Coupling of Size and Shape Equilibration in Lipid Monolayer Domains

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The time-dependent dynamics of domains formed in lipid monolayers has been investigated in the case of coexisting lipid phases of different molecular areas. In general, an applied nonequilibrium pressure gives rise to both size and shape changes of domains. In this work, it is shown how the two effects can be superposed, leading to transitions from circular domains to other shapes (such as harmonic modes $n = 2, 3, 4...$) depending on the value of the applied excess pressure. As the excess pressure changes, the symmetry numbers of the transitions change. The description of the transient states for the growth of circular domains allows one to predict the time for the appearance of the different n-fold distortions. It is shown how in principle a sequence of applied pressures can be used to produce domains with shapes derived from a given distortion symmetry, such as $n = 2$.

1. Introduction

Coexisting thermodynamic phases of lipid molecules at the air−water interface often exhibit discrete domains with a variety of sizes and shapes. These domains can be observed using epifluorescence microscopy.[1,2] Significant information on the phase behavior of lipids in monolayers can be obtained from observations of the properties of these domains as they depend on pressure and composition. While equilibrium properties of domains are relatively well-known from a theoretical point of view, the kinetics of equilibration have only been studied recently. In multicomponent systems, equilibration of domain size is limited by rates of molecular diffusion in the idealized case where no changes of pressure or molecular area is involved.[3] In the case of liquid domains, equilibration of domain shape can also limited by hydrodynamic flow involving drag in the aqueous subphase.[4] In the present work we first consider the rather hypothetical case of two incompressible liquids composed of one substance, where a circular central domain increases or decreases in size due to flow of the second liquid to or away from the central domain. In the Discussion we indicate how these calculations should be approximately applicable to coexisting liquids with multiple components, and to gas domains surrounded by liquid.

Sizes and Shapes of Domains. Figure 1 shows an idealized model that is used for calculating domain size equilibration. The model is relevant to experiments in which domain size change is brought about by monolayer compression or expansion. This figure depicts a single circular isotropic domain of black phase (B) surrounded by a white background phase (W). The average molecular areas in the two phases are fixed at the ratio: $\alpha = A_W/A_B$. The change in size of the circular domain involves fluid flow in the monolayer as well as in the subphase. In Figure 1 it is imagined that the trough is circular and can be expanded or contracted in diameter so as to maintain a constant pressure p_B at the trough edge. For clarity in the calculations it is imagined that increasing pressure results in an increase of

domain size, whereas for the gas domains discussed later decreases in pressure lead to increases in size of the central domain.

Figure 2 shows shape changes that might in principle accompany the increase in size of a domain. The domains of smaller radius grow in size until they reach certain critical radii: $e^{1/3}R_q, e^{2/3}R_q$, etc. When the domain radius reaches and exceeds the radius $e^{1/3}R_q$, it is then unstable with respect to the 2-fold distortion sketched in this figure. When the domain radius reaches and exceeds $e^{2/3}R_q$, it remains unstable with respect to 2-fold distortions and also becomes unstable with respect to 3-fold distortions, and so forth.[6,7]

Previous work has described both experimentally and theoretically the consequences of preparing a single circular domain under conditions where the radius exceeds one or more of the critical radii. Under these circumstances it is found experimentally that a single harmonic distortion forms at early times.[8,9] In these experiments the nonequilibrium domain sizes were prepared using an electric field, which was then subsequently removed to allow the domain to change shape. However, it is clear from qualitative considerations that in the case where monolayer compression is used to bring about size changes, one must consider the relative values of two rates, the rate of domain growth, and the rate of shape change. As discussed below, the rate of domain size change is determined by the applied pressure on the monolayer, and the rate of shape change is determined by the domain size.

The Stable Equilibrium Radius. For an isolated domain the radius of stable equilibrium is given by[6]

$$R_q = (e^3 \Delta/8) \exp(\lambda/m^2) \tag{1}$$

where λ is the line tension between the two phases, and m is the difference in dipole density between the two phases. The parameter Δ is an electrostatic dipole−dipole cutoff distance of the order of magnitude of nearest neighbor intermolecular distances. This is a stable equilibrium radius in the sense that a large number of weekly interacting domains should reach this radius under equilibrium conditions. The system is stable with respect to variations in domain radius as well as domain number.

