

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 the longest bending mode. Here, we present a Monte Carlo algorithm with update moves in which all the lipids are simultaneously displaced. 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 with linear size of ~ 50 nm and show reduction in the relaxation time by two orders of magnitudes when compared to conventional Monte Carlo. © 2008 American Institute of Physics. [DOI: 10.1063/1.2918736]

Biological membranes play a vital role in almost all cellular phenomena and are fundamental to the organization of the cell. Because of their remarkable complexity, computer models have become essential to the understanding of their structure and dynamics. Computer simulations of lipid and biological membranes can be broadly classified into (i) atomistic models which are limited in the size and time of problems that they can address by their huge computational workload¹ and (ii) coarse grained (CG) models that sacrifice most of the atomistic details to explore larger length and time scales. The field of simplified membrane simulations is more than 20 years old and goes back to the work of Kantor *et al.* on solid tethered membranes,² which was later extended to simulations of fluid membrane by considering dynamically triangulated networks.³ A few years later, molecular bead-spring lipid models were developed to elucidate micelle self-assembly in aqueous environment.⁴ Recently, a new class of CG molecular models have been introduced, in which bilayer membranes and vesicles are simulated without direct representation of an embedding solvent.⁵ This is accomplished by constructing intermolecular force fields that mimic effects of hydration. The development of implicit-solvent models constitutes an important advance in large scale membrane simulations, considering the fact that the number of solvent particles in explicit-solvent models is significantly larger than the number of lipids. These models now serve as platforms for simulations of complexes of membranes with proteins^{6,7} and DNA molecules.⁸

Existing implicit-solvent CG bilayer models employ an extremely simple representation of the lipids as short chains consisting of one hydrophilic bead (representing the head group) and two hydrophobic beads (representing the hydrocarbon tail), connected to each other by stiff springs. In earlier works, simulations of membranes consisting of $N \sim 1000$ lipids have been presented.⁹ Such simulations can be easily performed on a commodity personal computer (PC)/workstation. A membrane patch of 1000 lipids has the linear

size of about $L \sim 20$ nm (taking the area per lipid to be ~ 0.7 nm²), which is at the small-size end of the mesoscopic regime. Simulations of larger membranes would require more memory storage and CPU time. The memory needed for simulations of membranes containing $N \approx 10^4$ lipids is still significantly smaller than the memory available on a normal PC. The CPU time problem, however, is formidable. For tensionless membranes, the relaxation time of the longest bending mode scales as $\tau \sim L^4 \sim N^2$ [see Eq. (4) below]. Moreover, for particles interacting via short-range forces only, the CPU time per Monte Carlo (MC) or Brownian dynamics time step scales as N . Therefore, the total CPU time of the simulations grows as N^3 , from roughly 10 h for $N = 10^3$ (on an AMD Opteron 275 processor running at 2.2 GHz) to more than a year (!) for $N = 10^4$. In this work, we propose an improved MC scheme that considerably reduces these enormous computing times and, thus, permits simulations of membrane-based systems on larger length and time scales.

Recent computer simulations by Reynwar *et al.*⁷ demonstrate the slow relaxation problem in membrane simulations: In this work, the assembly of membrane inclusions by curvature-mediated interactions was studied.¹⁰ Calculating the interaction between a pair of inclusion requires that the equilibrium statistics of thermal fluctuations on the scale of the object pair separation distance are accurately measured. To access the regime of large separations, Reynwar *et al.* employed a CG implicit-solvent model, which permitted them to simulate a square membrane of 46 080 lipids (the largest membrane patch simulated to date) with a linear size of about $L \sim 130$ nm. Unfortunately, the membrane-mediated interactions cannot be computed at these large spatial scales because the temporal evolution of the corresponding bending modes is extremely slow. Therefore, the membrane in this study is decorated with 36 inclusions initially forming a square lattice with spacing $d = L/6 \sim 20$ nm, and the calculation of the forces is limited to this range.

The slowing down of single particle update schemes arises because the relaxation of large scale fluctuations re-

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quires a coordinated movement of all the lipids over increasingly larger distances. In lattice membrane models, this problem can be solved by using the Fourier representation of the membrane height field and updating one, randomly chosen, Fourier amplitude at a time.¹¹ (The method was originally proposed for lattice gauge models.¹²) The efficiency of this method relies on the fact that in 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

