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Distributed Replica Sampling

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Abstract: We present a simple and general scheme for efficient Boltzmann sampling of conformational space by computer simulation. Multiple replicas of the system differing in temperature T or reaction coordinate λ are simulated independently. In addition, occasional stochastic moves of individual replicas in T or λ space are considered one at a time on the basis of a generalized Hamiltonian containing an extra potential energy term or bias that depends on the distribution of all replicas. The algorithm is inherently suited for shared or heterogeneous computing platforms such as a distributed network.

Introduction

Despite rapid advances in computer technology, statistical sampling of systems governed by rugged potential energy surfaces remains a challenge, which underscores the need for efficient computational algorithms.[1−6] For example, the time scales of conformational transitions of biomolecular systems span many orders of magnitude. Many of these events are not directly accessible by atomistic computer simulations, precluding Boltzmann sampling of conformational space.

A number of statistical mechanical methods using generalized ensembles have been developed in recent years to enhance sampling efficiency. Some of these approaches are designed to induce a random walk either in temperature, potential energy, spatial coordinates, or transformation parameters in the Hamiltonian. In simulated tempering (ST),[7,8] a random walk in temperature is achieved by taking periodic steps from absolute inverse temperature β_i to β_j subject to acceptance of the following Metropolis Monte Carlo test:

$$p_{\text{accept}} = \min(1, \exp\{-[(\beta_j - \beta_i)E(\mathbf{q}) + (a_j - a_i)]\}) \quad (1)$$

where β_i and β_j are the inverse of the Boltzmann constant multiplied by absolute temperature, the potential energy $E(\mathbf{q})$ is a function of atomic coordinates $\mathbf{q}$, and a_i and a_j are weight factors that must be determined in advance using an iterative procedure. Similarly, the multicanonical algorithm (MUCA)[9,10] results in a random walk in potential energy space. Extending the Hamiltonian to include a transformation coordinate λ is another way to get around barriers because the higher dimensionality of phase space results in an increased number of alternate routes by which barriers can be avoided. A random walk along a transformation coordinate can be realized via adaptive umbrella sampling (AUS) methods,[11−15] where the Hamiltonian governing movement is defined as

$$H(\mathbf{q},\lambda) = E(\mathbf{q},\lambda) + U(\lambda) \quad (2)$$

In eq 2, the potential energy E is a function of atomic coordinates $\mathbf{q}$ and transformation coordinate λ, and $U(\lambda)$ is a biasing potential that must be adapted such that it removes any barriers that exist along the transformation coordinate. In ST, MUCA, or AUS, random walk behavior is achieved only once the system "adapts" or learns the correct weight factors for movement along the parameter of interest, a system-dependent procedure that introduces extra complexity as well as possible artifacts if not done carefully (see ref 16

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for more details). Furthermore, although adaptive methods clearly improve sampling uniformity along the coordinate, in some cases, uniform sampling may only be achieved in very long simulations because of ruggedness in orthogonal degrees of freedom.[17]

In the past decade, replica exchange (RE),[18−20] also known as multiple Markov chain or parallel tempering, has emerged as a powerful alternative to adaptive methods. In RE, multiple noninteracting copies or replicas of a system, each governed by the same potential energy function but differing in temperature, are simulated at once. Periodically, the simulations are halted, and replicas i and j with neighboring temperatures T_i and T_j are swapped with a probability given by the following Metropolis Monte Carlo condition:

$$p_{\text{accept}} = \min(1, \exp\{-[\beta_i - \beta_j][E(\mathbf{q}_j) - E(\mathbf{q}_i)]\}) \quad (3)$$

Temperature swaps cause each replica to undergo a random walk in temperature, providing a means (for any replica) to escape from a potential energy trap. Like adaptive methods, RE may also be used to attain a random walk in a parameter of the Hamiltonian,[21−23] λ. Swaps between adjacent replicas i and j are accepted with a probability given by

$$p_{\text{accept}} = \min(1, \exp\{-\beta[E(\mathbf{q}_i,\lambda_j) - E(\mathbf{q}_i,\lambda_i) + E(\mathbf{q}_j,\lambda_i) - E(\mathbf{q}_j,\lambda_j)]\}) \quad (4)$$