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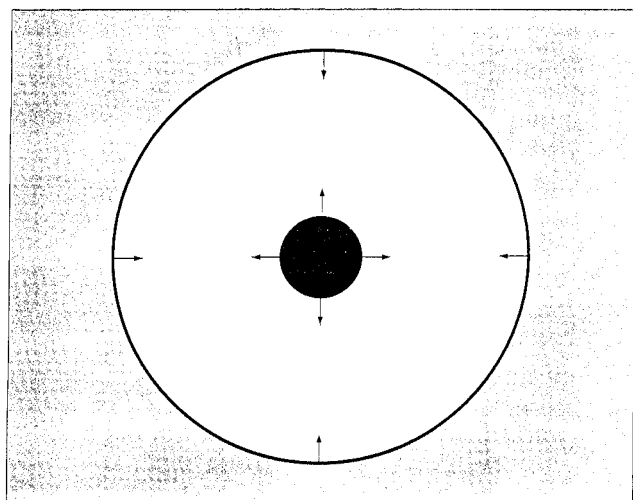
Figure 1. Idealized model for calculating domain size equilibration in lipid monolayers. The black circle represents a single circular domain of black phase (B) surrounded by a less dense white phase (W) of the same substance. If the size of the domain increases (outwardly directed arrows), there is monolayer flow toward the central domain (inwardly directed arrows). The trough is imagined to be circular and can expand or contract so as to maintain a constant pressure at the trough edge.
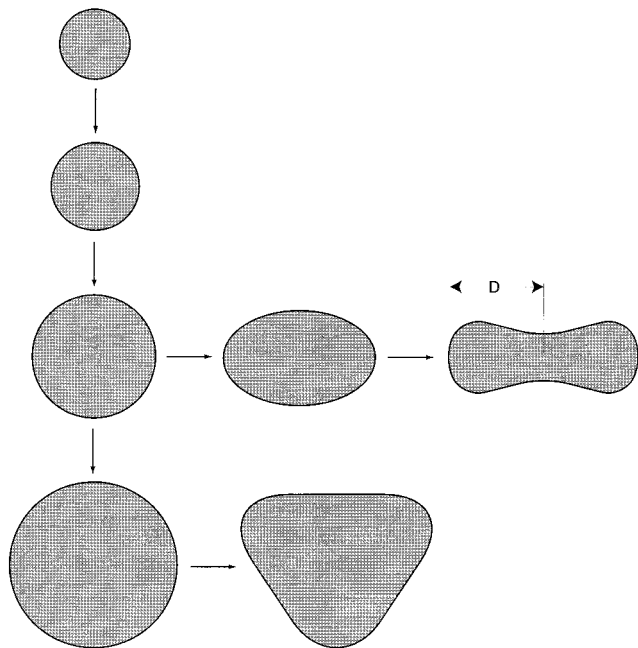

Figure 2. Shape changes during the growth of a circular domain. When the small domain of radius R exceeds the critical radius $e^{1/3}R_q$, it is unstable with respect to 2-fold distortions. When the circular domain radius exceeds $e^{2/3}R_q$, it continues to be unstable to 2-fold distortions and is also unstable to 3-fold distortions. $D(t)$ is defined as the total distance from the center of the circular domain to the point of maximum possible distortion (eq 12).

These conditions determine a stable equilibrium pressure p_{eq}^m. These values for the radius and pressure refer to a state of a domain termed *absolutely stable*. A circular domain can be *metastable* with respect to small changes in domain area for many values of the domain radius, at different pressures. Domains that are metastable in this sense are simply termed *stable* in the following.

Domain Growth Rate. For a domain in a monolayer with an externally applied nonequilibrium pressure, it is possible to calculate the rate of change of the radius. Figure 3 shows the
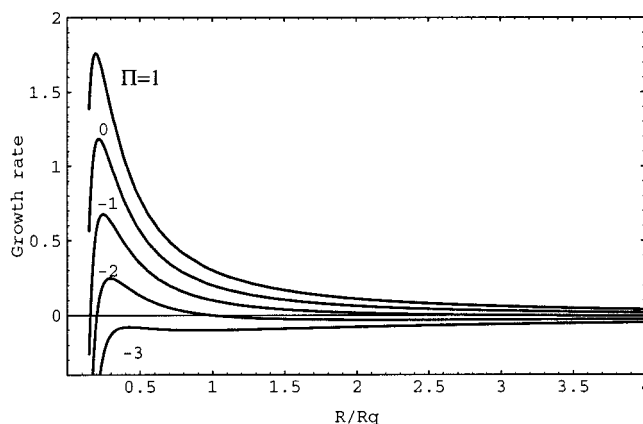

