Mode excitation Monte Carlo simulations of mesoscopically large membranes

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Solvent-free coarse grained models represent one of the most promising approaches for molecular simulations of mesoscopically large membranes. In these models, the size of the simulated membrane is limited by the slow relaxation time of longest bending mode. Here, we present a Monte Carlo algorithm with update moves in which all the lipids are displaced simultaneously. These collective moves result in fast excitation and relaxation of the long wavelength thermal fluctuations. We apply the method to simulations of a bilayer membrane of linear size \( \sim 50 \) nm and show reduction of the relaxation time by two orders of magnitudes when compared to conventional Monte Carlo.

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lattice simulations each Fourier mode of the membrane represents a single degree of freedom of the field and, therefore, large variations in their amplitudes will not be energetically costly and will have reasonable acceptance probabilities. Such large scale variations are prohibited in off-lattice molecular models by excluded volume interactions. Nevertheless, MC algorithms with collective update moves have been recently proposed for simulations of simple fluids [13, 14], exhibiting superior performance over conventional MC schemes. For molecular simulations of membranes and interfaces, we consider collective moves in which the coordinates of all the lipids are simultaneously updated according to the rule:

\[
(x, y, z)_{\text{new}} = \left(x_{\text{old}}, y_{\text{old}}, z_{\text{old}} + \sum_{i=1}^{m} \epsilon_i \cos(\bar{q}_i \cdot \bar{r} + \alpha_i)\right),
\]

where the sum runs over a set of \( m \) modes with wavevectors \( \bar{q} = (2\pi/L) \cdot (n_1, n_2) \); \( n_1, n_2 = 0, 1, 2, \ldots \). This set includes the modes with the smallest wavenumbers \( n^2 = n_1^2 + n_2^2 = 1, 2, 4, 5, 8, \ldots \). The random amplitude of the \( \ell \)-th mode in Eq. (1) is chosen from the interval \([-\epsilon^*_\ell, +\epsilon^*_\ell]\) (the magnitude of \( \epsilon^*_\ell \) is discussed below), while \( \alpha_i \) is a random phase chosen from a uniform distribution on \([0, 2\pi)\). Because this move is reversed by choosing the set of amplitudes \(-\epsilon_i\), and since the Jacobian of transformation described by Eq. (1) is unity, detailed balance is satisfied when the proposed mapping Eq. (1) is combined with Metropolis acceptance rule: \( p(\text{old} \to \text{new}) = \min(1, \exp(-\beta \Delta E)) \), where \( \beta = (k_B T)^{-1} \) is the inverse temperature and \( \Delta E \) is the energy difference between the “new” and “old” states.

The height function of the simulated membrane is calculated by dividing the area into \( M^2 = (L/l)^2 \) grid cell of size \( l \) (comparable to the width of the membrane), and averaging the height of all the lipids instantaneously located within each cell [15]. The Fourier transform of the discrete height function (defined on the set of points \( \{ \bar{r}_g \} \), each of which is located at the center of a grid cell

\[
h_{\bar{n}} = \sum_{\bar{r}_g} h(\bar{r}_g) e^{-2\pi i \langle \bar{n}, \bar{r}_g \rangle/L},
\]

includes \( M^2 \) modes, corresponding to \( \bar{n} = (n_1, n_2); n_1, n_2 = (-M/2) + 1, \ldots , M/2 \). In conventional MC simulations, all the modes are equally affected by the uncorrelated move attempts. Randomly displacing the lipids a vertical distance \( \epsilon \) within a MC time unit, would cause the amplitudes of all the Fourier modes [2] to change by \( |\delta h_{\bar{n}}| \sim M^2 \sigma^2 = (L/l)^2 \sigma^2 \), independently of \( n \). At large scales (small \( n \)), the behaviour of an undulating membrane can be described by Helfrich effective surface Hamiltonian which relates the elastic energy to the local curvature and the bending modulus, \( \kappa \). The power spectrum of the bilayer thermal fluctuations [16]

\[
\langle h_{\bar{n}}^2 \rangle = \frac{kT L^2}{\kappa (4\pi q^4/\kappa)^4} = \frac{kT L^6}{\kappa (2\pi n d)^4},
\]

strongly depends on \( n \). The conventional MC scheme generates diffusive dynamics in Fourier space, where for each mode the relaxation time (in MC time units)

\[
\tau_n \sim \left(\frac{\langle h_{\bar{n}}^2 \rangle}{(\delta h_{\bar{n}})^2}\right) \frac{kT L^4}{\kappa (\Delta^2 (2\pi)^n)^4} = \frac{kT L^4}{\kappa (\Delta^2 (2\pi)^n)^4}.
\]

The relaxation time of the mode with the smallest wavenumber, \( n = 1 \), grows as a fourth power of the linear size of the system.

