Phenomenological models of raft structure

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Abstract. We propose two phenomenological models describing the phase behavior of lipid-lipid systems and lipid-cholesterol systems in order to understand the "rafts" in cell membranes. In our models, the coupling between the lateral phase separation and the internal degree of freedom of a lipid membrane is considered. The calculated phase diagrams are in semiquantitative agreement with the experimental phase diagrams.

INTRODUCTION

Cell membranes are mainly composed of lipids, cholesterols (Chol), and proteins. Recent studies have shown that dynamical domains called "rafts" exist in the cell membranes in which the above components are inhomogeneously distributed [1]. These domains mainly consist of Chol and lipids with saturated hydrocarbon chains. The raft structure is related to the signaling and the material transfer in cells. For example, it is known that proteins are selectively included or excluded from the domains. The formation of raft structure has attracted both physical and biological interests.

It is considered that at least saturated lipid, unsaturated lipid and Chol are necessary to form rafts in cell membranes. In this paper, we focus on the saturated-unsaturated lipid systems and the lipid-Chol systems as a starting point to understand the rafts. We propose two simple phenomenological models describing the phase behavior of these systems. Within the mean-field treatment, we can produce the phase diagrams which are in semiquantitative agreement with the experimental ones.

MODELS

Saturated-Unsaturated Lipid Systems. It is kown that lipid bilayers exhibit first-order phase transition between the liquid crystalline phase and the gel phase. We call these two phases the disordered phase and the ordered phase, respectively. As the contributions to the total free energy of a bilayer membrane, we consider the mixing free energy of lipids ($f_1^{\ell\ell}$), and the stretching free energy of lipid chains ($f_2^{\ell\ell}$). The total free energy is approximated as the sum of these two energies: $f^{\ell\ell} = f_1^{\ell\ell} + f_2^{\ell\ell}$.

We use a lattice model to express the mixing free energy. The lattice size of saturated lipid and unsaturated lipid are assumed to be the same. Let us define the number of saturated lipid and unsaturated lipid by N_s and N_u, respectively, and the molar fraction of saturated lipids by $x = N_s/(N_s + N_u)$. Using the Bragg-Williams theory, the mixing free energy per lattice site is given by

$$f_1^{\ell\ell} = k_B T[x\log x + (1-x)\log(1-x)] + \frac{J}{2}x(1-x), \quad (1)$$

where k_B is the Boltzmann constant, T is the temperature, and $J > 0$ is the attractive interaction parameter.

Next we consider the stretching free energy of the lipid chains. To express the first-order phase transition, we use a Landau free energy [2]. The order parameter is defined by $\psi \equiv (\delta - \delta_0)/\delta_0$, where δ is the bilayer thickness, and δ_0 is that of the disordered phase. The stretching free energy of a lipid chain is then expressed by

$$f_2^{\ell\ell} = \frac{1}{2}a_2'[T - T^*(x)]\psi^2 + \frac{1}{3}a_3\psi^3 + \frac{1}{4}a_4\psi^4, \quad (2)$$

where we define as $a_2' > 0$, and require $a_3 < 0$ and $a_4 > 0$ to ensure the thicker ordered phase. The reference temperature $T^*(x)$ corresponds to the critical temperature if the cubic term is absent. Here we assume that $T^*(x)$ has a linear dependence on x: $T^*(x) = xT_s^* + (1-x)T_u^*$, where T_s^* and T_u^* are the reference temperatures of the single component bilayer composed of saturated and unsaturated lipids, respectively.

To obtain the phase diagram, we minimize $f^{\ell\ell}$ with respect to ψ first. Figure 1 (a) shows one of the typical phase diagrams of the saturated-unsaturated lipid systems. This type of the phase diagram was experimentally observed for aqueous dispersions of a DEPC-DPPC binary system.

