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Improving replica exchange using driven scaling

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Replica exchange is a powerful simulation method in which simulations are run at a series of temperatures, with the highest temperature chosen so phase space can be sampled efficiently. In order for swaps to be accepted, the energy distributions of adjacent replicas must have some overlap. This can create the need for many replicas for large systems. In this paper, we present a new method in which the potential energy is scaled by a parameter, which has an explicit time dependence. Scaling the potential energy broadens the distribution of energy and reduces the number of replicas necessary to span a given temperature range. We demonstrate that if the system is driven by the time-dependent potential sufficiently slowly, then equilibrium is maintained and energetic and structural properties are identical to those of conventional replica exchange. The method is tested using two systems, the alanine dipeptide and the trpzip2 polypeptide, both in water.

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I. INTRODUCTION

Many interesting molecular systems have important regions of conformational space separated by large energy barriers, which presents a challenge for molecular dynamics and Monte Carlo simulations. One general method to overcome the ergodicity problem is replica exchange (RE) (see Ref. 1 and references therein). In RE, a number of simulations of the system are run in parallel, so that the system with sampling problems (presumably under the conditions of interest) is linked to a system, which can easily overcome energy barriers (with an elevated temperature or a modified potential surface). Swaps between the different replicas are accepted with a probability that gives the correct Boltzmann weighting. In order for exchanges to be accepted, there has to be some overlap in the energy distributions of the replicas. This establishes how far apart in temperature the replicas can be and as the number of degrees of freedom, f_s , of the system increases, the number of replicas required to span the same temperature increases as approximately $f_s^{1/2}$.² The poor scaling of the method places practical limits on the system sizes that can be studied with RE. One of the largest studies is the folding of a 12 amino acid polypeptide with 3604 water molecules, which required 80 replicas to span a temperature range of 245–600 K, an average spacing between replicas less than 5 K.³ Other studies of similarly sized polypeptides require large number of replicas.^{4–6}

RE studies of larger systems, including small proteins, will require more efficient methods. A number of methods have been developed to reduce the number of replicas, which can involve quenching or annealing,^{7–11} the multicanonical algorithm (MUCA),^{12–14} simulated tempering (ST),^{15,16} and Hamiltonian RE.^{2,15,17–21} A method developed in our group, RE with dynamical scaling (REDS), shows promise as a general method for gaining efficiency.²² This method places be-

tween two distant replicas at temperatures T_A and T_B , a replica at an intermediate temperature, T_M , with an energy given by

$$E_\lambda(r) = \left[\frac{T_M}{T_A} \lambda + \frac{T_M}{T_B} (1 - \lambda) \right] E(r), \quad (1)$$

where $E(r)$ is the potential energy of the system. The variable λ is constrained in the interval from 0 to 1. If $\lambda=0$, then the Boltzmann weighting of the system is $\exp[-(T_M/T_B)E(r)/k_B T_M] = \exp[-E(r)/k_B T_B]$, or the same as that at the temperature T_B (where k_B is Boltzmann's constant). Because the configuration would have the same Boltzmann weighting for both replica B and the intermediate replica, an exchange between the two replicas would be accepted with probability one. The same would be true with replica A when $\lambda=1$. In this way, as λ varies from 0 to 1, the replica can exchange with both neighboring replicas, even if they have temperatures, which are widely separate. The variable λ is made to vary by treating it as a dynamical variable, with a mass and equations of motion, as is done in other λ -dynamics applications.^{23–31} In the first application of this method to the alanine dipeptide with 512 water molecules, the scaled replica was shown to replace about ten conventional replicas, reducing the number of replicas from 22 to 5. The method has some other advantages. Unlike other Hamiltonian RE methods, the modified replicas can give correct ensemble averages, for the entire range of temperature from T_A to T_B . The method can also be used in the isothermal-isobaric ensemble by scaling $E+PV$, where P is pressure and V is volume, rather than just E in Eq. (1).

One disadvantage of REDS over conventional RE is that in order to ensure that λ varies evenly between 0 to 1, a biasing potential must be used. The biasing potential would have to be determined prior to the simulation, increasing the setup time. Conventional RE also has setup time involved in the determination of the optimal set of temperatures to use.^{32–35} The other RE methods MUCA,^{12–14} ST,^{15,16} and

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quenching/annealing methods^{8,9,11} also require a biasing, or weight, factor, to ensure proper Boltzmann weighting. For the REDS method, the biasing potential can be constructed only from an estimate of the potential energy over the temperature range, T_A to T_B . In practice, a good biasing potential can be constructed from values of the potential energy at T_A , T_B , and T_M . Finding the potential energy is typically much easier than calculating the MUCA weights, which require the entropy over an energy range, or the ST weights, which require the Helmholtz free energy at different temperatures. The potential energy is particularly easy to estimate if the system's degrees of freedom are mostly water molecules, so the energy is dominated by the contributions from the water-water interactions, which can be calculated without advanced sampling techniques.