The relaxation of long wavelength modes can be accelerated by introducing collective MC moves which cause larger variations in their amplitudes. To eliminate the \( n^{-1} \) dependence of \( \tau_n \) and ensure that all the modes relax equally fast, we set the interval from which the random amplitudes in Eq. (1) are chosen to satisfy: \( \epsilon^*_n = \Delta/n^2 \) (see Eq. (1)). The value of \( \Delta \) can be determined empirically, by employing the usual criterion that the acceptance rate of the moves represented by Eq. (1) is approximately half. Notice, however, that because of the strong decrease of \( \epsilon^*_n \) with \( n \), significant improvement in the relaxation times should be expected only for the longer (also the slower) wavelength modes. Therefore, the sum in Eq. (1) can be limited to small wavenumbers while the relaxation of modes with larger values of \( n \) will continue to rely on single particle moves. The long wavelength modes are efficiently sampled by the new scheme because the magnitude of \( \Delta \) is independent of the system size. This can be understood by noting that the energy cost per unit area of a collective trial move is \( E/L^2 \sim C S^2 \), where \( S \sim (\Delta/L) \) is the induced strain and \( C \) is the relevant elastic modulus. The total deformation energy \( E \sim C \Delta^2 \) should be of the order of the thermal energy \( k_B T \), yielding \( \Delta^2 \sim (k_B T)/C \) which is indeed size-independent. The collective MC moves cause the amplitudes of the slow modes included in the sum in Eq. (1) to change by \( |\delta h_{\bar{n}}| \sim M^2 \delta \Delta = (L/l)^2 (\Delta/n^2) \) (see Eq. (2)) and, therefore, their relaxation times scale as

\[
\tau_n \sim \left(\frac{\langle h_{\bar{n}}^2 \rangle}{(\delta h_{\bar{n}})^2}\right) \frac{kT L^2}{\kappa \Delta^2 (2\pi)^n}.
\]

This time does not increase with decreasing the wavenumber \( n \) and, moreover, grows only as \( L^2 \sim N \) rather than \( L^4 \sim N^2 \). Furthermore, a single collective trial move requires the evaluation of \( O(N) \) (short range) pair-interactions, which makes them equally CPU time as \( O(N) \) single particle trial moves. Therefore, the CPU time per MC time unit required in schemes utilizing \( O(N) \) single-particle and \( O(1) \) collective mode excitation trial moves would scale as \( N^2 \), which is superior to conventional MC algorithms whose CPU time grows as \( N^3 \).

To demonstrate the validity and efficiency of the new algorithm, we carried out simulations using Reyewar et al. three-bead lipid model. The details of the intra- and intermolecular potentials are given in ref [17]. In our study we set the energy parameter of the Lennard-Jones (LJ) potential \( \epsilon = 1.05 k_B T \) and the range of the attractive tail-tail potential \( w_c = 1.35 \sigma \), where \( \sigma \) is the length
parameter of the LJ potential. For this choice of the parameters, the membrane is in the fluid phase. The intermolecular interactions were slightly modified from the original model to eliminate the occasional escape of lipids from the membrane plane, without affecting the rigidity and fluidity of the membrane. To verify that the newly proposed mode excitation Monte Carlo (MEMC) algorithm works correctly, we used it for MC simulations of square membranes with \( N = 1000 \) lipids and compared the results to those obtained by a conventional MC algorithm. The simulations were conducted in the constant surface tension ensemble \(^3\) [20], at vanishing surface tension. In the conventional algorithm, each MC time unit consisted of \( N \) displacement move attempts of lipids (including changes in the relative coordinates of the beads), \( N \) rotation move attempts, and two area-changing trial moves. The improved MEMC algorithm included two additional trial moves per MC time unit in which all the modes with wavenumbers \( n^2 \leq 8 \) in Eq. (1) are excited. The (normalized) distribution functions of the projected area per lipid, \( a/\sigma \), are shown by open circles and dashed line, respectively. The solid line indicates the asymptotic \( \langle |h_n|^2 \rangle \sim n^{-4} \) power law.