When data from all replicas are taken together, perfect sampling uniformity along the temperature or reaction coordinate is attained. Furthermore, no adaptation of a biasing potential is required because the weight factors are known a priori. In the realm of biomolecular studies, large-scale applications of RE have pushed back limitations in the scope of problems and the size of systems studied.[19,23−31] Recent studies have applied the method to folding a 46 amino acid protein domain,[32] and the approach has been extended to two-dimensional random walks in pressure and temperature.[31] The principal drawback of RE is that it requires a homogeneous and often large computing cluster to implement efficiently. Because the number of replicas required follows the square root of the number of degrees of freedom in the system,[18] the simulation of complex systems eventually becomes impractical.

Here, we present distributed replica (DR) sampling, a simple and general scheme for efficient Boltzmann sampling of conformational space by computer simulations. As in RE, multiple replicas of the system, covering a preassigned range in temperature or reaction coordinate space, are simulated independently. The main difference with RE is that, instead of performing pairwise exchanges of replicas, stochastic moves of individual replicas in T or λ space are considered one at a time. The target distribution of replicas is enforced by a generalized Hamiltonian containing an extra potential energy bias that depends on the distribution of all replicas. Contrary to adaptive methods, DR does not require preliminary determination of the bias. We show with a simple but relevant example that the DR algorithm leads to random-walk movement along the parameter of interest with an efficiency comparable to that of RE. Because it avoids the need for all replicas to run synchronously, DR is intrinsically suited for implementation on a shared or inhomogeneous computing platform such as a large-scale distributed network.

Method

Let us consider N noninteracting copies (or "replicas") of a system of interest, all of which are governed by an identical potential energy function, $E(\mathbf{q}_i,\lambda_i)$, where $\mathbf{q}_i$ represents the atomic coordinates of the atoms in replica i and λ_i is the coupling parameter for the reaction coordinate of interest (the reaction in question may be either an alchemical or a spatial transformation). The DR method makes use of an additional potential energy term, $D(\lambda_1,\lambda_2,...,\lambda_N)$, henceforth referred to as the distributed replica potential energy (DRPE), which enforces the distribution of replicas across the range of the transformation coordinate (i.e., an energy penalty is associated with a nonideal distribution). The generalized Hamiltonian for state $X = \{\mathbf{q}_1,\lambda_1,\mathbf{q}_2,\lambda_2,...,\mathbf{q}_N,\lambda_N\}$, combining all replicas together with the DRPE, is given by

$$\mathscr{H}_\lambda(X) = \sum_{i=1}^{N} E(\mathbf{q}_i,\lambda_i) + D(\lambda_1,\lambda_2,...,\lambda_N) \quad (5)$$

The weight factor for state X is given by

$$W(X) = \exp[-\beta\, \mathscr{H}_\lambda(X)] \quad (6)$$

We consider one λ move at a time. Suppose that the λ value of replica m is to be changed from λ_m to $\lambda_m + \delta\lambda_m$, thus taking state X to state X':

$$X = \{\mathbf{q}_1,\lambda_1,...,\mathbf{q}_m,\lambda_m,...,\mathbf{q}_N,\lambda_N\} \rightarrow X' = \{\mathbf{q}_1,\lambda_1,...,\mathbf{q}_m,\lambda_m + \delta\lambda_m,...,\mathbf{q}_N,\lambda_N\} \quad (7)$$

In order for the exchange process to converge toward the equilibrium distribution, it is sufficient to impose the detailed balance condition on the transition probability $p(X\rightarrow X')$:

$$W(X)\, p(X\rightarrow X') = W(X')\, p(X'\rightarrow X) \quad (8)$$

From eqs 5, 6, and 8, we have

$$\frac{p(X\rightarrow X')}{p(X'\rightarrow X)} = \exp(-\beta\Delta) \quad (9)$$

where

$$\Delta = E(\mathbf{q}_m,\lambda_m + \delta\lambda_m) - E(\mathbf{q}_m,\lambda_m) + D(\lambda_1,\lambda_2,...,\lambda_m + \delta\lambda_m,...,\lambda_N) - D(\lambda_1,\lambda_2,...,\lambda_m,...,\lambda_N) \quad (10)$$

