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Theoretical Models for One and Two Component Lipid Membranes

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1 Introduction

The cell membrane performs a vital function in the cell by allowing it to create a controlled chemical environment inside. Membranes are many component systems that exhibit complex phase behavior. The most common constituents of the membrane are phospholipids, decorated with proteins and other types of lipids. The proteins can cause phase separation, either directly, or by inducing local curvature [1], but for the purpose of this paper, we will consider only those effects present in one- and two- component phospholipid membranes with fully saturated fatty acids.

Unlike many of the systems studied in class, the lipids have a large number of relevant internal degrees of freedom. The phase behavior varies with the length (L) of the fatty acid chains, and the conformation of the chains. Each chain has L-3 internal, conformational degrees of freedom associated with the dihedral angle of each of the L-3 interior bonds (There are L-1 total bonds, but the most proximal bond is frozen at the temperatures of interest, and the most distal bond has (approximate) rotational symmetry.) See Figure 1.

The first question to ask is of course, how should we model the system? We will not attempt to construct a model with all of the molecular degrees of freedom, as in molecular dynamics, but will instead use a statistical approach. First, we consider what to use as the order parameter. For a one component membrane, there are two obvious choices: a distortion field $u(x)$ which represents the deviation in two dimensions from the zero temperature position of each molecule, suitably coarse-grained; and f, the fraction of bonds in the hydrocarbon chains that adopt the gauche conformation (refered to as S in the cited works, but I changed notation to avoid possible confusion with entropy). All other variables, such as conformations of the head group, deviations from planar geometry, etc., are assumed to be frozen out at relevant temperatures. For a two component system, we could introduce an Ising variable that is conserved globally to represent the identity of the molecule. Proceeding from the choice of order parameter, we can formulate a field theory with a Landau-Ginzberg type Hamiltonian, or formulate a lattice theory.

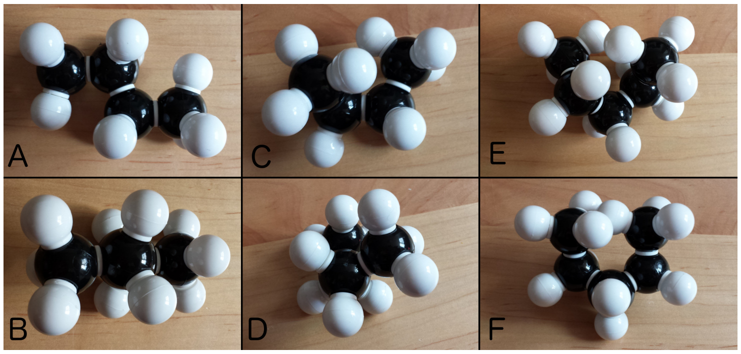

Figure 1. Space Filling Models of Hydrocarbon Chains. (A) (B) Butatne in the anti-conformation. The first and fourth carbon are positioned as far from each other as possible. (C) (D) Butane in the gauche conformation. This state is of higher energy than the anti-conformation. (E) (F) Pentane in the left-gauche, left-gauche and left-gauche, right-gauche conformations respectively. Having two gauche bonds of opposite chirality immediately adjacent to each other brings the terminal carbons into very close proximity. The energy of this state is large enough for it to be inaccessible at experimental temperatures.

2 Landau Models and Mean Field Theory

Our first approach will be to construct a mean-field theory using a Landau-Ginzberg type Hamiltonian. Most early theoretical models focused on the conformational degrees of freedom, assuming that translational freedom was frozen out near the phase transition. We will start our analysis by considering f to be the order parameter, and will only model the translational degrees of freedom implicitly. This order parameter differs from many that we have used previously in class. First, it is restricted to the range $[0,1]$. Second, it is not symmetric under translation or inversion ($-f$ is not in the domain of f). We will restrict our analysis to the mean-field approach, so we will ignore any gradient terms. Experimental evidence suggests that in addition to temperature, the length of the hydrocarbon chains is also relevant to the phase behavior of a lipid membrane, so we will expand the Hamiltonian to three terms. In accordance with the (lack of) symmetry of the system, our Hamiltonian is given by

$$\beta H[f(x)] = \int d^2x(af(x) + \frac{b}{2}f(x)^2 + \frac{c}{3}f(x)^3) \tag{1}$$

with $c > 0$. For equations of the above form that contain odd powers of the field, we must be careful to prevent the appearance of infinities at equilibrium. A simple mean field approach to the above Hamiltonian would yield at equilibrium

$f = -\infty$. Fortunately, we are saved by the restriction of the order parameter to lie in the range $[0, 1]$. At many values of the parameters in this model, we expect the value of the order parameter to saturate at either 0 or 1. The phase diagram of this model is presented in Figure 2.