In this manuscript, we present a variation of the REDS method in which λ , rather than being a dynamical variable, is given an explicit time dependence and made to cycle from 0 to 1 and back again over some time scale, τ . This eliminates the need to determine the biasing potential and only requires choosing τ . The system is now driven externally as λ changes. This manuscript presents the new method and its application to two different systems, the alanine dipeptide with 512 water molecules, and a 12 amino acid peptide, which has a stable fold (the trpzp2 peptide³⁶) with 2434 water molecules.

II. METHODS

In the RE with driven scaling (REDS2) method, some replicas have a time-dependent energy function [Eq. (1)] and others have the standard potential energy, $E(r)$. The parameter λ is given an explicit time dependence,

$$\lambda = \sin^2(\pi t/\tau), \quad (2)$$

so that λ ranges from 0 to 1 over a time scale τ . Exchanges between the configurations, r_M , of a driven replica at a temperature T_M and the configurations, r_N , of a normal replica at a temperature T_N , with T_N corresponding to either T_A or T_B in Eq. (1), are accepted so that they satisfy detailed balance. Detailed balance is given by

$$\rho(r_N, T_N)\rho(r_M, T_M)T(N \rightarrow M) = \rho(r_N, T_M)\rho(r_M, T_N)T(M \rightarrow N), \quad (3)$$

where $T(N \rightarrow M)$ is the transition probability for the exchange between N and M . The densities are, for the driven replica,

$$\begin{aligned} \rho(r_M, T_M) &= e^{-(\lambda T_M/T_A + (1-\lambda)T_M/T_A)E(r_M)/k_B T_M} / Z_M \\ &= e^{-(\lambda/T_A + (1-\lambda)/T_A)E(r_M)/k_B} / Z_M, \end{aligned} \quad (4)$$

and, for the standard replica,

$$\rho(r_N, T_N) = e^{-E(r_N)/k_B T_N} / Z_N, \quad (5)$$

with Z_j being the configurational partition function. Equation (4) is the major assumption of the REDS2 method. It assumes that the configurations are in equilibrium with the time-dependent Hamiltonian and do not show any hysteresis. This will be true in the limit that τ goes to infinity and would

be verified for finite values. Using Eqs. (4) and (5), detailed balance is then

$$\begin{aligned} e^{-(\lambda/T_A + (1-\lambda)/T_A)E(r_M)/k_B} e^{-E(r_N)/k_B T_N} / (Z_M Z_N) T(N \rightarrow M) \\ = e^{-(\lambda/T_A + (1-\lambda)/T_A)E(r_N)/k_B} e^{-E(r_M)/k_B T_N} / (Z_M Z_N) T(M \rightarrow N). \end{aligned} \quad (6)$$

The ratio of the transition probabilities is

$$T(N \rightarrow M) / T(M \rightarrow N) = e^{\Delta_{NM}}, \quad (7)$$

where

$$\Delta_{NM} = \left[\frac{\lambda(t)}{k_B T_A} + \frac{1-\lambda(t)}{k_B T_B} - \frac{1}{k_B T_N} \right] [E(r_M) - E(r_N)], \quad (8)$$

which can be satisfied with the Metropolis criteria,³⁷

$$P(N \leftrightarrow M) = \min(1, e^{\Delta_{NM}}). \quad (9)$$

$P(N \leftrightarrow M)$ gives the probability of switching the coordinates of replica M , r_M , with the coordinates of replica N , r_N . Equations (8) and (9) represent a special case of the acceptance criteria for Hamiltonian RE.² Because the modification of the Hamiltonian is simple, the resulting value for Δ_{NM} is close to that for conventional RE in which $\Delta_{NM} = (1/k_B T_M - 1/k_B T_N) \times [E(r_M) - E(r_N)]$. From Eq. (8) it is evident that exchanges will be accepted automatically when $\lambda(t) = 1$ with the replica at $T_N = T_A$ and when $\lambda(t) = 0$ with the replica at $T_N = T_B$.

The driven replica not only can bridge between two replicas far apart in energy, it can also, like the REDS method, generate ensemble averages over the temperature range from T_A to T_B .²² The canonical ensemble average of a property A at a temperature T_i is

$$\begin{aligned} \langle A \rangle_{T_i} &= \frac{\int dr A(r) e^{-E(r)/k_B T_i}}{\int dr e^{-E(r)/k_B T_i}} \\ &= \frac{\int dr d\lambda A(r) \delta(\lambda - \lambda_i) e^{-E(r)/k_B T_\lambda}}{\int dr d\lambda \delta(\lambda - \lambda_i) e^{-E(r)/k_B T_\lambda}}, \end{aligned} \quad (10)$$

where

$$T_\lambda = (\lambda/T_A + (1-\lambda)/T_B)^{-1}, \quad (11)$$

and, with $T_{\lambda_i} = T_i$,

$$\lambda_i = (1/T_i - 1/T_B) / (1/T_A - 1/T_B). \quad (12)$$

The denominator in the left side of Eq. (10) is related to the probability distribution of λ ,

$$\langle P(\lambda_i) \rangle = \int dr d\lambda \delta(\lambda - \lambda_i) e^{-E(r)/k_B T_\lambda} / Z_M, \quad (13)$$

and the numerator is related to

$$\langle A(\lambda_i) \rangle = \int dr d\lambda A(r) \delta(\lambda - \lambda_i) e^{-E(r)/k_B T_\lambda} / Z_M, \quad (14)$$

so that

$$\langle A \rangle_{T_i} = \langle A(\lambda_i) \rangle / \langle P(\lambda_i) \rangle. \quad (15)$$