This can be satisfied using the Metropolis Monte Carlo criterion:

$$p_{\text{accept}} = \min[1, \exp(-\beta\Delta)] \quad (11)$$

Like RE, the DR method may also be performed in temperature space. To this end, we first define $X = \{\mathbf{q}_1,\beta_1,...,\mathbf{q}_N,\beta_N\}$. The corresponding dimensionless generalized Hamiltonian is

$$\mathscr{H}_\beta^*(X) = \sum_{i=1}^{N} \beta_i\, E(\mathbf{q}_i) + D^*(\beta_1,\beta_2,...,\beta_N) \quad (12)$$

Table 1. Example of a Distributed Replica Potential Energy Calculation

index	1	2	3	4	5	6
nominal (or ideal) λ positions of replicas	0.0	0.1	0.2	0.4	0.6	1.0
current λ_i positions of replicas (after several λ moves and one effective λ swap)	0.0	0.2	0.11	0.4	0.6	1.0
$\lambda_{i,\text{sorted}}$ values after step 1 (sorting)	0.0	0.11	0.2	0.4	0.6	1.0
$\lambda_{i,\text{unit}}$ values after step 2 (spacing transformation)	1.0	2.1	3.0	4.0	5.0	6.0
DRPE result after step 3 (assuming $c = 0.1$ kcal/mol)	0.1 kcal/mol					

where the asterisk indicates a dimensionless quantity. The appropriate Monte Carlo acceptance probability of a move involving a change $\delta\beta_m$ in the inverse temperature of replica m is

$$p_{\text{accept}} = \min[1, \exp(-\Delta^*)] \tag{13}$$

where

$$\Delta^* = \delta\beta_m E(\mathbf{q}_m) + D^*(\beta_1,\beta_2,...,\beta_m + \delta\beta_m,...,\beta_N) - D^*(\beta_1,\beta_2,...,\beta_m,...,\beta_N) \tag{14}$$

Many possibilities exist for calculating the DRPE, and several variations were tested as a part of the development of this method. One that was found to work very well, which was used in the analysis reported here, is as follows. The DRPE function is calculated from three algorithmic steps: (1) The λ (or β) values for all replicas are sorted in ascending order. The following holds true for the new order, $\lambda_{i,\text{sorted}}$:

$$\lambda_{i,\text{sorted}} > \lambda_{i-1,\text{sorted}} \text{ for } i = 2 \text{ to } N \tag{15}$$

(2) The spacing system is transformed to a uniform unit spacing arrangement to give $\lambda_{i,\text{unit}}$:

$$\lambda_{i,\text{unit}} = f^{-1}(\lambda_{i,\text{sorted}}) \tag{16}$$

where f^{-1} is the inverse of a function f, which maps the replica index to the nominal λ value of that replica (i.e., the λ position where the replica started). Note that because replica indices are integers, f is constructed by linearly interpolating between adjacent points.

(3) This step involves the following equation:

$$D = c\sum_{i=1}^{N}\sum_{j=1}^{N}[(\lambda_{i,\text{unit}} - \lambda_{j,\text{unit}}) - (i - j)]^2 \tag{17}$$

where c is a parameter that scales the DRPE function for the purpose of adjusting the move acceptance probability. Note that the DRPE must necessarily be a state function (i.e., it must conserve energy). See Table 1 for an example DRPE calculation.

Note that the DRPE defined in eqs 15−17 acts to reinforce spacing between the λ_i values of the replicas, and it has no effect on the absolute positions of the λ_i values. Therefore, to prevent a concerted drift of all replicas away from the region of interest, a few extra nonmoving, nonsimulated dummy replicas can be included, typically positioned just beyond the endpoints.

A DR simulation is realized as follows. Initially, each replica i is created at a different position, λ_i, spanning the transformation coordinate, and is optionally equilibrated. The spacing between adjacent λ_i values is chosen on the basis of the application at hand and may be uniform or nonuniform. The following two steps are then iterated: (1) Each replica is run as an independent molecular dynamics or Monte Carlo simulation for a set period of time or number of steps, typically on its own CPU in a computing cluster. The method does not require all of the simulations to run simultaneously nor does it require simulations to finish (or be halted) in a coordinated manner as is typical in standard replica exchange algorithms. λ_i values are fixed during the course of these simulations. (2) Periodically, one replica is considered for a λ move. The probability of acceptance is $p(X \rightarrow X')$ (see eq 11).

