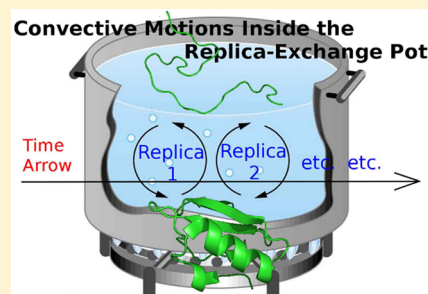


Convective Replica-Exchange in Ergodic Regimes

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ABSTRACT: In a recent article (*J. Comput. Chem.* **2013**, *34*, 132–140), convective replica-exchange (convective-RE) has been presented as an alternative to the standard even–odd transition scheme. Computations on systems of various complexity have shown that convective-RE may increase the number of replica round-trips in temperature space with respect to the standard exchange scheme, leading to a more effective sampling of energy basins. Moreover, it has been shown that the method may prevent the formation of bottlenecks in the diffusive walk of replicas through the space of temperature states. By using an ideal temperature-RE model and a classical harmonic-oscillator RE scheme, we study the performances of convective-RE when ergodicity is not broken and convergence of acceptance probabilities is attained. In this dynamic regime, the round-trip ratio between convective and standard-RE is at maximum ~ 1.5 , a value much smaller than that observed in nonergodic simulations. For large acceptance probabilities, the standard-RE outperforms convective-RE. Our observations suggest that convective-RE can safely be used in either ergodic or non-ergodic regimes; however, convective-RE is advantageous only when bottlenecks occur in the state-space diffusion of replicas, or when acceptance probabilities are globally low. We also show that decoupling of the state-space dynamics of the stick replica from the dynamics of the remaining replicas improves the efficiency of convective-RE at low acceptance probability regimes.



1. INTRODUCTION

Convective-RE¹ is a simulation method designed to enhance replica round-trip rate and to avoid the formation of replica diffusion bottlenecks through the states of a generalized ensemble.^{2–5} To achieve these benefits, convective-RE artificially forces each replica to perform round-trips through the states of the generalized ensemble. In doing so, global balance holds, and a stationary distribution can be reached. For the sake of clarity and to introduce a few key concepts, we will summarize the algorithm underlying the convective-RE by using the words of Spill and co-workers.¹

“In the RE method, N simulations of the same system are performed in parallel. Each simulation can be run in different ensembles [also called states], for example, at different temperatures, ... which are all controlled via a set of control parameters. Each state will be given a unique label for quick reference. For simplicity, the states’ labels are a monotonous function of the control parameters (in the canonical case, the lowest temperature is assigned label 1 and the highest is given label N). At a given exchange rate, adjacent states are allowed to exchange their conformations with a certain probability, given by the Metropolis criterion.⁶ We call a given conformation whose simulation temperature is a function of time a replica. Let S_i be the function that gives the state of replica i .

... The convective algorithm is constructed as follows. Before trying the first exchange, a replica is chosen at random; we will refer to it as the stick replica; other replicas are passive. Let i be the index of this stick replica, which is thus in state S_i at time 0. Upon the next exchange attempt, the transition matrix is chosen so as to

allow the stick replica to exchange with its right neighbor state, $S_i + 1$. If the exchange fails, the simulation of each replica is continued. The next exchange attempt is however performed using the same transition matrix. The transition matrix is not changed until the exchange with the stick replica is accepted; the stick replica eventually is in state $S_i + 1$. The exchange matrix is then changed to allow for an exchange between $S_i + 1$ and $S_i + 2$, and the same procedure is applied until the stick replica is in state N . At that point, the direction is reversed, and the transition matrices are chosen so that the stick replica can only go to lower state indices. Finally, when the stick replica reaches the lowest temperature state, the direction is reversed again and the same procedure is applied until the stick replica reaches its initial state S_i . The stick replica has then accomplished a round-trip in state space. Then, another replica, j , is chosen to be the stick replica and the same procedure is applied in turn until all replicas have been convective once, after which the stick replica is again replica i , j , and so forth.”

Convective-RE converges to the desired distribution. In the original article,¹ it is proven both analytically and numerically that convective-RE satisfies global balance for the Boltzmann distribution. Also, it is easily seen that in this method, as in any replica-exchange method with N states, there is a nonzero probability of reaching any state from any other state after $N - 1$ moves, so the sampling is regular. These two conditions ensure⁷ that there is a unique stationary limit to the Markov chain, which is the Boltzmann distribution.

