

How Efficient Is Replica Exchange Molecular Dynamics? An Analytic Approach

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Abstract: Replica exchange molecular dynamics (REMD) has become a standard technique for accelerating relaxation in biosimulations. Despite its widespread use, questions remain about its efficiency compared with conventional, constant temperature molecular dynamics (MD). An analytic approach is taken to describe the relative efficiency of REMD with respect to MD. This is applied to several simple two-state models and to several real proteins—protein L and the B domain of protein A—to predict the relative efficiency of REMD with respect to MD in actual applications. In agreement with others, we find the following: as long as there is a positive activation energy for folding, REMD is more efficient than MD; the effectiveness of REMD is strongly dependent on the activation enthalpy; and the efficiency of REMD for actual proteins is a strong function of the maximum temperature. Choosing the maximum temperature too high can result in REMD becoming significantly less efficient than conventional MD. A good rule of thumb appears to be to choose the maximum temperature of the REMD simulation slightly above the temperature at which the enthalpy for folding vanishes. Additionally, we find that the number of replicas in REMD, while important for simulations shorter than one or two relaxation times, has a minimal effect on the asymptotic efficiency of the method.

Introduction

Replica exchange (RE),^{1–4} also known as simulated tempering, has become a standard method for enhancing relaxation in any system with rugged energy landscapes. This method has been applied to study a diverse number of systems including biomolecules, spin-glasses, lattice quantum chromodynamics, phylogenetic trees, and polymer melts. The variant known as replica exchange molecular dynamics (REMD),⁵ in particular, is widely used in biosimulations.^{6–45} Despite this, questions have been raised about the efficiency of REMD relative to conventional, constant temperature molecular dynamics (MD).^{46,47} A number of biomolecular simulations have investigated this issue. For example, Periole and Mark⁴⁸ compared REMD with conventional simulation of a β -heptapeptide in explicit solvent and found that “for determining the relative populations at the lower temperature

(275–300 K), [REMD] was at least eight times more efficient than conventional MD for this system”. Zhang, Wu, and Duan⁴⁹ studied a 21-residue helix-forming peptide in implicit solvent and reported that “REMD can significantly enhance the sampling efficiency by 14.3 ± 6.4 , 35.1 ± 0.2 and 71.5 ± 20.4 times at, respectively, ~ 360 , ~ 300 , and ~ 275 K in comparison to the regular MD.” Sanbonmatsu and Garcia⁷ studied the pentapeptide Met-enkephalin in explicit solvent and found that REMD samples “approximately five times more configurational space than constant temperature MD simulations of the same duration”, which suggests an increase in efficiency of REMD by at least a factor five. Rao and Caflisch⁵⁰ studied a 20-residue antiparallel beta-sheet protein using both conventional MD and REMD. They found that the average folding time over all replicas using REMD was $0.064\text{--}0.067\ \mu\text{s}$, and the average folding time using conventional MD near the folding temperature was $0.085\ \mu\text{s}$. Seibert et al. used long REMD and MD simulations of a small beta-hairpin (Chignolin) in explicit water to estimate relative

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efficiency.⁵¹ It was found that REMD simulations equilibrate in a few hundreds of nanoseconds per replica compared with a folding time using conventional MD of 1–2 μ s. Extensive REMD simulations of the α -helical Trp-cage protein produced similar results:⁴⁴ using REMD, relaxation occurred after about 100 ns of simulation per replica in a system that takes a few μ s to equilibrate with conventional MD.

This evidence suggests that relaxation of biological molecules with REMD is faster than in conventional MD, and for a few select systems, there are indications that REMD simulations may relax an order of magnitude or more quickly than with conventional MD. The relatively small increase in REMD efficiency observed for some biological systems has been attributed to the lack of large activation enthalpies for protein folding,^{46,47} which is consistent with the analysis presented in this manuscript.

In order to better understand the relaxation behavior of REMD simulations and the effects of the temperature distribution and exchange frequency, several authors have constructed semianalytic models from master equations. For example, Zheng et al.⁵² constructed a Markov state model of a protein REMD simulation to estimate its actual efficiency and the effect of different parameter choices on this efficiency. The most significant finding was that choosing the maximum temperature too large may actually decrease the efficiency of REMD; a result confirmed by the analysis presented here. Trebst et al.⁵³ used a similar model to improve REMD efficiency by optimizing the temperature distribution. And, simulations and Markov state modeling by Sindhikara et al.⁵⁴ were used to study the effects of exchange frequency on REMD simulations. These authors found that for most biological simulations, large gains in REMD efficiency can arise by increasing the exchange frequency. Considering these results, which have shown that the efficiency of REMD depends sensitively on the maximum temperature, temperature spacing and exchange frequency, it is not surprising that quite different results have been found regarding the efficiency of REMD compared with MD.

Semianalytic models such as these give us the ability to rapidly optimize simulation parameters; however, an analytic approach to this problem may help us to better answer a number of questions such as: how does the efficiency of REMD depend upon the particular system being studied; how does the number of replicas needed for the simulation impact its efficiency; and how does the choice of temperatures especially T_{\max} affect the efficiency of REMD. An analytic approach is developed in this manuscript to help address these questions. This analysis is quite general and can be adapted to analyzing the efficiency of REMD applied to nearly any system as well as analyzing the numerous variants of RE and REMD that have been developed.

