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# Efficiency of exchange schemes in replica exchange

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ABSTRACT

In replica exchange simulations a fast diffusion of the replicas through the temperature space maximizes the efficiency of the statistical sampling. Here, we compare the diffusion speed as measured by the round trip rates for four exchange algorithms. We find different efficiency profiles with optimal average acceptance probabilities ranging from 8% to 41%. The best performance is determined by benchmark simulations for the most widely used algorithm, which alternately tries to exchange all even and all odd replica pairs. By analytical mathematics we show that the excellent performance of this exchange scheme is due to the high diffusivity of the underlying random walk.



## 1. Introduction

The replica exchange (RE) method [1–3] has become a standard approach in molecular simulation to efficiently sample the rough energy landscapes of biomolecules in solution at a target temperature $T_1$ (see e.g. Ref. [4]). In RE simulations, $N$ simulation systems (replicas) are parallely propagated in time using Monte Carlo (MC) or molecular dynamics (MD) algorithms. For the standard temperature RE method in particular, the replicas $i \in \{1,\ldots,N\}$ are identical with the exception of the respective simulation temperatures $T_i$. At a predefined temporal spacing an exchange between two replicas $i$ and $j$ is attempted and is accepted with the Metropolis [5] probability

$$p_{ij} = \min\{1, \exp[(\beta_j - \beta_i)(E_j - E_i)]\}, \quad (1)$$

where $E_i$ and $E_j$ are the current potential energies of the replicas at the corresponding inverse temperatures $\beta_i = 1/k_B T_i$ and $\beta_j = 1/k_B T_j$, respectively. Here, $k_B$ denotes Boltzmann's constant. The exchange probability given by Eq. (1) satisfies the detailed balance condition and therefore guarantees that the ensembles sampled by the individual replicas remain undisturbed by the exchange.

Due to the exchanges, each replica performs a random walk through the temperature space $[T_1, T_N]$. During the high temperature phases of its trajectory, a replica crosses potential energy barriers more rapidly, leading in many cases (a relevant counter example has been given in Ref. [6]) to a faster convergence, compared to a straight forward simulation, of the statistical sampling at the lower temperatures. Here it is crucial for an optimal statistical sampling at the low temperatures that the replicas cycle between low and high temperatures as frequently as possible [7–11]. As we will demonstrate below, the sizes of these round trip rates strongly depend on the detailed algorithm by which the replica pairs are selected for attempting an exchange.

A widely used exchange scheme [12–14] divides the set $\mathcal{N} \equiv \{(i, i+1) \mid i = 1,\ldots,N-1\}$ of next neighbors in the temperature ladder into the two subsets $\mathscr{E} \subset \mathcal{N}$ and $\mathscr{O} \subset \mathcal{N}$, where $\mathscr{E}$ contains all 'even' pairs $(2j, 2j+1) \in \mathcal{N}$ and $\mathscr{O}$ contains the 'odd' pairs $(2j-1, 2j) \in \mathcal{N}$. Exchanges are attempted alternatingly for the members of $\mathscr{E}$ and $\mathscr{O}$. Because of the deterministic pattern of exchange trials, we will call this method the deterministic even/odd algorithm (DEO).

We will also consider a variant of DEO which, instead of alternatingly attempting exchanges among all even and all odd replica pairs, randomly chooses with equal probability one of the subsets $\mathscr{E}$ and $\mathscr{O}$. Due to the stochastic selection of exchange sets, we call this method the stochastic even/odd algorithm (SEO). As we will show, the SEO scheme was implicitly assumed by a number of authors when theoretically deriving rules for optimal temperature ladders [7,11]. Another reason for analyzing the SEO algorithm is that an exchange scheme equivalent to SEO is the straightforward choice when implementing simulated tempering [15].

Besides DEO also other exchange schemes have been discussed in the literature. The all-pair exchange (APE) method suggested by Brenner et al. [16] considers all possible exchange pairs including non-next neighbors. Finally, the very simple random next neighbor (RNN) algorithm [16,17] chooses with equal probability at every exchange step a single pair from the set $\mathcal{N}$ of next neighbors and attempts an exchange for this pair.