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The ability of convective-RE to explore conformational space was tested in systems of different degrees of complexity: alanine dipeptide in implicit solvent, the GB1 β -hairpin in explicit solvent and the $A\beta_{25-35}$ homotrimer in a coarse grained representation.¹ Comparison of convective-RE with the standard method, namely the deterministic even-odd exchange scheme,⁸ revealed that convective-RE significantly enhances sampling of energy landscapes, and increases the number of replica round-trips through temperature space. Sampling efficiency and number of replica round-trips are known to be correlated⁹⁻¹² in generalized ensemble^{13,14} approaches such as RE, and increasing the number of round-trips is often a means of enhancing exploration of conformational space. Given that convective-RE forces (stick) replicas to perform round-trips through state space, it seems surprising that replica round-trip rates increase in GB1 β -hairpin and $A\beta_{25-35}$ systems while they decrease in the less complex alanine dipeptide system.¹ In fact, the ratio between convective and standard-RE round-trip rates goes from 48 and 8 for GB1 β -hairpin and $A\beta_{25-35}$ systems, respectively, to 0.65 for the alanine dipeptide. In this case, the standard method even outperforms convective-RE. Although these observations point to some dependence of the performances of convective-RE on the complexity of the system, a precise rationalization is difficult owing to the nonergodic regime to which GB1 β -hairpin and $A\beta_{25-35}$ systems are subjected. In the latter systems, ergodicity breaking is revealed by a couple of observations: (i) the number of new structures detected during standard and convective-RE simulations are still increasing at the end of the simulation (see Figure 3 of ref 1) and (ii) in the convective-RE simulation, an anomalous correlation between average potential energies and populations of conformational basins has been observed (see Table 1 and related discussion of ref 1).

We notice that for the above cases, ergodicity breaking is not intrinsic to the systems or somehow generated by a sort of unsuitability of the simulation algorithm. Rather, it is a consequence of the small simulation time with respect to the times that would be necessary to get a completely convergent sampling. Furthermore, a common drawback of RE simulations of complex systems lies in the fact that conformations are not decorrelated between successive exchanges (which happened every 3 to 6 ps in ref 1). This correlation may dramatically increase the time needed to reach ergodicity in these systems. We note that the broken ergodicity in GB1 β -hairpin and $A\beta_{25-35}$ simulations prevented from getting sound quantitative evaluations of the performances of convective-RE.

In the present article, we tackle the above aspect of the problem by exploiting two benchmark systems presenting ergodic behavior, for which convergence of the acceptance probabilities of replica exchanges and number of replica round-trips is almost achieved. We also consider a third case where a local bottleneck is present in the diffusive walk of replicas through state space. In particular, we will explore how the acceptance probability of replica exchanges, modulated by the number of replicas, affects the number of replica round-trips in convective-RE compared to the standard method.

Finally, we will show that it is possible to improve the efficiency of convective-RE, by supplying the convective scheme with an algorithm aimed at decoupling the dynamics of stick and passive replicas through state space.

2. SETUP OF BENCHMARK SIMULATIONS

The first benchmark case consists of a series of ideal RE simulations in temperature space in which the potential energies of each replica are sampled according to a Gaussian probability:

$$\rho_i(E) = \frac{1}{T_i \sqrt{2\pi C}} \exp \left[-\frac{(E - CT_i)^2}{2CT_i^2} \right] \quad (1)$$

where E is the potential energy of the replica lying in the state at temperature T_i and C is the system heat capacity, which we assume to be constant.¹⁵ Note that in eq 1, C denotes the (extensive) heat capacity in units of Boltzmann constant k_B and refers to the potential energy part of the total energy. In order to get equal average acceptance probabilities for the exchanges between neighboring replicas, the spacing law of temperatures is¹⁶

$$T_i = T_{\min} \left(\frac{T_{\max}}{T_{\min}} \right)^{\frac{i-1}{N-1}} \quad (2)$$

where $[T_{\min}, T_{\max}]$ is the temperature range covered by the N states/replicas of the generalized ensemble, with temperature index $i = 1, \dots, N$. For both convective and standard-RE algorithms we have performed several RE simulations with a number of replicas N ranging from 8 to 100, but with a fixed temperature range $T_{\min} = T_1 = 300$ K to $T_{\max} = T_N = 1500$ K and with temperature spacing according to eq 2. In these simulations, replica potential energies E are drawn at each RE step from the distributions given by eq 1, with $C = 500$ for the heat capacity. The Metropolis criterion⁶ is applied to evaluate the outcome of the exchange attempts. In order to get convergent estimates of both acceptance probabilities and number of replica round-trips, long simulations lasting 10^7 steps have been carried out. Replica exchanges are attempted at every step.