Background

Considering the extensive use of REMD and numerous descriptions of it in the existing literature, only a brief review will be provided here. REMD is an attempt to enhance sampling by allowing two simulations or *replicas* to exchange their temperatures. This additional dynamical freedom allows the system to relax more quickly than at a fixed

temperature. In REMD, the probability for two replicas (1 and 2) out of N replicas to exchange temperature is proportional to

$$\rho = \min\{1, e^{\Delta\beta\Delta E}\}$$

where $\Delta\beta$ is the difference in inverse temperatures between replicas 1 and 2 and ΔE is the difference in their potential energies. This exchange probability is chosen to maintain the appropriate equilibrium distribution; however, the form of this exchange probability limits the temperature spacing of neighboring replicas. It is usually necessary to increase the number of replicas N as the square root of the system size.^{55,10} For small peptides and proteins in explicit solvent, this typically means several tens of replicas are needed to span a few hundred degrees in temperature.

Theory

The objective of this analysis is to determine the efficiency of REMD relative to conventional MD. Relative efficiency is defined the number of *statistically independent conformations* generated by REMD using a fixed *amount of computation* divided by the number of statistically independent conformations that can be generated by standard MD with the same amount of computation. For REMD to be useful, it should have efficiency greater than or equal to 1.

The analysis will avoid as much as possible delving into the details of molecular dynamics codes. It is assumed that the amount of computation is proportional both to the amount of simulated real time and to the number of simulations. For example, the amount of computation for N simulations each of length t will be the same amount of computation as a single simulation of length Nt . The efficiency losses due to communication among processors will be ignored. These efficiency losses may be large for some methods such as spatial decomposition. Because these losses are strongly dependent upon the particular simulated system, MD program and machine, these losses will not be included in an initial analysis. The issue of efficiency lost to communication bottlenecks will be briefly addressed later.

Two types of relative efficiency will be considered. In the first measure of relative efficiency E_1 , it is assumed that we are interested in all temperatures ranging from T_{\min} to T_{\max} , the minimum and maximum temperatures of the REMD. For this comparison, both REMD and conventional MD require N separate simulations—one at each temperature. The only difference is that REMD allows for temperature exchanges and conventional MD does not.

In the second measure of relative efficiency E_2 , it is assumed that we are only interested in the behavior at a single temperature T . In this case, the other temperature simulations in REMD only exist to help the sampling at T , and we consider the conformations generated at different temperatures to have no value. A simulation at temperatures other than T can provide some additional statistics about the equilibrium properties at T through reweighting techniques. The additional amount of information contributed by reweighting is strongly system dependent and normally limited to nearby temperatures, so information provided by reweighting will also not be considered. The temperature T at

which we are most interested is often T_{\min} but may be another temperature such as the melting temperature T_m . The relative efficiency depends upon the temperature of interest. It will be assumed throughout the rest of the manuscript that the temperature of interest is T_{\min} .

Relative efficiency has been defined as the ratio of the number of statistically independent samples generated by REMD and MD. But, what exactly is meant by *the number of statistically independent samples*? The difficulty is that MD and REMD both produce samples that are correlated in time and not statistically independent. For most biosimulations, the longest relaxation time characterizes the folding/unfolding conformational equilibrium. Following common practice, the number of statistically independent samples $n(t)$ of a simulation of time t will be defined from the asymptotic dependence of the variance in the estimated average folded/unfolded population \bar{f} with time

$$\sigma^2(\bar{f}) \propto \frac{1}{n(t)} \quad (1)$$

If f has a normalized autocorrelation function $C(t)$ then it can be shown^{56,57} that the number of statistically independent samples $n(t)$ generated by a simulation of length t is

$$n(t) = \frac{t}{\tau_{\text{int}}} \quad (2)$$

where τ_{int} is the integrated autocorrelation time. In the limit of frequent sampling and long times^{56,57}

$$\tau_{\text{int}} = 2 \int_0^\infty C(t') dt' \quad (3)$$

For a system with a single, exponential relaxation time τ_{relax} , the normalized autocorrelation time has the form $C(t) = \exp[-t/\tau_{\text{relax}}]$, and

$$\tau_{\text{int}} = 2\tau_{\text{relax}} \quad (4)$$

For systems with multiple relaxation times, it is important to fully evaluate eq 3 rather than assume that eq 4 holds. Multiple relaxation times occur frequently in nonprotein systems and for protein systems with intermediate states. Also, for simulations in which Monte Carlo rather than MD is used to generate moves, the definition of τ_{int} (eq 3) should be modified to incorporate the possibility of significant decorrelation within a single sample time.⁵⁷

To calculate efficiency, we need to determine $n(t)$ for both conventional MD and for REMD. The efficiency of REMD relative to MD is then defined to be

$$E = \frac{n_{\text{REMD}}(t)}{n_{\text{MD}}(t)} \quad (5)$$

The values of $n_{\text{REMD}}(t)$ and $n_{\text{MD}}(t)$ depend upon the type of efficiency being calculated. For efficiency E_1 , the independent conformations generated at all the temperatures from T_{\min} to T_{\max} are included. For efficiency E_2 only conformations generate at T_{\min} are included.

Before proceeding with a detailed analysis, it is useful to consider generally how $n_{\text{REMD}}(t)$ and $n_{\text{MD}}(t)$ arise in simple, two-state protein systems. Two-state protein systems are proteins with two macrostates: an unfolded state (U) and a folded (F) state. These two macrostates are separated by

a single folding transition state barrier (TS). There exists a single unimolecular rate to transition from U to F (k_f) and a single unimolecular rate to transition from F to U (k_u). The system relaxes with a single relaxation rate given by

$$k_{\text{relax}} = k_u + k_f \quad (6)$$

Real proteins have other relaxation rates; however, in the absence of intermediates, these other relaxation rates are presumed to be several orders of magnitude larger than k_{relax} . In this manuscript, the analysis will be restricted to these idealized two-state proteins.