Both $\langle A(\lambda_i) \rangle$ and $\langle P(\lambda_i) \rangle$ can be calculated from the driven replica. Equation (15) is valid only if Eq. (4) is valid, that is, if the coordinates are in equilibrium with the time-dependent

potential. It is worth emphasizing that the driven replicas remain at a constant temperature, only the potential is being scaled in a way that can give ensemble averages over a range of temperatures. The method does not involve varying the temperature over some range, as in ST, or using temperature quenches.

A. Simulation details

Two different systems were used. The first is the alanine dipeptide using the OPLS-AA/L potential^{38,39} with 512 TIP4P (Ref. 40) water molecules. This was simulated using out our own program with a time step of 1 fs, SHAKE to constrain all bonds, Ewald for long-ranged electrostatic interactions, and Nosé–Hoover chains for thermostating. To examine how well the REDS2 method performs, we will compare the results using conventional RE with 22 replicas and REDS2 with 5 replicas, 3 conventional replicas (at $T=300$, 420, and 600 K), and 2 driven replicas (at $T=350$ and 494 K). These are the same temperatures used in a previous study with conventional RE and REDS (Ref. 22) and were chosen according to the relation $T_i=T_0 \exp(i\epsilon)$ as proposed by Sugita and Okamoto.⁴¹ The REDS2 method used a time constant, τ , equal to 50 ps, except as noted. Simulations were run twice for each method, once with all replicas in a $C7_{eq}/C5$ configuration ($\phi=-60^\circ$ and $\psi=-150^\circ$) and once with all replicas in a α_R/β_2 configuration ($\phi=-60^\circ$ and $\psi=0^\circ$). Each replica of the 22 replica system was simulated for 6 ns for a total simulation time, counting all the 22 replicas and both initial conditions, of 264 ns. Each replica for the 5 replica system with the REDS2 method was simulated for 16 ns for a total simulation time of 160 ns.

The second system is the 12 amino acid trpzip2 (Ref. 36) peptide using the ff99SB^{42,43} force field [shown to accurately reproduce the trpzip2 structure for trpzip2 (Ref. 43)] with 2434 TIP3P (Ref. 40) water molecules and one chloride ion for charge neutrality. The trpzip2 simulations were done by our own modifications to the AMBER9 suite of programs.⁴⁴ These simulations used 1 fs time step, SHAKE, particle mesh Ewald, and a Langevin heat bath to maintain a constant temperature. For the trpzip2 system, the REDS2 method was compared to the REDS method. Both methods used replicas to span a temperature range from 250 to 600 K. This is similar to the temperature range of 250 to 640 K used in a previous RE simulation, which had about the same system size (with 2433 water molecules) and required 62 replicas.⁵ Our implementation of REDS2 used 10 replicas (five scaled at 273, 320, 369, 436, and 533 K and five unscaled at 300, 343, 400, 480, and 600 K) and $\tau=200$ ps (except as noted). The REDS method used 16 replicas (eight scaled at 261, 286, 313, 343, 379, 424, 450, and 514 K and eight unscaled at 273, 300, 327, 360, 400, 450, 514, and 600 K). The REDS method used a mass for λ equal to 0.1 kcal/mol/ps. In addition, rather than enforcing the condition that λ stays in the interval from 0 to 1 by changing variables as done previously,²² we placed elastic hard walls at $-\epsilon$ and $1+\epsilon$, with $\epsilon=0.005$ Å.³¹ The scaled replicas have T_A and T_B values equal to the temperatures of the adjacent replicas; for the

