Model for Lamellar Phases of Interacting Lipid Membranes

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We solve in mean-field approximation a model describing the lamellar phases of lyotropic liquid crystals as stacks of interacting bilayer membranes. The model is a synthesis of a Landau-Ginzburg theory of membrane-melting transitions and a continuum treatment of the molecular forces acting between bilayers. The resulting phase diagrams include both planar and modulated phases and are in semiquantitative agreement with experimental observation on neutral lipids. The approach highlights the role of interactions in the thermodynamic behavior of membrane systems.

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Lamellar liquid crystals of hydrated lipid bilayers are good model systems for the study of interacting membranes. As is the case for isolated membranes (e.g., vesicles), the individual lipid bilayers which constitute the lamellae may undergo many structural phase transitions as a function of temperature. In the multilayer systems, however, such *intra*membrane phase transitions are often strongly modified by *inter*lamellar interactions.[1] An understanding of this effect appears crucial to the development of a realistic theory of interacting and fluctuating membranes. In this Letter we study an example of a structural phase transition modified by membrane interactions. We show that a simple synthesis of two theoretical ingredients, a Landau theory of intramembrane melting transitions,[2] and a well-known continuum model of molecular forces,[3] provides a semiquantitative account of thermodynamic properties of the lamellar phases, and may serve as a possible starting point for a more detailed theory of interacting membranes.

The phase diagrams presented in Figs. 1(a) and 1(b)

are the main results of a mean-field treatment of the model. They include three of the observed[4] phases of lamellar crystals: (i) the fluid, disordered L_α phase, (ii) a solidlike, ordered L_β phase, and (iii) the intermediate modulated ("rippled") P_β phase. These diagrams were computed using typical values of the phenomenological parameters which enter the theory. They can all be deduced from thermodynamic and structural measurments obtained with existing experimental techniques.[1,4] The topology and the main characteristics of the diagrams in Fig. 1 bear a strong resemblance to those found in neutral phospholipids. In particular, the variations of the L_α-L_β and L_α-P_β ("main") transitions and of the L_β-P_β ("pre") transition with the water volume fraction are in accord with experimental observations. The theory thereby shows explicitly the important role played by water-mediated "hydration" interactions in the physics of membrane systems.

We proceed now to a brief summary of the model.[5] The melting transitions in lipid membranes have been
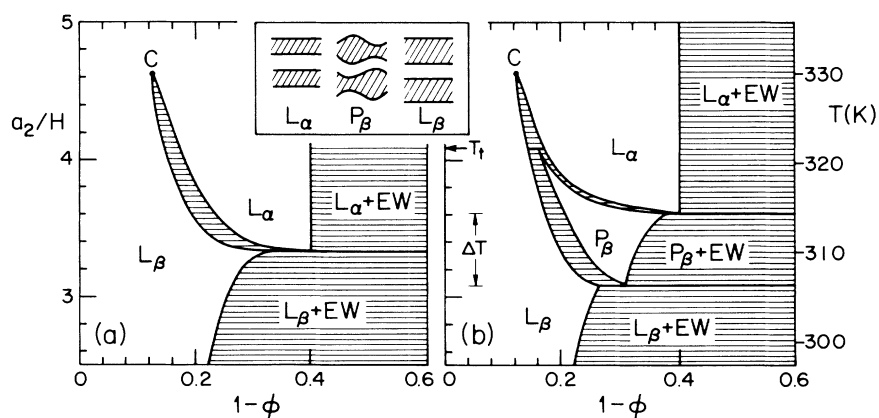

FIG. 1. Temperature-composition phase diagrams of multilamellar bilayer membranes, with ϕ the volume fraction of lipid. Inset: schematic drawings of the thin (L_α), modulated (P_β), and thick (L_β) phases. EW denotes a phase of nearly pure ("excess") water. Vertical scales are those of the bare Landau coefficients (left) and in absolute degrees (right) as deduced from typical values of the model parameters.

the subject of numerous experimental studies, particularly in light of their possible biological relevance. Many experiments reveal that at these transitions the bilayer thickness δ exhibits jump discontinuities.[1] We therefore base our continuum theory on a *scalar* order parameter $\psi \equiv [\delta(T) - \delta_0]/\delta_0$, where δ_0 is a reference thickness, taken here as that of the fluid phase. Scattering studies of the multilamellar systems,[6] freeze-fracture microscopy,[7] as well as micromechanical experiments[8] on isolated membranes show that the P_β phase is characterized by a one-dimensional modulation (with a wavelength $\lambda_r \simeq 10$–20 nm). We thus allow the order parameter ψ to vary with the position vector $\mathbf{x}$ within the membrane.

$$\mathcal{H}_0[\psi] = \int d^2x \{ \tfrac{1}{2}\Sigma(\nabla\psi)^2 + \tfrac{1}{2}K(\nabla^2\psi)^2 + \tfrac{1}{2}a_2\psi^2 + \tfrac{1}{3}a_3\psi^3 + \tfrac{1}{4}a_4\psi^4 \} . \tag{1}$$

