Chemical Physics Letters 478 (2009) 80–84

Contents lists available at ScienceDirect

Chemical Physics Letters

journal homepage: www.elsevier.com/locate/cplett

Efficiency of exchange schemes in replica exchange

Martin Lingenheil, Robert Denschlag, Gerald Mathias, Paul Tavan *

Lehrstuhl für BioMolekulare Optik, Ludwig-Maximilians-Universität, Oettingenstr. 67, 80538 München, Germany

ARTICLE INFO

Article history:
Received 1 April 2009
In final form 9 July 2009
Available online 12 July 2009

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

* Corresponding author. Fax: +49 89 2180 9220.
E-mail address: tavan@physik.uni-muenchen.de (P. Tavan).

0009-2614/$ - see front matter © 2009 Elsevier B.V. All rights reserved.
doi:10.1016/j.cplett.2009.07.039

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 α 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_{acc} is about 23% [20]. Consistently, Kone and Kofke [7] obtained the same value for p_{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_{acc}, the average number n_{ex} of actual exchanges per REMC step is equal to p_{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_{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_{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].

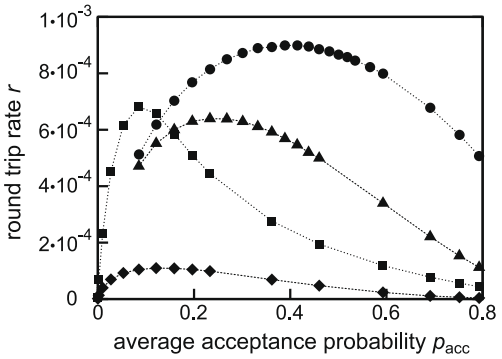

Fig. 1. The round trip rates r measured for the four different exchange schemes and a system with $C = 500$ as a function of the average acceptance probability p_{acc}: RNN (diamonds), APE (squares), SEO (triangles), DEO (circles). The dotted lines connecting the symbols are a guide for the eye.

As demonstrated by the circles in Fig. 1 the closely related DEO algorithm, performs everywhere better than SEO although both algorithms feature the same number n_{ex} of exchanges per REMC step for every choice of $p_{acc}(N)$. This improved performance of DEO is particularly pronounced at large p_{acc}, i.e. at large ladder sizes N. According to Fig. 1 the maximal DEO round trip rate $r_{max} = 9.0 \cdot 10^{-4}$ is found at $p_{acc} \approx 41\%$.

These findings suggest that the theory behind the optimizations performed by Kone and Kofke [7] as well as by Nadler and Hansmann [11] does apply to SEO but not to the established and widely used DEO scheme.

4. Diffusive properties

4.1. Elementary process

To understand why DEO performs better than SEO, we analyzed the associated random walks performed by the replicas in the temperature space. A random walk is a sequence of statistically independent random experiments which we will call its elementary processes (EPs). After n EPs the displacement $X \equiv \sum_{i=1}^{n} \Delta_i$ of the random walker is the sum of the displacements Δ_i in the individual EPs. Since X is a sum of n identically distributed, statistically independent random variables Δ_i, its variance $\sigma^2(X)$ is given by $n\sigma^2(\Delta)$ [21], where $\sigma^2(\Delta)$ is the variance of the EP. If $\langle d \rangle$ is the average duration of the random walk's EP, then its diffusivity, i.e. the gain in variance per unit time, is given by

$$D = \sigma^2(\Delta)/\langle d \rangle. \tag{6}$$

4.2. Diffusivity of SEO

In the SEO scheme, the EP may have the following three outcomes: (i) The replica moves one step upward ($\Delta = +1$) on the temperature ladder with a total probability $p_{\pm} p_{acc}$, where $p_{\pm} = 0.5$ is the probability of selecting the replica pair sets $\mathscr{E}$ or $\mathscr{O}$, respectively. (ii) The replica moves one step downward ($\Delta = -1$) on the ladder with the same probability. (iii) The replica does not move at all ($\Delta = 0$) with the rejection probability $1 - p_{acc}$. Thus, the variance of the EP is

$$\sigma^2(\Delta) = p_{\pm} p_{acc} \left[(+1)^2 + (-1)^2 \right] + (1 - p_{acc}) 0^2 = p_{acc} \tag{7}$$

and its average duration is $\langle d \rangle = 1$. According to Eq. (6), the diffusivity of the SEO algorithm is then

$$D_{SEO} = p_{acc}. \tag{8}$$

Thus, in SEO a replica performs a simple random walk on the temperature ladder as is usually assumed in theoretical analyses of the RE approach [7,9,11,22].