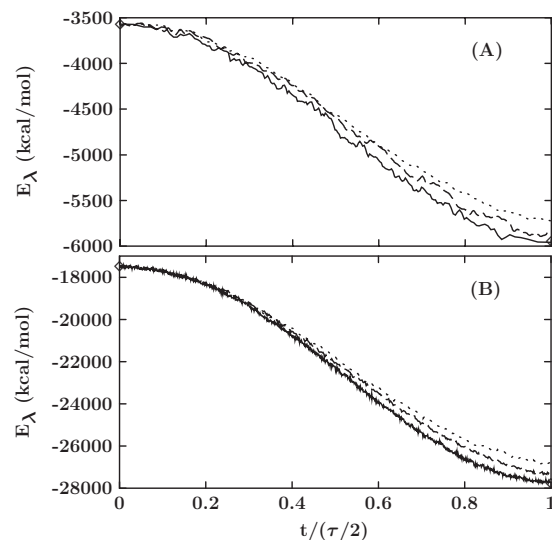


FIG. 1. Scaled energy, E_λ vs time for (a) the alanine dipeptide system with $\tau=1$ (dotted line), 2 (dashed line), and 20 ps (solid line) and (b) the trpzip2 system with $\tau=5$ (dotted line), 10 (dashed line), and 40 (solid line) ps. The diamonds show the equilibrium values for E_λ .

scaled replica with the lowest temperature, T_A equals 250 K. All replicas for both methods started from an unfolded state, which was generated by starting with the folded structure of trpzip2,³⁶ running at 640 K for 1.2 ns, and then equilibrating this unfolded structure at lower temperatures. The REDS results represent 10 ns per replica and the REDS2 results represent 14 ns per replica.

III. RESULTS

In order to implement the REDS2 method, a value for τ must be chosen. It is important that τ , which determines the time scale for the Hamiltonian scaling, is not too short, so the coordinates of the system can stay in equilibrium. Proximity to equilibrium can be checked by monitoring properties of the system as a function of λ . Using Eq. (15) properties of the driven replica can be related to the properties from standard simulations at the appropriate temperature. Energies are used to check closeness to equilibrium, rather than structural properties, since the equilibrium structure is not always known and reaching equilibrium for structural properties can be slow. If we start simulations with coordinates equilibrated at λ equal to 0 and run until λ equals 1 (this will be a time equal to $\tau/2$), we can compare different values of τ . Figure 1 shows E_λ versus time for both the alanine dipeptide and trpzip2 systems, both with the same scaling parameters ($T_A=300$, $T_B=420$, and $T_M=350$ K). The systems are equilibrated with λ equal to 0, which gives coordinates equivalent to a temperature of 420 K and an energy equal to $(350 \text{ K}/420 \text{ K}) \langle E \rangle_{420 \text{ K}}$, or the energy at 420 K times a scaling factor. As time goes to $\tau/2$, λ goes to 1 and the energy should approach $(350 \text{ K}/300 \text{ K}) \langle E \rangle_{300 \text{ K}}$. The curves for the alanine dipeptide show τ equal to 1, 2, and 20 ps. With τ the coordinates are in equilibrium with E_λ and values greater than 20 ps are essentially the same. The curves for trpzip2

show τ equal to 5, 10, and 40 ps. For this system, the coordinates appear to be in equilibrium for τ greater than or equal to 40 ps.

The value of τ required to maintain equilibrium is system dependent, as shown in Figure 1. The trpzip2 system is a factor of 4 or 5 larger than the alanine dipeptide system, largely due to the difference in the number of water molecules (2434 compared to 512). The required τ increases by about a factor of 2 (20 to 40 ps), going from the alanine dipeptide to the trpzip2 system. This time scale is related to the energy fluctuations. The energy for both systems is dominated by water-water interactions because water molecules make up the large majority of degrees of freedom. The most significant factor for the energy difference is the number of water molecules, rather than the different solutes. Fluctuations in the energy, δE , are related to the heat capacity through $\delta E^2 = k_B T^2 C_V$, and so, because the heat capacity increases with the number of particles, N , δE increases only as $N^{1/2}$. Fluctuations as a fraction of the energy, which increases linearly with N , decrease as $N^{-1/2}$. (This is evident in Fig. 1 in which the short time oscillations of the energy are larger for the alanine dipeptide than for the trpzip2 system.) Fluctuations of size $\delta E/E$ will be less likely by a factor of $N^{-1/2}$ and the time we have to wait for these fluctuations increases. The difference in $N^{1/2}$ between the trpzip2 and the alanine dipeptide systems is about a factor of 2, consistent with the factor of 2 difference in the τ values.

These results are encouraging and show that the system can be driven at reasonable time scales, from 20 to 40 ps, for a large temperature difference (120 K). For the REDS method with the same temperature scaling and the same alanine dipeptide system, λ varies from 0 to 1 over a time scale of about 20 ps (see Fig. 1 of Ref. 22).⁴⁵ This agrees well with the REDS2 value for τ . The time scale for λ dynamics is determined by energy fluctuations, which act as a force to move λ , and the choice of a mass for the λ variable. This means that under the influence of the energy fluctuations of the system, λ can vary from 0 to 1 on the same time scale as it can be driven using the REDS2 method. Any faster than this and the system will be out of equilibrium.