Figure 3. Domain growth rate as a function of radius and normalized pressure Π. The domain radius is scaled relative to the stable equilibrium radius given by eq 1. The scaled pressure is proportional to the difference between the applied monolayer pressure $p(B)$ and the equilibrium pressure defined in eq 2. The smaller values of R/R_q at which the growth rate is zero (called R_u/R_q) are points of unstable equilibrium, while the larger values (called R_s/R_q) correspond to states of metastable equilibrium, except $R/R_q = 1$ which is a state of stable equilibrium. Time is given in units of $|\tau_0|$, given in eq 4.

circular domain growth for different values of the applied normalized excess pressure Π defined as

$$\Pi = \frac{[p^m(B) - p_o^m](a - 1)R_q}{m^2} \tag{2}$$

Here $p^m(B)$ is the applied pressure at the position of the domain barrier $r = B$, and p_o^m is the equilibrium pressure of a domain of very large radius $(R \to \infty)$.[4] For some values of the radius, R_u and R_s, the growth rate is zero. For each value of the normalized excess pressure Π, the radius R_u is unstable (small perturbations of the radius will grow), while the radius R_s is stable (small perturbations will decay). For positive values of the normalized excess pressure, the radius evolves to infinity: there is no stable value R_s.

The time evolution of the radius of a circular domain can be obtained by solving the following nonlinear evolution equation (eq 36 of ref 4 taking $R(t)/R_q$ as the time dependent variable).

$$\frac{dR(t)/R_q}{dt} = t_0^{-1}\frac{\Pi(R(t)/R_q) + \ln(R(t)/R_q) + 2}{(\ln(R(t)/R_q) + \ln(8R_q/d))(R(t)/R_q)^2} \tag{3}$$