The other benchmark case consists of RE simulations in which the states are described by one-dimensional harmonic oscillators, whose Hamiltonians depend parametrically by a factor λ_i entering both in the equilibrium position and in the force constant of the oscillators: $H_i(x) = 1/2K(\lambda_i)(x - \lambda_i)^2$. At each step, the replica coordinates, x_i , are picked according to a Boltzmann distribution with $\beta^{-1} = k_B T = 1$:

$$\rho_i(x) = Z^{-1} \exp(-H_i(x)), \quad (3)$$

with Z being the partition function of the system. In all simulations, the parameter λ_i ranges from $\lambda_1 = 0$ to $\lambda_N = 40$ in equally spaced steps, i.e., $\Delta\lambda = \lambda_{i+1} - \lambda_i = 40/(N - 1)$. Two series of simulations have been performed with different definition of $K(\lambda_i)$: A-simulations, in which $K(\lambda_i) = 1$ for all states $i = 1, 2, \dots, N$; and B-simulations, in which

$$K(\lambda_i) = 1 + 30 e^{-(\lambda_i - 10)^2} \quad (4)$$

This choice for $K(\lambda_i)$ allows us to introduce a bottleneck in correspondence of few states associated with λ_i around the value of 10. For example, in a B-simulation with 32 replicas, eq 4 gives rise to the $K(\lambda_i)$ sequence shown in Figure 1a. In a standard B-simulation, such a sequence leads to an acceptance probability bottleneck mainly localized at the transitions $\lambda_8 \leftrightarrow \lambda_9$ and $\lambda_9 \leftrightarrow \lambda_{10}$ (see Figure 1b). For these two transitions, the average acceptance probabilities are in fact 2.4×10^{-4} and 2.7×10^{-4} .

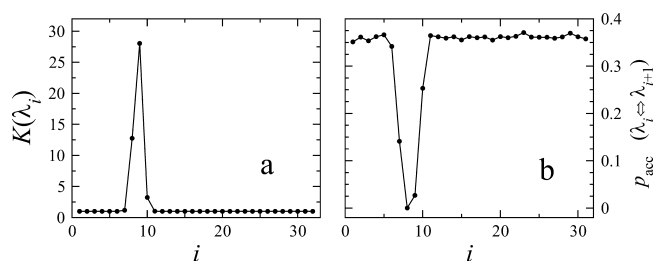


Figure 1. (a) Sequence of the $K(\lambda_i)$ parameter as a function of the index i employed in a B-simulation with 32 replicas. (b) Acceptance probability p_{acc} of replica transitions $\lambda_i \leftrightarrow \lambda_{i+1}$ as a function of the index i computed from a standard-RE B-simulation with 32 replicas.

10^{-2} , respectively, versus values of about 0.36 for replica transitions far from the bottleneck.

Like in temperature-RE simulations, a series of A-simulations have been performed with N ranging from 8 to 100, each lasting 10^7 steps. At every step, the replica coordinates x are drawn according to eq 3 and simultaneously a replica exchange is attempted. B-simulations are instead 3.4×10^5 steps long, with N ranging from 32 to 96. The setup of B-simulations has been devised to mimic a system where all parameters, i.e. $\Delta\lambda$, $K(\lambda_i)$ and N , yield acceptance probabilities comparable to those of typical atomistic simulations in the generalized ensemble^{17–19} (see Figure 1b). Also the number of steps has been chosen to get simulation times consistent with state-of-the-art atomistic simulations. For example, with a number of attempted replica-exchanges of 3.4×10^5 and considering that replica exchanges are typically performed every few ps in atomistic simulations, our B-simulations would cover times of the order of 10^2 – 10^3 ns. In the specific case that replica exchanges are attempted every 6 ps, as in $A\beta_{25-35}$ simulations of ref 1, our simulation time would correspond to slightly more than $2 \mu\text{s}$ (versus $0.5 \mu\text{s}$ of $A\beta_{25-35}$ simulations). Since all above quantities take realistic values, we expect that the number of round-trips is comparable to that of atomistic simulations. On the other side, we notice that, owing to the relatively small number of steps in B-simulations, the average round-trip numbers may not be large enough to allow precise evaluations. This aspect can be particularly critical in those B-simulations that are affected by low acceptance probabilities around the bottleneck. Therefore, in order to confirm our outcomes, we also performed B-simulations with standard and convective-RE schemes lasting 10^7 steps, in which the number of round-trips is expected to increase by a factor of about 30 with respect to B-simulations 3.4×10^5 steps long.