The unfolding and folding rates, k_u and k_f , are given by a standard Arrhenius-like relationships

$$\begin{aligned} k_f &= k_0 \exp[-\Delta\beta\Delta G_f^\ddagger] \\ k_u &= k_0 \exp[-\Delta\beta\Delta G_u^\ddagger] \end{aligned} \quad (7)$$

where $\Delta G_f^\ddagger = G_{\text{TS}} - G_u$ is the free energy of activation for folding and $\Delta G_u^\ddagger = G_{\text{TS}} - G_f$ is the free energy of activation for unfolding. β is the inverse temperature, and k_0 is a rate prefactor assumed to have no temperature dependence. The number of statistically independent samples generated by an MD simulation of total real time t can be determined from eqs 2, 4, 6, and 7.

In a REMD simulation, each replica moves both in temperature and in its conformational space. If there are N replicas in a REMD simulation, then there are N trajectories in temperature and conformation space. These trajectories interact because of the requirement that no two of them can occupy the same temperature simultaneously. This interaction introduces correlations between the different replicas: the motion of replica i in temperature space depends upon the potential energies that the other replicas have at any moment. If the interaction between replicas could be ignored, then the analysis of a REMD simulation would be greatly simplified because it would become N statistically independent simulations of the system in temperature and conformational space.

Are there conditions under which the interactions between replicas can be minimized and perhaps ignored? Let us suppose that (i) N is large and (ii) the system is close to equilibrium. These two conditions guarantee that at any time the set of replicas have nearly an equilibrium distribution in enthalpy. Then the dynamics of a single replica—say replica i —may be determined by assuming that the other replicas are chosen from their equilibrium distribution. Under these conditions, it is reasonable to suppose that each replica moves nearly independently on the single-replica, equilibrium free energy surface in temperature and conformational space.

For an illustration of this single-replica, equilibrium surface, let us consider the one-dimensional two-state system shown in Figure 1a. This system has a single conformational coordinate x . The single-replica, equilibrium free energy surface is shown in Figure 1b. This equilibrium free energy surface can be determined from the relationship between free energy and probability

$$e^{-\beta G(x,\beta)} \propto p(x,\beta) \quad (8)$$

$G(x,\beta)$ is the free energy of the microstate with conformational coordinate x and inverse temperature β . $p(x,\beta)$ is the

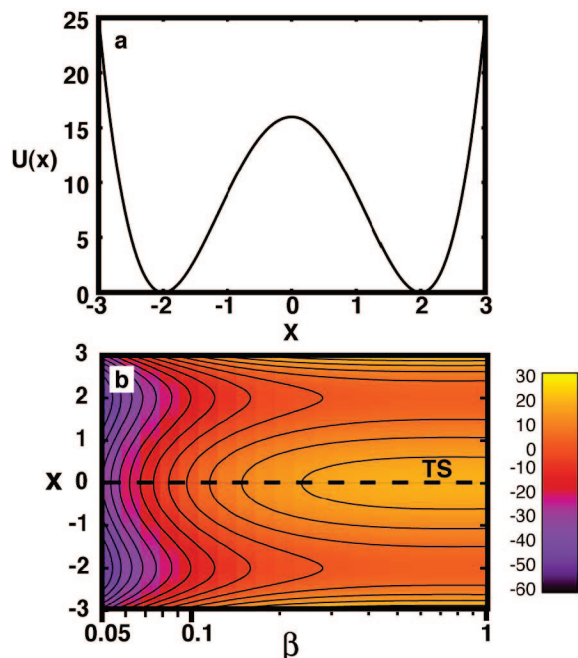


Figure 1. (a) Simple one-dimensional potential of the form $U(x) = (x^2 - 4)^2$, which is a model two-state system and (b) its two-dimensional free energy contours as a function of inverse temperature β and x assuming that replicas are uniformly distributed in temperature from $T = 1$ to 200. Dimensionless units are used. Contours are drawn every 5 units of energy. This is an example of the free energy surface seen by a single replica in a REMD simulation. The relaxation rate of a replica in a REMD simulation is determined by the flux across the transition state (TS) boundary. Motion along the β axis is normally fast compared with motion along x , which allows us to replace this two-dimensional free energy surface with an effective one-dimensional temperature-averaged surface along x (not shown).

probability density. At a fixed inverse temperature β , the probability density p at conformation x is given by a Boltzmann distribution

$$p(x|\beta) = \frac{1}{\Omega_\beta} e^{-\beta H(x)} \quad (9)$$

where H is the enthalpy of conformation x . In equilibrium, the probability distribution of an individual replica is given by

$$p(x, \beta) = p(x|\beta)p(\beta) = \frac{1}{\Omega_\beta} e^{-\beta H} p(\beta) \quad (10)$$

where $p(\beta)$ is the distribution of inverse temperatures chosen for the REMD simulation. Equations 8 and 10 lead us to a definition for the free energy of

$$e^{-\beta G(x, \beta)} = \frac{\frac{1}{\Omega_\beta} e^{-\beta H(x)} p(\beta)}{\int \frac{1}{\Omega_\beta} p(\beta) d\beta} \quad (11)$$

The constant in the denominator is chosen for convenience so that the integral of eq 11 over inverse temperature has a value of 1 for any state x with $E = 0$. The choice of this constant does not affect our calculation of relative efficiency.

When there are many replicas near equilibrium, the number of statistically independent conformations generated by a REMD simulation should be nearly equal to N statistically uncoupled replicas, where each replica has a relaxation spectrum determined by its dynamical motion on the equilibrium free energy surface $G(x, \beta)$. In other words

$$n_{\text{REMD}}(t) = N \frac{t/N}{\tau_{\text{int}}} = \frac{t}{\tau_{\text{int}}} \quad (12)$$

because there are N replicas; each replica is simulated for a time t/N , and each replica has the same relaxation spectrum with integrated autocorrelation time τ_{int} .