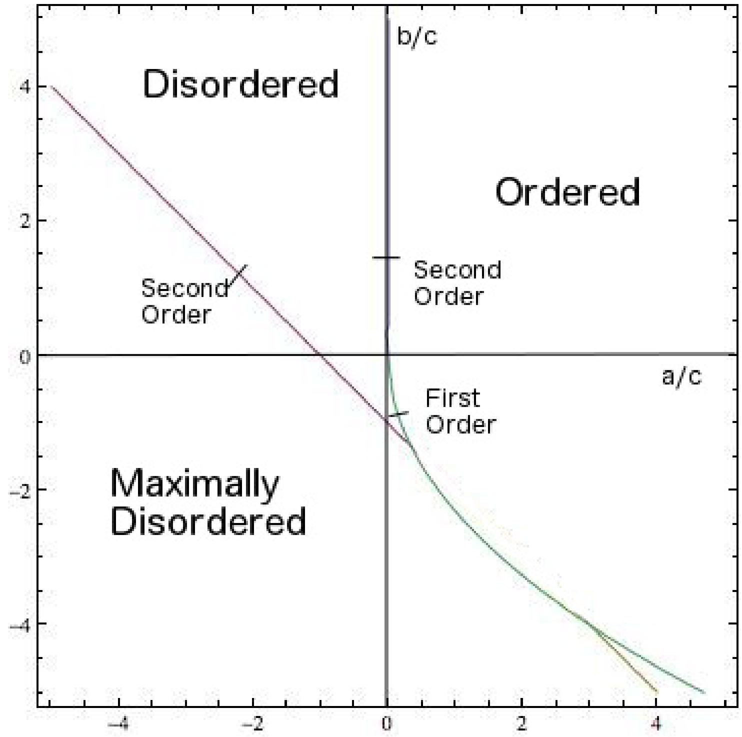

Figure 2. The phase diagram of the third order model. The ordered phase corresponds to an order parameter $f = 0$. The maximally disordered phase saturates at $f = 1$. The disordered phase corresponds to an order parameter of $f = -\frac{b}{2c} + \sqrt{\frac{b^2}{4c^2} - \frac{a}{c}}$

Intuition suggests that $f = 0$ membranes correspond to the gel phase and $f \neq 0$ membranes correspond to the liquid phase, but models based on a conformational degree of freedom exclusively can not give yield translational and orientational correlation functions, and so the assignment of one phase as liquid and the other as solid is tentative. In fact, experiments [2] have shown that for certain lipid systems, the ordered-disordered chain transition can occur independently of the liquid-gel transition, so the most general model would include a translational order parameter coupled to the conformational order parameter.

To develop a sense of how the parameters a, b, and c depend on temperature and length of the lipid chains, we can construct a phenomenological model. The argument that follows is derived from the paper by Priest [3]. The entropy change in the ordered-disordered transition is dominated by conformational entropy of the lipid chains. The entropy, derived using the transfer matrix in Appendix A, is given by

$$S = (L-3)2\sqrt{2}(f - f^2) \tag{2}$$

The conformational energy per bond is just equal to the number of gauche bonds times the energy per gauche bond

$$\beta E_{conform} = f\frac{(L-3)}{k_b T}\epsilon \tag{3}$$

In a microscopic model, the hardest term to take into account is how the chain conformation induces energy changes by perturbing the density. While the previous two terms of the model have an exact microscopic interpretation, this term will necessarily be phenomenological. We would expect that the density of the membrane is most sensitive to the conformation in the vicinity of the ground state, i.e., that the density would change more per gauche bond added when the chain is relatively straight than when it already has kinks. Also, for longer chains, we would expect a larger change in density. Priestly implements these restrictions by assuming an equation of the form