4.3. Diffusivity of DEO

In contrast, the random walk imposed on a replica by the DEO algorithm is more complex. Let us first assume an infinite temperature ladder. For this situation, Fig. 2A sketches the logic of the exchanges. Assume that, in the odd REMC step j, the replica at rung i moves along the blue arrow upwards to rung $i+1$. Then, in the following even step $j+1$, it will be once again considered for an upward exchange toward rung $i+2$ because DEO deterministically selects the red arrows for this exchange trial. As long as the exchange trials are successful, the replica keeps moving upward. This movement stops with the first exchange failure and, subsequently, the direction of the DEO replica movement is reversed. Thus, from the perspective of a single replica, the random walk

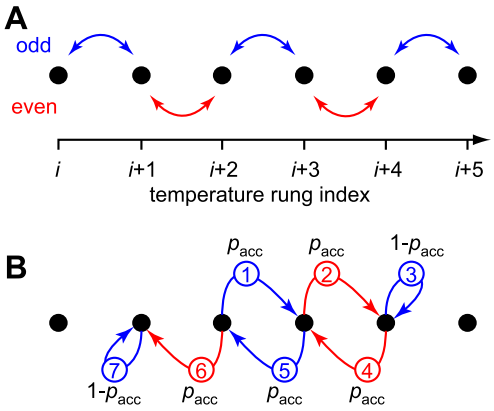

Fig. 2. (A) DEO exchanges within a temperatures ladder. The rungs $i, i+1, \ldots$ of the ladder are marked by black dots. The replica pairs which occupy the rungs joined by the blue double arrows are considered for exchange in odd REMC steps. Red double arrows refer to even REMC steps. (B) An example for an EP. The upward march consists of $k = 2$ successful steps, a failure in step 3, and of a downward march with $k' = 3$ successful steps terminated by a failure in step 7. The probability of each step is indicated at the corresponding arrow. (For interpretation of the references in colour in this figure legend, the reader is referred to the web version of this article.)

consists of alternating upward and downward marches of variable lengths. Note that these lengths may also be zero if already the first exchange fails.

We define the EP of DEO as a pair consisting of an upward march and the following downward march. Let $k \in \mathbb{N}_0$ denote the number of successful upward steps, $k' \in \mathbb{N}_0$ the number of successful downward steps, and $l \equiv k + k'$ the sum of both. Fig. 2B shows a typical example for such an EP. This EP causes a net displacement $\Delta_{k,l} \equiv k - k' = 2k - l = -1$ and takes $d_{k,l} \equiv k + k' + 2 = l + 2 = 7$ steps. The probability of the EP shown in Fig. 2B is the product of all indicated probabilities belonging to the terminated upward $[p_{acc}^2(1 - p_{acc})]$ and downward marches $[p_{acc}^3(1 - p_{acc})]$.

The general formula for the probability of k successful upward steps, k' successful downward steps, and two unsuccessful exchange trials is

$$p_{k,l} \equiv p_{acc}^{k+k'} (1 - p_{acc})^2 = p_{acc}^{l} (1 - p_{acc})^2. \tag{9}$$

Thus, the variance of the EP is

$$\sigma^2(\Delta) = \sum_{l=0}^{\infty} \sum_{k=0}^{l} p_{k,l} \Delta_{k,l}^2 = \frac{2 p_{acc}}{(1 - p_{acc})^2}, \tag{10}$$

and the average duration of the EP is

$$\langle d \rangle = \sum_{l=0}^{\infty} \sum_{k=0}^{l} p_{k,l} d_{k,l} = \frac{2}{1 - p_{acc}}. \tag{11}$$

From Eq. (6) we finally obtain for the DEO diffusivity

$$D_{DEO} = \frac{p_{acc}}{1 - p_{acc}}. \tag{12}$$

A comparison with Eq. (8) demonstrates that D_{DEO} is by a factor of $1/(1 - p_{acc}) > 1$ larger than D_{SEO}.