$$\tau_0^{-1} = \frac{\pi m^2}{2(a - 1)hR_q^2} \tag{4}$$

η is the viscosity of the aqueous subphase. The quantity δ is a hydrodynamic cutoff assumed to be of the order of molecular dimensions. The numerical calculations let $\boldsymbol{ln}(8R_q/\delta) = 10$, where it is assumed that δ is of the order of molecular dimensions. The time constant τ_0 is of the order of 1 s using typical order-of-magnitudes (cgs-esu units), $m \approx 10^{-4}$, $(\alpha - 1) \approx 1$, $\eta \approx 0.01$ and $R_q \approx 10^{-3}$. Figure 4 represents different solutions of eq 3. If the initial radius at $t = 0$ is between R_u and R_s, the instability grows toward R_s (new stable value of the radius). This value of R_s depends on the normalized excess pressure Π. Several initial conditions are considered for each value of the pressure. It is shown that, for every initial condition, the radius increases, and slowly approaches the stationary radius (Figure 4a). For a given pressure, different initial conditions
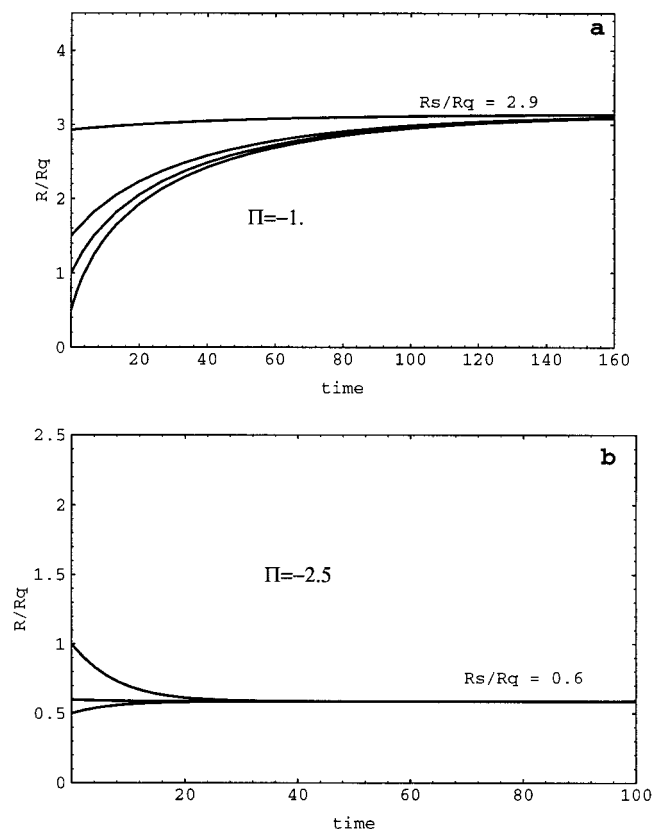
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Figure 4. Time evolution of radii of circular domains for different initial conditions. The normalized excess pressure Π is defined in eq 2. (a) $\Pi = -1$ and three different initial conditions for R. The radius increases rapidly at first and then more slowly toward the stationary value $R_s/R_q = 2.9$. (b) $\Pi = -2.5$. The radius increases (decreases) for initial values below (above) the stationary value $R_s/R_q = 0.6$. Time is in units of $|\tau_0|$, given in eq 4.
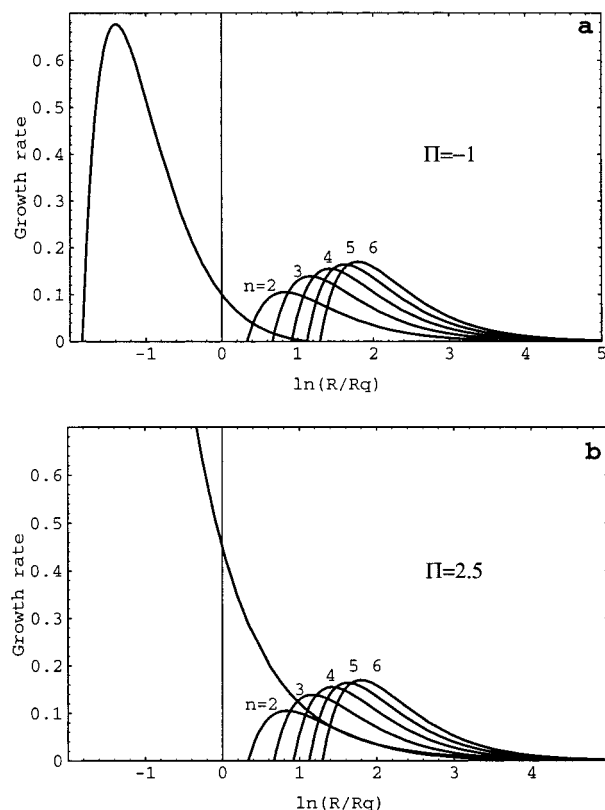

Figure 5. Superposition of size and shape growth rates. A circular domain grows at rate $1/\tau(R)$ and changes shape at the rates for the different n harmonic modes $1/\tau_n$. The growth rate for the harmonic modes is independent of the pressure Π. The different radii R_n are defined as the radii at which the circular domain become unstable to harmonic distortion n. For $\Pi = -1$, Figure 5a shows a first intersection between the growth rate for circular domain and the growth rate for mode $n = 2$ at $1/\tau(R) = 1/\tau_2$. For increasing values of R, $1/\tau(R) < 1/\tau_2$. For $\Pi = 2.5$, Figure 5b shows another scenario where the first intersection is for $1/\tau(R) = 1/\tau_3$. For increasing values of R, $1/\tau(R) < 1/\tau_3$.

converge to the same stationary state. If the initial radius is equal to R_s, the system is stable (horizontal line). If the initial radius is larger than R_s, the radius decreases (Figure 4b).

Equation 3 was derived for the case where the central domain is an isotropic solid, or an incompressible liquid, where there is no flow within the domain.[4] With sticking boundary conditions there is accordingly a discontinuity in the aqueous flow field just under the monolayer, and this requires the use of the cutoff parameter δ that appears in this eq 3. If the central domain is a "gas", then there is no such restriction on the aqueous flow field at the monolayer gas−liquid boundary. Even so, the hydrodynamic flows in the two cases are likely to be similar, at least in the approximation used to derive eq 3.

Rates of Domain Shape Change. With increasing circular radius the domain becomes unstable with respect to shape distortions. Indeed, it has been shown that there is a time-dependent instability of nearly circular lipid domains to harmonic modes ($n = 2, 3, 4$, etc).[9] Proper treatment of this instability requires a description of the interplay between viscous dissipation, line tension, and electrostatic forces. As the domain radius increases, it has been predicted (and observed experimentally) that the symmetry number n of the most rapidly growing mode increases.[8,9] This means that larger domains tend to produce shapes characterized by larger n. The two types of dynamic change can be superposed. Figure 5 represents this superposition for two different values of the normalized pressure.