To determine τ_{int} for two-state protein-like systems, the relaxation behavior of the system on the free energy surface $G(x, \beta)$ must be determined. Two additional simplifying assumptions will be made to facilitate this calculation. First, it will be assumed that for a two-state protein-like system, $G(x, \beta)$ will also exhibit a two-state character with a single dominant relaxation time. This is obviously true for the simple two-state system shown in Figure 1. It seems reasonable that this will be true for all two-state systems provided there remains a significant folding/unfolding barrier from T_{min} to T_{max} . Second, in order to estimate that relaxation time, the free energy surface $G(x, \beta)$ will be replaced by a temperature averaged effective free energy surface $G_{\text{eff}}(x)$. This replacement is justified by the fact that under most conditions at which REMD is run—especially in biological simulations—the motion in conformational space x is slow compared to motion in inverse temperature β . $G_{\text{eff}}(x)$ can be found by integrating eq 11 over the inverse temperature

$$e^{-G_{\text{eff}}(x)} = \frac{\int \frac{1}{\Omega_\beta} e^{-\beta H(x)} p(\beta) d\beta}{\int \frac{1}{\Omega_\beta} p(\beta) d\beta} \quad (13)$$

A similar relation characterizes the effective free energy $G_{\text{eff},i}$ of macrostate i with free energy $G_i(\beta)$ at inverse temperature β

$$e^{-G_{\text{eff},i}} = \frac{\int \frac{1}{\Omega_\beta} e^{-\beta G_i(\beta)} p(\beta) d\beta}{\int \frac{1}{\Omega_\beta} p(\beta) d\beta} \quad (14)$$

The relaxation rate (or relaxation spectrum) can be estimated from the dynamics on this temperature averaged effective free energy surface.

At this point, it is useful to consider some concrete systems in detail. The simplest two-state system has wells with identical energies and entropies separated by a high barrier with enthalpy of activation ΔH . This system is essentially equivalent to that shown in Figure 1. This model is unlike most proteins, because the unfolded (U) state and folded (F) states have identical energies and enthalpies; however, this model does have characteristics similar to many smaller peptides with a discrete number of stable conformational states such as Met-enkephalin.

Let us first determine $n_{\text{MD}}(t)$ for a single simulated temperature (efficiency E_2). From eqs 2, 4, 6, and 7, the

number of statistically independent conformations generated by a simulation of time t and at inverse temperature β is

$$n_{\text{MD}}(t) = \frac{1}{2} k_{\text{relax}}(\beta) t \quad (15)$$

This assumes that $\tau_{\text{int}}(\beta) = 2\tau_{\text{relax}}(\beta)$.

Let us now consider $n_{\text{MD}}(t)$ for computing E_1 . $n_{\text{MD}}(t)$ is the number of statistically independent conformations generated at all temperatures from T_{min} to T_{max} . If there are N independent simulations, the total simulation time t must be apportioned among the simulations at each temperature. In order to generate the same statistical error at each temperature, the time spent on each simulation should be divided unequally: more time should be spent on simulations that have a longer correlation time, and less time should be spent on simulations with a shorter correlation time. The fraction of time spent on the simulation at an inverse temperature of β should be proportional to $\tau_{\text{int}}(\beta) = 2\tau_{\text{relax}}(\beta)$, so if the total simulation time is t , then the simulation at inverse temperature β should ideally be run for a time

$$t(\beta) = t \frac{\tau_{\text{relax}}(\beta)}{\sum_{i=1}^N \tau_{\text{relax}}(\beta_i)} \quad (16)$$

and the number of independent conformations generated from the simulation at each β will be

$$n(\beta) = \frac{t(\beta)}{2\tau_{\text{relax}}(\beta)} = \frac{t}{2 \sum_{i=1}^N \tau_{\text{relax}}(\beta_i)} \quad (17)$$

If there are N separate temperatures being simulated, the total number of conformations generated is N times this amount

$$n_{\text{MD}}(t) = \frac{Nt}{2 \sum_{i=1}^N \tau_{\text{relax}}(\beta_i)} = \frac{t}{2 \langle \tau_{\text{relax}} \rangle_{\beta}} \quad (18)$$

Let us now consider the REMD simulations. A REMD simulation consists of N replicas or copies of the system. If each replica is simulated for a time t/N , then the total number of independent configurations generated in a REMD simulation is

$$n_{\text{REMD}}(t) = \frac{t}{\tau_{\text{int}}} = \frac{k_{\text{REMD}} t}{2} \quad (19)$$

written in terms of the relaxation rate k_{REMD} of a single replica of the REMD simulation. k_{REMD} can be determined from the dynamics on the effective free energy surface determined using eq 14.

Each replica contributes to the statistics at each temperature, and each replica relaxes with the same rate k_{REMD} ; consequently, every temperature has the same slowest relaxation rate. This means that a REMD simulation can never be in equilibrium unless all replicas are in equilibrium together. In practice, this slow relaxation rate may not be observed in the higher-temperature replicas, because the degree to which a low-temperature replica contributes to the statistics at high temperature may be very small.

In conventional MD, simulations at one temperature do not provide any information about the behavior at another temperature (assuming reweighting methods are not considered); consequently, if one is only interested in the behavior at T_{min} , it is inefficient to spend time simulating temperatures other than this. The data generated by these simulations is wasted. Is the same true for REMD simulations: is it less efficient to use more replicas—larger N ? A simple argument suggests that increasing the number of replicas N has a minimal impact on the efficiency of REMD. In REMD, each replica moves in conformational space and temperature space simultaneously. The distribution in this combined space is controlled by a single relaxation barrier and relaxation rate, which is the slowest relaxation rate for the whole system. The distribution at a single fixed temperature is a projection of this distribution in conformation and temperature space; consequently, the relaxation rate of this distribution must be the same (or faster) than the relaxation rate of each replica.

