Simulations of Interacting Membranes

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The liquid crystalline model biomembrane system consisting of a stack of interacting membranes is studied by the newly developed Fourier Monte Carlo simulation technique. In comparison to perturbation theory, substantial quantitative discrepancies are found that affect determination of interbilayer interactions. A harmonic theory is also routinely used to interpret x-ray scattering line shapes; this is shown to be valid because the distance dependence of the simulated correlation functions can be fairly well fit by the harmonic theory.

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Stacks of lipid bilayers (see Fig. 1) are model systems for biomembranes that are much studied for two reasons. First, such stacks diffract fairly well and this facilitates determination of the structure of individual membranes, which is of primary interest in biophysics. However, these stacks are not crystals with the long range order that is assumed in traditional biophysical analysis, but smectic liquid crystals with quasi-long-range order. Therefore, quantitative use of the scattering intensity for structure determination requires correction for the fluctuations endemic in such systems [6,7]. A harmonic theory [2,3] that predicts power law tails in the scattering line shapes fits membrane data very well [4,5], but the anharmonicities that are inherent in realistic potentials have remained a concern for quantitative interpretation [6,7], even though a renormalization group analysis suggested that such effects are small [8].

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For hard confinement the effective interbilayer force is a minimum. The contrasting regime, sometimes called the soft confinement regime [10], it is usually supposed that the primary interbilayer interactions for dipolar lipids are the attractive van der Waals potential and the repulsive hydration potential,

\[ V(z) = -\frac{H}{12\pi z^2} + A\lambda e^{-z/\lambda}, \]

where \( z \) is the local distance between two membranes. These interactions are significantly anharmonic, to the extent that the potential of a membrane midway between two neighboring membranes (at the dashed positions in Fig. 1) may have a maximum instead of a minimum. The contrasting regime, sometimes called the hard confinement regime, consists of only excluded volume or steric interactions between neighboring membranes. That regime is appropriate when \( a \) is of order 100 Å because the hydration force is short range (\( \lambda \approx 2a \)). For hard confinement the effective interbilayer force is the entropic fluctuation pressure which decays as \( a^{-3} \) [12]. Fluctuation forces also exist in the soft confinement regime, and are determined by our simulations.

In addition to the interbilayer interactions in Eq. (1), the energy of each membrane includes a bending term, proportional to the square of the local curvature of the membrane. Let \( u_m(x,y) \) be the local displacement of the \( m \)th membrane from its average position as shown on Fig. 1. Periodic boundary conditions are imposed in the plane of each membrane and also along the stack, so that \( u_{m+1} \equiv u_0 \). The membranes can collide, but cannot overlap, so that \( u_{m+1} + a \geq u_m \), where \( a \) is the average distance between membranes. The Hamiltonian of the stack is

\[ H = \sum_{m} \left[ K \frac{\partial^2 u_m}{\partial x^2} + K \frac{\partial^2 u_m}{\partial y^2} \right] + \sum_{m} \frac{\lambda}{\pi} e^{-u_m/\lambda}. \]
then:

$$H = \frac{M-1}{2} \sum_{m=0}^{M-1} \int \left[ \frac{K_c}{2} (\Delta u_m)^2 + V(u_{m+1} + a - u_m) \right] dx dy$$  \hspace{1cm} (2)$$

The simulation method, called the Fourier Monte Carlo method, was developed for single membranes between hard walls \[13\] and is easily extended to stacks of membranes. Each membrane in the stack is represented by a complex array of dimensions \(N \times N\) of Fourier displacement amplitudes. Instead of moving one lattice site at a time, moves are made in Fourier space and a whole membrane is displaced in each move. This allows larger moves and faster equilibration, without incurring large increases in the bending energy. One difference with our previous simulations \[13\] is that a fixed osmotic pressure \(P\) ensemble is employed instead of the previous fixed \(a\) ensemble, so that \(a\) is obtained as a function of \(P\) rather than vice versa. Of course, use of the \(P\) ensemble is fundamentally no different, but it does have better convergence properties that we now discuss.

Simulations performed systematically as a function of lattice size, density of lattice points, and number of membranes in the stack show that accurate results for infinite, continuous membranes in infinite stacks can be obtained at one \(P\) in real time of the order of one day on a Pentium Pro PC. The most sensitive finite-size parameter is the “density” of each membrane \(N/L\), since when \(N\) is varied from 6 to 32, the root mean square fluctuation in nearest neighbor spacing, defined as \(\Delta\), can easily change by 40%, and the changes in \(a\) are also significant. This is shown in Fig. 2 which also shows that accurate values can be obtained by extrapolation. By comparison, variations with lateral system size \(L\) at fixed \(N/L\) are negligible (\(\approx 0.2\%\) for \(L \geq 700 \text{Å}\)), as are variations with \(M\) (\(\approx 1\%\) for \(M \geq 8\)) for \(a\) and \(\Delta\).

It may be noted that stacks of several membranes (\(M \approx 4\)) have been previously considered \[14,16\], but mostly for the critical phenomenon of unbinding; this occurs in the limit of large average membrane spacing, where the van der Waals interaction is the main one, in addition to the spatial constraints. We have also performed simulations in the hard confinement regime and obtained results for the Helfrich fluctuation free energy \(c_{f \ell} T^2/K_c a^2\) with \(c_{f \ell} \approx 0.1\), in agreement with \[14,13\].