Next, we tested the improvement in computational efficiency by simulating larger membranes consisting of \( N = 9000 \) lipids. The cross sectional area of the simulation cell was divided into a \( 16 \times 16 \) grid and the (discrete) height function was evaluated every 50 MC time units. The Fourier transform of height function \(^2\) was then computed and the amplitudes off all the modes with wavenumbers \( n^2 \leq 29 \) were recorded. The relaxation times were calculated by fitting the time autocorrelation function: \( C_n(\Delta t) = \langle |h_n(t)h_n(t+\Delta t)|/\langle |h_n(t)|^2 \rangle \) to a double exponential function: \( C_n(\Delta t) = a \exp(-\Delta t/\tau_{n,1}) + (1-a) \exp(-\Delta t/\tau_{n,2}) \). The double exponential decay has been originally conjectured by Seifert and Langer [19], and was recently observed in simulations of Shkulipa et al. [20]. In our simulations, the dissipation of the bending energy accounts for the slow relaxation mechanism characterized by \( \tau_{n,1} \equiv \tau_n \), while the smaller relaxation time \( \tau_{n,2} \) may be associated with intermonolayer friction. The latter mechanism was found to play only a relatively minor role in the decay of all the investigated modes. Due to the large statistical noise and in order to reduce the cross correlation between the two relaxation times, the fit to a double exponential form was limited to time intervals \( \tau_{n,1} \ll \Delta t < \tau_n \). The uncertainties in \( \tau_n \) (typically \( \pm 20 \% \)) were determined by comparing the fit results obtained for different fitting intervals. In the MEMC algorithm, each MC time unit consisted of (on average): \( N \) translations, \( N \) rotations, 2 area-changing, and 18 mode (with wavenumbers \( n^2 \leq 13 \)) excitation trial moves. The conventional MC algorithm included only the first three move types applied with \( N : N \equiv 2 \) proportions; however, each MC time unit of the conventional algorithm consisted of almost \( 8N \) trials in order to make the CPU time per MC time unit of both algorithms the same. The results of our analysis of the relaxation times are summarized in Fig. [3]. The MEMC algorithm eliminates the slowing down of the long wavelength modes (solid squares), causing them to relax at very similar rates. The relaxation times of the short modes which are not excited (open squares) follow the \( \tau_n \sim n^{-4} \) power law (dashed lines), which is also obeyed by the modes when the conventional MC algorithm is applied (open circles). At small length scales the MEMC algorithm is almost 4 times slower than the conventional scheme because each MC time unit of the latter includes...
almost 4 times more single particle moves. The relaxation of the total bilayer area (not shown), which is quite fast, is also slowed down by a factor of 4. The relaxation times of the long (excited) modes are considerably reduced and become comparable to the relaxation times of the longest modes among those which were not excited by the collective update moves. In comparison to the conventional scheme, the relaxation of the $n = 1$ modes is improved by a factor of about 50, from an estimated one year of CPU time to less than a week. The simulations extended over a period of about 10 weeks and, therefore, our estimates of the long scales slow relaxation times for the conventional MC algorithm (solid circles) is based on extrapolation of the $\tau_n \sim n^{-4}$ power law rather than on direct numerical evaluation.

It is interesting to compare the efficiency of the MEMC algorithm with alternative computational algorithms for constant temperature simulations. MEMC is clearly more efficient than constant temperature molecular dynamics (MD) algorithms which at sufficiently large scales become Brownian in nature and effectively behave like conventional MC simulations \cite{11}. Improved relaxation behavior is achieved when the MD simulations are run with a momentum-conserving thermostat \cite{22} that, on long length and time scales, reproduce the correct hydrodynamic behavior $\tau \sim L^3$ \cite{23}. When the CPU time per time step is considered, one finds that the computational complexity of such simulations grows as $N^{2.5}$. This is better than conventional MC and MD but still inferior to the MEMC algorithm whose complexity grows as $N^2$. In the lattice membrane simulations \cite{11}, the CPU time per MC time step grows as $N^3$ (since there are $O(N)$ Fourier modes and the variation of each is a collective move that requires the calculation of $O(N)$ interaction terms), which makes it comparable to MEMC simulations of tensionless membranes when each lattice point represents a microscopic area element of the membrane. However, when the membrane is under tension or in the presence of an external harmonic potential, the power spectrum for small wavenumbers are given by $\langle |h_{n\parallel}|^2 \rangle \sim n^{-2}$ and $\langle |h_{n\perp}|^2 \rangle \sim n^0$, respectively \cite{16}. Repeating the argument that leads from Eq. (2) to Eq. (3), one finds $\tau_n \sim L^0$ rather than $\tau_n \sim L^2$ in Eq. (4) and, therefore, the required CPU time for MEMC simulations of such membranes would grow only linearly with $N$. This demonstrates that the MEMC algorithm is asymptotically faster not only than other algorithms for continuum (molecular) membrane simulations, but also than the Fourier MC algorithm for lattice simulations.

To summarize, we introduce an improved MC algorithm for simulations of mesoscopically large membranes. The new algorithm utilizes collective update moves that lead to fast excitation and relaxation of the long wavelength bending modes. The slow relaxation of these modes in conventional MC and MD schemes is the most severe constraint that limits the size of the simulated membranes in solvent-free coarse grained models. The efficiency of the new algorithm is demonstrated by simulations of a membrane patch of 9000 lipids, where a 50-fold decrease in the relaxation time was measured as compared to a conventional MC algorithm with only single particle moves. Implicit solvent bilayer models combined with improved sampling techniques, such as the mode excitation algorithm presented here, can serve as the basis for large scale CG simulations of complexes of bilayer membranes with additional biological components.

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