Morphology and Phase Behavior of Two-Component Lipid Membranes

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Abstract The stability and shapes of domains with different bending rigidities in lipid membranes are investigated. These domains can be formed from the inclusion of an impurity in a lipid membrane or from the phase separation within the membrane. We show that, for weak line tensions, surface tensions and finite spontaneous curvatures, an equilibrium phase of protruding circular domains or striped domains may be obtained. We also predict a possible phase transition between the investigated morphologies.

Key words lipid membrane · phase separation · phase transition

Introduction

Living cells are enclosed by a plasma membrane which distinguishes the cells' contents from the environment. Classical and oversimplified models of the cell reduce the plasma membrane to a bilayer of one species of lipid molecule [1–4]. More recently, increased attention has been paid to the properties of multi-component bilayer membranes. The reasons are as follows. On the one hand, biological membranes are complex and inhomogeneous systems that are usually mixtures of lipid species, intercalated molecules such as cholesterol, and many intra-membrane proteins [5, 6]. Processes such as budding, shape transformations and raft formations are believed to involve local inhomogeneities in these mixtures [7–12]. On the other hand, lipid mixtures have been shown to play an important role in a variety of biomedical and biophysical applications, such as efficient drug delivery, controlled genes and biosensors [13–15].

Lipids can diffuse freely in biological membranes, and, under appropriate conditions, membrane phases may separate [16]. Phase separations play important roles in biological systems, since they may be responsible for changes in biological functions of membranes such as the formation of functional rafts [17, 18]. Phase separations have been studied

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theoretically in two-component fluid membranes with spherical [19–21], planar [22–25], and cylindrical shapes, and other complex topologies [26, 27]. The shape transformations of a domain boundary of a two-component lipid membrane have also been investigated [28]. On the other hand, experimental studies on two- or three-component systems have revealed domain formations [7–12] and confirmed their roles played in membrane shape transformations such as budding [11, 12].

In this paper, the equilibrium shapes and stabilities of domains in flat membranes (or giant vesicles with dimensions much larger than the domain sizes) are investigated. We focus on the strong-segregation limit, i.e., the situation where the mixture is far from its critical temperature and the components are well segregated, forming sharp domain walls between pure A and B domains. However, the membrane shape at the domain boundary is smooth [22]. In contrast to former research [22–25], the difference in bending rigidities of the two components is the focus of this paper. We show that, for membranes under weak tension, stable caplets and striped phases can form. The caplet phase is composed of a hexagonal arrangement of monodisperse circular domains of the A component surrounded by the B component. These caplet configurations are analogous to droplet phases observed in bulk liquids. The striped phase is composed of a periodic arrangement of stripes of A and B components. We also demonstrate the possibility of a phase transition from a mesophase of circular caplets to those of protruding stripes either with increasing area fraction of the minority component or with increasing ratio of bending rigidity of two components.

The structure of this paper is as follows: In the section titled “Description of Model”, a detailed description of the model is devoted to defining the total free energy functional. The equilibrium shape equation and boundary conditions are derived, and solutions for caplets and striped domains are investigated. In the section titled “Dilute Limit”, results in dilute limit and concentrated regimes are presented and discussed. Finally, in “Summary and Conclusions” the conclusions are drawn.

Model and Basic Equations

Description of model

A single idealized two-component membrane consisting of incompatible amphiphiles a and b is considered in Figure 1. The membrane is defined as a two-dimensional surface with a

Figure 1 Schematic view of lipid membrane composed of two amphiphiles a and b .

phenomenological parameter ϕ , which is defined as the fraction of the surface area occupied by component a , i.e., $\phi = \text{area}(a)/(\text{area}(a) + \text{area}(b))$.

When the mixture separates, the components form domains. Two typical domain morphologies are investigated, as shown in Figure 2. These morphologies are idealizations of actual structures that may exhibit disordered textures of polydisperse or irregular domains. These are the following [22–25]:

- (i) Quasi-one-dimensional periodic arrangement of stripe-like domains, with A -phase stripes of width $2x_0$ embedded inside B -phase stripes with total width $2X_0$. The stripe length is L , and the projected area of an element is $2X_0L$.
- (ii) Monodisperse circular domains of A -phase (caplets). For caplets, we take a Wigner-Seitz cell with A -phase radius r_0 and B -phase total radius R_0 . The circular Wigner-Seitz cell approximation leads to a lower bound for the free energy of a less symmetric structure, such as a hexagonal array. The projected area of an element is πR_0^2 .