$$\beta E_{density} = \frac{L-L'}{k_b T}\left(W(f-f')^2 - Z(f-f')^3 - Wf'^2 - Zf'^3\right) \tag{4}$$

where W, Z and L' are fit parameters, and f' is the predicted fraction gauche bonds in polyethylene (the $L \to \infty$ limit) at its melting point. One more of these parameters can be set by examining the case of polyethylene, but this model still has two free parameters that must be fit to the data. The complete model is therefore

$$\beta F = \beta E_{conform} + \beta E_{density} + S \tag{5}$$

Consequently, the dependence of a, b and c and the temperature and chain length can be determined to be

$$a = \frac{(L-3)\epsilon - (L-L')(2Wf' + 3zf'^2)}{k_b T} + (L-3)2\sqrt{2} \tag{6}$$

$$b = 2\left(\frac{(L-L')(W+3Zf')}{k_b T} - (L-3)2\sqrt{2}\right) \tag{7}$$

$$c = \frac{-3(L-L')Z}{k_b T} \tag{8}$$

The free parameters in the model limit its predictive power, but it can still be useful to describe qualitative phase behavior. Sugar and Monticelli use a verision of this model that is adapted for two component systems to examine the phase behavior of two component membrane[4] [5]. By fitting the parameters of the model to one mixture, they predict the nature (Azeotropic, Eutectic, Peritectic, etc.) of the phase transition.

The predicted behavior of the mean-field model needs to be taken with a grain of salt, and this model in particular. First, mean-field models ignore fluctuations, which we have seen are important in low dimensions. More importantly, however, this model predicts that the order parameter will saturate with all bonds in the gauche conformation. In the high temperature limit, we would expect the gauche fraction at 0.5, as this should have maximal internal entropy. The error is glaring enough that the entire approach should probably be reformulated in terms of a different conformational order parameter. One common model for the internal degrees of freedom is the Pink model [6]. It is a ten state model that allows up to three gauche bonds before complete melting. Some details of the model are summarized in Table **??**, but the model will not be discussed in detail.

Table 1. The States of the Pink Model

State	Length(C-C bond units)	Degeneracy	Internal Energy
all-trans G	L-1	1	0
int 1	L-2	4	E_g
int 2	L-3	4	E_g
int 3	L-4	4	E_g
int 4	L-2	2L-12	2 E_g
int 5	L-3	2L-16	2 E_g
int 6	L-4	2L-20	2 E_g
int 7	L-3	8L - 64	3 E_g
int 8	L-4	16L - 160	3 E_g
melted E	20.4(L-1)/34.0	$D_E(L)$	$E_E(L)$

3 Lattice Simulations and Correlation Functions

The previous models are not particularly useful for determining the component correlation functions of the system, as they include do not include gradient terms. The most common method to take into account spatial variations is to run Monte Carlo Lattice Simulations [8] [9]. These models tend to have many free parameters that are experimentally inaccessible. The model presented by Ehrig et. al. is

$$\Delta G = \Delta N_1^F(\Delta E_1 - T\Delta S_1) + \Delta N_2^F(\Delta E_2 - T\Delta S_2) + \Delta N_{11}^{GF} w_{11}^{GF} + \Delta N_{22}^{GF} w_{22}^{GF} + ...$$

$$\Delta N_{12}^{GG} w_{12}^{GG} + \Delta N_{12}^{FF} w_{12}^{FF} + \Delta N_{12}^{GF} w_{12}^{GF} + \Delta N_{21}^{GF} w_{21}^{GF} (9)$$

From this model, you can extract phase diagrams, spatial correlation functions, and the heat capacity (from the variance of the enthalpy). A representative state of the simulation is shown in Figure 3, reproduced on a 10 × 10 lattice using the values given in Ehrig et. al.