There are no restrictions on the intervals between replica move attempts, although some optimal interval will exist for a given application. Frequent move attempts allow a greater mobility of the λ_i values, but at the cost of increased overhead. The distance by which λ_i changes during a λ move is also not restricted and can be optimized for the application at hand.

Test Application

The performance of the DR method is illustrated with a two-dimensional model system designed such that a significant energy barrier exists in a degree of freedom x orthogonal to a reaction coordinate λ. As depicted in Figure 1, the reaction involves the conversion of a double-well potential to a single well. A total of 51 replicas spaced uniformly along the reaction coordinate, each initially at $x = -1$, were constructed. For each replica, the particle evolved on the 1D energy landscape governed by Monte Carlo moves at a temperature of 298 K with a fixed step size of 0.01. A total of 10^7 moves along x were simulated per replica. The calculation was performed with fully independent replicas, with DR, and with RE. After 10 steps elapsed for all DR replicas (20 steps for RE), a λ move (or a swap between neighbors) was attempted for one replica (or one replica pair) chosen at random, giving the particles a chance to move in the λ dimension. When either DR or RE was used, each replica experienced on average about 19 600 move attempts along λ (one swap event in RE is equivalent to two λ moves in DR).

Sequential moves of DR replicas in λ space are illustrated in Figure 2. An effective random walk is achieved by individual replicas over the entire simulation (Figure 2b). The occasional rapid replacement of one replica by another is tantamount to a pairwise exchange reminiscent of RE (Figure 2a). However, the fact that DR replicas move one at

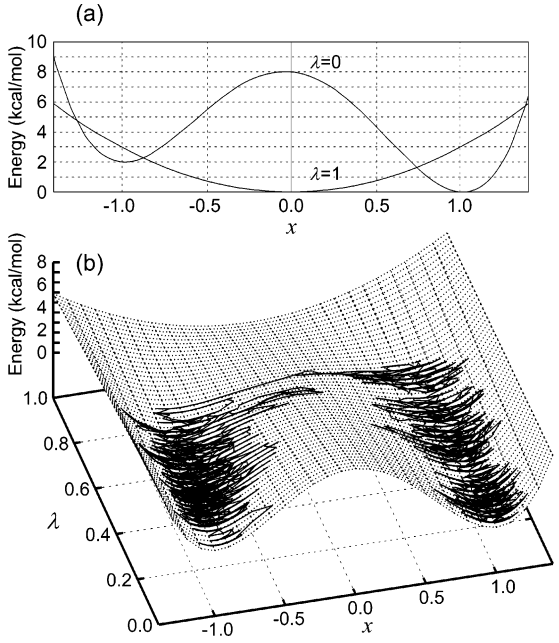

Figure 1. Model potential energy surface used to test DR sampling. (a) The energy profile gradually switches from a bistable well at $\lambda = 0$ (with minima at $x \approx \pm 1$) to a single well at $\lambda = 1$ and $x = 0$. (b) Two-dimensional representation; a DR trajectory illustrating barrier avoidance by diffusion in λ space is also shown.

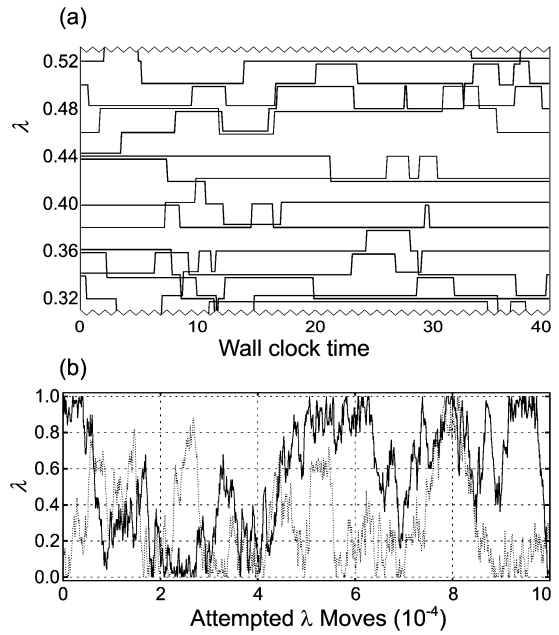

Figure 2. Diffusion of distributed replicas in λ space. (a) Representative trajectories of a few DR replicas over a small interval of wall-clock time corresponding to approximately 40 move attempts. Lines were slightly shifted vertically for clarity. (b) Two representative complete trajectories illustrate a random walk in λ.