For phase-separated membranes under weak tension, the total free energy is given by

$$F = F_b + F_\lambda + F_\sigma \quad (1)$$

where F_b , F_λ and F_σ are the energy contributions from the bending elasticity, the membrane surface tension, and the line (interfacial) tension between two phases, respectively. These three contributions are modeled by [3, 4]

$$F_b = \sum_{i=A,B} \int_{S_i} \frac{k_c^i}{2} (2H - c_0)^2 dS, \quad F_\lambda = \sum_{i=A,B} \lambda \int_{S_i} dS, \quad F_\sigma = \sigma \oint_{\partial S} dl \quad (2)$$

where $i = A, B$ denotes the regions of a membrane occupied by the A and B components, respectively. k_c^i is the bending rigidity, λ and σ are the surface and line tension. H denotes the mean curvature of the membrane, and c_0 the spontaneous curvature. S describes the membrane surface, and ∂S represents the boundaries of the domains.

In this paper, we focus on the difference of the bending rigidity of the two components and relax the constraints inside the bilayers. For simplicity, the spontaneous curvature c_0 , the surface tension λ , and the Gaussian curvature rigidity $\bar{k}$ are taken to be the same for each component. Since the topology of a membrane does not change, the term containing

Figure 2 A sketch of the stripe and caplet morphologies. (a) A linear array of A -phase stripes with width $2x_0$ (black) in the matrix of B -phase (grey). (b) A hexagonal array of A -phase caplets with radius r_0 (black) in the matrix of B -phase (grey). The dashed lines in each figure show the appropriate Wigner-Seitz cell boundaries.

the Gaussian curvature contributes a constant [21] and has therefore been omitted in the bending elasticity.

Euler-Lagrange equations

In the case of caplet domains, we use the Monge gauge representation with a polar coordinate system [22–25], as shown in Figure 3.

Considering a single caplet domain, for given material parameters, we obtain minimum energy height profiles $h(r)$, where r is the radius along the contour, and then minimize the resulting free energy over the domain dimension. This representation is valid for surfaces that are nearly flat with only gradual variations of h , and allows the approximation,

$$2H = c(r) = \nabla^2 h = \frac{1}{r} \frac{\partial}{\partial r} \left(r \frac{\partial h}{\partial r} \right), \quad (3)$$

$$dS = \left[1 + (\nabla h)^2 \right]^{1/2} dS_p, \quad dS_p = 2\pi r dr$$

where S_p is the projected membrane area. Then, the total energy with respect to a flat reference state can be written as

$$F = 2\pi \sum_{i=A,B} \frac{k_c^i}{2} \int_{S_i} \left[(\nabla^2 h_i)^2 - 2c_0 \nabla^2 h_i + \frac{1}{2} c_0^2 (\nabla h_i)^2 \right] r dr$$

$$+ 2\pi \sum_{i=A,B} \frac{\lambda}{2} \int_{S_i} (\nabla h_i)^2 r dr + \sigma 2\pi r_0. \quad (4)$$

The variation of F over h leads to the lowest order in h such that

$$\delta F = 2\pi \sum_{i=A,B} \int_{S_i} f_{e-l}^i(\delta h_i) r dr + \delta h(r_0) f_{hr}(r_0) + \delta h(R_0) f_{hR}(R_0)$$

$$+ \delta h'(r_0) \Gamma_r(r_0) + \delta h'(R_0) \Gamma_R(R_0) \quad (5)$$

in terms of the following forces f and torques Γ :

$$f_{hr}(r) = 2\pi r \left[-k_c^A c_A' + k_c^B c_B' + \left(\frac{k_c^A}{2} c_0^2 + \lambda \right) h_A' - \left(\frac{k_c^B}{2} c_0^2 + \lambda \right) h_B' \right], \quad (6a)$$

$$f_{hR}(R) = 2\pi R \left[-k_c^B c_B' + \frac{1}{2} k_c^B c_0^2 h_B' + \lambda h_B' \right], \quad (6b)$$

$$\Gamma_r(r) = 2\pi r [k_c^A c_A - k_c^B c_B - k_c^A c_0 + k_c^B c_0], \quad (6c)$$

$$\Gamma_R(R) = 2\pi R k_c^B [c_B - c_0]. \quad (6d)$$

The Euler-Lagrange equations, which determine the profile $h(r)$, are

$$k_c^i (\nabla^2 \nabla^2 h_i) - \left[\frac{k_c^i}{2} c_0^2 + \lambda \right] \nabla^2 h_i = 0. \quad (7)$$

Figure 3 Parameterization of the axial symmetric caplet domain.

