Resolution Exchange Simulation

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We extend replica exchange simulation in two ways, and apply our approaches to biomolecules. The first generalization permits exchange simulation between models of differing resolution — i.e., between detailed and coarse-grained models. Such “resolution exchange” can be applied to molecular systems or spin systems. The second extension is to “pseudo-exchange” simulations, which require little CPU usage for most levels of the exchange ladder and also substantially reduces the need for overlap between levels. Pseudo exchanges can be used in either replica or resolution exchange simulations. We perform efficient, converged simulations of a 50-atom peptide to illustrate the new approaches.

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The simulation of biomolecules with $10^4 - 10^5$ degrees of freedom has become routine, thanks to the accessibility of powerful computing resources, the development of reliable simulation software, and standardized empirical potential energy functions. For many biological applications, such as binding free energy estimation, it is desirable to generate an equilibrated ensemble of conformations. In principle, standard Monte Carlo (MC) and molecular dynamics (MD) algorithms are perfectly ergodic, and therefore will eventually generate such ensembles. In practice, the $\mu$s — sec timescale, which describes biologically relevant fluctuations, is not within reach of computation even for small proteins.

Two broad strategies have been developed to address this problem. In one approach, dating to the earliest computational studies of proteins[1, 2], coarse-grained protein representations are adopted. This strategy continues to be popular[3, 4].

A second class of strategies attempts directly to enhance sampling of atomic-resolution models, including multiple time step methods[5, 6], replica exchange[7]/parallel tempering[8, 9, 10], and other generalized ensemble techniques[11]. Parallel tempering (PT), which employs a ladder of replicas simulated at increasing temperatures, is widely used for state-of-the-art molecular dynamics simulations, but presently is limited to small proteins[12], as the resources required increase rapidly with the system size.

This Letter presents two new tools for biomolecular simulation, by extending the PT approach and exploiting the speed of coarse-grained models. The first extension is a “resolution exchange” (res-ex) algorithm which — instead of using high-temperature simulation to increase sampling, as does PT — uses inexpensive coarse-grained models to cross barriers. Boltzmann-weighted ensembles are produced. The algorithm is implemented in close analogy to PT, and can also be applied to magnetic systems (e.g., the Ising model). The res-ex approach is natural for proteins, and indeed the kernel of the idea was suggested in the early days of protein simulation[1]. More recently, the approach has been implemented in an ad hoc way, without proper statistical weighting[3]. A rigorous method to calculate free energy differences between all-atom and coarse-grained models was demonstrated by Warshel and coworkers[13].

Our res-ex approach is conceptually related to work on Ising systems by Brandt and coworkers (e.g., [14, 15]). The res-ex approach is distinguished, however, by its simplicity, its ready applicability to biomolecules, and the ability to employ arbitrary coarse-grained Hamiltonians.
We also introduce “pseudo-exchange” (ps-ex) processes which should significantly improve the efficiency of any type of exchange simulation, whether one swaps temperatures (as in PT), Hamiltonians or resolution (res-ex). Pseudo-exchanges are performed between a simulation in progress and one which has already been completed. The key advantage of ps-ex is that it permits uneven distribution of CPU time among levels of the exchange ladder. Because all exchange simulations are limited by the sampling obtained at the highest level — i.e., highest temperature (for PT) or lowest resolution (res-ex) — the bulk of CPU time should be devoted to this top level. Although an uneven distribution of CPU time among levels (replicas) would be awkward in a truly parallel implementation, it is natural and highly efficient in a serial ps-ex simulation. Furthermore, there is essentially no disadvantage to multiple independent runs, as compared to a single parallel simulation.

Resolution Exchange Theory. The key idea behind res-ex is that, in addition to swapping temperature labels (PT) or parameters of the Hamiltonian, one can also swap a subset of configurational coordinates. A well-chosen subset of coordinates of a detailed model can comprise the full set of coordinates for a coarse-grained model, as we demonstrate below.