4.4. Round trip rates

The above analysis has yielded diffusivities on infinite temperature ladders. However, what we want to know are round trip rates r on finite ladders. Such a rate r is the inverse of 2τ, where τ is the mean first passage time required for a replica to diffusively cross the complete ladder. Therefore, r should be proportional [21] to the diffusivity D as long as the EPs of the underlying random walk are commensurate with the ladder size N. For the SEO scheme with

its step sizes of 0 or ±1 this requirement is automatically fulfilled. However, DEO features at decreasing probabilities also EPs of arbitrarily increasing step sizes. Therefore, the proportionality $r_{\mathrm{DEO}} \propto D_{\mathrm{DEO}}$ is expected to hold only within a certain approximation.

Nadler and Hansmann [9] have calculated r assuming a SEO random walk directly from the corresponding master equation [21]. Inspection of Eq. (8) demonstrates that their result for the rate

$$r_{\mathrm{SEO}} = \frac{p_{\mathrm{acc}}}{2N(N-1)} \tag{13}$$

actually exhibits the expected proportionality $r_{\mathrm{SEO}} \propto D_{\mathrm{SEO}} = p_{\mathrm{acc}}$. If we assume such a proportionality also for DEO we get $r_{\mathrm{DEO}} = r_{\mathrm{SEO}} D_{\mathrm{DEO}}/D_{\mathrm{SEO}}$. Hence with Eqs. (8), (12), and (13), we expect for DEO the round trip rate

$$r_{\mathrm{DEO}} = \frac{p_{\mathrm{acc}}}{(1-p_{\mathrm{acc}})2N(N-1)}. \tag{14}$$

4.5. Comparison with measured rates

In Fig. 3, we compare the round trip rates $r(p_{\mathrm{acc}})$ thus analytically calculated with rates measured in our test simulations (see Fig. 1). The dashed line in Fig. 3 is the SEO prediction of Eq. (13), where we have additionally used the unique relation between N and p_{acc} given by Eqs. (5) and (3). The agreement with the measured rates (triangles in Fig. 3) is perfect as expected. Also for DEO our expectations are met. As expected, the approximation Eq. (14) (solid line) deviates only a little from the measured rates (circles).

The deviation between Eq. (14) and the measurements noted for DEO must decrease with increasing ladder size, because for large ladders all those EPs which try to reach beyond the ladder boundary become less frequent. Fig. 4 illustrates this decrease for three different average acceptance probabilities. The figure compares a round trip rate r_{RW} measured in extended DEO random walks on ladders of increasing size N with the rate r_{DEO} from Eq. (14). Due to the decrease, the depicted ratio $r_{\mathrm{RW}}/r_{\mathrm{DEO}}$ approaches the value one with growing N for all values of p_{acc}. Fig. 4 suggests that Eq. (14) is an upper limit for the actual round trip rate r_{RW} and that the overestimate of r_{RW} by r_{DEO} increases with p_{acc}. We note that at $N = 10$ and $p_{\mathrm{acc}} = 0.4$ the deviation is less than 10%.

4.6. Optimal temperature ladders

The analytical approximation Eq. (14) for the DEO round trip rate r together with the unique correspondence between p_{acc} and

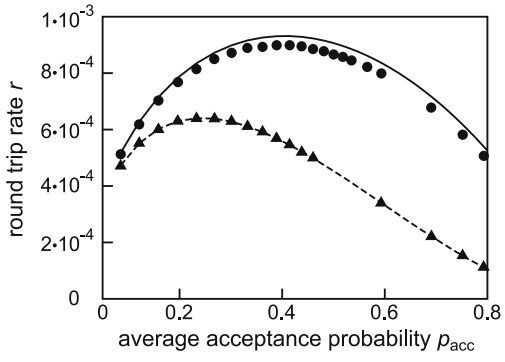

Fig. 3. Analytically calculated round trip rates r_{SEO} (Eq. (13), dashed line) and r_{DEO} (Eq. (14), solid line) as functions of the average acceptance probability p_{acc}. Values measured in our test simulations are adopted from Fig. 1. The SEO values (triangles) perfectly match Eq. (13), whereas the DEO values (circles) slightly deviate from Eq. (14).