In the case of the striped phase, the analogous set of equations for the stripe morphology is given by the same method:

$$\frac{f_{hr}}{L} = -k_c^A c_A' + k_c^B c_B' + \left(\frac{k_c^A}{2} c_0^2 + \lambda \right) h_A' - \left(\frac{k_c^B}{2} c_0^2 + \lambda \right) h_B', \quad (8a)$$

$$\frac{f_{hR}}{L} = -k_c^B c_B' + \frac{1}{2} k_c^B c_0^2 h_B' + \lambda h_B', \quad (8b)$$

$$\frac{\Gamma_r}{L} = k_c^A c_A - k_c^B c_B - k_c^A c_0 + k_c^B c_0, \quad (8c)$$

$$\frac{\Gamma_R}{L} = k_c^B (c_B - c_0), \quad (8d)$$

$$k_c^i (\nabla^2 \nabla^2 h_i) - \left[\frac{k_c^i}{2} c_0^2 + \lambda \right] \nabla^2 h_i = 0. \quad (8e)$$

Notice that here h is a function of the Cartesian coordinate x and the Laplacian $\nabla^2 = d^2/dx^2$.

Boundary conditions

In this section, we will explicitly describe the boundary conditions for the two-dimensional caplet case; the same conditions hold for the one-dimensional stripe case.

The boundary conditions are specified by the forces and torques applied to the membrane. There is no applied torque at the interface r_0 and R_0 , so we have

$$\Gamma_r(r_0) = 0, \quad (9a)$$

$$\Gamma_R(R_0) = 0. \quad (9b)$$

Equations 9a, 9b relate the mean curvature to the spontaneous curvature of the membrane, which has been discussed in the references [29, 30]. Next, we assume there are no vertical forces applied to the membrane,

$$f_{hr}(r_0) = 0, \quad (10a)$$

$$f_{hR}(R_0) = 0. \quad (10b)$$

However, it is straightforward to show that these force equilibrium boundary conditions are in fact proportional to first integrals of the Euler-Lagrange equations [4, 24],

$$f_h(r) = k_c c'(r) - \left(\frac{k_c}{2} c_0^2 + \lambda \right) h'(r) = \int dr \left\{ k_c (\nabla^2 \nabla^2 h) - \left[\frac{k_c}{2} c_0^2 + \lambda \right] \nabla^2 h \right\} = \text{const}. \quad (11)$$

Since $f_h(r)$ is constant for all r , the boundary condition at the junction, Eq. 10a, is irrelevant and we are left with Eq. 10b. A similar result applies for the stripe case.

To completely specify this problem we need a few more conditions. Symmetry about the domain center requires

$$h'_A(0) = h'''_A(0) = 0. \quad (12)$$

Another condition on the derivative of the profile $h'(r_0)$ results from the requirement of a well-defined energy. If h' has a discontinuity at the boundary, then the curvature has a δ function as the boundary is crossed. This leads to a nonphysical and singular energy in the region of the junction $r = r_0$. Hence we are led to our final boundary condition

$$h'_A(r_0) = h'_B(r_0). \quad (13)$$

For completeness, we reproduce the relevant boundary conditions that remain after recognizing the redundancy of Eq. 10a. For the single-domain problem, from Eqs. 6b–6d we have,

$$k_c^B c'_B(\infty) = \left[\frac{1}{2} k_c^B c_0^2 + \lambda \right] h'_B(\infty), \quad (14a)$$

$$c_B(\infty) = c_0, \quad (14b)$$

$$k_c^A c_A(r_0) - k_c^B c_B(r_0) = k_c^A c_0 - k_c^B c_0. \quad (14c)$$

For the multi-domain problem the boundary conditions must be modified. We still have Eqs. 12 and 13 above, but instead of boundary conditions at $R = \infty$, we impose a symmetric profile at the Wigner-Seitz cell boundaries:

$$c'_B(R_0) = h'_B(R_0) = 0 \quad (15)$$

replacing Eqs. 14a and 14b.

Because the Euler-Lagrange equations and boundary conditions depend only on derivatives of h , we will solve for the slope $\eta = dh/dr$ instead of the height profile. The three equations 14a, 14b (or Eq. 15 and 14c, together with the three conditions of Eqs. 12

and 13, give us six conditions. The Euler-Lagrange equations (Eq. 7) are two three-order differential equations for η_i , which have six constants. Hence we have a closed set of equations which determine the height profiles $h_A(r)$ and $h_B(r)$. Finally, we determine the domain size r_0 by minimizing the total free energy (after substituting the solution into the original free energy) over r_0 .