3. RESULTS AND DISCUSSION

In Figure 2a, we report the number of round-trips per replica, n_{rt} , as a function of the average acceptance probability, p_{acc} , obtained from standard and convective-RE simulations performed in λ space (A-simulations) and in temperature space (temperature-RE simulations). The acceptance probability has been modulated by varying the number N of replicas in the simulations. The trends of the curves obtained from temperature and λ -space simulations are similar because the sampling of potential energy and replica coordinates, respectively, occurs according to Normal distributions (eqs 1 and 3). In convective-RE, the maximum performance is reached at $p_{\text{acc}} \simeq 0.28$, versus $p_{\text{acc}} \simeq 0.4$ of standard-RE.⁸ It is worth noting that, at small p_{acc} values, convective-RE outperforms standard-RE, whereas the opposite occurs at large p_{acc} . The

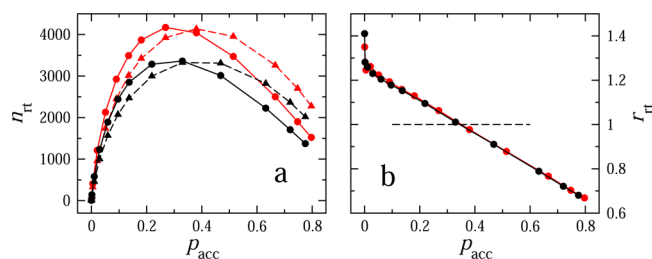


Figure 2. (a) Number of round-trips per replica, n_{rt} , as a function of the average acceptance probability, p_{acc} , calculated from temperature-RE simulations and A-simulations (red and black colors, respectively) with various numbers of replicas (circles and triangles from left to right represent simulations performed with $N = 8, 10, 12, 14, 16, 18, 20, 24, 30, 40, 60, 80, 100$). Simulations using the standard method are reported with triangles, while simulations using convective-RE are reported with circles. (b) Ratio between the numbers of replica round-trips estimated with convective-RE and standard simulations, $r_{\text{rt}} = [n_{\text{rt}}]_{\text{conv}}/[n_{\text{rt}}]_{\text{stand}}$, in temperature-RE simulations and A-simulations (red and black colors, respectively). The dashed line indicates the crossover regime.

crossover regime falls at $p_{\text{acc}} \simeq 0.35$ for both types of simulations.

The performances of convective and standard-RE can be compared by plotting the ratio of the number of replica round-trips estimated by the two methods, that is, $r_{\text{rt}} = [n_{\text{rt}}]_{\text{conv}}/[n_{\text{rt}}]_{\text{stand}}$, as a function of p_{acc} . The plots are shown in Figure 2b. We note that, for temperature-RE simulations in the regime of very small p_{acc} values ($\sim 3.2 \times 10^{-4}$), n_{rt} for convective-RE is 1.35 times greater than n_{rt} for standard-RE. Similar outcomes are obtained in λ -space simulations ($r_{\text{rt}} \simeq 1.4$ at $p_{\text{acc}} \simeq 5.4 \times 10^{-5}$). In both cases, the ratio r_{rt} , though significantly greater than 1, is about 1 order of magnitude smaller than that gained from nonergodic simulations of atomistic systems.¹ Interestingly, the standard method appears to be more efficient than convective-RE when p_{acc} is large, and reaches $r_{\text{rt}} \simeq 0.67$ for $p_{\text{acc}} \simeq 0.78$. These observations are roughly consistent with the outcomes of ref 1. In fact, under the well-grounded assumption that crossover is not attained in the simulations of GB1 β -hairpin and $A\beta_{25-35}$,²⁰ we may argue that p_{acc} is in average smaller for GB1 β -hairpin than for $A\beta_{25-35}$ from the fact that the number of round-trips per replica, that is, $n_{\text{rt}}/\text{Simul.Time}$, is smaller in the standard-RE simulation of the former system ($n_{\text{rt}}/\text{Simul.Time} = 3.1 \times 10^{-4}$ found in standard-RE simulation of GB1 β -hairpin, versus 9.2×10^{-3} found in standard-RE simulation of $A\beta_{25-35}$). Thus, on the basis of our results, a greater r_{rt} is expected for the GB1 β -hairpin simulation. Indeed, this is in agreement with the outcomes of ref 1 ($r_{\text{rt}} = 48$ for GB1 β -hairpin versus $r_{\text{rt}} = 8$ for $A\beta_{25-35}$). Moreover, the much larger number of round-trips per replica achieved in the standard-RE simulation of alanine dipeptide points to a p_{acc} even greater than that of the $A\beta_{25-35}$ simulation. Considering that $r_{\text{rt}} = 0.65$, we may argue that, in the case of the alanine dipeptide, crossover regime has been largely surpassed.