A general exchange process is constructed by considering two independent simulations of a protein (or a spin system) carried out in parallel, each sampling its own distribution \( \pi_1 \) or \( \pi_2 \). In common cases, the distributions will be given by \( \pi_i(\Phi_i, x; k; T_i) = \exp(-U(\Phi_i, x; k)/k_B T_i) \), where a configuration is composed of coordinates \( \{\Phi, x\} \) which include an arbitrarily chosen “coarse” subset \( \Phi \), and where \( k \) denotes the parameters of the potential function \( U \) and \( k_B T \) is the product of Boltzmann’s constant and the temperature. A general exchange process consists of a swap of a set of the arguments of the \( f \) functions: swapping \( T_1 \leftrightarrow T_2 \) leads to PT, and swapping \( k_1 \leftrightarrow k_2 \) values leads to Hamiltonian exchange. To achieve resolution exchange, one can swap values of the set of coarse coordinates, \( \Phi_1 \leftrightarrow \Phi_2 \), noting that the corresponding potential parameters \( k_\Phi \) need not match in the two systems. It is indeed possible to swap an arbitrary combination of coordinates and parameters.

Specializing, for clarity, to resolution exchange, we consider independent simulations governed by a “high resolution” potential function \( U_H(\{\Phi, x\}) \) and a coarse-grained (low-resolution) potential \( U_L(\{\Phi\}) \). Occasionally, we attempt an exchange move by swapping the \( \Phi \) subset. The set \( \{\Phi, x\} \) may be, for example, all the atomic coordinates of a protein, while the subset \( \{\Phi\} \) may be only the coordinates of the backbone. For a spin system, \( \{\Phi\} \) may correspond to a block backbone, and \( x \) to the orientations of the local spins relative to the block spin.

To develop the exchange criterion, assume that at an exchange point the system is characterized by a high-resolution configuration \( \{\Phi_a, x_a\} \) and a low-resolution configuration \( \{\Phi_b\} \). Attempting to exchange the \( \{\Phi\} \) subset yields the trial conformations \( \{\Phi_b, x_a\} \) and \( \{\Phi_a\} \). Because the simulations are independent, the weight of the composite system is given by the simple product \( \pi_\text{tot} = \pi_1 \pi_2 = \pi_H \pi_L \), and detailed balance will be satisfied if we accept such moves with a Metropolis rate \( \min[1, R] \), where \( R \) is given by

\[
R = \frac{\pi_1(\text{new}) \pi_2(\text{new})}{\pi_1(\text{old}) \pi_2(\text{old})} = \frac{\pi_H(\Phi_b, x_a) \pi_L(\Phi_a)}{\pi_H(\Phi_a, x_a) \pi_L(\Phi_b)} \tag{1}
\]

The analogy to PT and Hamiltonian exchange is clear, but we have now extended the approach.

Naturally, there are limitations on the types of models which can be successfully exchanged, much as PT temperature increments are limited. In the results presented below, we successfully performed exchanges between all-atom and united-atom models of a peptide.

**Pseudo-exchange simulation.** The res-ex and PT algorithms are motivated by the likelihood that the “top level” simulation (i.e., lowest resolution or highest \( T \)) will more rapidly cross barriers and converge to an equilibrium ensemble of conformations. While the associated convergence time is expected to be quite long, even for the top level, it is far from clear that the attainment of an equilibrium ensemble at a lower level requires the same length of simulation. Indeed, given that barriers should be crossed many times at the top level, significantly less simulation time should be required at the lower levels of the exchange ladder. Our results show this to be true. Yet it would seem impossible to allot a priori appropriate CPU resources among the various ladder levels in a conventional parallel exchange simulation.

A “pseudo exchange” process is the key to efficiently distributing computing time among ladder levels. The first step is to generate a well-sampled ensemble at the top level (highest temperature or lowest resolution) and randomly re-order this trajectory (FIG. 1b). While such shuffling preserves the distribution of states of the original trajectory, the shuffled trajectory exhibits a feature key for exchange simulation: extremely rapid barrier hops, as in FIG. 11.

One now performs a ps-ex simulation with the shuffled trajectory. As with conventional exchange, one runs an independent lower level simulation (FIG. 11), but now exchanges are performed with the shuffled top-level trajectory. The identical Metropolis criterion is used — i.e., or its PT analog. If the exchange attempt is successful, the new lower-level trajectory is continued from the accepted configuration, and the top-level trial configuration is simply discarded. The process is repeated as long as necessary.