Solutions

In the case of caplet domains, we consider circular domains of inner radius r_0 and outer radius R_0 , and the mean curvature is $c(r) = \nabla^2 h = h'' + h'/r$. The Euler-Lagrange equations can be written as

$$k_c^i (rc_i'' + c_i') - \left[\frac{k_c^i}{2} c_0^2 + \lambda \right] rc_i = 0. \quad (16)$$

Here $i = A, B$ denotes phase A and B . Equation 16 may be integrated to give

$$r \left\{ k_c^i c_i' - \left[\frac{k_c^i}{2} c_0^2 + \lambda \right] h_i' \right\} = \text{const.} \quad (17)$$

Since $c_A'(0) = h_A'(0) = 0$ and $c_B'(R_0) = h_B'(R_0) = 0$ by symmetry, the constant vanishes. In terms of slope, $\eta = dh/dr$, Eq. 17 becomes

$$\eta_i'' + \frac{1}{r} \eta_i' - \left[\frac{1}{2} c_0^2 + \frac{\lambda}{k_c^i} + \frac{1}{r^2} \right] \eta_i = 0. \quad (18)$$

For convenience, we introduce the dimensionless variables, $\tilde{R}_0 = R_0 c_0$, $\rho = rc_0$, $\tilde{\lambda} = \lambda / (k_c^A c_0^2)$, $\alpha = k_c^B / k_c^A$, $\tilde{\omega}_A^2 = 1/2 + \tilde{\lambda}$, $\tilde{\omega}_B^2 = 1/2 + \tilde{\lambda}/\alpha$ and $\tilde{\sigma} = \sigma / (k_c^A c_0)$. Then Eqs. 18 and 14c become:

$$\frac{\partial^2 \eta_i}{\partial \rho^2} + \frac{1}{\rho} \frac{\partial \eta_i}{\partial \rho} - \left[\tilde{\omega}_i^2 + \frac{1}{\rho^2} \right] \eta_i = 0, \quad (19)$$

$$\left[\frac{\partial \eta_A}{\partial \rho}(\rho_0) + \frac{1}{\rho_0} \eta_A(\rho_0) \right] - \alpha \left[\frac{\partial \eta_B}{\partial \rho}(\rho_0) + \frac{1}{\rho_0} \eta_B(\rho_0) \right] = 1 - \alpha. \quad (20)$$

Implementing the boundary conditions will yield the following profiles:

$$\frac{\eta_A}{\eta_0} = \frac{I_1(\tilde{\omega}_A \rho)}{I_1(\tilde{\omega}_A \rho_0)}, \quad \frac{\eta_B}{\eta_0} = \frac{K_1(\tilde{\omega}_B \rho) - CI_1(\tilde{\omega}_B \rho)}{K_1(\tilde{\omega}_B \rho_0) - CI_1(\tilde{\omega}_B \rho_0)}, \quad (21)$$

$$C = \frac{K_1(\tilde{\omega}_B \tilde{R}_0)}{I_1(\tilde{\omega}_B \tilde{R}_0)}, \quad (22)$$

$$\eta_0 = \frac{(1 - \alpha) I_1(\tilde{\omega}_A \rho_0)}{\tilde{\omega}_A I_0(\tilde{\omega}_A \rho_0) + \alpha \tilde{\omega}_B I_1(\tilde{\omega}_A \rho_0) \frac{K_0(\tilde{\omega}_B \rho_0) + CI_0(\tilde{\omega}_B \rho_0)}{K_1(\tilde{\omega}_B \rho_0) - CI_1(\tilde{\omega}_B \rho_0)}}, \quad (23)$$

where I_0 , I_1 , K_0 and K_1 are modified Bessel functions [31]. The dimensionless total free energy of the caplet phase is given by

$$f = \frac{F}{2\pi k_c^4} \approx \tilde{\sigma}\rho_0 + (1 - \alpha) \left(\frac{1}{4}\rho_0 - \eta_0 \right) \rho_0 + \left(\frac{\alpha}{4} + \frac{\tilde{\lambda}}{2} \right) \tilde{R}_0^2. \quad (24)$$