In spite of this qualitative agreement between the present study and the results of ref 1, we notice the very large quantitative difference in the r_{rt} values. To explain such differences one could suppose that the ratio r_{rt} goes asymptotically to infinity as p_{acc} goes to zero, but this is not strongly supported by the quite large n_{rt} , and hence the non-negligible values of p_{acc} , observed in the simulations of $A\beta_{25-35}$. On the other hand, such an asymptotic regime would not be of

great relevance in practice, because it would be reached when the number of round-trips is too small to make the RE simulation really effective. In fact, in the limit of zero p_{acc} , the number of round-trips per replica in convective-RE becomes negligible, so that all benefits of the method would be lost. For example, the number of round-trips per replica in convective-RE A-simulations obtained by using 8 replicas is 6.9, while r_{rt} is only ~ 1.4 . Probably, to obtain r_{rt} values of the order of 10, simulations with 1 or less round-trips per replica should be performed.

In light of these observations, and also considering that convective-RE preserves ergodicity,¹ the outcomes of ref 1 could be interpreted as due to the lack of convergence in the computed n_{rt} . On the other side, the relatively high number of round-trips observed especially in the $A\beta_{25-35}$ simulation leaves open the question about the achievement of convergence. Some answer to this problem could be obtained by increasing enormously the simulation time and decreasing the rate of replica-transition attempts as well, which is, however, out of the reach of current computational resources.

The relative performance of standard and convective-RE in the presence of a bottleneck in replica-transitions can be appreciated in Figure 3a, where we report n_{rt} as a function of

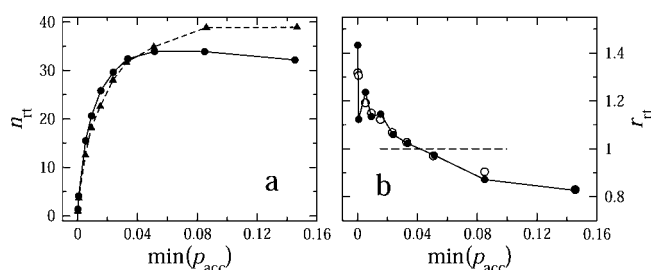


Figure 3. (a) Number of round-trips per replica, n_{rt} , as a function of the minimum acceptance probability, $\min(p_{\text{acc}})$, calculated from B-simulations with various numbers of replicas (from left to right, data of simulations with $N = 32, 38, 48, 52, 56, 60, 64, 70, 80, 96$ are reported). B-simulations using the standard method are reported with triangles, while B-simulations using convective-RE are reported with circles. (b) Ratio between the numbers of replica round-trips estimated with convective-RE and standard B-simulations, $r_{\text{rt}} = [n_{\text{rt}}]_{\text{conv}}/[n_{\text{rt}}]_{\text{stand}}$, as a function of $\min(p_{\text{acc}})$ (filled circles). The r_{rt} quantity calculated from B-simulations of 10^7 steps is reported for comparison (open circles). The dashed line marks the crossover regime ($r_{\text{rt}} = 1$).

the minimum acceptance probability among all replica transitions, $\min(p_{\text{acc}})$, computed for B-simulations. We point out that, in the presence of a bottleneck in the replica transitions, the overall diffusion of the replicas through state space is regulated by the lowest acceptance probability occurring at bottleneck transition itself. In this situation, $\min(p_{\text{acc}})$ rather than the p_{acc} (which is averaged over all replica transitions) becomes more appropriate to monitor the n_{rt} trend. The behavior of the curves of Figure 3a looks like that of Figure 2a, though the crossover regime is moved down to $\min(p_{\text{acc}}) \simeq 3.3 \times 10^{-2}$ (see ref 21). Similarly, the performances of the convective-RE relative to the standard method can be better appreciated from the r_{rt} versus $\min(p_{\text{acc}})$ plot reported in Figure 3b. At small values of $\min(p_{\text{acc}})$, the curve shows a quite noisy behavior due to poor convergence arising from the small number of simulation steps. As a matter of fact, increasing the number of steps from 3.4×10^5 to 10^7 , a more regular, but substantially identical, trend is observed (open circles in Figure