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

where the sum runs over a set of m modes with wave vectors $\vec{q} = (2\pi/L) \cdot (n_1, n_2)$, $n_1, n_2 = 0, 1, 2, \dots$. This set includes the modes with the smallest wavenumbers $n^2 = n_1^2 + n_2^2 = 1, 2, 4, 5, 8, \dots$. The random amplitude of the i th mode in Eq. (1) is chosen from the interval $[-\epsilon_i^*, +\epsilon_i^*]$ (the magnitude of ϵ_i^* will be discussed below), while α_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: $p(\text{old} \rightarrow \text{new}) = \min(1, \exp(-\beta\Delta E))$, where $\beta = (k_B T)^{-1}$ is the inverse temperature and ΔE 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 by 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 $\{r_g\}$, each of which is located at the center of a grid cell),

$$h_{\vec{n}} = \sum_{\vec{r}_g} h(\vec{r}_g) e^{-2\pi i(\vec{n} \cdot \vec{r}_g)/L}, \quad (2)$$

includes M^2 modes, corresponding to $\vec{n} = (n_1, n_2)$, $n_1, n_2 = (-M/2) + 1, \dots, M/2$. In conventional MC simulations, all the modes are equally affected by the *uncorrelated* move attempts. Randomly displacing the lipids by a vertical distance ϵ within a MC time unit would cause the amplitudes of all the Fourier modes [Eq. (2)] to change by $(\delta h_n)^2 \sim M^2 \epsilon^2 = (L/l)^2 \epsilon^2$, independently of n . At large scales (small n), the behavior 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 κ . The power spectrum of the bilayer thermal fluctuations,¹⁶

$$\langle |h_n|^2 \rangle = \frac{kTL^2}{\kappa l^4 |\vec{q}|^4} = \frac{kTL^6}{\kappa (2\pi n l)^4}, \quad (3)$$

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)

$$\tau_n \sim \frac{\langle |h_n|^2 \rangle}{(\delta h_n)^2} = \frac{kT}{\kappa} \frac{L^4}{l^2 \epsilon^2 (2\pi n)^4}. \quad (4)$$

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^{-4} dependence of τ_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 $\epsilon_i^* = \Delta/n^2$ [see Eq. (4)]. The value of Δ can be empirically determined 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 in ϵ_i^* with n , significant improvement in the relaxation times should be expected only for the longer (and 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 Δ 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 $\dot{E}/L^2 \sim CS^2$, 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 $|\delta h_n| \sim M^2 \Delta = (L/l)^2 (\Delta/n^2)$ [see Eq. (2)] and, therefore, their relaxation times scale as

$$\tau_n \sim \frac{\langle |h_n|^2 \rangle}{(\delta h_n)^2} = \frac{kT}{\kappa} \frac{L^2}{\Delta^2 (2\pi)^4}. \quad (5)$$

This time does not increase with decreasing 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 $\mathcal{O}(N)$ (short-range) pair interactions, which makes them equally CPU time consuming as $\mathcal{O}(N)$ single particle trial moves. Therefore, the CPU time per MC time unit required in schemes utilizing $\mathcal{O}(N)$ single particle and $\mathcal{O}(1)$ 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 by using the three-bead lipid model of Reynwar *et al.* 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 po-

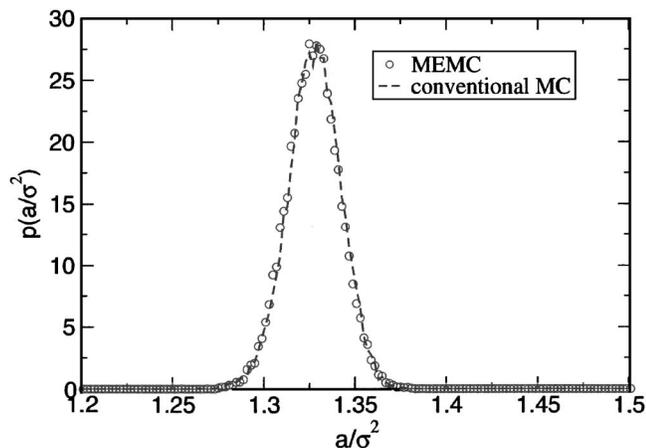


FIG. 1. The normalized distribution functions p of the projected area per lipid a/σ^2 , where σ is the length parameter of the bead-bead LJ potential.

tential $w_c = 1.35\sigma$, where σ 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 MC* (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,¹⁸ 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, $a = 2L^2/N$, obtained from the conventional and improved simulations are plotted in Fig. 1. Within negligible computational uncertainties, the two distribution functions are indistinguishable, which confirms that both algorithms generate the same statistical ensembles. The power spectrum $\langle |h_n|^2 \rangle$ of the height fluctuations is plotted in Fig. 2. The conventional and improved algorithms give identical results, including the asymptotic $\langle |h_n|^2 \rangle \sim n^{-4}$ power law. From Eq. (3) (setting the mesh size to $l=L/8$), we calculate the bending modulus of the bilayer $\kappa \approx 8k_B T$, in consistency with the values measured in Ref. 17.