Note that the DEO scheme does not permit a reverse move immediately after a successful replica swap in contrast to SEO, APE, and RNN. Therefore, it does not satisfy detailed balance and one may ask whether DEO can interfere with canonical sampling. However, Manousiouthakis and Deem [23] have shown that the equilibrium statistics, which is generated by the intermittent MD

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or MC simulation, is preserved if the sampling procedure satisfies a less strict 'balance condition'. This condition holds if each individual exchange trial satisfies local detailed balance, which is implied by the Metropolis criterion Eq. (1) for even and for odd exchanges. Thus, DEO represents a valid sampling strategy.

In this Letter we will systematically check as to how the different exchange algorithms affect the diffusion of the replicas through the temperature space. This check will provide a rule for the optimal setup of RE simulations. For this purpose we will first introduce basic notions of the RE approach and a benchmark MC system. Using the benchmark system we will then compare the round trip rates obtained with the four different exchange schemes. Because of the practical importance of the DEO algorithm, we will subsequently identify the reasons for its superior performance by analytical mathematics.

## 2. Theoretical basics

It is general consensus that the distances of the $N$ rungs $T_i$ within the temperature ladder should be chosen to yield equal average acceptance probabilities $\langle p_{i,i+1}\rangle = p_{\mathrm{acc}}$ for the exchanges between neighboring replicas $i$ and $i+1$ [3] provided that the simulated system does not undergo a phase transition within the range of the temperature ladder [8,9]. If the system's heat capacity $C$ is constant, which is approximately true for explicit solvent systems [18], then, following Okamoto et al. [19], the spacing law for equal average acceptance probabilities is

$$T_i = T_{\min}\cdot\alpha^{i-1}, \tag{2}$$

with the minimal temperature $T_{\min}$ and a constant ratio $\alpha = T_{i+1}/T_i$ of neighboring temperatures.

Given a certain temperature range $[T_{\min}, T_{\max}]$ to be spanned by a simulation, the choice of the number $N$ of replicas automatically determines the temperature ratio $\alpha$ through

$$\alpha(N) = (T_{\max}/T_{\min})^{1/(N-1)}. \tag{3}$$

Next we assume Gaussian probability distributions

$$\rho(E_i) = \frac{1}{\sqrt{2\pi C T_i}}\exp\left[-\frac{(E_i - CT_i)^2}{2CT_i^2}\right] \tag{4}$$

for the potential energies $E_i$ at the various temperatures $T_i$ because these distributions are as typical for explicit solvent simulations as a constant heat capacity $C$. Note that, in Eq. (4), $C$ denotes the (extensive) heat capacity in units of Boltzmann's constant $k_B$ and refers to the potential energy part of the total energy.

With the potential energy distributions given by Eq. (4), the geometric temperature spacing by Eqs. (2) and (3), and the acceptance criterion by Eq. (1), the average acceptance probability according to Kone and Kofke [7] is

$$p_{\mathrm{acc}} = \mathrm{erfc}\left[\sqrt{C}\,\frac{\alpha(N)-1}{\alpha(N)+1}\right], \tag{5}$$

where $\mathrm{erfc}(x') = 2/\sqrt{\pi}\int_{x'}^{\infty}\exp(-x^2)\mathrm{d}x$ is the complementary error function.

For a predefined temperature range $[T_{\min}, T_{\max}]$, Nadler and Hansmann [11] recently derived a formula to optimize an RE simulation setup with respect to the round trip rate $r$, i.e., to the average number of round trips a replica performs per unit time. In this optimal ladder spanning the interval $[T_{\min}, T_{\max}]$, the average acceptance probability $p_{\mathrm{acc}}$ is about 23% [20]. Consistently, Kone and Kofke [7] obtained the same value for $p_{\mathrm{acc}}$ when optimizing the diffusion of a replica on the temperature ladder. Most recently, however, we observed in sample simulations employing the DEO scheme that the allegedly optimal value $p_{\mathrm{acc}} \approx 23\%$ led to suboptimal round trip rates [20]. This surprising observation sparked our curiosity and led us to compare different exchange schemes using a very simple benchmark simulation system.