3b). The value of r_{rt} ranges from ~ 1.4 at $\min(p_{\text{acc}}) \simeq 2.2 \times 10^{-4}$ (~ 1.3 , in better convergence conditions) to ~ 0.83 at $\min(p_{\text{acc}}) \simeq 0.15$ (practically unchanged, in better convergence conditions). With respect to the uniform distribution of acceptance probabilities enforced in A-simulations, the presence of a bottleneck does not change significantly the performances of convective-RE relative to the standard method. Convective-RE is better than standard-RE when low acceptance probabilities occur, due to a nonuniform p_{acc} distribution featured by the presence of a bottleneck¹ (see Figure 1b).

However, small acceptance probabilities imply low round-trip rates also in convective-RE, which may prevent the RE scheme from being effective. For example, in B-simulations, the best performances of convective-RE with respect to standard-RE ($r_{\text{rt}} \simeq 1.4$) is obtained with 32 replicas, yielding $\min(p_{\text{acc}}) = 2.2 \times 10^{-4}$. Unfortunately, this acceptance probability leads to a small number of round-trips ($n_{\text{rt}} \simeq 1.3$), which can typically be increased by changing the number of replicas. In our case, to obtain a workable n_{rt} value, for example, $n_{\text{rt}} \simeq 15$, we would have needed to increase the number of replicas to 48. With this number of replicas, the ratio r_{rt} lowers to ~ 1.2 . A further increase of N , for example, $N = 64$, yields a satisfactory number of round-trips ($n_{\text{rt}} \simeq 32$), but the advantages of convective-RE almost disappear ($r_{\text{rt}} \simeq 1$). In summary, by doubling the number of replicas from 32 to 64, the round-trip rate increases by more than a factor of 20 with a practically complete loss of the advantages of convective-RE with respect to standard RE.

Another interesting aspect of convective-RE observed in $A\beta_{25-35}$ simulation¹ was the almost unexpected distribution of the number of round-trips between stick and passive replicas. Among the 706 round-trips globally observed in the $A\beta_{25-35}$ simulation, 435 were realized by stick replicas, while the remaining 271 round-trips were accomplished by passive replicas. Interestingly, this number is still three times greater than in the standard simulation, during which only 88 round-trips were counted. This fact was explained by observing that replica exchanges are correlated in convective-RE: “When the stick replica crosses the bottleneck, a passive replica crosses it as well, but in the other direction.” This behavior is not confirmed by the current B-simulations, as shown in Figure 4, where we report n_{rt} as a function of $\min(p_{\text{acc}})$ for the standard and convective-RE, detailing the contributions to the total number of round-trips from stick and passive replicas. We note that, at variance with the $A\beta_{25-35}$ simulation data, at higher values of $\min(p_{\text{acc}})$ the contribution of passive replicas to n_{rt} is greater than that of the stick replica; also, that each contribution is smaller than the number of round-trips in the standard-RE.

4. COMBINING CONVECTIVE-RE WITH A RANDOM PAIR-REPLICA SELECTION SCHEME

The efficiency of convective-RE with respect to the standard even-odd scheme stems from generating replica exchanges aimed at moving a single replica, the so-called stick replica, along one of the two possible directions in state space. When the upper (or lower) end state is reached, exchanges are attempted to guide the stick replica in the opposite direction, that is, toward the other end state. This process is repeated until the stick replica completes a round-trip. During this forced walk, the other replicas, called passive replicas, are “constrained” to move according to the stick replica, on the basis of an even-odd scheme. When the acceptance probabilities are globally large, the constrained motion of passive replicas prevents their free diffusion through the states, eventually