The respective values of R_n have been given previously[6] and are

$$R_n = R_q \exp(x_n) \tag{5}$$

where $x_n = 1/3, 2/3$, and $2.76/3$, etc., respectively, for $n = 2, 3$, and 4, etc.

When $\ln(R/R_q) \geq 1/3$, the circular domain is unstable to a 2-fold distortion. At larger values of $\ln(R/R_q)$, the circular domain is unstable with respect to higher harmonic distortions. So we can conclude that the symmetry number of the observed first distortion will likely depend on the value of Π. The growth rate of the nth-harmonic mode of a nearly circular domain is given by (eq 3.7 of ref 9 taking R/R_q as the variable):

$$1/t_n = \frac{4m^2}{\pi\eta R_q{}^2} \frac{n^2(n^2 - 1)(\ln(R/R_q) - \ln(R_n/R_q))}{(2n + 1)(2n - 1)(R/R_q)^2} \tag{6}$$

The quantity $4m^2/\pi\eta R_q{}^2$ is equivalent to the inverse time constant $\tau_0{}^{-1}$ given by eq 4 taking the factor $\pi/2 \approx 4/\pi$ and $|a - 1| \approx 1$. Equation 6 is only valid for small perturbations ϵ_n of the radius of the circular domain. This equation was derived in a linear stability analysis for $\epsilon_n(t) \approx \exp(t/\tau_n)$, while eq 3 is valid for any finite value of the radius. Two remarks have to be made here: first, the intrinsic rate of growth of the harmonic modes is independent of the applied pressure. Second, the

evolution of each of the harmonic modes from some unstable initial state is treated as taking place at constant domain area.

Consider Figure 5a. Starting, for instance, from a value of the radius so that $\ln(R/R_q) = -1.5$, the domain grows rapidly, and then more slowly until at approximately $\ln(R/R_q) = 1$ the circular domain stops growing. However, before this condition of no-growth is realized, the value $\ln(R/R_q) = \frac{1}{3}$ for the instability of a circular domain with respect to 2-fold distortion is reached. Thus the domain starts to have a 2-fold distortion and continues to grow. To the extent that the distortion remains small, the two effects can be superimposed (the respective velocity fields are additive). When $1/\tau_2 > 1/\tau(R)$, the 2-fold distortion is the dominant mode. The situation in Figure 5b is quite different. The 3-fold distortion starts when $\ln(R/R_q) = 2/3$, and there is a superposition of two modes ($n = 2$ and $n = 3$).

The derivation of eq 6 assumes that the two phases involved are both liquid. The calculation is not valid for a viscous solid. The rate in eq 6 is likely to be approximately valid for a gaseous central domain as the hydrodynamic flows in the aqueous subphase must be similar.

Combined Growth and Shape Change. To follow the time evolution of the coupled process, we considered that eq 6 can be expressed as $(1/(R_n/R))\mathrm{d}(R_n/R_q)/\mathrm{d}t$ at small times. The radius R_n/R_q for the evolution of the nth mode is defined as follows:

$$R_n/R_q = (1 + \epsilon_n(t)\cos n\phi)\exp(x_n) \qquad (7)$$

where $\epsilon_n(t)$ is a small dimensionless parameter $\epsilon_n(t) < 1$, and ϕ the azimuthal angle ($\phi = 0$ for the direction of maximal elongation). So for $n = 2$, the distortion will grow at $\phi = 0$ and decay at $\phi = \pi/2$. For small perturbations around the circular shape, the infinitesimal change in (R_n/R_q) is[9]

$$\frac{1}{\epsilon_n}\,\mathrm{d}\epsilon_n/\mathrm{d}t = \frac{1}{\tau_n} \qquad (8)$$

with $1/\tau_n$ given by eq 6 where $R(t)/R_q$ has been replaced by the solution of eq 3. Equation 8 has an exponential solution:

$$\epsilon_n(t) = \epsilon_n(0)\exp((t - t_n)/\tau_n) \qquad (9)$$

where t_n is the time at which the nth harmonic begins to grow. Indeed, the onset of the harmonic modes is not at $t = 0$, but at time t_n at which the radius R/R_q for the growth of the circular domain is at least equal to R_2/R_q for $n = 2$, R_3/R_q for $n = 3$, etc.