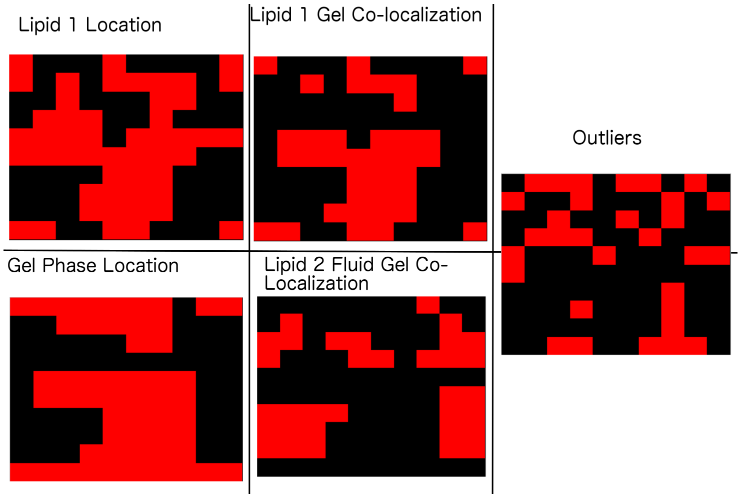

Figure 3. A representative state of the simulation for x = 0.5, and T = 310K showing phase separation. The outliers figure shows that the system is fairly well partitioned into a Lipid-1 rich gel phase and a Lipid-2 rich fluid phase.

4 Conclusion

Modeling of cell membranes is complex problem with a rich array of phase behaviors. The coupling of the internal degrees of freedom to the translational and orientational degrees of freedom make the system hard to represent without resorting either to phenomenological approaches or to introducing many fitting parameters. Recent advances in computing have made the problem easier to address, but a full theory that takes into account the curvature of the membrane, the dozens of different lipids present in the membrane, and coupling to membrane bound proteins and to the cytoskeleton still remains out of our grasp.

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A Derivation of Lipid Chain Entropy

To derive the conformational entropy of the lipid chains, we will assume a three state model. The Hamiltonian is given by

$$\beta H = \sum_i \epsilon(\delta_{\sigma_i,1} + \delta_{\sigma_i,2}) + E(\delta_{\sigma_i,1}\delta_{\sigma_{i+1},2} + \delta_{\sigma_i,2}\delta_{\sigma_{i+1},1}) \tag{10}$$

where ϵ is the energy difference between the gauche and anti- conformations, and E is the energy associated with having a right handed gauche bond followed by a left handed gauche bond (or vice versa). We will let E tend to infinity as this conformation has significant steric clashing (see Figure 1). The free energy of the chain can be solved exactly in the limit of a long chain using the transfer matrix method. The transfer matrix is given by

$$T = \begin{pmatrix} 1 & e^{-\epsilon/2} & e^{-\epsilon/2} \\ e^{-\epsilon/2} & e^{-\epsilon} & 0 \\ e^{-\epsilon/2} & 0 & e^{-\epsilon} \end{pmatrix} \tag{11}$$

which has eigenvalues $\lambda = a, a + 1/2(a + 1 - \sqrt{a^2 + 6a + 1}), a - 1/2(a + 1 - \sqrt{a^2 + 6a + 1})$, where $a \equiv e^{-\epsilon}$. Consequently, the free energy per bond is given by

$$-\frac{\beta F}{L-3} = ln(1/2) + ln(a + 1 + \sqrt{(a+1)^2 + 4a}) \tag{12}$$

The energy per bond is

$$\frac{\beta E}{L-3} = \epsilon f = \frac{1}{L-3}\beta\frac{\partial(\beta F)}{\partial \beta} = -\frac{ln(a)}{2(L-3)}\left(1 + \frac{a-1}{\sqrt{(1+a)^2 + 4a}}\right) \tag{13}$$

Using the previous equation to replace a with f, and taking the difference between the Energy per bond and the free energy per bond, we can get the entropy per bond (in units of the Boltzmann Constant)

$$\frac{S}{L-3} = (1+x)ln\left(\frac{1-x+\sqrt{2x^2+2}}{1+x}\right) + \frac{1-x}{2}ln\left(\frac{1+x+\sqrt{2x^2+2}}{1-x}\right) \tag{14}$$

which can be expanded around $f = 1/2$ to third order to yield

$$S = (L-3)\left(-\frac{\sqrt{2}}{2}(1-2f)^2 + ln(1+\sqrt{2})\right) \tag{15}$$

or dropping the constant terms

$$S = (L-3)2\sqrt{2}(f-f^2) \tag{16}$$