The equilibrium domain size is evaluated by [24]

$$\frac{\partial f}{\partial \rho_0} = \frac{\tilde{\sigma}}{(1 - \alpha)} + \frac{\rho_0}{2} - \frac{d\eta_0}{d\rho_0} \rho_0 - \eta_0 = 0, \quad (25a)$$

$$\frac{\partial f}{\partial \tilde{R}_0} = \left(\tilde{\lambda} + \frac{\alpha}{2} \right) \tilde{R}_0 - (1 - \alpha) \frac{d\eta_0}{d\tilde{R}_0} \rho_0 = 0. \quad (25b)$$

In the case of the stripe phase, the domain morphology is a stripe of width $2x_0$ embedded inside a majority stripe with total width $2X_0$. The curvature is d^2h/dx^2 , and the Euler-Lagrange equations are:

$$k_c^i \left(\frac{d^4 h_i}{dx^4} \right) - \left[\frac{k_c^i}{2} c_0^2 + \lambda \right] \frac{d^2 h_i}{dx^2} = 0. \quad (26)$$

As is the same with the caplet case, we only need the slope $\eta = dh/dx$. Equation 26 may be integrated once, with integration constant zero. This leaves the following Euler-Lagrange equations:

$$\frac{d^2 \eta_i}{d\xi^2} - \tilde{\omega}_i^2 \eta_i = 0, \quad (27)$$

where we have introduced the new dimensionless variables, $\Xi = X_0 c_0$ and $\xi = x c_0$. Implementing the boundary conditions, we get the solutions

$$\eta_A = \eta_0 \frac{\sinh(\tilde{\omega}_A \xi)}{\sinh(\tilde{\omega}_A \xi_0)}, \quad \eta_B = \eta_0 \frac{\sinh \tilde{\omega}_B (\Xi - \xi)}{\sinh \tilde{\omega}_B (\Xi - \xi_0)}, \quad (28)$$

$$\eta_0 = \frac{1 - \alpha}{\tilde{\omega}_A \coth \tilde{\omega}_A \xi_0 + \alpha \tilde{\omega}_B \coth \tilde{\omega}_B (\Xi - \xi_0)}. \quad (29)$$

Here, $\sinh$ and $\coth$ are the hyperbolic functions that satisfy the boundary conditions. The dimensionless total free energy for the stripe phase is given by

$$f = \frac{F}{2k_c^4 L c_0} \approx \tilde{\sigma} + (1 - \alpha) \left(\frac{1}{2} \xi_0 - \eta_0 \right) + \left(\frac{\alpha}{2} + \tilde{\lambda} \right) \Xi. \quad (30)$$

The equilibrium domain size is also evaluated by

$$\frac{\partial f}{\partial \xi_0} = \frac{1}{2} - \frac{d\eta_0}{d\xi_0} = 0, \quad (31a)$$

$$\frac{\partial f}{\partial \Xi} = \left(\frac{\alpha}{2} + \tilde{\lambda} \right) - (1 - \alpha) \frac{d\eta_0}{d\Xi} = 0. \quad (31b)$$

Results and Discussion

Dilute limit

The general solutions to the Euler-Lagrange equations are given above. Before discussing the phase behavior in the concentrated case, we discuss the dilute limit for weak surface tension and line tension of the membrane, where several approximations simplify the results.

The dilute limit is valid for two cases, one when the concentration of the A component is small, and a single domain is formed in the membrane; the other, when the domains are separated by more than the characteristic length of the B phase. Taking the limits $\tilde{R}_0 \rightarrow \infty$ and $\Xi \rightarrow \infty$, the solutions may be deduced to

$$\frac{\eta(\rho)}{\eta_0} = \begin{cases} \frac{I_1(\tilde{\omega}_A \rho)}{I_1(\tilde{\omega}_A \rho_0)} & \rho \leq \rho_0 \\ \frac{K_1(\tilde{\omega}_B \rho)}{K_1(\tilde{\omega}_B \rho_0)} & \rho \geq \rho_0 \end{cases} \quad (\text{Caplets}) \quad (32)$$

and

$$\frac{\eta(\xi)}{\eta_0} = \begin{cases} \frac{\sinh(\tilde{\omega}_A \xi)}{\sinh(\tilde{\omega}_A \xi_0)} & \xi \leq \xi_0 \\ \exp \tilde{\omega}_B (\xi_0 - \xi) & \xi \geq \xi_0 \end{cases} \quad (\text{Stripes}) \quad (33)$$

where

$$\eta_0 = \begin{cases} \frac{(1-\alpha)I_1(\tilde{\omega}_A \rho_0)K_1(\tilde{\omega}_B \rho_0)}{\tilde{\omega}_A I_0(\tilde{\omega}_A \rho_0)K_1(\tilde{\omega}_B \rho_0) + \alpha \tilde{\omega}_B I_1(\tilde{\omega}_A \rho_0)K_0(\tilde{\omega}_B \rho_0)} & (\text{Caplets}) \\ \frac{1-\alpha}{\tilde{\omega}_A \coth \tilde{\omega}_A \xi_0 + \alpha \tilde{\omega}_B} & (\text{Stripes}) \end{cases} \quad (34)$$