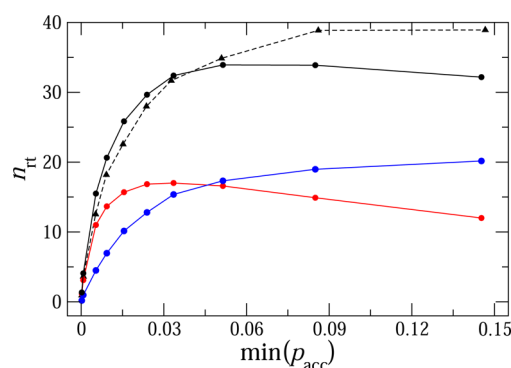


Figure 4. Number of round-trips per replica, n_{rt} , as a function of the minimum acceptance probability, $\min(p_{acc})$, calculated from B-simulations (3.4×10^5 steps) with various numbers of replicas (from left to right data of simulations with $N = 32, 38, 48, 52, 56, 60, 64, 70, 80, 96$ are reported). Simulations using the standard method are reported with triangles. For convective-RE simulations, the total n_{rt} and the contributions from stick and passive replicas are shown (black, red, and blue circles, respectively). The n_{rt} values obtained with B-simulations of 10^7 steps differ from those reported here by a factor of ~ 30 , but the overall behavior remains practically unchanged (data available upon request).

leading to a significant reduction of the number of round-trips (Figures 2 and 3). This constrained motion of passive replicas has instead no dramatic effects as bottlenecks occur, because, in such a case, the dynamics of replicas is dominated by the convective component of the motion. However, in the presence of bottlenecks, we expect that constraining passive replicas to the stick one, somehow slows down the walk diffusion of the former. In fact, passive replicas will continue to swap between two states, without a resultant net diffusion, until the stick replica will overcome the bottleneck.

Based on the above observations, we envisage a possibility of improving the diffusion of passive replicas through the space of states by decoupling their dynamics from that of the stick replica. This can be realized by supplying the convective (even–odd) scheme with a stochastic criterion to choose the replica pairs that must undergo attempted exchanges. This strategy basically allows decoupling between passive and stick replicas, so that the exchanges involving the passive replicas are independent of each other and, especially, independent of the stick replica. A pseudocode related to this random-convective exchange scheme is reported in Table 1.

The round-trip efficiency ratios, r_{rt} (see above for definition), obtained from temperature-RE simulations, A-simulations and B-simulations using the random-convective scheme are compared in Figure 5 with the convective even–odd approach.¹ Overall, we note that, when convective and random-pair selection schemes are combined, r_{rt} increases, but only in the regime of low acceptance probability. In this regime, the increase of efficiency of the random-convective scheme with respect to the convective even–odd method, is relevant in percentage, even if it appears quite modest in absolute terms. The opposite trend, that is, a decrease of efficiency of the random convective-RE, is observed for large acceptance probabilities.

In light of the previous discussion, the former behavior is not surprising. On the contrary, the loss of performance of the random convective-RE at large acceptance probabilities has a more subtle origin, which can be understood by imagining the performances of the three algorithms, standard even–odd,

Table 1. Pseudo-code for the Random Convective-RE Scheme

set	$M = \text{number of states (replicas)}$	
set	$s = \text{stick replica}$	
loop	$\text{for } t = 1, 2, \dots, T$	($T = \text{no. of tried exchanges needed to obtain a round-trip of replica } s$)
set	$\text{allpairs}(i) = 1 \ \forall i = 1, \dots, M - 1$	($i \equiv \text{pairs of states}$)
set	$\text{xchpairs}(i) = 0 \ \forall i = 1, \dots, M - 1$	($i \equiv \text{pairs of states}$)
set	$\text{xchpairs}(n) = 1$	($n = \text{pair of states involved in the exchange of the stick replica } s$)
set	$\text{allpairs}(n) = 0$	
set	$\text{allpairs}(n - 1) = 0$	(if $n - 1 \in \text{state-pair domain}$)
set	$\text{allpairs}(n + 1) = 0$	(if $n + 1 \in \text{state-pair domain}$)
while	$\text{allpairs}()$ not null:	
pick	at random a pair of states p	
if	$\text{allpairs}(p) = 0$, go to previous step	
set	$\text{xchpairs}(p) = 1$	
set	$\text{allpairs}(p) = 0$	
set	$\text{allpairs}(p - 1) = 0$	(if $p - 1 \in \text{state-pair domain}$)
set	$\text{allpairs}(p + 1) = 0$	(if $p + 1 \in \text{state-pair domain}$)
end while		
make	replica exchanges	(Attempt replica exchanges involving state-pairs for which $\text{xchpairs}() = 1$)
end		
select	another stick replica s	
start	loop again	

