Simulations of Simplified Cell Membranes

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Abstract:

Macroscopic properties of cell membranes can be simulated using a simple, flexible, solvent-free model. Each amphiphilic lipid composing the membrane is represented as a chain of five beads governed by four potential energy parameters. The simulations are conducted according to Metropolis Monte Carlo algorithms, effectively minimizing the free energy of the system. Obtaining the proper parameters such that the membrane remains structurally intact has been a challenge, as pores have developed in many of the simulated membranes. The bending rigidity falls within ranges similar to biological systems. Also, when simulated with a large bending parameter, the molecules in the membrane assumed a tilted structure seen in gel membranes.

Introduction:

Cell membranes are composed of amphiphilic lipids, which self assemble into a flexible bilayer arrangement. The cell membrane is involved in many important cell processes that occur on scales greater than 100 nm^2, although cell size is much larger. Some of these processes include but are not limited to protein aggregation and trafficking, cell motility, endo- and exocytosis, and cell division. Alzheimer's Disease has been linked to aggregation of proteins in the cell membrane. Undulations in the membrane are important in influencing these processes, and thus, the flexibility of the membrane, or bending rigidity, is an important area of study.

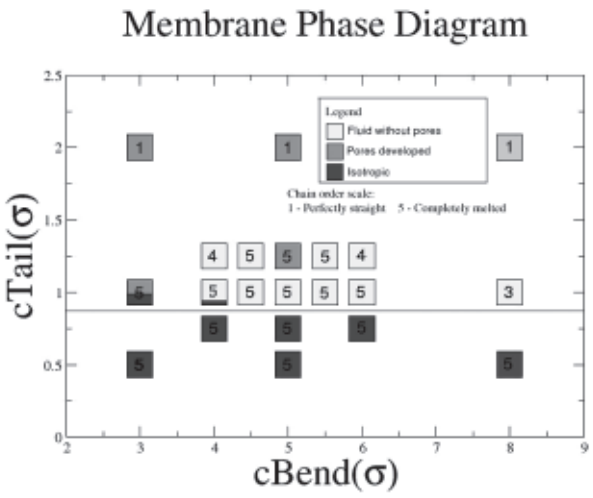

Figure 1: Pores develop unpredictably in this parameter space search.

Experimental testing of cell membranes can often be too expensive, difficult, or even impossible to perform under certain conditions. Computer simulations of membranes can alleviate some of these obstacles. However, they present their own set when faced with decisions on how to begin modeling the membrane. Precise atomistic simulations, although useful for small systems, cannot be used in larger systems because of the computationally expensive calculations required. Alternatively, models that are too coarse grained have had certain properties outside of biological ranges. For example, the rigid, solvent free model proposed by Brannigan was found to have a bending rigidity off by an order of magnitude [1].

An acceptable model will be computationally efficient, yet still exhibit cell processes that occur on length scales greater than 100 nm^2. Also, the model should be equipped to account for multiple types of lipids, and inclusions such as cholesterol and proteins, all of which are found in real membranes. Finally, the model should be tunable to simulation parameters such as molecular flexibility and intermolecular attractions.

The purpose of this project was to check the newly developed flexible, solvent free model against experimental data by examining the flexibility of the simulated membranes. The quantification of the flexibility of a membrane is the bending rigidity (K_c), which is defined by how much energy is required to bend the membrane. Real membranes have a bending rigidity that lies between 10-80ε, where $\varepsilon = 4*10^{-21}$ J [2].

Procedure:

The model examined in this paper represents each lipid as a chain of five beads. The second bead is special, accounting for a membrane's amphiphilicity with implicit solvent. The chains in this model are flexible, but don't stretch. Lipid interactions are governed by four potential energy parameters: an excluded volume interaction (c_{core}) enforces shape and prevents overlap of lipids; a long range attraction (c_{long}) is calculated for the 2nd bead giving the bilayer a skin; a short range attraction (c_{tail}) governs the hydrophobic tail attraction; and a molecular bending interaction (c_{bend}) discourages the beads from overlapping

because the energy is at a minimum when the chain is perfectly straight. This model has the capacity to accommodate different types of lipids, as well accommodate inclusions such as proteins and cholesterol.

The simulations were conducted using between 392 and 800 molecules. The simulations were run at constant tension as opposed to constant area, where the dimensions of the bounding box of the membrane can fluctuate, more accurately simulating a real membrane. The long range and excluded volume interaction parameters were held constant, while the effect of a variable tail attraction and bending parameter on the membrane were studied to identify a parameter space.