a time also leads to overlaps of two or more replicas and temporary gaps in λ space. The DRPE function acts to enforce spreading of the replicas in λ space. On average, sampling is close to the target uniform distribution (Figure 3a). There is a nonlinear relationship between the root-mean-square deviation from uniformity and the acceptance ratio

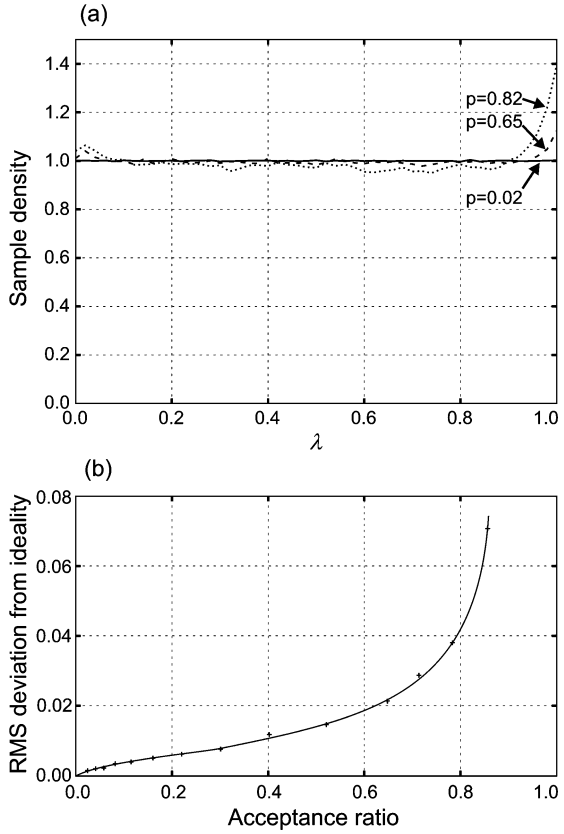

Figure 3. Relationship between sampling profiles and acceptance ratios in DR simulations. (a) Sampling profiles along the reaction coordinate λ obtained from three DR simulations, each with 51 replicas but differing in acceptance ratio, $p =$ 0.02, 0.65, and 0.82. (b) Root-mean-square deviation from sampling uniformity as a function of acceptance ratio. The lines are included to guide the eye.

(Figure 3b). Both of these quantities are controlled by the stiffness of the DRPE function (i.e., by the scaling constant c in eq 17). While sampling uniformity is achieved only for an infinitely forbidding DRPE ($c \rightarrow \infty$), deviations from the target distribution only become significant for relatively large acceptance ratios (loose DRPE). With intermediate acceptance ratios (i.e., 20−70%), the DR method nearly achieves the desired sampling profile.

In the limit of independent replicas, severe deviations from the theoretical sampling distribution along x are evident at small values of λ (Figure 4). For some replicas, the energy barrier prevents crossings altogether during the entire simulation, trapping the particle in the metastable well at $x = -1$. Considerably longer simulations would be necessary to achieve statistical convergence. The energy barrier can be bypassed if the system is allowed to evolve freely on pathways through λ space as well as x. The sampling distributions obtained using DR (with an acceptance ratio of 65%) and RE simulations are shown in Figure 4c,d. Both cases show dramatic improvements in sampling efficiency over independent replicas (Figure 4b) and good agreement with the theoretical distribution (Figure 4a). Accordingly, these two simulations yield mean force and free energy profiles within the statistical error from each other (Figure 5), indicating that DR is as efficient as RE in the given test