The way in which energy fluctuations propagate is different between conventional RE and REDS, on the one hand, and REDS2, on the other. In conventional RE, if there is a fluctuation to a lower energy structure for the high temperature replica, that structure will tend to be exchanged with that of the lower temperature replica as determined by the RE Metropolis criteria. How far that structure moves through the replicas depends on how its energy compares to that of the other replicas. In REDS, the structure will propagate downward by λ dynamically changing from zero to one (if $T_A < T_B$), which will happen if the force on λ moves it in that direction. The force is due to the difference in the energy of that structure and the biasing potential, which has been parametrized to represent an average energy for that value of λ . So for both RE and REDS, movement of a structure from high to low temperature first requires a fluctuation to a low energy structure for the high temperature replica, then a comparison of that energy with the energy of other replicas or with the biasing potential. In the REDS2 method, the energy

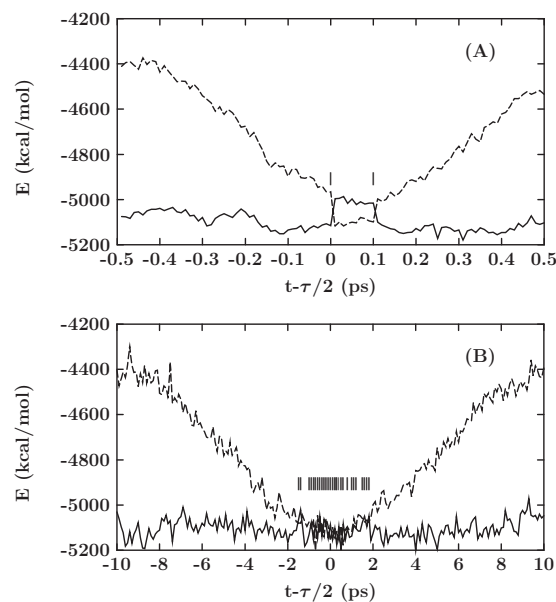


FIG. 2. Energy vs time for two replicas of the alanine dipeptide system, with the $T=300$ K (solid line) and the driven replica ($T_A=300$ K, $T_B=420$ K, and $T_M=350$ K) with (a) $\tau=1$ ps and (a) $\tau=20$ ps. Vertical lines indicate the points at which exchanges were accepted.

of the structure is not used to propagate λ . The propagation is driven and the energy fluctuations are induced by the driven potential. The energy is used to accept swaps, using Eq. (9), but if λ equals 1, the swap will be accepted with probability one because Δ_{NM} will equal 0. If structure is out of equilibrium, either because it has been driven too fast or because it caught in a local minimum, then it will be accepted regardless of its energy at $\lambda=1$.

This is illustrated in Fig. 2(a), in which the system is out of equilibrium and swaps are attempted every 0.1 ps. The swap at $t=\tau/2$ (when λ equals 1) is accepted even though the scaled replica has appreciably higher energy than the unscaled replica. The next attempt is also accepted, which removes the high energy structure from the 300 K replica and after that, because λ is not equal to one, swaps will not be accepted with the higher energy configuration. By taking frequent swap attempts, these structures out of equilibrium will be eliminated. Of course, the structure will be retained for the duration of a swap attempt (here 0.1 ps) and will make an incorrect contribution to ensemble averages at this temperature, even if it is for a small time. If the driven replica is in equilibrium, then swaps will be accepted not only when $t=\tau/2$ but also for a range of time when the energies of the two replicas are close, as shown in Fig. 2(b). In this trajectory, 27 swaps are accepted over about a 4 ps interval, as indicated by the vertical lines, giving an acceptance ratio of about 50% over the 4 ps interval. When t is between $\tau/2 - 0.6$ and $\tau/2 + 0.6$ ps every swap is accepted. There is an equal chance that either configuration eventually ends up at the lower temperature, depending on whether an odd or even number of swaps is accepted during this interval. On the other hand, if the system is driven out of equilibrium, the higher energy configuration will not end up at the lower temperature as long as more than the one swap attempt when λ equals 1 is made.

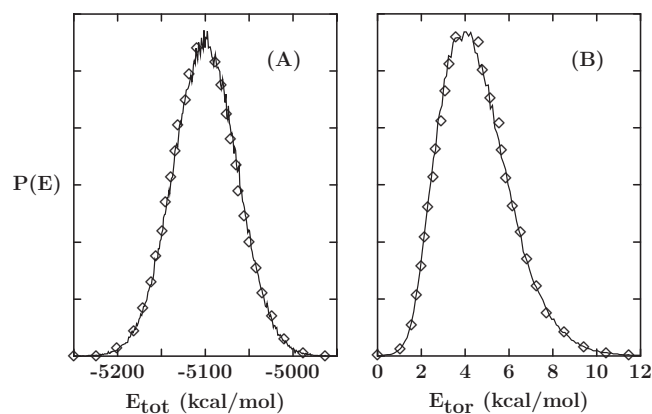


FIG. 3. Distribution of energy at 298 K for the alanine dipeptide system for 5 replica REDS2 (solid lines) and 22 replica RE (diamonds) for (a) the total energy and (b) the torsional energy.