These above reasoning suggests that $n_{\text{REMD}}(t)$ for a single temperature is the same as for all the temperatures, i.e., whether we are computing E_1 or E_2 . This is equivalent to asserting that *in the limit of a long simulation* the number of replicas used for a REMD simulation is irrelevant to its efficiency. This assertion is well-recognized when all the replicas have the same temperature: dividing the simulation into N separate shorter simulations generates the same amount of conformational sampling as one single simulation, provided that the system has a single dominant relaxation time.^{58,59} However, this same property holds for REMD simulations because the temperature variation and conformational change are coupled: temperature relaxation is controlled by conformational change, so they have the same relaxation time.

But, what if we are not in the limit of a long simulation? Dividing the simulation in N separate simulations can be a significant problem if one is unable to simulate longer than k_{REMD} . In this case, the separate simulations are not long enough to lose memory of their initial conditions. For many biosimulations, the total simulation time is only a few multiples of the relaxation time. In these cases, REMD may be at a disadvantage; however, asymptotically the residual error should be similar whether performing N simulations of length t/N or one simulation of length t .

Putting the results together (eqs 18 and 19)

$$E_1 = \frac{t k_{\text{REMD}}}{t \langle \tau_{\text{relax}} \rangle_{\beta}} = k_{\text{REMD}} \langle \tau_{\text{relax}} \rangle_{\beta} \quad (20)$$

The subscript relax indicates the relaxation time at a fixed inverse temperature and the subscript REMD indicates the relaxation rate of a fixed replica. The efficiency E_2 is given by a similar product (eqs 15 and 19)

$$E_2 = \frac{k_{\text{REMD}} t}{k_{\text{relax}}(\beta_{\text{max}}) t} = k_{\text{REMD}} \tau(\beta_{\text{max}}) \quad (21)$$

To determine k_{REMD} , the distribution of inverse temperatures in the replica simulation must be specified. For the purposes of calculation, the distribution of inverse temperatures will be assumed to be uniform from $\beta_{\text{min}} = 1/T_{\text{max}}$ to $\beta_{\text{max}} =$

$1/T_{\min}$. In other words, $p(\beta) = 1/\Delta\beta$, where $\Delta\beta = \beta_{\max} - \beta_{\min}$ for all values of β from β_{\min} to β_{\max} .

If the population of the transition state is negligible at all temperatures, then $\Omega_\beta = 2$. The effective free energy of each well is 0, and the effective free energy of the transition state is

$$G_{\text{eff}} = -\ln \int_{\beta_{\min}}^{\beta_{\max}} e^{\Delta S/R} e^{-\beta \Delta H} \frac{1}{\Delta\beta} d\beta \\ = -\ln \left[e^{\Delta S/R} \frac{e^{-\beta_{\min} \Delta H} - e^{-\beta_{\max} \Delta H}}{\Delta\beta \Delta H} \right] \quad (22)$$

In the limit that $\beta_{\min} = \beta_{\max}$, this reverts to the expected result that

$$G_{\text{eff}} = \beta_{\max} [\Delta H - T_{\max} \Delta S] \quad (23)$$

Equations 6, 7, and 22 then lead to

$$k_{\text{REMD}} = 2k_0 e^{-\Delta G_{\text{eff}}} = 2k_0 \frac{e^{\Delta S/R} [e^{-\beta_{\min} \Delta H} - e^{-\beta_{\max} \Delta H}]}{\Delta\beta \Delta H} \quad (24)$$

In the limit that T_{\max} is large, the relaxation rate is asymptotically equal to

$$k_{\text{REMD}} = 2k_0 \frac{e^{-\beta_{\min} \Delta G(\beta_{\min})}}{\Delta\beta \Delta H} \quad (25)$$

Using the calculated value of the relaxation rate from eqs 24 and 21, we can find the relative efficiency of REMD for our toy two-well system

$$E_2 = k_{\text{REMD}} \tau_{\text{relax}}(\beta_{\max}) \\ = \left[2k_0 \frac{e^{\Delta S/R} [e^{-\beta_{\min} \Delta H} - e^{-\beta_{\max} \Delta H}]}{\Delta\beta \Delta H} \right] \left[\frac{1}{2k_0 e^{\Delta S/R} e^{-\beta_{\max} \Delta H}} \right] = \frac{e^{\Delta\beta \Delta H} - 1}{\Delta\beta \Delta H} \quad (26)$$

which is shown for a specific choice of parameters in Figure 2. A similar calculation tells us

$$E_1 = k_{\text{relax}} \langle \tau_{\text{relax}} \rangle_\beta = \left[2k_0 \frac{e^{\Delta S/R} [e^{-\beta_{\min} \Delta H} - e^{-\beta_{\max} \Delta H}]}{\Delta\beta \Delta H} \right] \int_{\beta_{\min}}^{\beta_{\max}} \frac{1}{\Delta\beta} \frac{1}{2k_0 e^{\Delta S/R} e^{-\beta' \Delta H}} d\beta' = 2 \frac{[\cosh(\Delta\beta \Delta H) - 1]}{(\Delta\beta \Delta H)^2} \quad (27)$$

which is also shown in Figure 2.