The flexibility of the membrane was studied by investigating the effect of the molecular bending parameter, C_{bend}, on K_c. To do this, the discrete points comprising the membrane were turned into a mesh surface using Delaunay Triangulation, and then were interpolated such that K_c can be found by fitting the Fourier mode of this surface according to:

$$F(x) = \frac{1}{K_c * x^2}$$

Results:

In the parameter space search, three basic phases were found (see Figure 1): the membrane fell apart and became isotropic; the membrane developed pores; and the membrane remained stable and fluid. As intramolecular bending is discouraged (a higher C_{bend}), average box length decreases continuously (see Figure 2b). This is logical because stiffer chains can pack more closely. However, the bending rigidity is not continuous with increasing C_{bend} (see Figure 2a). The reasons for this are not readily apparent, although data must be collected at greater resolution before any conclusions can be made. When large values for C_{bend} were used, the membrane formed a tilted, yet highly ordered gel phase (see Figure 3). This is significant because this ordering has been seen experimentally [2] and is an indicator the flexible, solvent free model is behaving appropriately.

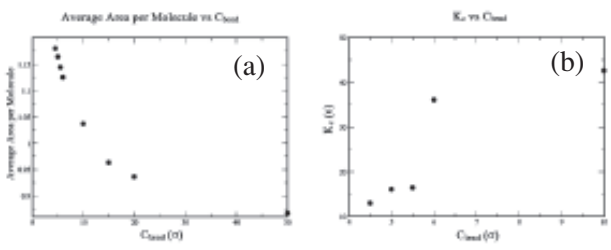

Figure 2: The average area decreases continuously with increases of C_{bend}. However, K_c exhibits a large increase with C_{bend} = ~6.0.

Conclusions:

This project verified that the bending rigidity for the flexible model is within appropriate biological ranges, as well as the effect of molecular flexibility on total membrane flexibility. K_c increases with an increase in the molecular bending parameter, which is consistent with theory: it should be harder to bend the membrane when each molecule is stiffer. Also, further parameter searches should be conducted, possibly at different temperatures, to see if other phases of lipid membranes can be simulated, i.e., a vesicle.

Acknowledgments:

Grace Brannigan, Frank Brown, Lawrence Lin, Howard Wong, NSF

References:

[1] G. Brannigan and F. L. H. Brown, 2004, "Solvent-free simulation of fluid membrane bilayers," Journal Of Chemical Physics, vol. 120, p. 1059

[2] U. Seifert and R. Lipowsky, Structure and Dynamics of Membranes, ed. R. Lipowsky and E. Sackmann (Elsevier Science, 1995), vol. 1.

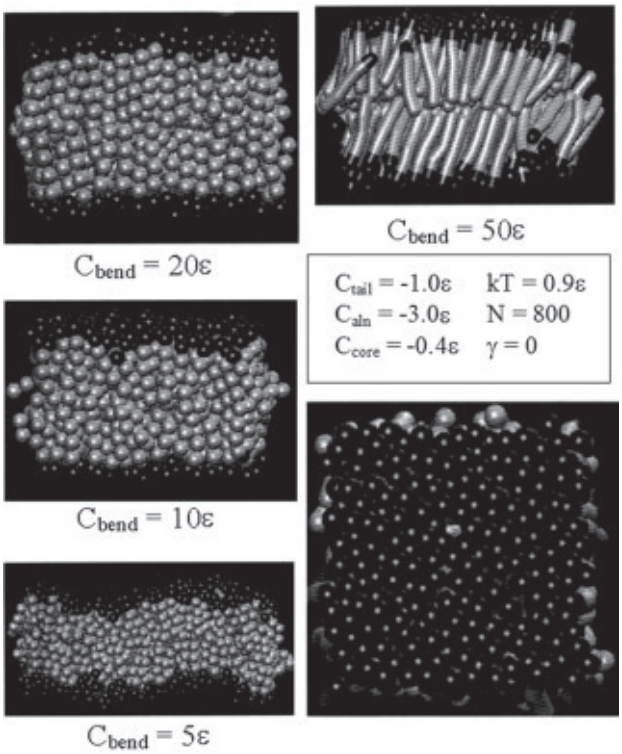

Figure 3: As molecular bending is increased (lowering C_{bend}), the entire membrane gets more flexible. The bottom membrane, C_{bend}=5ε exhibits clear undulations. The top membrane, C_{bend}=50ε, formed a tilted gel phase that has been seen experimentally.