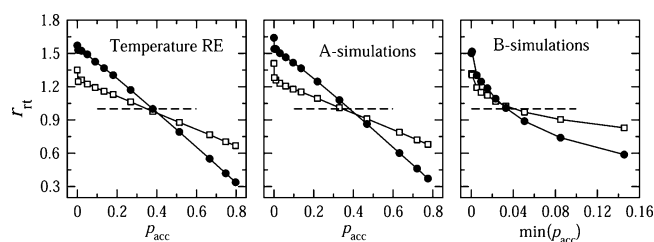


Figure 5. Ratio between the numbers of replica round-trips estimated with convective and standard RE simulations, $r_{rt} = [n_{rt}]_{conv}/[n_{rt}]_{stand}$, as a function of p_{acc} (temperature-RE and A-simulations) and $\min(p_{acc})$ (B-simulations). In each panel, the even–odd and random convective schemes are compared (open squares and filled circles, respectively). The dashed line marks the crossover regime ($r_{rt} = 1$). For B-simulations, results obtained with 10^7 steps are reported.

convective even–odd and random-convective, in the limit of $p_{acc} \sim 1$. Under this assumption, using the standard even–odd as well as the convective even–odd schemes leads to a very fast round-trip rate. In such cases, in fact, a round-trip takes exactly $2N$ attempted replica exchanges, where N is the number of states in the simulation. Note that this is the maximum efficiency one can get from RE simulations in terms of round-trip rate. These performances cannot clearly be obtained by using the random-convective scheme, because the random choice of pairs of replicas to be exchanged can easily invert their walk in the space of states. Consistently with the present results, it is worth noting that loss of efficiency was also observed in the so-called stochastic even–odd scheme,⁸ which

has strong analogies with the random-convective sequence of Table 1.

5. CONCLUDING REMARKS

In this article, we have investigated the performances of the convective transition scheme¹ for RE simulations relative to the standard even–odd deterministic approach. Calculations have been carried out in ideal fully ergodic conditions by means of toy-model simulations. Overall, our calculations show that, when ergodicity and convergence are both in place, the performances of convective-RE, in terms of replica round-trip rate, do not exceed 1.5 times the ones obtained with the standard replica-transition scheme. Above some crossover value of the acceptance probability, p_{acc} , which occurs below the optimal p_{acc} value²² in simulations with uniform p_{acc} distribution, standard even–odd algorithm starts to be competitive with convective-RE, outperforming the latter as large p_{acc} values are attained. Similar results are obtained if a bottleneck in replica transitions is present. These observations are consistent with the results reported in ref 1, though the performances of convective-RE seem to be much less striking than those observed in more complex systems. Although the true reasons of these discrepancies are not completely understood, we believe that uncertainties in round-trip rates due to the loss of ergodicity arising from the shortness of the simulations (with respect to the dynamics needed to get effective sampling), may play some role. Therefore, it would be interesting to evaluate the performances of convective-RE in complex systems when round-trip rate reaches satisfactory convergence, which may occur only by performing micro-second scale simulations.

Furthermore, an attempt at improving the performances of convective-RE has been done by devising a stochastic scheme to select the passive replica pairs undergoing exchanges. The exchange mechanism, based on decoupling the diffusion motions of stick and passive replicas through the state space, proved to be effective with respect to the even–odd convective scheme as bottlenecks are present or the acceptance probabilities are globally low. Conversely, the stochastic selection criterion makes the efficiency significantly worse at high acceptance probability regimes.

In summary, we have shown that, when bottlenecks occur in RE simulations due to low acceptance probabilities arising, for example, from a not optimized spacing between the states, or when the acceptance probabilities are globally low due to small numbers of states/replicas, the use of even–odd convective-RE or random convective-RE schemes leads to improvements in the round-trip rate. The benefits of convective schemes are lost if the acceptance probabilities are globally large.

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Notes

The authors declare no competing financial interest.

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- (20) In this case the occurrence of a crossover should be evaluated considering the plot of n_{rt} versus the smallest p_{acc} , because n_{rt} would depend basically on the replica transition $\lambda_i \leftrightarrow \lambda_{i+i}$ with lowest probability.
- (21) A comparison of B-simulations with A-simulations is however improper because in the former case acceptance probabilities are not distributed uniformly.
- (22) In the present context, the optimal p_{acc} is the one for which the number of round-trips is maximum.