A good choice of the exchange frequency is important with the REDS2 method. For conventional RE, any calculated properties should be independent of the exchange frequency, although some choices may lead to more optimal sampling.^{46–50} For the REDS2 method, it is important that the exchange frequency not be out of phase with the driven Hamiltonian, so that attempts are made when λ is near zero or one. In addition, during the interval when λ is near these extremes, more than one attempt would be advantageous, so the exchange frequency should be much less than the period for the driven Hamiltonian, $1/\tau$.

Once suitable values of τ were found, the performance of the REDS2 method can be examined for the alanine dipeptide and the trzip2 systems, with conditions as described above. The REDS2 method should give the same distribution of energies and the same average energy as a function of temperature as conventional RE or other methods. It should also give the same distribution of structures. The distribution of energies at 298 K for the alanine dipeptide shows close agreement between REDS2 and RE for the total energy, as shown in Fig. 3(a). The distributions are essentially identical; the total energy is almost completely due to the water interactions, so this agreement shows just the water degree of freedom are in equilibrium. Fig. 3(b) shows the distribution of the torsional energy, which comes from the peptide only and represents the slow degrees-of-freedom with the highest barriers. This also shows good agreement between REDS2 and RE, indicating that the torsional degrees-of-freedom are also in equilibrium. The trzip2 system shows good agreement for the total and torsional energy between the REDS2 and REDS methods (Fig. 4), so for this larger system, the coordinates appear to be in equilibrium with the time-dependent potential, as well.

Ensemble averages over a range of temperatures can be calculated from a single REDS2 replica using Eq. (15). Figure 5 compares the total and torsional energy from the scaled replicas from REDS2 with the RE results. This entire temperature range of 300 K is determined from the data from only two scaled replicas, which is being compared to the data from 22 conventional replicas. The two are in good agreement. Similar plots for the trzip2 system are shown in Fig. 6 comparing 10 replica REDS2 and 16 replica REDS.

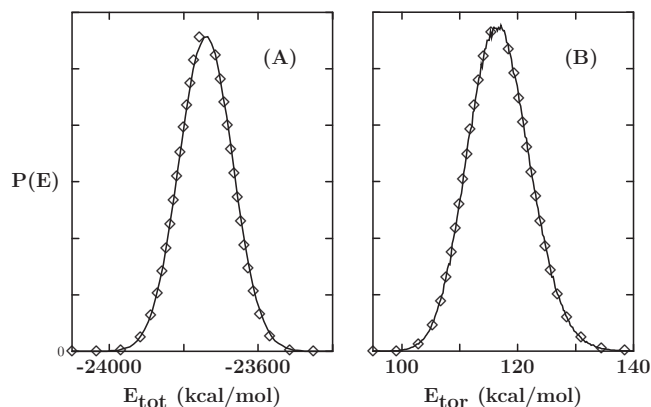


FIG. 4. Distribution of energy at 298 K for the trzip2 system for 10 replica REDS2 (solid lines) and 16 replica REDS (diamonds) for (a) the total energy and (b) the torsional energy.

The agreement between the methods is close for both systems, indicating that the scaled replicas are in equilibrium over the entire λ range.

In addition to correct energies, the REDS2 method should also give the correct structures. The structures of the alanine dipeptide can be split up into four regions in the Ramachandran diagram.⁵¹ The two most populated regions are $C7_{eq}/C5$ and $\alpha_R/\beta2$ and, as mentioned previously, we started two sets of simulations with all replicas with one of the two regions. We can then examine the cumulative average of the population fraction, X , for each structure as a function of time. Figure 7 compares the population of the $C7_{eq}/C5$ region from the RE and REDS2 simulations. To make a fair comparison, the total simulation time for each method is used. This is equal to the simulation time for a single replica times the number of replicas, giving the total CPU time used by each method. The population fractions take a long time to converge (as is evident from Fig. 7) because, rather than finding a single structure, the simulations need to make enough transitions among the structures to give the correct populations. The RE simulations starting

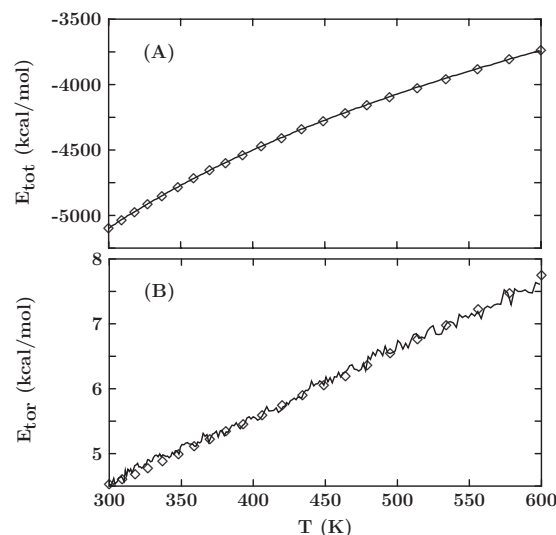


FIG. 5. Average energy as a function of temperature for the alanine dipeptide system for 5 replica REDS2 (solid lines) and 22 replica RE (diamonds) for (a) the total energy and (b) the torsional energy.