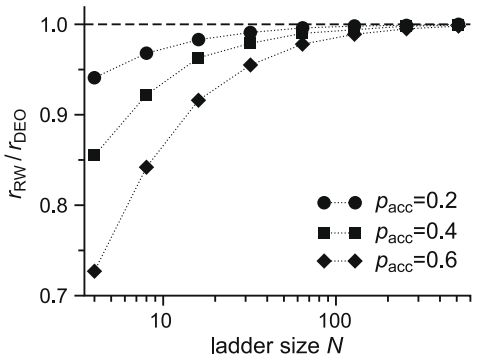

Fig. 4. Ratio of a measured round trip rate r_{RW} (calculated with a fixed acceptance probability p_{acc} from extended DEO random walks on different ladder sizes N) to the rate r_{DEO} given by Eq. (14). Ratios are shown for $p_{\mathrm{acc}} = 0.2$ (circles), $p_{\mathrm{acc}} = 0.4$ (squares), $p_{\mathrm{acc}} = 0.6$ (diamonds). The dotted lines connecting the symbols serve to guide the eye.

N (Eqs. (3) and (5)) enables us now to determine temperature ladders with a maximal r_{DEO}. Here we assume that a temperature range $[T_{\min}, T_{\max}]$ for an RE simulation and a system with known heat capacity C are given. For our benchmark system, we find the maximum of r_{DEO} at the acceptance rate $p_{\mathrm{acc}} = 40.5\%$. This prediction closely agrees with our MC measurements (Figs. 1 and 3) which identified the maximal r at the ladder size $N = 20$ corresponding to an average acceptance probability $p_{\mathrm{acc}} = 41.4\%$.

In a previous study [20], we found empirically for the same benchmark system that r is quite well approximated by the expression

$$r_\kappa \equiv c\kappa(p_{\mathrm{acc}}) \approx c' p_{\mathrm{acc}}/[N(p_{\mathrm{acc}}) - 1] \tag{15}$$

with system dependent constants c and c'. From Eqs. (15), (3), and (5) one finds that the maximum of r_κ is at $p_{\mathrm{acc}} = 44.4\%$, which is also close to the MC value $p_{\mathrm{acc}} = 41.4\%$.

As we have seen, the two apparently different analytical approximations Eqs. (14) and (15) yield quite similar predictions for the optimal p_{acc}. This puzzling result raises questions, which are resolved by Fig. 5. The figure shows the ratio $r_\kappa/r_{\mathrm{DEO}} = c'N(p_{\mathrm{acc}})(1-p_{\mathrm{acc}})$ as a function of p_{acc}. It demonstrates that for large p_{acc} the two expressions become equivalent and remain close at smaller p_{acc}. This similarity is more pronounced for very small systems (dashed line) than for larger ones (solid line). We would like to stress that the solid line is representative for all large systems with heat capacities $C > 500$ (data not shown).

By Eq. (15), r_κ is proportional to $1/(N-1)$, which is characteristic for a directed motion with constant velocity, whereas r_{DEO} is

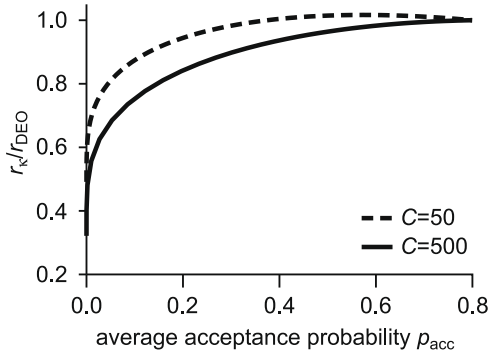

Fig. 5. The ratio $r_\kappa/r_{\mathrm{DEO}}$ as a function of the average acceptance probability p_{acc} for two systems with heat capacities $C = 50$ (dashed line) and $C = 500$ (solid line), respectively.

by Eq. (14) proportional to $1/[N(N-1)]$, which is typical for a diffusive motion. If the temperature ladders become so small that the EPs of the DEO random walk hit the ladder boundaries very frequently, then the approximation Eq. (14) is expected to become worse. For such small ladders one can expect that the constant velocity expression Eq. (15) becomes more accurate. To check this expectation, we calculated the p_{acc} of maximal r by Eq. (14) and Eq. (15) for the small system ($C = 50$). For this system the constant velocity expression Eq. (15) predicts 42.6%, the diffusion expression Eq. (14) yields 43.5% whereas the target value obtained through MC is 41.5% (corresponding to a ladder size $N = 7$). Thus, even for very small temperature ladders our analytical approximation r_{DEO} still predicts the location of the maximal round trip rate at nearly the same accuracy as the educated guess r_κ put forward in Ref. [20], while it is somewhat better for larger systems.