Figure 4 The free energy difference Δf is extrapolated as a function of parameter α for caplet and stripe phases. The parameters are set such that $\tilde{\lambda} = 0.5$ and $\tilde{\sigma} = 0.02$.

Figure 5 Equilibrium domain size as a function of parameter α for caplet and stripe phases. The parameters are set such that $\tilde{\lambda} = 0.5$ and $\tilde{\sigma} = 0.02$.

Substituting these profiles into Eqs. 25a and 31a, the equilibrium domain size is obtained. The free energy difference between the caplet (or stripe) phase and the equilibrium flat phase may be written as

$$\Delta f = \begin{cases} -(1 - \alpha)\eta_0\rho_0 & (\text{Caplets}) \\ -(1 - \alpha)\eta_0 & (\text{Stripes}). \end{cases} \quad (35)$$

Figure 4 shows the relation between the free energy difference and the parameter α . Other independent dimensionless parameters are set as $\tilde{\lambda} = 0.5$ and $\tilde{\sigma} = 0.02$. We can easily find that the caplet phase is stable with respect to the striped one for $\alpha < 0.25$, while the stripe phase is unstable with respect to the flat one for $\alpha > 0.5$; there is a first-order transition between the caplet phase and the stripe phase for $\alpha = 0.25$.

In Figure 5, the domain size is expressed as a function of α in the dilute limit. The solid line denotes the stable phase. Caplets are stable for $\alpha = 0.25$, and stripes are stable for $0.25 < \alpha < 0.5$. For $\alpha > 0.5$, the stable state is a macroscopically phase-separated flat phase.

Figure 6 Phase diagram as a function of the A component area fraction ϕ and parameter α ; other parameters are set such that $\tilde{\lambda} = 0.5$ and $\tilde{\sigma} = 0.02$. The region below the solid line is the caplet phase, the region between the solid and dotted lines is the stripe phase, and that above the dotted line is the flat phase.

Finite concentration

For finite concentrations of two components, a regular array of monodisperse domains is assumed, each within cell dimensions determined by the concentration. We approximate the hexagonal Wigner-Seitz cell through a set of circular domains with equal area. The solutions are given by Eqs. 21–23 and 28–29, with corresponding domain size given by Eqs. 25a, 25b, and 31a, 31b, for a set of controlling parameters.

Figure 6 expresses the A component area fraction ϕ as a function of parameter α . Other independent dimensionless parameters are set at $\tilde{\lambda} = 0.5$ and $\tilde{\sigma} = 0.02$. With increasing parameter α there is a first-order transition from circular caplets to stripes and then from stripes to the flat phase. When $\alpha < 0.35$, there is also a transition from caplets to stripes and then to the flat phase with increasing ϕ . When $0.35 < \alpha < 0.5$, a transition from flat phase to stripes is found with decreasing ϕ .

Discussion

Gózdź and Gompper [23], and Harden and Mackintosh [24, 25] have performed a similar calculation in a different “slice” of parameter space. The former considered phases with different signs of spontaneous curvature and predicted a variety of budding, stripe and circular domains under weak tension. The latter studied phase behavior with just one spontaneous curvature and revealed a budding transformation from stable protruding circular domains to spherical buds with increasing line tension. It is difficult to compare their results directly with ours. In our model, we assume that the membrane is under weak surface and line tension, and find that the different bending rigidities of the lipid components may also induce the first-order transition between the caplet phase and the stripe phase.

The transition from caplets to stripes that occurs at small surface and line tension with increasing ratio of bending rigidity $\alpha = k_c^B/k_c^A$ and composition ϕ can be understood in simple physical terms. With increasing the ratio of bending rigidity, the difference of physical properties between the two components becomes less and less, and boundaries should become more mild. For stripes, this represents a smaller curvature on the boundary than for caplets. Thus, stripes are preferred at large α . Alternatively, the unit cell in stripe and caplet morphologies scales as $X_0 \sim 1/\phi$ and $R_0 \sim 1/\sqrt{\phi}$, respectively. With increasing ϕ , the constraints on the membrane profiles due to the shrinking unit cell boundaries become more costly in the caplet phase than the stripe phase, thereby favoring the stripe phase at large ϕ .