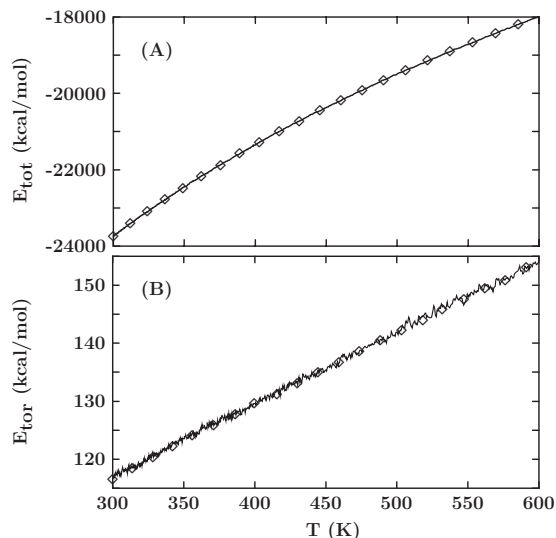


FIG. 6. Average energy as a function of temperature for the trpzip2 system for 10 replica REDS2 (solid lines) and 16 replica REDS (diamonds) for (a) the total energy and (b) the torsional energy.

from the different initial conditions are still not converged after 22×6 ns of total simulation time. The REDS2 simulations agree with each other more closely, after 5×14 ns, but it is not clear if the RE and REDS2 simulations are converging to the same value. Slow convergence is partially due to biases of the initial configurations, which are all either $X(\alpha_R/\beta_2)$ equal to 0 or 1. If we use only the second half of the data, assuming that we have reached equilibrium at this point and just need to accumulate enough transitions among structures, then we get good agreement between the two methods (Table I). This agreement indicates that the REDS2 method is giving the correct distribution of structures for the alanine dipeptide system. (For the trpzip2 system, the simulations will have to go much longer than the times simulated here to achieve convergence for structural properties.)

The efficiency of RE is dependent on the time it takes to

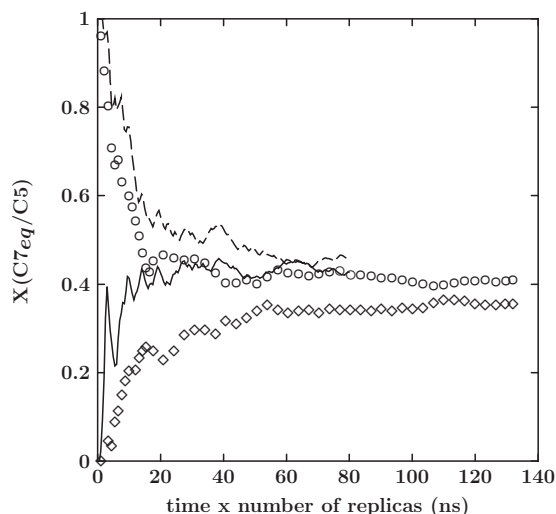


FIG. 7. The population of the $C7_{eq}/C5$ structure for the alanine dipeptide at $T=298$ K for 5 replica REDS2 (lines) and 22 replica RE (symbols). The diamonds and solid line represent the simulation that started in the α_R/β_2 configuration and the circles and dashed line in the $C7_{eq}/C5$ structure.

TABLE I. The populations of four structures of the alanine dipeptide using data from the last half of the simulation.

Method	$C7_{eq}/C5$	α_R/β_2	α_L	$C7_{ax}$
REDS2	0.40 ± 0.04	0.57 ± 0.04	0.025 ± 0.008	0.003 ± 0.002
RE	0.39 ± 0.02	0.57 ± 0.02	0.034 ± 0.010	0.005 ± 0.002

cycle from the highest temperature to the lowest. Figure 8 follows the temperature of a selected replica for 10 ns. The transitions among the temperatures follow a regular pattern, with rapid transitions between neighboring replicas at times when λ is near 0 and 1 followed by no transitions for a period of $\tau/2$ when λ is between 0 and 1 (τ equals 0.2 ns). An analysis of all the data from the trpzip2 simulations shows that it takes 5 ± 1 ns for a replica to move from 273 to 600 K, which is consistent with Fig. 8, where the replica goes from 273 to 600 and back in about 10 ns. This is at least as fast as conventional RE for the same system, as shown in Fig. 2 of Ref. 5. For the alanine dipeptide system, the REDS2 method takes 0.16 ± 0.02 ns to go from 300 to 600 K, about the same as conventional RE, which takes 0.18 ± 0.02 ns. This value for RE is faster than the value of 0.8 ± 0.1 ns for the system reported previously.²² That simulation attempted exchanges every 1 ps rather than 0.1 ps, as done here, demonstrating that smaller exchange frequencies may lead to more efficient sampling, as suggested elsewhere.⁴⁹ The replicas using REDS2 method move through temperature space about as fast as conventional RE, but with fewer replicas.

