E_0, V)}$$

(71)

and the latter is given by (see Eq. (25))

$$W_{\text{ST}}(E_0, V, \Lambda_m) = \exp(-\beta_m E_{m(i)} + f_m).$$

(72)

We can use MREM for free energy calculations. We first describe the free energy perturbation case. The method is referred to as replica-exchange free energy perturbation (REFEP) [82]. The potential energy is given by

$$E_{j}(q) = E_j(q) + \lambda(E_j(q) - E_j(q))$$

(73)

where $E_j$ and $E_k$ are the potential energy for a “wild-type” molecule and a “mutated” molecule, respectively. Note that this equation has the same form as Eq. (66).

Our replica-exchange simulation is performed for $M$ replicas with $M$ different values of the parameters $\Lambda_m \equiv (T_m, \lambda_m)$. Since $E_{m(i)}(q) = E_j(q)$ and $E_{m(i)}(q) = E_k(q)$, we should choose enough $\lambda_m$ values distributed in the range between 0 and 1 so that we may have sufficient acceptance of replica exchange. From the simulation, $M$ histograms
\[ N_m(E_I, E_F) \] or equivalently \( N_m(E_I, E_F) \), are obtained. The Helmholtz free energy difference of “mutation” at temperature \( T (= 1/k_B T) \), \( \Delta F \equiv \Delta F_{I,J} \), can then be calculated from

\[
\exp(-\beta \Delta F) = \frac{Z_{E_I,E_F}^{(I,J)}}{Z_{E_I,E_F}^{(I,J)}},
\]

where \( P_{E_I,E_F}^{(I,J)} = n(E_I, E_F) \exp(-\beta E_N) \), are obtained from the WHAM equations of Eqs. (69) and (70).

We now describe another free energy calculations based on MREME applied to umbrella sampling, which we refer to as replica-exchange umbrella sampling (REUS) [82]. The potential energy is a generalization of Eq. (66) and is given by

\[
E_{\lambda}(\xi) = E_0(\xi) + \sum_{\ell=1}^{L} \lambda(\ell) V_{\ell}(\xi),
\]

where \( E_0(\xi) \) is the original unbiased potential, \( V_{\ell}(\xi) \) are the biasing (umbrella) potentials, and \( \lambda(\ell) \) are the corresponding coupling constants (\( \lambda = (\lambda(1), \ldots, \lambda(L)) \)).

Introducing a “reaction coordinate” \( \xi \), the umbrella potentials are usually written as harmonic restraints:

\[
V_{\ell}(\xi) = k_{\ell}(\xi - \xi_{\ell}^{(0)})^2, \ell = 1, \ldots, L,
\]

where \( k_{\ell} \) are the strengths and \( \xi_{\ell}^{(0)} \) are the midpoints of the restraining potentials. We prepare \( M \) replicas with \( M \) different values of the parameters \( \lambda_m = (\lambda_{m,1}, \ldots, \lambda_{m,L}) \), and the replica-exchange simulation is performed. Since the umbrella potentials \( V_{\ell}(\xi) \) (Eq. (76) are all functions of the reaction coordinate \( \xi \) only, we can take the histogram \( n_m(E_0, \xi) \) instead of \( n(E_0, E_I, \xi) \). The WHAM equations of Eqs. (69) and (70) can then be written as [82]

\[
n_m(E_0, \xi) = \sum_{\ell=1}^{L} \sum_{\xi_{\ell}^{(0)}} n_m(E_0, \xi) \exp(-\beta E_N),
\]

and for each \( m = 1, \ldots, M \)

\[
\exp(-\beta E_N) = \sum_{\xi_{\ell}^{(0)}} n(E_0, \xi) \exp(-\beta E_N).
\]

The expectation value of a physical quantity \( A \) with any potential-energy parameter value \( \lambda \) at any temperature \( T \) (= 1/k_B T) is now given by

\[
\langle A \rangle_{E_0} = \frac{\sum_{E_0} A(E_0) P_{E_0}^{(I,J)}(E_0, \xi)}{\sum_{E_0} P_{E_0}^{(I,J)}(E_0, \xi)}
\]

where \( P_{E_0}^{(I,J)}(E_0, \xi) = n(E_0, \xi) \exp(-\beta E_N) \) is obtained from the WHAM equations of Eqs. (77) and (78).

The potential of mean force (PMF), or free energy as a function of the reaction coordinate, of the original, unbiased system at temperature \( T \) is given by

\[
W_{E_0}(\xi) = -k_B T \ln \left[ \sum_{E_0} P_{E_0}^{(I,J)}(E_0, \xi) \right],
\]

where \( \{0\} = (0, \ldots, 0) \).

We now present two examples of realization of REUS. In the first example, we use only one temperature, \( T \), and umbrella potentials. We prepare replicas so that the potential energy for each replica includes exactly one umbrella potential (here, we have \( M = L \)).