At this point, a few observations are possible. First, the efficiency is strongly system dependent. Systems with relaxation controlled by large enthalpy barriers will be greatly enhanced by REMD; systems with small enthalpy barriers will be only weakly improved by REMD. This point has previously been emphasized by others.^{46,47} Second, the relative efficiency is always greater than 1 for this particular system provided that there is a positive activation barrier. REMD is always more efficient than regular MD. Third, the efficiency is solely a function of $\Delta\beta \Delta H$, which is not surprising, since these are the only two characteristic energy scales in this system.

In the limit that $\Delta\beta \Delta H$ is large, E_1 and E_2 are asymptotically equal to

$$E_1 : \frac{1}{(\Delta\beta \Delta H)^2} e^{\Delta\beta \Delta H} \\ E_2 : \frac{1}{\Delta\beta \Delta H} e^{\Delta\beta \Delta H} \quad (28)$$

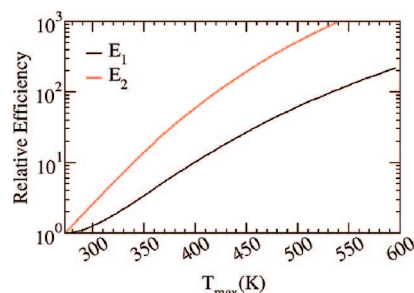


Figure 2. Theoretical relative efficiencies (E_1 and E_2) for REMD for a two-state system with two wells with identical entropies and energies separated by a single barrier with an activation free energy of 10 kcal/mol. Biologically, this model is most similar to a small peptide with two stable conformational minima. Replicas are assumed to be uniformly distributed in inverse temperature with a minimum temperature of 273 K and a maximum temperature of T_{\max} .

Naively, one might have guessed that for large activation barriers the efficiency of REMD would be equal to the ratio of relaxation rate at T_{\max} to the relaxation rate at T_{\min} , that is

$$\frac{k(T_{\max})}{k(T_{\min})} = \frac{e^{-\beta_{\min} \Delta H}}{e^{-\beta_{\max} \Delta H}} = e^{\Delta\beta \Delta H} \quad (29)$$

The actual efficiency of REMD is significantly less than this for both E_1 and E_2 . The factor $\Delta\beta \Delta H$ accounts for the effective fraction of replicas available to cross the transition state barrier. As the energy of the barrier increases and as the temperature spread increases, the effective fraction decreases.

A more protein-like model has two-wells (U and F) separated by a single barrier, and these wells have different entropies and energies. The same approach can be used to estimate the relative efficiency in this system. In particular, eq 14 is used to determine the effective free energy of the U, F, and TS states. These effective free energies are used with eqs 6 and 7 to determine k_{REMD} . This is then used in eqs 20 and 21 to determine the relative efficiencies. For more complex protein-like models, eq 14 must be evaluated numerically for each state (U, F, and TS).

It is assumed that the TS and U states have enthalpies ΔH_{TS} and ΔH_{U} relative to the F state and entropies ΔS_{TS} and ΔS_{U} relative to the F state. ΔS_{U} is fixed by maintaining the melting temperature at 300 K. In addition, the TS barrier is assumed to have a negligible contribution to the partition function relative to the F and U states. The principal difference between this model and real proteins is the lack of relative heat capacities among the various states. The relative efficiency E_2 for this protein-like model is shown in Figure 3. (Efficiency E_1 is not shown because it is qualitatively similar and normally of less interest.) Figure 3 shows that both the unfolding enthalpy ΔH_{U} and the activation enthalpy for folding $\Delta H_{\text{f}}^\ddagger$ can affect the relative efficiency of REMD. It can be rigorously shown that the activation entropy of folding has no effect on the relative efficiency for this model under the assumption that the contribution of the TS state to the partition function is negligible.

As in the previous model, the efficiency of REMD is always greater than conventional MD at T_{\min} . The actual gain

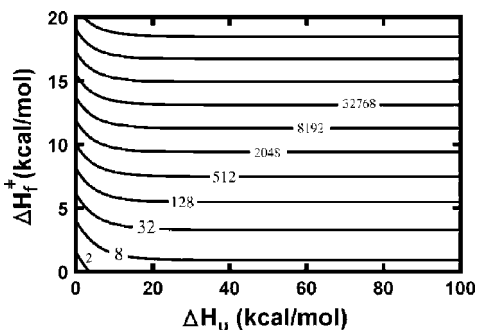


Figure 3. Constant relative efficiency (E_2) contours for a simple, two-state, protein-like kinetic model with fixed enthalpies and entropies of activation and folding. Unlike the model of Figure 2, the two wells are not assumed to have the same energy or entropy. Contours are labeled by their relative efficiency. They are spaced logarithmically in efficiency. ΔH_u is the enthalpy of unfolding. The melting temperature is fixed at 300 K, which fixes the value of ΔS_u . ΔH_f^\ddagger is the activation enthalpy of folding. The value of ΔS_f^\ddagger is chosen small enough to make the population of the transition state negligible for all values of ΔH_f^\ddagger ; the precise value of ΔS_f^\ddagger has no effect on the relative efficiency of REMD. Relative efficiency is computed for a REMD simulation with evenly spaced inverse temperatures spanning the temperature range from 273 to 500 K.

is a strong function of the activation energy for folding. For even modest barriers (~ 5 kcal/mol) for folding, the rate enhancement of REMD can be significant. Interestingly, even in the absence of an activation enthalpy for folding, REMD can be more efficient than conventional MD because elevating the temperature can reduce the unfolding time, which contributes to the overall relaxation rate.