IV. CONCLUSIONS

The REDS2 method can improve the efficiency of RE by reducing the number of replicas, from 22 to 5 for the alanine dipeptide and about 60 to 10 for the trpzip2 system. The method combines conventionally simulated replicas at some temperatures with driven replicas using a time dependent potential. The driven replicas, in addition to bridging conventional replicas separated by large temperature differences,

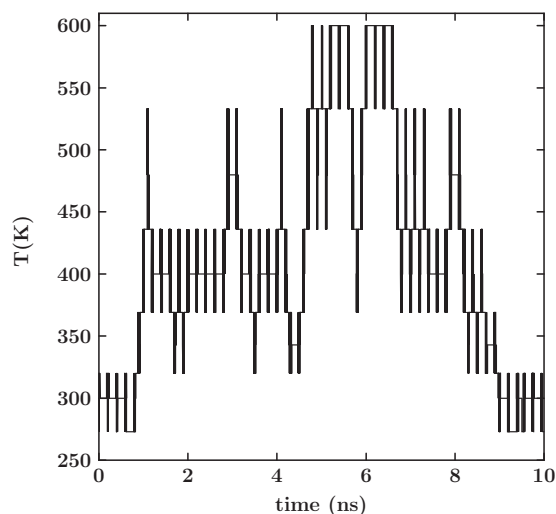


FIG. 8. The temperature of a selected replica as a function of time for the trpzip2 system.

also give ensemble averages over a range of temperatures. The REDS2 method is easy to implement and easy to add to simulation packages like AMBER and, because the driven replicas run at the same time as the conventional replicas, the method parallelizes as well as standard RE. These features have common with the REDS method.²² The difference is that the REDS2 method does not require a biasing potential to ensure even sampling. Rather, it requires a single parameter, τ , which determines the time scale for the variations in the potential energy. The parameter needs to be chosen so that the system is in equilibrium, which can be determined by running for a period $\tau/2$ and seeing if the energy matches values from conventional simulations at the relevant temperatures (see Fig. 1). If appropriate values for τ are used, then the REDS2 method successfully reproduces the energies and structures for the alanine dipeptide and the trpzip2 systems.

The method provides a solution to the problem caused by the poor system size scaling of RE. For conventional RE, as the number of degrees of freedom, f_s , increases, the number of replicas required to span the same temperature increases as approximately $f_s^{1/2}$.² For REDS2, the same number of replicas could in principle span the same temperature range, but the value of τ would need to increase. The alanine dipeptide and tripzip2 systems are different in size by a factor of 4.75 (mostly due to an increase in the number of water molecules) and the value of τ necessary to maintain equilibrium increases by about a factor of 2. This implies that τ scales as $f_s^{1/2}$, consistent with how energy fluctuations depend on system size, as discussed above. This dependence of τ means it would take longer for replicas to cycle through the range of temperatures as f_s increases. Conventional RE would also take longer to cycle as f_s increases because there are more replicas. The results of this study for the alanine dipeptide found that the cycle times for RE and REDS2 are about the same, if swap attempt frequencies for RE are optimal. The time scales for both methods are ultimately driven by the inherent energy fluctuations of the system, so, while it could be different for other systems, it make sense that the cycle times are comparable. Taking all this together suggests that the REDS2 method scales better than conventional RE by a factor of $f_s^{1/2}$, from the increase in the number of replicas in RE. For large systems, which can have average spacings of less than 5 K between replicas,³ REDS2 can be implemented to have spacing between replicas of about 50 K, as done here for the trpzip2 system.

An optimization of the temperature gaps spanned by the driven replicas and the form of the time dependence of the scaling variable λ was not attempted and better choices could be made. In this study, λ varies as $\sin^2(\pi t/\tau)$, which has the effect of moving λ more slowly at the end points (near 0 and 1). This allows for plenty of replica swaps at the end points, but it may be better to vary λ at a constant rate, e.g., by a triangle wave. Another possibility would be to pause the conventional replicas while the driven replicas are moving between the two limits when exchanges are unlikely. These variations may make the REDS2 method more efficient.

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⁴⁵In Fig. 1 of Ref. 22, the x-axis is incorrectly labeled. It should read 0.02, 0.04, 0.06, 0.08, and 0.10.

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⁵¹The $C7_{eq}/C5$ region is defined as $\phi < 0$ or $\phi > 130$ and $\psi < -110$ or $\psi > 80$; α_R/β_2 is $\phi < 0$ or $\phi > 130$ and $-110 < \psi < 80$; α_L is $0 < \phi < 130$ and $-60 < \psi < 90$; and $C7_{ax}$ is $0 < \phi < 130$ and $\psi < -60$ or $\psi > 90$.