Our work shares some common features with previous theoretical studies. Undulating stripe and hexagonal phases in weakly segregated two-component membranes were first studied theoretically using a phenomenological coupling of local membrane composition and shape [32, 33]. These phases are analogous to the strongly segregated stripe and caplet phases discussed in this paper. Moreover, Yin *et al.* [34] have recently studied the equilibrium configurations of biomembranes with heterogeneous rigidities, and revealed that the rigidity gradient is an initial “drive force” that may destabilize the biomembrane and induce shape transformations. One of the post-bifurcation modes presented in [34] is qualitatively similar to our caplet mesophases.

We estimate the region of domain stability for the following values of the parameters in our model: $k_c^A = 25k_B T \approx 100 \text{ pN} \cdot \text{nm}$, $k_c^B = 5 \sim 10k_B T \approx 20 \sim 40 \text{ pN} \cdot \text{nm}$, $c_0^{-1} = 100 \text{ nm}$. The order of magnitude of the line tension σ may approach 10 pN [35]. When membrane rupture occurs, the surface tension λ is on the order of 10 pN/nm [36]. Here, we consider that the membrane is under weak tension, and choose $\lambda \approx 0.5 \times 10^{-2} \text{ pN/nm}$; then, the

dimensionless parameters $\tilde{\lambda} = 0.5$ and $\tilde{\sigma} = 0.02$ are set, which are in the range of parameter space described in reference [24]. Thus, we may find the caplet domains of 100 nm in size, as in [37], are stable for $\alpha = 0.2$ and stripe domains of 25 nm in size are stable for $\alpha = 0.4$.

Summary and Conclusions

In summary, the shapes and phase behaviors of two-component membranes of planar topology have been investigated within the framework of the curvature model. The physics of two-component membranes reveals new qualitative features, which are absent in pure membranes. First, a rich variety of stable phases has been discovered. These are caplet, stripe and macroscopically flat phases for two-component membranes. Second, the shape of the domain has been shown to be strongly influenced by the composition ϕ . Finally, first-order phase transitions between the caplet, stripe and flat phases are predicted with increasing bending rigidity ratio.

It should be noted that the present theory model only coincides qualitatively with some experimental results. Quantitative experiments are still necessary to confirm the reliability and correctness of the model.

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References

1. Singer, S.J., Nicolson, G.L.: The fluid mosaic model of the structure of cell membranes. *Science* **175**, 720–731 (1972)
2. Lipowsky, R., Sackmann, E.: *Handbook of Biological Physics*, vol.1. Elsevier, Amsterdam (1995)
3. Seifert, U.: Configurations of fluid membranes and vesicles. *Adv. Phys.* **46**, 13–137 (1997)
4. Ou-Yang, Z.-C., Liu, J.-X., Xie, Y.-Z.: *Geometric Methods in the Elastic Theory of Membranes in Liquid Crystal Phases*. World Scientific, Singapore (1999)
5. Veatch, S.L., Keller, S.L.: Organization in lipid membranes containing cholesterol. *Phys. Rev. Lett.* **89**, 2942–2950 (2002)
6. Gennis, R.B.: *Biomembranes*. Springer, Berlin (1989)
7. Gaus, K., Gratton, E., Kable, E.P.W., Jones, A.S., Gelissen, I., Kritharides, L., Jessup, W.: Visualizing lipid structure and raft domains in living cells with two-photon microscopy. *Proc. Natl. Acad. Sci. USA*. **100**, 15554–15559 (2003)
8. Rauch, C., Farge, E.: Endocytosis switch controlled by transmembrane osmotic pressure and phospholipid number asymmetry. *Biophys. J.* **78**, 3036–3047 (2000)
9. Veatch, S.L., Polozov, I.V., Gawrisch, K., Keller, S.L.: Liquid domains in vesicles investigated by NMR and fluorescence microscopy. *Biophys. J.* **86**, 2910–2922 (2004)
10. Leidy, C., Wolkers, W.F., Jorgensen, K., Mouritsen, O.G., Crowe, J.H.: Fabrication of nanometer-sized protein patterns using atomic force microscopy and selective immobilization. *Biophys. J.* **80**, 1891–1899 (2001)
11. Veatch, S.L., Keller, S.L.: Separation of liquid phases in giant vesicles of ternary mixtures of phospholipids and cholesterol. *Biophys. J.* **85**, 3074–3083 (2003)
12. Baumgart, T., Hess, S.T., Webb, W.W.: Imaging coexisting fluid domains in biomembrane models coupling curvature and line tension. *Nature* **425**, 821–824 (2003)
13. Lasic, D.D.: *Liposomes in Gene Delivery*. CRC Press, Boca Raton, FL (1997)
14. Lasic, D.D., Papahadjopoulos, D.: *Medical Applications of Liposomes*. Elsevier, Amsterdam (1998)
15. Sackmann, E.: Supported membranes: Scientific and practical applications. *Science* **271**, 43–48 (1996)
16. Keller, S.L., Pitcher, W.H., III, Huestis, W.H., McConnell, H.M.: Red blood cell lipids form immiscible liquids. *Phys. Rev. Lett.* **81**, 5019–5022 (1998)