To gain some more insight into the relative contributions of k_f and k_u to the total replica relaxation rate k_{relax} (k_{REMD}), the dependence of these rates on T_{max} for one choice of model parameters ($\Delta H_u = 20$ kcal/mol; $\Delta H_f^\ddagger = 5$ kcal/mol) is shown in Figure 4. Because the activation enthalpy for unfolding (25 kcal/mol) is much larger than the activation enthalpy for folding (5 kcal/mol), the unfolding rate increase more rapidly with T_{max} than the folding rate. At low temperatures the relaxation rate is controlled by the folding rate, so the primary effect of a REMD simulation when T_{max} is low is to increase the folding rate; however, when T_{max} is large, the primary effect is to increase the unfolding rate. The crossover between these two effects occurs in this model about 25 K above the melting temperature (300 K).

An important property of real proteins not included in this model is the existence of relative heat capacity differences ΔC_U and ΔC_{TS} of the U and TS states relative to the F state. These heat capacities can strongly affect the behavior because they work to reduce the activation enthalpy for folding at high temperatures. At a high enough temperature, the activation enthalpy for protein folding usually becomes negative. In this regime, the folding rate is determined solely by an entropic search for the native state. This does not correspond to a conventional Arrhenius picture of diffusion controlled by an enthalpic barrier, although it is described by a similar “Arrhenius-like” rate equation. The existence of a negative activation enthalpy strongly affects the efficiency of REMD simulation.

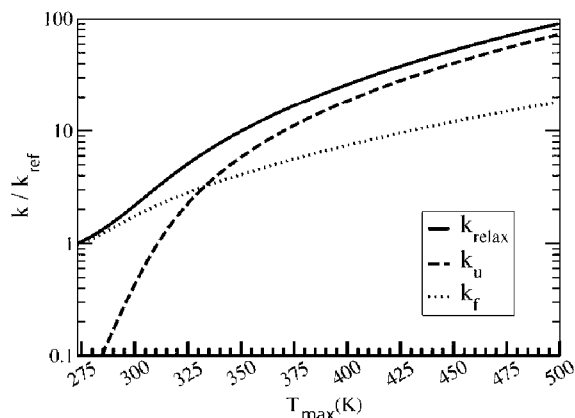


Figure 4. Variation in the unfolding rate (k_u), the folding rate (k_f), and the relaxation rate (k_{relax}) of the replicas in a REMD simulation as a function of the maximum temperature of the simulation. Rates are shown relative to the relaxation rate at 273 K. The model used is the two-state protein-like model with no heat capacities, an unfolding enthalpy of $\Delta H_u = 20$ kcal/mol, and an activation enthalpy for folding of $\Delta H_f^\ddagger = 5$ kcal/mol. The entropy of the unfolded state is determined so that the melting temperature is fixed at 300 K.

Table 1. Measured Enthalpy, Entropy, and Heat Capacity of the Transition State and Unfolded State of Protein L Relative to the Native State at 295 K^a

	ΔH (kcal/mol)	ΔS (kcal/(mol K))	ΔC_p (kcal/(mol K))
transition state (TS)	26.8	0.03	0.19
unfolded state (U)	20.1	0.05	0.77

^a These values are used to estimate the relative efficiency E_2 of REMD (Figure 5).

To illustrate the effects of a nonzero heat capacity, let us consider an actual protein. Protein L is a commonly used model system for protein for folding studies. The thermodynamic properties of protein L have been measured⁶⁰ and are shown in Table 1. Following the same procedure as before, numerical integration is used to determine the relative efficiency E_2 as a function of the maximum temperature T_{max} of the replicas. This is shown in Figure 5. It is assumed that inverse temperatures are uniformly distributed from the minimum to maximum inverse temperature.

Unlike simpler models for which relative efficiency is always greater for a larger T_{max} , protein L shows a maximum efficiency for an intermediate T_{max} . This maximum efficiency occurs slightly above the temperature at which the activation enthalpy for folding vanishes, which appears to be a good rule of thumb for choosing a value of T_{max} . At temperatures for which the activation enthalpy is negative, increasing temperature would be expected to be counterproductive, slowing the search rate; in contrast, for any positive activation enthalpy, increasing the temperature should make barrier crossing more rapid. The same behavior is exhibited by the F13W/G29A mutant of the B domain of staphylococcal protein A (protein A) when modeled from its thermodynamic data⁶¹ (data not shown). The relative efficiency E_2 for a REMD simulation of protein A starts at a value of 1, peaks at 6.4 when T_{max} is 326 K, and declines as T_{max} is increased further. The peak efficiency occurs close to

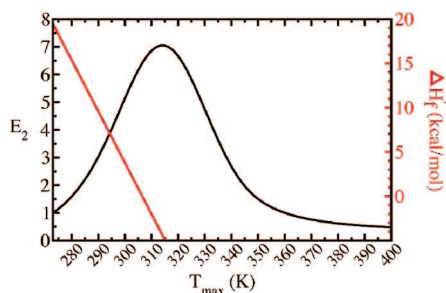


Figure 5. Relative efficiency E_2 of a REMD simulation of protein L with inverse temperatures uniformly distributed from $1/273$ K to $1/T_{\max}$. Although REMD can produce significant increases in efficiency, the amount of rate enhancement varies strongly with the maximum temperature. In particular, a maximum temperature that is too high can actually result in a decrease in the relaxation rate because of the existence of heat capacities that reduce the activation energy of folding. The maximum relative efficiency of REMD occurs when T_{\max} is chosen slightly above the temperature at which the activation free energy of folding disappears. This appears to be a good rule of thumb for choosing T_{\max} of a REMD simulation.

and slightly above the temperature, 318 K, at which the activation enthalpy vanishes.