## 3. Benchmark simulations

For each of the four algorithms, DEO, SEO, APE, and RNN, we performed several RE Monte Carlo (REMC) benchmark simulations with differing numbers $N$ of replicas but with a fixed temperature range $T_{\min} = T_1 = 300$ K to $T_{\max} = T_N = 800$ K and with the temperatures $T_i$ spaced as given by Eq. (2). In these simulations we drew the potential energies $E_i$ of the replicas at each REMC step from the distributions given by Eq. (4) choosing $C = 500$ for the heat capacity. Then, one of the four algorithms was used to decide which exchanges should be considered, and the Metropolis criterion Eq. (1) was applied to evaluate the outcome of the exchange attempts. Every simulation comprised $S = 10^7$ REMC steps. A round trip was counted if one of the replicas had traveled the complete way from $T_1$ to $T_N$ and back again. With the total number $R$ of round trips counted during a simulation, the round trip rate is $r \equiv R/NS$.

Fig. 1 presents the measured round trip rates $r$ as functions of $p_{\mathrm{acc}}(N)$. The shown efficiency profiles $r(p_{\mathrm{acc}})$ of the various algorithms are markedly different. The simple RNN algorithm (diamonds in Fig. 1) shows by far the weakest performance and has its maximum round trip rate $r_{\max} \approx 10^{-4}$ at $p_{\mathrm{acc}} \approx 12\%$. Because the RNN algorithm chooses only one pair from the set $\mathcal{N}$ of next neighbors for an exchange trial and because this trial is successful with an average acceptance probability $p_{\mathrm{acc}}$, the average number $n_{\mathrm{ex}}$ of actual exchanges per REMC step is equal to $p_{\mathrm{acc}}$.

Compared with the RNN scheme, the more refined APE algorithm (squares in Fig. 1) yields much higher round trip rates with a maximal performance $r_{\max} \approx 6.8\cdot 10^{-4}$ at $p_{\mathrm{acc}} \approx 9\%$. At this value of $p_{\mathrm{acc}}$, the average APE number of exchanges ($n_{\mathrm{ex}} = 0.55$) exceeds that of RNN ($n_{\mathrm{ex}} = 0.09$) by roughly a factor of 6. According to Fig. 1, here the APE round trip rate $r$ is about 6.5 times higher than that of RNN. Hence, compared to RNN, the better performance of APE is mainly due to the larger value of $n_{\mathrm{ex}}$, and the inclusion of non-next neighbor exchanges within APE seems to be of minor importance.

At $p_{\mathrm{acc}} \approx 23\%$ the round trip rate of the SEO algorithm assumes its maximum value $r_{\max} = 6.4\cdot 10^{-4}$ (triangles in Fig. 1). At this point SEO exchanges nearly three times more pairs ($n_{\mathrm{ex}} = 1.45$) per REMC step than APE at its respective $r_{\max}$. Nevertheless, the maximal APE rate is higher than that of SEO. Interestingly, for SEO the position of $r_{\max}$ in Fig. 1 perfectly agrees with the 23% acceptance probability predicted by the optimization formula of Nadler and Hansmann [11,20] and with the point of maximal diffusivity predicted by Kone and Kofke [7].

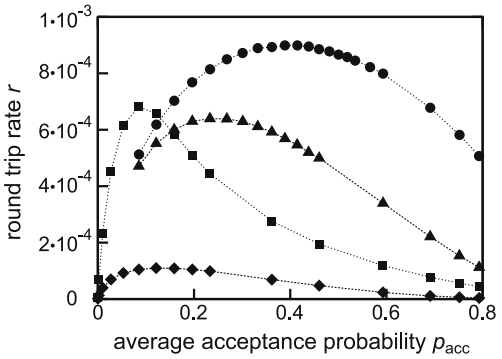


**Fig. 1.** The round trip rates $r$ measured for the four different exchange schemes and a system with $C = 500$ as a function of the average acceptance probability $p_{\mathrm{acc}}$: RNN (diamonds), APE (squares), SEO (triangles), DEO (circles). The dotted lines connecting the symbols are a guide for the eye.