Review of “Monte Carlo Simulation of Two-Component Bilayers: DMPC/DSPC Mixtures” by I.P. Sugár, T.E. Thompson, and R.L. Biltonen

Introduction

Lipid, primarily phospholipid, bilayers are the principal component of biomembranes. In their paper, Sugár et al. use a simple triangular lattice model to describe a mixed dimyristoylphosphatidylcholine (DMPC)/distearoylphosphatidylcholine (DSPC) bilayer and apply Monte Carlo methods to simulate the observed excess heat capacity versus temperature curves of the two-component bilayer and to investigate the lateral distribution of the components in the bilayer. The authors note that previous studies have established that mixtures of DMPC and DSPC exhibit positive deviations from ideality, implying that, during phase transitions, “the minor phase forms small clusters in a continuum of the major phase.” The implications of this fact to the function of biomembranes, which are primarily composed of multi-component rather than single-component bilayers, are numerous. Of particular significance is the tendency of these clusters to promote localization of membrane proteins based on the affinity of the proteins for specific lipids. The lateral distributions of bilayer components during phase transition, and the properties related to these distributions, are thus of particular relevance. The authors note that Monte Carlo methods are well suited to simulation of the lateral distributions, providing information not attainable with previous experimental methods for analysis of bilayer thermodynamics.

Theory, Model, and Simulation Method

Lattice Configuration and Theoretical Development of System Properties

Each monolayer of the DMPC/DSPC bilayer is modeled as a triangular lattice with one acyl chain occupying each of N lattice points. The lattice configuration is characterized by a square matrix, S, and a connection vector, c, which lists the lattice positions of the connected acyl chains. Based on S and c, the number of a given component in a given state and the number of nearest neighbor acyl chains are characterized. To eliminate finite size effects in the simulations, the authors determine minimum lattice sizes, above which the calculated excess heat capacity is, according to the authors, “practically independent from the lattice size,” and only choose lattice sizes larger than the minimums.

The authors use these parameters to develop relevant properties of the system, in the canonical ensemble: the energy of a given configuration, which the authors assume to be constant and independent of the rotational isomers in the acyl chain, the degeneracy of the energy level, and the probability of configuration S in thermodynamic equilibrium, which is given by:

\[ p(S) = \frac{f(S)e^{-E(S)/kT}}{Q(N,T,V)} = \frac{e^{-\chi(S)/kT}}{Q(N,T,V)} \]

where \( Q(N,T,V) \) is the partition function in the canonical ensemble, which, for a one-component bilayer, is:

\[ Q(T,N) = [1 + e^{-(\Delta E - T\Delta S)/kT}]^N \]

if the Gibbs free energy of mixing, \( w_{\text{gl}} \), is equal to zero. The authors define the function \( \chi(S) \) as:

\[ \chi(S) = E(S) - kT \ln f(S) \]

which they reduce to a configuration-dependent function, \( \chi_c \), which contains ten unknown parameters: the change in energy for both components, the change in entropy for both components, and six energy values for
the short-range van der Waals interactions. The authors go into substantial detail on the methods used to obtain these parameters, using experimental heat capacity curves from single component multilamellar vesicles for the one-component parameters and experimental heat capacity curves from a binary mixture of DMPC and DSPC to estimate the two-component parameters. The excess heat capacity is determined using the partition function:

\[ C_v = \frac{1}{kT^2} \frac{\partial^2 \ln Q}{\partial \beta^2} \]

Monte Carlo Simulations

For the Monte Carlo simulations, Sugár et al. generate trial configurations of the two-component bilayer system through a three-step process. The first step involves changing the state of random acyl chains from gel to fluid or vice versa, the second involves swapping randomly selected molecules of different lipid components, and, finally, the third step involves the rotation of randomly selected acyl chain pairs relative to each other. The trial configuration, \( S_{\text{trial}} \), is then tested by:

\[ \text{RAN} \leq \exp[-\{ \overline{X}(S_{\text{trial}}) - \overline{X}(S_{\text{orig}}) \} / kT] \]

where RAN is a pseudorandom number distributed between zero and one. If the inequality holds, then \( S_{\text{trial}} \) is acceptable, otherwise \( S_{\text{orig}} \) is retained. Using this method, the system is driven towards thermodynamic equilibrium, which will be the Boltzmann distribution over the configurations. The authors determine that 4N/3 reorientation steps are necessary for each orientation to be accessible to each molecule at least once. The authors then run 6000 Monte Carlo cycles, followed by a further 6000 for which data is collected to determine the quantities of interest. This method is used over a range of 50 different temperatures to obtain the excess heat capacity curve and over a range of mole fractions.

Results

Type of Transition

Sugár et al. determine the type of transition that is undergone in transitioning from the gel to liquid phase for the two-component system from the distribution function of the fluctuating extensive parameters. For all mole fractions, they find that the energy distributions change from bimodal at small lattice sizes to unimodal at large lattice sizes, indicating that, at the thermodynamic limit, the gel-fluid transition is continuous. The authors note that a previous study, by Risbo et al. (1995), produced contrasting results in regards to the continuous nature of the gel-fluid transition but argue that the results obtained in this paper are more likely to be accurate because the canonical ensemble is more appropriate for this application than the grand canonical ensemble used by Risbo et al.

Agreement of Experimentally Determined and Calculated Temperatures for Gel-Fluid Transition

The authors go into some detail in comparing their results versus experimental results for a variety of temperatures in the gel-to-fluid transition, as well as in checking the consistency of their temperatures. In each case, they determine that there is excellent agreement in the temperature data. They also present melting curves of both components in a variety of DMPC/DSPC mixtures, finding that the curves are sigmoidal.

Lipid Compositions in the Gel-Fluid Coexistence Region

The mole fractions of DSPC in the fluid and gel states are calculated and plotted versus temperature. As expected, the results indicate that the composition of the gel clusters is approximately equal to the total composition at low temperatures and that the composition of the liquid clusters is approximately equal to the
Statistics on Gel and Liquid Clusters

At the end of every Monte Carlo cycle, snapshots of the system are analyzed using a cluster counting algorithm to obtain cluster size distributions, cluster numbers, and percolation frequencies. The results indicate that, above the gel percolation threshold temperature, the bilayer contains only small gel clusters and the size distribution is unimodal whereas, below the gel percolation threshold temperature, large gel clusters appear and the cluster size distribution is bimodal. Conversely, below the fluid percolation threshold temperature, the bilayer contains only small fluid clusters and the size distribution is unimodal whereas, above the temperature, large fluid clusters appear in a bimodal distribution. The authors compare the percolation threshold temperatures with the peak positions of the excess heat capacity curve and find that they are in good agreement. Furthermore, results are compared against experimental results obtained using the fluorescence recovery after photobleaching method and good agreement is again observed. The cluster compositions are also determined and, generally, it is found that the DSPC mole fraction increases with increasing cluster size in small gel clusters while it decreases with increasing cluster size in large gel clusters. The opposite is found for liquid clusters. The authors propose that this trend is due to “the inhomogeneous distribution of the components in the different cluster types;” the data indicates that the mole fraction of DSPC is significantly higher in the inside of gel clusters than on the periphery and that the opposite is true for liquid clusters.

Conclusion

Ultimately, Sugár et al. determine that a two-component, two-state lattice model used with Monte Carlo methods is sufficient to accurately simulate the thermodynamic behavior of mixed DMPC/DSPC bilayers in the gel-liquid transition region.