5. Summary

We have investigated the round trip rate performance of four different exchange algorithms. Our results demonstrate that the DEO algorithm yields the highest round rates over a wide range of average acceptance probabilities p_{acc}. Thus, using the DEO algorithm is not only a common but also a good practice in the application of replica exchange. This conclusion not only applies to replica exchange but also to simulated tempering [15]. Note, however, that according to our results (Fig. 1) the APE algorithm [16] might be an interesting alternative if one is interested in high round trip rates using minimally sized temperature ladders [20].

Examining the DEO random walk analytically we have shown that the reason for the higher DEO round trip rates compared with those of its randomized variant (SEO) is the intrinsically higher diffusivity of the corresponding random walk. Since the diffusivity advantage of DEO over SEO becomes larger with increasing p_{acc}, the acceptance probability maximizing the round trip rate is shifted from $p_{acc} \approx 20\%$ (SEO) to $p_{acc} \approx 40\%$ (DEO).

Finally, we have shown that the educated guess Eq. (15), which empirically had been determined to be a good optimization measure for the DEO round trip rates [20], yields results nearly equivalent to those of our analytical approximation Eq. (14).

Acknowledgement

This work was supported by the Deutsche Forschungsgemeinschaft (SFB 533/C1 and SFB 749/C4).

References

[1] K. Hukushima, K. Nemoto, J. Phys. Soc. Jpn. 65 (1996) 1604.
[2] U.H.E. Hansmann, Chem. Phys. Lett. 281 (1997) 140.
[3] Y. Sugita, Y. Okamoto, Chem. Phys. Lett. 314 (1999) 141.
[4] D.J. Earl, M.W. Deem, Phys. Chem. Chem. Phys. 7 (2005) 3910.
[5] N. Metropolis, A.W. Rosenbluth, M.N. Rosenbluth, A.H. Teller, E. Teller, J. Chem. Phys. 21 (1953) 1087.
[6] R. Denschlag, M. Lingenheil, P. Tavan, Chem. Phys. Lett. 458 (2008) 244.
[7] A. Kone, D.A. Kofke, J. Chem. Phys. 122 (2005) 206101.
[8] S. Trebst, M. Troyer, U.H.E. Hansmann, J. Chem. Phys. 124 (2006) 174903.
[9] W. Nadler, U.H.E. Hansmann, Phys. Rev. E 75 (2007) 026109.
[10] W. Nadler, J.H. Meinke, U.H.E. Hansmann, Phys. Rev. E 78 (2008) 061905.
[11] W. Nadler, U.H.E. Hansmann, J. Phys. Chem. B 112 (2008) 10386.
[12] T. Okabe, M. Kawata, Y. Okamoto, M. Mikami, Chem. Phys. Lett. 335 (2001) 435.
[13] M.J. Abraham, J.E. Gready, J. Chem. Theory Comput. 4 (2008) 1119.
[14] D. van der Spoel et al., Gromacs User Manual version 3.3, 2005. www.gromacs.org.
[15] R. Denschlag, M. Lingenheil, P. Tavan, G. Mathias, J. Chem. Theory Comput., submitted for publication.
[16] P. Brenner, C.R. Sweet, D. VonHandorf, J.A. Izaguirre, J. Chem. Phys. 126 (2007) 074103.
[17] F. Calvo, J. Chem. Phys. 123 (2005) 124106.
[18] B. Paschek, H. Nymeyer, A.E. Garcia, J. Struct. Biol. 157 (2007) 524.
[19] Y. Okamoto, M. Fukugita, T. Nakazawa, H. Kawai, Protein Eng. 4 (1991) 639.
[20] R. Denschlag, M. Lingenheil, P. Tavan, Chem. Phys. Lett. 473 (2009) 244.
[21] C.W. Gardiner, Handbook of Stochastic Methods, 2nd edn., Springer, Berlin, 1985.
[22] W. Nadler, U.H.E. Hansmann, Phys. Rev. E 76 (2007) 065701(R).
[23] V.I. Manousiouthakis, M.W. Deem, J. Chem. Phys. 110 (1999) 2753.