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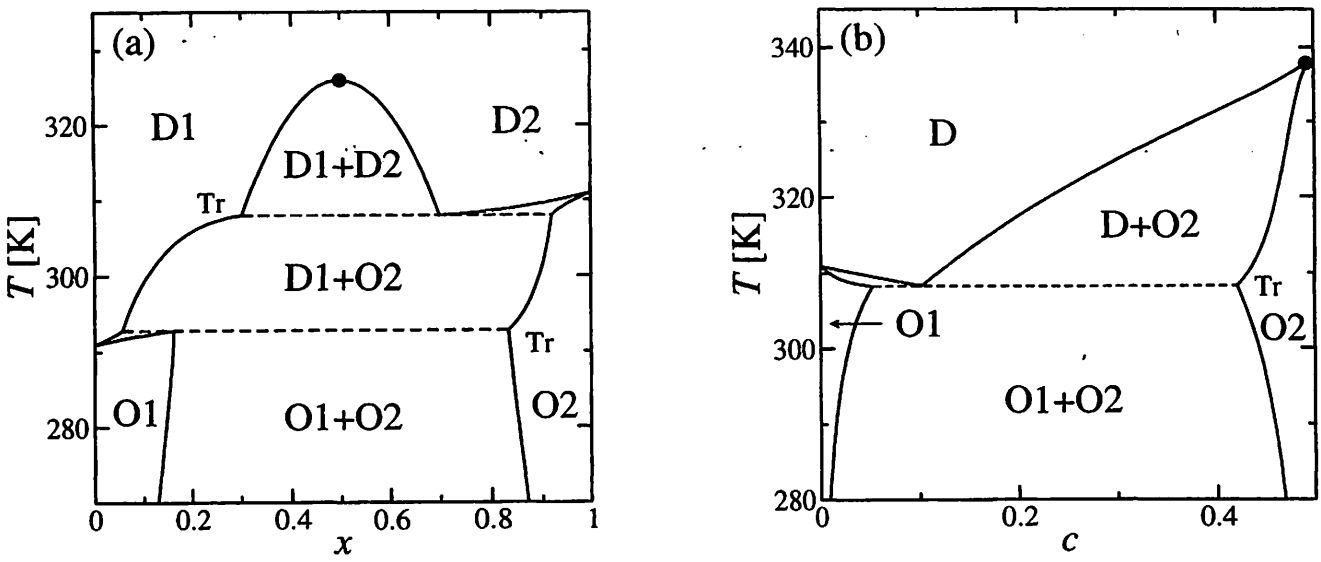

FIGURE 1. The numerically calculated phase diagrams for (a) the saturated-unsaturated lipid system, and (b) the lipid-Chol system. The critical point is indicated by a filled circle, and the triple point by Tr. The ordered and the disordered phase are denoted by O and D, respectively. The parameters are $J = 1.8 \times 10^{-20}$J, $a_2' = 2.4 \times 10^{-21}$J, $a_3 = -1.1 \times 10^{-18}$J, $a_4 = 2.2 \times 10^{-18}$, $T_s^* = 260$K, $T_u^* = 240$K, $\Gamma_1 = 4.0 \times 10^{-20}$J, $\Gamma_2 = 1.7 \times 10^{-19}$J, $T^* = 260$K.

Lipid-Cholesterol system. For the lipid-Chol systems, it is known that phase separation occurs. At low Chol concentration, the high temperature disordered phase and the low temperature ordered phase are stable. At high Chol concentration, the so-called *liquid-ordered* (*lo*) phase which is peculiar to this system exists. In order to explain the phase behavior of the lipid-Chol systems, the "dual effect" of the Chol has been suggested. Due to the rigid molecular structure of the cholesterol, the hydrocarbon chain in the ordered phase becomes disordered, whereas it becomes ordered in the disordered phase. The phase diagram of the lipid-Chol system was reported for a mixture of DPPC and Chol [3]. The two-phase coexisting state between the disordered phase and the *lo*-phase is the basic structure of the rafts in cell membranes.

We consider three contributions to the total free energy of a bilayer. These are the mixing free energy between lipid and Chol ($f_1^{\ell c}$), the stretching free energy of lipid chains ($f_2^{\ell c}$), and the coupling energy ($f_3^{\ell c}$). The total free energy is approximated as the sum of these three energies: $f^{\ell c} = f_1^{\ell c} + f_2^{\ell c} + f_3^{\ell c}$.

Since the two-phase coexistence region is limited for $c < 0.5$ in the experiment [3], we assume that all the cholesterols form dimers with lipids. Following the Flory-Huggins theory, the mixing free energy becomes

$$f_1^{\ell c} = k_B T[c \log 2c + (1-2c)\log(1-2c)], \qquad (3)$$

where c is the molar concentration of Chol and is restricted to $c < 0.5$.

The stretching free energy of lipid chains can be expressed as before:

$$f_2^{\ell c} = \frac{1}{2}a_2'[T - T^*]\psi^2 + \frac{1}{3}a_3\psi^3 + \frac{1}{4}a_4\psi^4, \qquad (4)$$

where T^* is a constant.

The simplest but still meaningful coupling energy to account for the above mentioned dual effect of Chol can be phenomenologically expressed by

$$f_3^{\ell c} = \frac{1}{2}\Gamma_1 c\psi - \frac{1}{2}\Gamma_2 c^2\psi, \qquad (5)$$

where $\Gamma_1 > 0$ and $\Gamma_2 > 0$ are the constants. We assume that the presence of Chol decreases the chains ordering at low Chol concentration and increases the chains ordering at high Chol concentration. Since both of the coupling terms are linear in ψ, they act as an external field on the order parameter ψ. The second term in Eq. (5) has a tendency to eliminate the first-order transition, and it overwhelms the first term at high Chol concentration. We consider that this effect explains the existence of the *lo*-phase. Figure 1 (b) shows one of the typical phase diagrams of the lipid-Chol systems. The O2-phase corresponds to the *lo*-phase.

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