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 16×16 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 of all the modes with wavenumbers $n^2 \leq 29$ were recorded. The relaxation times were calculated by fitting the time autocorrelation function, $C_n(\Delta t) = \langle |h_n(t)h_n(t + \Delta t)| \rangle / \langle |h_n(t)|^2 \rangle$, 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 exponen-

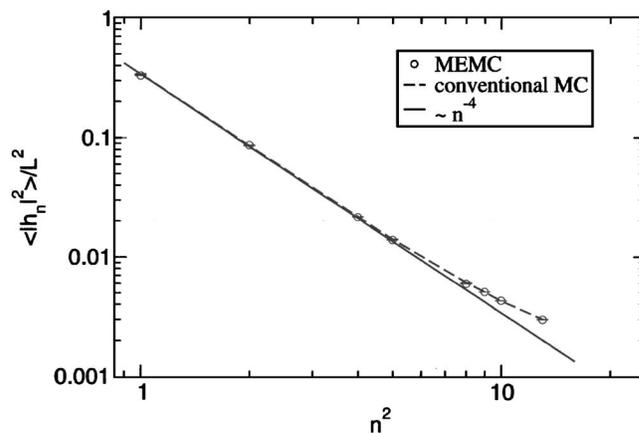


FIG. 2. Fluctuation spectrum of a membrane of $N=1000$ lipids. Results of the conventional and improved algorithms are shown by open circles and dashed line, respectively. The solid line indicates the asymptotic $\langle |h_n|^2 \rangle \sim n^{-4}$ power law.

tial decay has been originally conjectured by Seifert and Langer¹⁹ 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 of 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 $\tau_{n,2} \ll \Delta t < \tau_n$. The uncertainties in τ_n (typically $\pm 20\% - 25\%$) were determined by comparing the fit results obtained for different fitting intervals. In the MEMC algorithm, each MC time unit consisted of the following (on average): N translations, N rotations, two 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 $N:N:2$ proportions; however, each MC time unit of the conventional algorithm consisted of almost $8N$ trails 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 four times slower than the conventional scheme because each MC time unit of the latter includes almost four 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 with the conventional scheme, the relaxation of the $n=1$ modes is improved by a factor of about 50, from an estimated 1 year of CPU time to less than a week. The

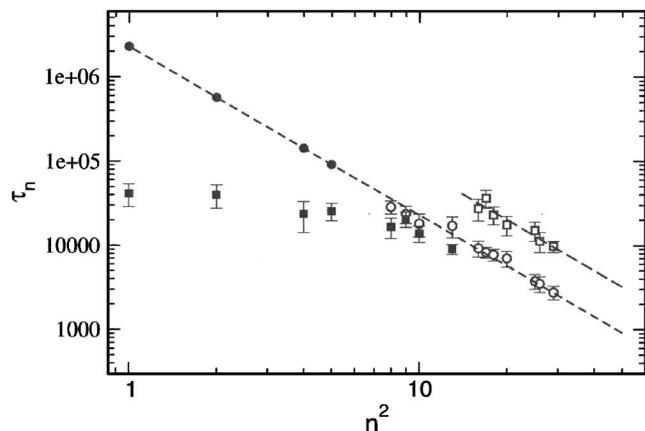


FIG. 3. Relaxation times of undulatory bending modes as a function of the wavenumber n . Conventional MC results are plotted by circles (open: results numerically obtained and solid: results evaluated by extrapolation). MEMC results are plotted by squares (open: unexcited modes and solid: excited modes). Dashed lines: Fits to the $\tau \sim n^{-4}$ scaling law.

simulations extended over a period of about 10 weeks and, therefore, our estimates of the relaxation times of the long modes 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 similar to conventional MC simulations.²¹ Improved relaxation behavior is achieved when the MD simulations are run with a momentum-conserving thermostat²² that, on long length and time scales, reproduces the correct hydrodynamic behavior $\tau \sim L^3$.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,¹¹ the CPU time per MC time step grows as N^2 (since there are $\mathcal{O}(N)$ Fourier modes and the variation of each is a collective move that requires the calculation of $\mathcal{O}(N)$ 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 is given by $\langle |h_n|^2 \rangle \sim n^{-2}$ or $\langle |h_n|^2 \rangle \sim n^0$, respectively.¹⁶ Repeating the argument that leads from Eqs. (2) to (5), one finds $\tau_n \sim L^0$ rather than $\tau_n \sim L^2$ in Eq. (5) 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 CG 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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