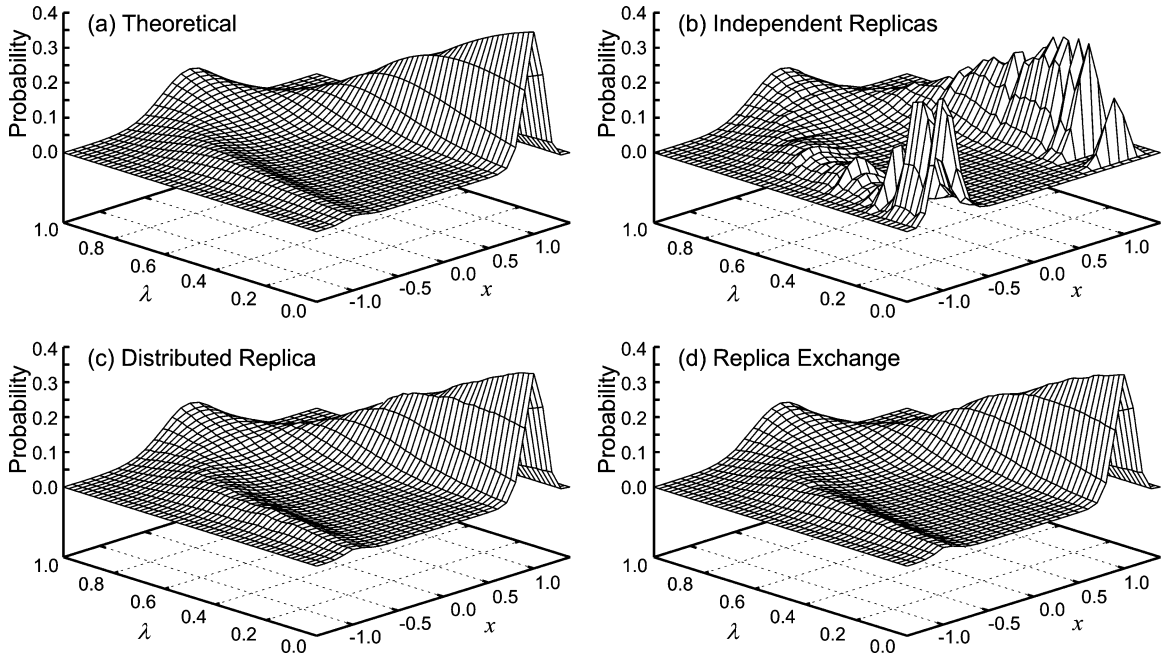

Figure 4. Sampling distribution for the model system depicted in Figure 1: exact (analytical) distribution (a) and distributions obtained with 51 replicas spanning the range $\lambda = 0-1$, successively from independent replicas (no λ move) (b), from DR with a 65% acceptance ratio (c), and from RE (d).

case. Importantly, the equally good agreement with the exact solution also shows that DR is as accurate as RE.

The effectiveness of the DR method is compromised at both low and high acceptance ratios. If the ratio is low, the systematic sampling error is large because of poor sampling along x (as is illustrated by the results obtained with independent replicas; see Figures 4b and 5). If the acceptance is high (soft DRPE), then the replicas accumulate in regions of lower energy (i.e., at the endpoints in the present case) and statistical sampling errors along λ grow due to the fact that high-lying regions do not get sampled effectively. Thus, it is desirable to strike a balance between the acceptance ratio and the deviation from the target distribution. In the present case, an acceptance ratio as high as 65% leads to acceptable deviations from sampling uniformity and to accurate results (see Figures 4 and 5). By comparison, it should be noted that 96% acceptance is achieved in the RE simulations on the same set of replicas. By construction, RE never departs from sampling uniformity; the desired acceptance ratio is modulated instead by trial simulations with different numbers and spacings of replicas. With DR, the step size taken by λ during a replica move can be optimized for the application at hand. This can be done either a priori or on the fly. Step sizes can be any distance and can be made as small as required in order to decrease the system energy penalty and increase the acceptance probability.