Namely, in Eq. (75) for \( \lambda = \lambda_m \), we set

\[
\delta_{\ell,m} = \delta(\xi_{\ell}^{(0)} - \xi_{m}^{(0)}),
\]

where \( \delta_{\ell,m} \) is Kronecker’s delta function, and we have

\[
E_{\lambda_m}(\xi) = E_0(\xi) + \sum_{\ell=1}^{L} \lambda_{m,\ell} V_{\ell}(\xi).
\]

We exchange replicas corresponding to “neighboring” umbrella potentials, \( V_{\ell} \) and \( V_{\ell+1} \).

The acceptance criterion for replica exchange is given by Eq. (46), where Eq. (68) now reads (with the fixed inverse temperature \( \beta = 1/k_B T \)) [82]

\[
\Delta = \beta (E_0(\xi_{\ell}^{(0)}) - E_0(\xi_{\ell+1}^{(0)})),
\]

where replica \( i \) and \( j \) respectively have umbrella potentials \( V_{\ell} \) and \( V_{\ell+1} \) before the exchange.

In the second example, we prepare \( N_T \) temperatures and \( L \) umbrella potentials, which makes the total number of replicas \( M = N_T \times L \). We can introduce the following relabeling for the parameters that characterize the replicas:

\[
(\lambda_1, \ldots, \lambda_M) \rightarrow (\lambda_{T_{B}}), (I_{B}, j_{B}).
\]

The potential energy is given by Eq. (82) with the replacement: \( m \rightarrow J \). We perform the following replica-exchange processes alternately:

1. Exchange pairs of replicas corresponding to neighboring temperatures, \( T_I \) and \( T_{I+1} \) (i.e., exchange replicas \( i \) and \( j \) that respectively correspond to parameters \( \lambda_{I,J} \) and \( \lambda_{I+1,J} \)). (We refer to this process as \( T \)-exchange.)

2. Exchange pairs of replicas corresponding to “neighboring” umbrella potentials, \( V_I \) and \( V_{I+1} \) (i.e., exchange replicas \( i \) and \( j \) that respectively correspond to parameters \( \lambda_{I,J} \) and \( \lambda_{I,J+1} \)). (We refer to this process as \( \lambda \)-exchange.)

The acceptance criterion for these replica exchanges is given by Eq. (46), where Eq. (68) now reads [82]

\[
\Delta = \beta (E_0(\xi_{\ell}^{(0)}) - E_0(\xi_{\ell+1}^{(0)})),
\]
for $T$-exchange, and
\[ \Delta = \beta R (V_J(q_j^i) - V_J(q_j^{i+1}) - V_J(q_j^{i+1}) + V_J(q_j^{i})) \]
for $\lambda$-exchange. By this procedure, the random walk in the reaction coordinate space as well as in the temperature space can be realized.

3. Conclusions

In this article we have reviewed uses of generalized-ensemble algorithms for both Monte Carlo simulations and molecular dynamics simulations. A simulation in generalized ensemble realizes a random walk in potential energy space, alleviating the multiple-minima problem that is a common difficulty in simulations of complex systems with many degrees of freedom.

Detailed formulations of the three well-known generalized-ensemble algorithms, namely, multicanonical algorithm, simulated tempering, and replica-exchange method, were given.

We then introduced five new generalized-ensemble algorithms that combine the merits of the above three methods. We refer to these methods as replica-exchange multicanonical algorithm, replica-exchange simulated tempering, multicanonical replica-exchange method, simulated tempering replica-exchange method, and multidimensional replica-exchange method, the last of which also led to replica-exchange free energy perturbation and replica-exchange umbrella sampling.

The question is then which method is the most recommended. We have recently studied the effectiveness of MUCA, REM, REMUCA, and MUCAREM in the protein folding problem [88]. Our criterion for the effectiveness was how many times the random walk cycles between the high-energy region and low-energy region are realized within a fixed number of total MC (or MD) steps. We found that once the optimal MUCA weight factor is obtained, ST (and REST) has more random walk cycles than REM[84,109]. Moreover, we compared the efficiency of Berg’s recursion [69], Wang–Landau method [21,22], and MUCA/MUCAREM as methods for the multicanonical weight factor determination in two-dimensional 10-state Potts model and found that the three methods are about equal in efficiency [118–120].

Hence, the answer to the above question will depend on how much time one is willing to (or forced to) spend in order to determine the MUCA or ST weight factors. Given a problem, the first choice is REM because of its simplicity (no weight factor determination is required). If REM turns out to be insufficient or too much time-consuming (like the case with first-order phase transitions), then other more powerful algorithms such as those presented in the present article are recommended.

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References

5423.
1818–1820.
[116] B.A. Berg, Markov Chain Monte Carlo Simulations and Their
in the Physical Sciences: Celebrating the 50th Anniversary of the
Metropolis Algorithm, American Institute of Physics, Melville,
2003, pp. 248–260; cond-mat/0308119.