Similar Hamiltonians with a scalar order parameter have been introduced to study modulated phases of isolated membranes.[10] The temperature dependence of the coefficients is assumed to reside solely in a_2: $a_2 = a_2'(T - T_0)$, with T_0 a reference temperature which is the critical temperature of a uniform system in the absence of a cubic term. For $a_3 \neq 0$ the model leads to a first-order transition between the L_α ($\psi = 0$) and L_β ($\psi > 0$) phases. The modulated P_β phase appears between the L_α and L_β phases if the coefficient Σ in Eq. (1) is more negative than a characteristic value $\Sigma_0(K, \{a_i\})$. The wave vector of the modulation is then of order $q^* \equiv (|\Sigma|/2K)^{1/2}$. In the present work, we shall limit the space of solutions $\psi(\mathbf{x})$ to one-wave-vector trial functions[10] $\psi = \psi_0 + \eta_0 \cos(q^* x)$ (which include both the planar and P_β phases; see inset in Fig. 1).[11] The model (1) predicts that at the P_β–L_α transition $q^* > 0$, except if $\Sigma = a_2 = a_3 = 0$, which corresponds to a so-called *Lifshitz point*. At this point the wavelength of the modulation diverges.[12] An explanation of the molecular mechanism by which the coefficient Σ can be negative lies beyond the scope of this paper. One possible scenario invokes[10,13] a coupling between the conformation of the chains and the curvature of the lipid/water interface; it is also conceivable that the interactions between the polar headgroups of the lipids and water could favor modulated structures.[5]

The second ingredient of the model is a continuum theory of molecular interactions between membranes. For neutral lipid bilayers the molecular potential (per unit area), V_{mol}, includes two terms: (i) the (nonretarded) van der Waals attraction which, for layers of thickness δ and separation d, can be written as[3]

$$V_1(d,\delta) = -W[d^{-2} - 2(d+\delta)^{-2} + (d+2\delta)^{-2}], \tag{2}$$

where $W \simeq 10^{-22}$–10^{-21} J is the Hamaker constant, and (ii) the so-called "hydration" repulsion[1] which decays exponentially with d, and for *flat* layers can be written as

$$V_2(d) = H \exp(-d/\lambda_h), \tag{3}$$

The choice of the order parameter as a simple scalar is a drastic simplification since the lipid molecules possess many degrees of freedom: hydrocarbon chain conformation, molecular tilt, and positional ordering. In order to account fully for different symmetries[9] of the lamellar phases, as well as the detailed nature of different phase transitions, future theories must consider more elaborate order parameters. The present approach reveals, however, that *many aspects of the global phase behavior can be explained without reference to the detailed molecular structure of the membranes.*

In order to describe the melting transitions within an *isolated* membrane we introduce a phenomenological Landau-Ginzburg Hamiltonian[2]

where H is a constant of order 0.1–1 J/m^2, and $\lambda_h \simeq 0.25$ nm. The hydration interaction may be described within the framework of a well-known continuum model[14] in which the repulsion arises from the ordering of the water molecules by the membrane surfaces. This Landau-Ginzburg Hamiltonian for a polarization variable P (related to the dipolar order of water molecules) reads

$$\mathcal{H}_h \propto \int d^3x [(\nabla P)^2 + \lambda_h^{-2}P^2], \tag{4}$$

and leads to the effective potential (3) for $d > \lambda_h$ when solved in a finite-thickness slab geometry with appropriate boundary conditions at the membrane surfaces. As discussed below, Eq. (4) permits us to generalize the hydration repulsion (3) to the geometry of modulated phases, treated self-consistently in the one-wave-vector approximation. The analogous generalization of van der Waals forces for undulated geometries is neglected here since over most of the phase diagram the modulated hydration forces are dominant.[5]

Equation (1) and the molecular potential $V_{mol} = V_1 + V_2$ define completely the model:

$$\mathcal{H} = \sum_i \mathcal{H}_0(T, \psi_i) + \sum_{i<j} \int d^2x_i \, V_{mol}(\psi_i, \psi_j, d_{ij}), \tag{5}$$

where ψ_i is the internal order parameter of layer i (connected to its thickness δ_i). Molecular interactions are well approximated as pairwise additive and acting between nearest-neighbor lamellae. We implicitly assume here that the layers have the same value of order parameter ψ and spacing d; the interesting possibility of more complicated structures in which the fluid and solid layers coexist will be studied elsewhere. The model (5) is solved within a mean-field approximation neglecting fluctuations both in the in-plane order (ψ) and in the interlamellar spacing (d). This last approximation means that we completely neglect fluctuation-induced "steric" repulsions[15] which can—under some conditions—lead to complete separation (*unbinding*[16]) of the membranes.

Under these assumptions we can invoke the geometrical relationship $\delta/d = \phi/(1-\phi)$, where ϕ is the lipid volume fraction,[17] and write the free energy density as a function of T and ϕ, with ψ as a variational parameter whose equilibrium value is determined numerically. Note that both van der Waals and hydration interactions depend then on ψ and ϕ; e.g., Eq. (3) can be written as $V_2 = H\exp[-(1-\phi)(1+\psi)\delta_0/\phi\lambda_h]$.