17. Kinnunen, P.K.J.: On the principles of functional ordering in biological membranes. *Chem. Phys. Lipids* **57**, 375–399 (1991)
18. Edidin, M.: Lipid microdomains in cell surface membranes. *Curr. Opin. Struct. Biol.* **7**, 528–532 (1997)
19. Taniguchi, T., Kawakatsu, K., Andelman, D., Kawakatsu, T.: Phase transitions and shapes of two component membranes and vesicles II; weak segregation limit. *J. Phys. II France* **4**, 1333–1362 (1994)
20. Jülicher, F., Lipowsky, R.: Domain induced budding of vesicles. *Phys. Rev. Lett.* **70**, 2964–2967 (1993)
21. Jülicher, F., Lipowsky, R.: Shape transformation of vesicles with intramembrane domains. *Phys. Rev. E* **53**, 2670–2683 (1996)
22. Gózdź, W.T., Gompper, G.: Phase behavior of two component membranes. *Colloids Surf. A: Physicochem. Eng. Aspects* **208**, 241–251 (2002)
23. Gózdź, W.T., Gompper, G.: Shape transformation of two component membranes under weak tension. *Europhys. Lett.* **55**, 587–593 (2001)
24. Harden, J.L., MacKintosh, F.C., Olmsted, P.D.: Budding and domain shape transformations in mixed lipid films and bilayer membranes. *Phys. Rev. E* **72**, (2005)
25. Harden, J.L., MacKintosh, J.L.: Shape transformations of domains in mixed fluid films and bilayer membranes. *Europhys. Lett.* **28**, 495–500 (1994)
26. Gózdź, W.T., Gompper, G.: Composition driven shape transformation of membranes of complex topology. *Phys. Rev. Lett.* **80**, 4213–4216 (1998)
27. Gózdź, W.T., Gompper, G.: Shapes and shape transformations of two-component membranes of complex topology. *Phys. Rev. E* **59**, 4305–4316 (1999)
28. Diamant, H., Witten, T., Gopal, A., Lee, K.: Unstable topography of biphasic surfactant monolayers. *Europhys. Lett.* **55**, 171–177 (2000)
29. Capovilla, R., Guven, J., Santiago, J.A.: Lipid membranes with an edge. *Phys. Rev. E* **66**, (2002)
30. Capovilla, R., Guven, J.: Stresses in lipid membranes. *J. Phys. A: Math Gen.* **35**, 6233–6247 (2002)
31. Abramowitz, M., Stegun, I.A.: *Handbook of Mathematical Functions*. Dover, New York (1972)
32. Leibler, S.: Curvature instability in membranes. *Journal de Physique* **47**, 507–516 (1986)
33. Leibler, S., Andelman, D.: Ordered and curved meso-structures in membranes and amphiphilic films. *Journal de Physique* **48**, 2013–2018 (1987)
34. Yin, Y., Chen, Y., Ni, D., Shi, H., Fan, Q.: Shape equations and curvature bifurcations induced by inhomogeneous rigidities in cell membranes. *J. Biomech.* **38**, 1433–1440 (2005)
35. Lipowsky, R., Dimova, R.: Domains in membranes and vesicles. *J. Phys.: Condens. Matter* **15**, S31–S45 (2005)
36. Boal, D.: *Mechanics of the Cell*. Cambridge University Press, Cambridge, England (2002)
37. Backmark, T.R., Elender, G., Lasic, D.D., Sackmann, E.: Conformational transitions of mixed monolayers of phospholipids and poly (ethylene oxide) lipopolymers and interaction forces with sol-surfaces. *Langmuir* **11**, 3975–3987 (1995)