Pseudo-exchange processes are useful for several reasons: (i) ps-ex processes may be used with any exchange simulation; (ii) much lower acceptance ratios are still efficient because frequent pseudo-exchange attempts are inexpensive in a serial scheme; and (iii) because of the weaker acceptance ratio requirements, larger gaps among ladder levels (e.g., \( T \) increments in PT) can be tolerated.
form potential used for the low-resolution simulation. The low-resolution simulations were carried out with a friction coefficient of 91 ps$^{-1}$ at 300 K. Langevin dynamics were used, with a friction coefficient of 91 ps$^{-1}$. The all-atom butane molecule was simulated in vacuum for 1 nsec reference trajectory. Plotted is the distribution of the C-C-C-C dihedral, $\phi_1$, which measures the populations of the three conformers. The res-ex simulations reproduce the equilibrium distribution, as measured in the comparison simulation, regardless of the potential used for the low-resolution simulation. The low-resolution model was a one-dimensional potential of the form $A \cos(3\phi) + B \sin(\phi)$, where $\phi$ is the C-C-C-C dihedral. The asymmetric potential, shown in (b), has $A = B = 1$, while the symmetric potential in (c) has $A = 1$ and $B = 0$.

**Res-ex for a peptide: Dileucine peptide.** We also tested the res-ex/ps-ex method on the dileucine peptide (ACE-(Leu)$_2$-NME; “leucine dipeptide”). Though still a long way from a full size protein, 50 atom dileucine allows us to address a number of issues which need to be considered before tackling a full size protein. A united atom (UA) representation, which omits nonpolar hydrogens, is a natural choice for the low-resolution model. For dileucine, this reduces the number of atoms from 50 in an all-atom (AA) representation to 24 in UA.

The goal is to generate efficiently a converged ensemble of conformations for all-atom dileucine, using the ps-ex/res-ex protocol. We assess convergence by considering the free energy difference between the two dominant conformations, distinguished by rotations about the $\psi_1$ angle of leu1 and the $\phi_2$ angle of leu2. Transitions between these two basins are hampered by a significant barrier, and therefore occur rarely (approx. 1/3 nsec$^{-1}$ at 300 K for AA). We define the “$\alpha$” conformations by $-105 < \psi_1 < 0$ and $-145 < \phi_2 < -25$, and the “$\beta$” conformations by $30 < \psi_1 < -155$ and $-160 < \phi_2 < -40$.

The AA dileucine molecule was modelled with the OPLSaa force field. For UA dileucine, we used a slightly modified version of the OPLSaa force field, altering a few of the bond length and bond angle parameters to match those in the all-atom force field; these simple changes reduce the likelihood of exchange-induced steric clashes. Both simulations were carried out with the TINKER v. 4.2 simulation package, using Langevin dynamics with a 91 ps$^{-1}$ friction coefficient, a 1 fs integration timestep and GB/SA implicit solvation.

Implementing the res-ex/ps-ex strategy, we first carried out a simulation of united-atom dileucine (FIG. 1(a)). We then randomly reshuffled this trajectory (FIG. 1(b)) in order to generate a pseudo-trajectory with much more

![FIG. 2: The res-ex algorithm produces canonical sampling despite a poor coarse-grained potential. (a) Probability densities $P(\phi)$ for butane. Reference data obtained from standard simulation are indicated by the solid line. The res-ex simulation with the asymmetric potential in (b) is plotted with triangles, and the res-ex simulation with the symmetric potential in (c) is plotted with circles.](Image)

**FIG. 2: The res-ex algorithm produces canonical sampling despite a poor coarse-grained potential. (a) Probability densities $P(\phi)$ for butane. Reference data obtained from standard simulation are indicated by the solid line. The res-ex simulation with the asymmetric potential in (b) is plotted with triangles, and the res-ex simulation with the symmetric potential in (c) is plotted with circles.**

![FIG. 3: Res-ex simulation accelerates equilibration among dileucine peptide substates. Dashed lines show running estimates of the inter-substate $\Delta G_{\alpha\beta}$ as a function of time for 8 independent, 40 nsec trajectories, and the solid line shows the estimate of $\Delta G_{\alpha\beta}$ from 600 nsec of standard simulation. Each symbol with error bars gives the average and range of 8 independent res-ex simulations, displaced from the origin to reflect total CPU time (measured in all-atom timesteps), including investment in the united atom simulation. The efficiency gain can be estimated by the relative ranges of the $\Delta G_{\alpha\beta}$ estimates.](Image)

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frequent $\alpha \leftrightarrow \beta$ transitions than are observed in the original trajectory. This randomized trajectory (still Boltzmann distributed) is then used to generate the all-atom trajectory (FIG 1(c)) via the res-ex protocol. Notice that $\alpha \leftrightarrow \beta$ transitions are observed far more frequently in the all-atom trajectory with exchange (about 30/nsec) than without (about 1/3 nsec, FIG 1(d)).