The strong dependence of efficiency on the choice of T_{\max} and on the enthalpy of folding is the most plausible explanation for the large differences between the estimated efficiency of REMD simulations. Close attention should be paid to the type of problem to which one is applying REMD as well as the choice of T_{\max} . Estimation of the optimal T_{\max} can be made from experimental measurements of the thermodynamic properties of the folded, unfolded, and transition states; however, one should be cautious that these values are approximately reproduced using the molecular dynamics force field. These results also suggest that the performance advantages of REMD on systems with explicit solvent may be very different from the performance advantages with implicit solvent, because, in many implicit solvent models, entropic nonpolar solvation effects are represented as enthalpic contributions to the free energy leading to different activation enthalpies.

The folding and unfolding contributions to the relaxation rate can be determined for the REMD simulation of protein L (Figure 6). Like the simpler protein model without relative heat capacities, the primary rate enhancement of REMD arises at lower values of T_{\max} from increases in the folding rate. However, unlike the simpler model, enhancement of the unfolding rate makes a relatively minor contribution to the overall rate enhancement of REMD.

The analysis that has been presented is predicated upon the fact that motions in temperature are fast relative to conformational changes. Many biomolecular simulations have been run in a suboptimal manner in which temperature exchanges are relatively infrequent.⁵⁴ An analysis similar to the one presented here may be applicable; however, in this suboptimal regime one must examine the relaxation behavior on the full $G(x, \beta)$ surface. Additionally, the existence of additional correlations between replicas under very high

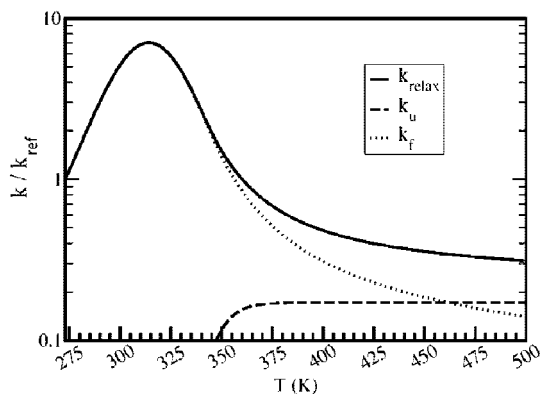


Figure 6. Variation in the unfolding rate (k_u), the folding rate (k_f), and the relaxation rate (k_{relax}) of the replicas in a REMD simulation of protein L as a function of the maximum temperature of the simulation. Rates are shown relative to the relaxation rate at 273 K.

exchange rates that might lead to slowing cannot be definitively ruled out.

Up to this point, the issue of additional computational losses from spatial decomposition in conventional MD has not been addressed. In essence, the results so far have been a comparison of REMD with MD on a single processor. When calculations are run on N processors simultaneously, conventional MD incurs additional losses due to communication bottlenecks that REMD will not. For conventional MD, the actual speedup with a conventional decomposition approach will not normally be N but γN , where γ is equal to the ratio of actual speedup to theoretically possible speedup. For this reason, even if the theoretical efficiency of REMD as we have calculated it is no better than conventional MD, the actual efficiency of REMD on N processors is often greater than conventional MD by a factor of $1/\gamma$.

Summary and Conclusion

In summary, an analytic approach has been developed for analyzing REMD simulations. This analysis is applicable for conditions under which individual replicas are only weakly interacting. Under these conditions, a REMD simulation can be analyzed as a collection of N noninteracting simulations moving in both conformational space and in temperature. The dynamics in conformation and temperature for a single replica is determined by the structure of the equilibrium free energy surface $G(x, \beta)$. Beginning from this surface (defined via eq 11), one can in principle determine the relaxation spectrum and the integrated autocorrelation time, which can be used to determine the relative efficiency of REMD.

To simplify calculations, the timescale separation between temperature motion and conformational change can be used to reduce the equilibrium free energy surface $G(x, \beta)$ to an effective free energy surface $G_{\text{eff}}(x)$ by integrating out the temperature degrees of freedom. Applying this approach to a number of two-state protein models demonstrates that the relative efficiency of REMD is a strong function of the activation enthalpy; however, REMD is always more efficient for these models than conventional, constant temperature MD provided that the activation enthalpies for folding and unfolding are positive

throughout the temperature range. Analysis of models with thermodynamic parameters of real proteins—protein L and the B domain of protein A—indicates that the peak REMD efficiency occurs for a value of T_{\max} slightly above the temperature at which the activation enthalpy for folding vanishes. If T_{\max} is increased beyond this, the relative efficiency of REMD begins to drop. Eventually, the relative efficiency of REMD can become negative, making this a critically important parameter choice for a REMD simulation.

Assuming that protein L and the B domain of protein A are representative of the small proteins for which REMD is used, REMD appears to be significantly more efficient than conventional MD. For the optimal choice of T_{\max} REMD is respectively 7 and 6.4 times more efficient than conventional MD for these proteins. This does not include efficiency losses due to parallelization, which in practical circumstances strongly favor REMD simulations. Additionally, REMD has the benefit of providing accurate temperature dependent statistics to determine the relative enthalpies of different conformational states.

Because the dynamics of replicas are controlled by a single transition state barrier on the $G(x, \beta)$ surface, the asymptotic efficiency of REMD is nearly independent of the number of replicas. However, because biological simulations are usually run for only a few multiple of the relaxation rate, dividing the simulation time among the multiple replicas can be detrimental.

The analysis presented in this manuscript is solely for two-state proteins. A similar analysis can be carried out for proteins with intermediates or nonprotein systems. For this analysis, it is important to carefully determine the integrated autocorrelation time, because a single relaxation time is no longer dominant. Also, when motion in temperature is not fast compared to conformational change, the full $G(x, \beta)$ surface should be used for analysis rather than the effective surface $G_{\text{eff}}(x)$. Replica methods involving parameters other than temperature can also be analyzed in a similar manner.

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