Although this is not apparent in the simple model system tested here, another advantage of DR over RE is expected in applications where a large energy penalty is associated with λ moves (such as in simulations involving atomic displacements in dense media). Because the exchange of two replicas is associated with two separate conformational energy penalties (one for each replica), the probability of accepting a move is the product of two small probabilities. This ultimately leads to low mobility in λ space and, thus,

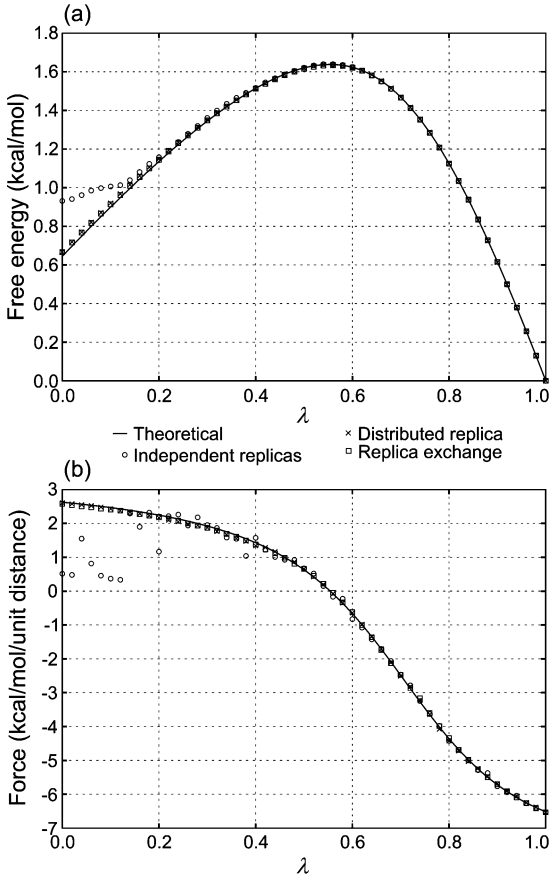

Figure 5. Potential of mean force (a) and mean force (b) acting on the particle along the reaction coordinate. The theoretical curves are shown with continuous lines; results obtained from independent replicas (circles), from distributed replica sampling (crosses), and from replica exchange (squares) are also shown. In the latter two cases, the size of the symbols is larger than the statistical sampling error.

poor sampling efficiency. The energy penalty for an exchange can be reduced by decreasing the spacing between nominal λ values of the replicas and, thus, increasing the number of replicas that span the reaction coordinate. However, smaller separation distances between replicas also hamper coordinate mobility. In contrast, replica moves in the DR method are associated with a single conformational energy penalty because, although the DRPE is analogous to a potential energy, it is not generally a function of system complexity. Furthermore, the severity of this penalty can be adjusted to some extent through the DRPE scaling constant *c*. For this reason, the sampling efficiency in DR is expected to be better than that in RE as the system complexity increases, although only in applications involving a spatial reaction coordinate and a dense medium. This advantage does not exist in temperature space.

Concluding Discussion

We report a simple yet powerful simulation technique that can be used in a range of applications utilizing both physical and alchemical transformations as well as in exhaustive sampling where a random walk in temperature is key. The method is of comparable efficiency to that of RE. Because it shares essential characteristics with RE, DR could be used with similar extensions. For example, it could be combined advantageously with adaptive-type methods such as ST and MUCA.[24−28]

The essential advantage of DR over RE lies in the ease of implementation on computer platforms. Traditional RE methods require dedicated CPUs in a homogeneous computing system. This is due to the need for replicas to finish simultaneously so that a swap event can occur. Thus, efficient implementation on shared or unreliable computing clusters or on large-scale distributed computing systems is very difficult to realize because CPUs often sit idle, waiting for other replicas to finish a simulation segment. For this reason, efforts to distribute replica exchange simulations have focused on minimizing this wait time through an optimized allocation of jobs on the basis of CPU speed.[33−35]

As the need for a larger number of replicas increases (in cases of complex systems), the feasibility advantage of DR over RE rises. Because DR undergoes replica jumps rather than replica exchanges, no CPU need ever wait for others to finish. A 100% utilization of all available CPU resources is thus realized. Furthermore, the method is not sensitive to changes in CPU speed or CPU availability, both of which cannot be considered fixed on most clusters. DR will continue running even if some replicas are suspended because of a drop in the number of available CPUs. DR sampling is, therefore, a different approach designed from the ground up to naturally suit shared or large-scale distributed computing platforms.

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