It is important to stress that in principle there exist enough independent structural and thermodynamic measurements to fix unambiguously the values of all material constants of the model. The diagram in Fig. 1(a) (with $\Sigma > \Sigma_0$), which has no ripple phase, is like that found in many phosphatidylethanolamines[18]; that in Fig. 1(b) (with $\Sigma < \Sigma_0$) resembles the phase behavior of phosphatidylcholines.[4,19] In the absence of a *complete* set of such measurements on any *single* phospholipid system, we have used typical values for the intermediate-length phospholipids. In order to do this (i) we have fixed values of $H \simeq 0.1$ J m^{-2}, $\lambda_h \simeq 0.25$ nm, and $W = 1.8 \times 10^{-21}$ J based on osmotic stress measurements,[1] and (ii) from calorimetric and x-ray diffraction studies of lamellar crystals coexisting with ("excess") water, we have adopted the typical values of the ripple wavelength $\lambda_r \simeq 10$–15 nm [20] and of the latent heat Q and order-parameter jumps of L_α-L_β (phosphatidylethanolamine) or L_α-P_β (phosphatidylcholine) transitions (with $T_m \simeq 310$ K) as $Q \simeq 25$ kJ mole^{-1} and $\Delta\psi \simeq 0.3$,[20] with $\delta_0 \simeq 3.5$ nm. The choices (i) and (ii) are sufficient to obtain a family of phase diagrams as a function of a_2 and ϕ (see Fig. 1). In addition, one can fix the temperature scale by adjusting the position of the triple point at $T_t \simeq 320$ K and a typical value (see Ref. 18) of the temperature range in which the P_β phase coexists with excess water: $\Delta T \simeq 10$ K [see Fig. 1(b)].

The existence of a triple point in Fig. 1(b) at which all three lamellar phases coexist is a direct consequence of the modification of the hydration forces due to the modulation of the membranes. In fact, a generalization[5] of the theory (4) for a sinusoidal modulation leads to an additional repulsion term proportional to q^{*2}, which may be written as $H_1[\nabla\psi(\mathbf{x})]^2$, with $H_1 \sim H\exp(-d/\lambda_h)$. Therefore, the effective gradient-squared coefficient in Eq. (1) is of the form $\Sigma_{\rm eff} = \Sigma + H_1$ and becomes less negative with decreasing d. This also implies that the modulation wave vector q^* decreases exponentially with d, for separations near the coexistence with excess water. The recent experiments by Wack and Webb[20] on phosphatidylcholines indeed confirm this prediction, finding the shift of λ_r scaling as $\exp(-d/\xi)$, with $\xi \simeq 0.23$ nm $\simeq \lambda_h$. Similarly, the observation[21] that λ_r does not vary significantly with temperature (for fixed spacing d) is in full agreement with the results of the calculations. The typical amplitude of the modulation, found in the model to be $(0.2$–$0.4)\delta_0$, appears to be of the order of that found in experiments.[6,7]

The present model predicts that the L_α-L_β coexistence occurs with very narrow tielines, with an exponential increase of T_m upon decreasing water content, and with a typical shift of the melting temperature of some 10–20 K upon nearly complete dehydration. All of these features are clearly observed in experiment.[18] In the theory based on a scalar order parameter, the L_α-L_β coexistence line may terminate at the critical point C.[22] The two branches of the spinodal lines emanating from C then lie within fractions of a degree of the phase boundaries. We believe that this proximity can be connected to the observations of *pseudocritical* phenomena[23] in multilamellar systems: Even if the phase boundary is crossed far from the critical point, one may observe the growth of fluctuations in the vicinity of these spinodals. Such a scenario is *distinct* from those[24] invoking an intrinsic pseudocriticality of the melting transition of an *isolated* membrane. In our calculation $T_0 \simeq 260$ K of Eq. (1) lies far away from the melting temperature T_m. Let us note, however, that one may easily decrease $T_m - T_0$ by decreasing the hydrocarbon chain length n. In fact, it is observed that the L_α-L_β transition then becomes more weakly first order. By extrapolation, Q and $\Delta\psi$ would vanish for $n = n^* \simeq 9$–10,[4,20] and the estimated melting temperature $T_m(n^*)$ would lie very close to T_0. Thus, for very short-chain molecules the pseudocriticality may indeed be connected to finite-size effects within single membranes. Decreasing n could also permit an approach to the Lifshitz point of the model (1) at which the ripple wavelength λ_r would diverge.

The model described here accounts for many of the observed characteristics of lamellar crystals despite the simplifications in the choice of the order parameter and the description of the modulated phase. It should be further developed to include the effects of thermal fluctuations and the more complicated nature of the order parameter(s). From the experimental point of view it is desirable to have a complete set of measurements of a *single* phospholipid system, as well as systematic studies of the phase behavior of lipids with varying chain length n. Such measurements would permit a *quantitative* check of the model presented here (or its possible modifications), and thus contribute to the detailed understanding of interacting membrane systems.

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