Assessing convergence and efficiency of a protein simulation are generally difficult tasks. Fortunately, the situation here is relatively simple, as we can consider the free energy difference between the $\alpha$ and $\beta$ states: $\Delta G_{\alpha\beta} = 0.690k_BT$, with the wrong sign. This is an important point, as it is known that united atom models do not reproduce all atom behavior. More important for res-ex simulation is that the coarse-grained model explores conformational space more rapidly, as well as being “exchangeable” with the more detailed model.

It is clear that the res-ex simulations reproduce the $\Delta G_{\alpha\beta}$ estimated from the standard simulations. This is accomplished despite the failure of the united atom model to reflect correctly the populations of the $\alpha$ and $\beta$ states: $\Delta G_{\alpha\beta}(\text{united atom}) = -1.25 \pm 0.40k_BT$, with the wrong sign. This is an important point, as it is known that united atom models do not reproduce all atom behavior. More important for res-ex simulation is that the coarse-grained model explores conformational space more rapidly, as well as being “exchangeable” with the more detailed model.

It is further clear that the res-ex results are generated with significantly higher efficiency. For a given amount of CPU time (nsec in FIG 13), the res-ex estimates exhibit high accuracy with a greatly reduced uncertainty. For example, 5 nsec of resolution exchange simulation generated an estimate for $\Delta G_{\alpha\beta} = -1.25 \pm 0.40k_BT$, while 75 nsec of standard simulation are required to reach a comparable level of accuracy and precision, indicating a 15-fold savings in CPU time. We emphasize that our analysis gives a true efficiency estimate, since it includes the total CPU time, rather than the cost for one of many parallel simulations.

The acceptance ratio of attempted pseudo exchange moves need not be 20%, as conventional wisdom dictates. Indeed, even a very small fraction of accepted exchanges can greatly enhance efficiency, provided those exchanges generate novel conformations. The goal is to optimize diffusion in conformation space, not acceptance ratio. In res-ex trajectories presented here the average acceptance ratio was only 0.156%. Nonetheless, high efficiency is obtained because successful exchanges with a shuffled top-level trajectory are very likely to generate novel conformations, at a fraction of the cost of standard simulation.

**Discussion.** We have introduced two extensions of parallel-tempering/replica-exchange which show promise for improved efficiency of biomolecular simulations. “Resolution exchange” enhances sampling of an expensive, high-resolution model using a cheaper, coarse-grained model with the resolution exchange protocol. Generalization to a ladder of models is formally trivial. The sampling in the high-resolution model satisfies detailed balance, and therefore generates an equilibrium ensemble. The further introduction of the “pseudo-exchange” process permits the bulk of computer resources to be invested in sampling and crossing barriers at the top level of the exchange ladder (highest temperature or lowest resolution), and only incremental additional simulation is required at lower levels.

The treatment of even larger, more complex molecules will be the subject of future research. We emphasize that our efficiency gains were obtained using only a two-level ladder, implying that much greater efficiency is possible with additional levels — which can be added at small cost via pseudo-exchange. A long-term goal is to develop a full ladder of reduced, exchangeable models, extending up to the “united residue” level, because even UA computations require long simulation times. For temperature-based exchange, a PT implementation of the pseudo-exchange approach can be applied to explicitly solvated proteins with only a minimum of modification to common software packages. Our own preliminary PT/ps-ex simulations indicate, interestingly, that successful dileucine exchanges can easily be implemented with temperature gaps of 200 K or more. Ultimately, resolution and temperature exchange might be combined for high-efficiency simulations of biomolecules.

Two limitations should be mentioned. First, we do not expect the present algorithm to enable exchange between continuum and explicit solvent representations. However, the present degree of undersampling of proteins, when using continuum solvent representations, warrants pursuit of this problem in its own right. A second limitation is that, to be exchangeable, two models must be sufficiently “similar”: there should be overlap between low-energy coarse variable conformations. Yet, a process of incremental coarsening—changing part of a molecule at a time, and which we have already implemented for dileucine (data not shown)—will minimize this difficulty for larger systems.

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