![FIG. 2. Effect of finite density (\(N = 6, \ldots, 32\)) on \(a\) (solid squares) and \(\Delta\) (open circles and right hand ordinate) for realistic interaction parameters given in \[17\] and for \(P = 10^8\text{erg/cm}^3\).](image1)

![FIG. 3. Simulation results (symbols) and perturbation theory (lines) for \(\Delta\) and \(\log P\) versus \(a\) for the parameter set in \[17\] with attractive interaction (solid squares and lines) and with no attractive interaction (open circles and dashed lines).](image2)
the theory also agree for \( P(a) \) when there is no attractive van der Waals interaction. However, at larger \( a \), the simulated \( \Delta \) increases with \( a \) faster than the perturbation approximation for either intermembrane potential. A large difference between the simulation results and the perturbation theory occurs when the potential has an attractive van der Waals part. The theory predicts that \( a_0 = 25.8 \) for \( P = 0 \), more than 5 larger than the true value \( a_0 = 20.2 \pm 0.1 \) obtained by simulation. It is also of interest to compare the values of \( \mu \equiv (\Delta/a)^2 \) to the hard confinement values. In Fig 3 the range of \( \mu \) is also of interest to compare the values of \( \Delta \) at large \( a \), but considerably smaller than the hard confinement estimates 0.16 – 0.21.

In the harmonic theory the bare interbilayer interactions are approximated with a compression modulus \( B \). In Fig. 4 a value of \( B = 1.9 \times 10^4 \text{erg/cm}^4 \) was chosen to match the large \( k \) end of the \( M = 32 \) curve. The resulting \( \Delta(k) \) profile allows one to see that \( \Delta \approx \Delta(1) \) is in fact a good proxy for describing the long-range correlations, since the difference between \( \Delta \), implied by the “harmonic curve”, and the actual \( \Delta \) for the stack is about only 0.2 \( \text{Å} \), i.e. relatively small compared to \( \Delta = 4.6 \text{Å} \). Another way to see how interactions are renormalized from short to long range is to compute, for different \( k \), the implied strength \( B(k) \) of the harmonic potential that would result in the same value of \( \Delta(k) \) as obtained by simulations for a stack with realistic interactions. The bottom panel of Fig. 4 presents a plot of the harmonic value of \( B(k) \) required to give the simulation value of \( \Delta(k) \). This shows that, for large \( k \), the system can be reasonably well approximated by one with harmonic interactions with constant \( B \).

How is it that the harmonic theory works quite well for the correlation functions in the preceding paragraph and not so well for \( P \) and \( \Delta \) in Fig. 3? The answer is that the perturbation theory does not yield the best value of \( B \); for the example in Fig. 4 the theory yields a larger \( B = 5.4 \times 10^3 \text{erg/cm}^4 \) which accounts for the smaller value of \( \Delta \) in Fig. 4.

We turn finally to the entropic fluctuation pressure in a stack of membranes, which is defined to be the difference between the applied pressure, and the pressure due to the bare van der Waals and hydration interactions. Perturbation theory \( \lambda_\text{fl} \), experiment \( \lambda_\text{fl} \) and simulations on a single membrane between hard walls \( \lambda_\text{fl} \) all agree that the decay of the fluctuation pressure is closer to exponential, with a decay length \( \lambda_\text{fl} \), although the value of \( \lambda_\text{fl} \) found in both experiment and simulations is larger than the perturbation theory prediction \( \lambda_\text{fl} = 2 \lambda \). Fig. 5 shows the same result for simulations of stacks.
A long range goal is to obtain values of the interbilayer interaction parameters; the traditional analysis \[9\] uses osmotic pressure \( P(a) \) data, which has recently been supplemented by fluctuation \( \Delta(a) \) data. One of the main results of this paper indicates that the \( \Delta \) data are indeed valid, even though the analysis of the basic x-ray scattering data is based on a harmonic theory. However, the intrinsic anharmonic nature of realistic interactions between bilayers in stacks makes it difficult to devise quantitatively accurate analytic or perturbation theories. We show here that the Fourier Monte Carlo method is sufficiently fast that it provides a viable alternative. Indeed, it is now possible to consider using it as part of a comprehensive data analysis program to determine the best values of the fundamental interaction parameters.

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\[ \begin{align*}
\Delta(k) &= [\text{Å}] \\
B(k) &= 1.9\cdot10^{13} \text{erg/cm}^3 \\
\end{align*} \]

FIG. 5. Root mean square fluctuations \( \Delta(k) \) between \( k \)th neighbor membranes for a stack with different numbers \( M \) of membranes and for the parameter set in \[17\] (except that \( L = 1400\text{Å} \) at \( P = 3.16\cdot10^6 \text{erg/cm}^3 \)). Also shown is \( \Delta(k) \), exactly computed for the case of harmonic interactions with compression modulus \( B = 1.9\cdot10^{13} \text{erg/cm}^3 \). The bottom figure shows the effective harmonic compression modulus \( B(k) \) for each \( k \) and \( M \).

\[ \begin{align*}
\log_{10} P_f \text{ [erg/cm]} = a \text{ [Å]} \\
\end{align*} \]

FIG. 6. Simulation results for \( P_f \) vs. \( a \) for the parameter set in \[17\] and also for \( H = 0 \). The slope is \( \lambda_f = 4.34 \text{Å} \).

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