If we assume that the domain has small shape fluctuations that are in thermal equilibrium, then the value of $\epsilon_n(0)$ can be estimated by equating the energy[9] of a small distortion $E(\epsilon_n)$ to $kT/2$:

$$E(\epsilon_n) = \frac{1}{2}R^2\epsilon^2\left[\frac{\pi m^2(n^2-1)}{R}\ln\left(\frac{R_n}{R}\right)\right]$$

$$\epsilon_n(0) = \sqrt{\frac{kT}{\pi m^2(n^2-1)R_{\mathrm{init}}\ln(R_n/R_{\mathrm{init}})}} \qquad (10)$$

As long as $R < R_n$, for example, by a factor of 2 or more, the $\epsilon_n(0)$ values are estimated to be about 1%. There is a series of $\epsilon_2(t - t_2)$, $\epsilon_3(t - t_3)$, etc. For example, we have

$$\epsilon_3(0)/\epsilon_2(0) = \sqrt{3/8} \qquad (11)$$

The total distance $D(t)$ shown in Figure 2 from the center of the domain to the point of maximum possible distortion is given

by

$$\frac{D(t)}{R_q} = \frac{R(t)}{R_q}\left(1 + \sum_{n=2}\epsilon_n(t)\right) \qquad (12)$$

In Figure 6 we have represented the superposition of increase of domain radius and domain distortion, for different values of the normalized pressure Π. Figure 6a is for $\Pi = -1$ and initial condition $R(0)/R_q = 0.5$. As the radius of the circular domain increases, at time t_2 when the system first becomes unstable to a 2-fold distortion, we have from eq 6 that $1/\tau_2 = 0$. As time increases, $1/\tau_2$ increases, thus the exponent in eq 9 increases more rapidly than linearly. When $1/\tau_2 > 1/\tau(R)$, the 2-fold distortion becomes even more pronounced as time proceeds. Figure 6b corresponds to a positive value of the normalized excess pressure ($\Pi = 2.5$). As the radius of the circular domain increases, the 2-fold distortion starts at $t = t_2$, but increases more slowly, so that the system develops also a 3-fold distortion at time $t = t_3$ (as expected in Figure 5b) with a superposition of the different modes according to eq 12. The description of the transient states allows one to predict the time t_n for the appearance of the different n-fold distortions.

Discussion

Unfortunately there is no known monolayer system that conforms perfectly to the specific approximations used in our model calculations. Binary mixtures of lipids that give coexisting liquid phases show the pressure-dependent shape transitions described here, but pressure changes also produce composition changes that potentially affect line tension and dipole density.[8,11] However along steep binodal boundaries of the two-liquid pressure−area phase diagrams the composition changes associated with domain area changes are minimal, and an approximate equality of the chemical potentials near the domain boundary can be assumed, at least for slow compression or expansion of the monolayer.[8] In these cases decreasing the pressure results in an increase in domain area.

The liquid−gas two-phase system is also likely to conform approximately to our calculations. In this case the aqueous hydrodynamic flow in the subphase below the gas phase is not identical to that for a liquid domain (with sticking boundary conditions at the domain-water interface), but should be similar. Here local equilibrium at the gas−liquid interface is assumed. Again, decreasing monolayer pressure results in an increase in domain area.

The largest uncertainty in calculations of this type is the free energy surface for domain shapes, and the possibility of abrupt shape transitions not considered above. This can be illustrated by unpublished work from this laboratory on gas domains in a liquid monolayer composed dimyristoylphosphatidylcholine and 10 mol % gramacidin are shown in Figure 7. It will be seen that on domain expansion small circular domains expand, show large thermal fluctuations, and shape transitions to "dogbone" shapes that have 2-fold symmetry. Under these experimental conditions the domain growth rate is low and thermal fluctuations are superimposed on the domain shape throughout the increase of domain size. The large amplitude of these fluctuations is likely related to the double potential minimum surface for 2-fold distortions for domain radii $R < e^{1/3}R_q$.[10] The "first-order transition" suggested by these potential surface calculations is sometimes captured by apparent jumps in domain shape, from largely circular to dogbone. Note the domain in the lower right-hand side of Figure 7. It is possible that this transition is thermally excited for domain radii below radius corresponding
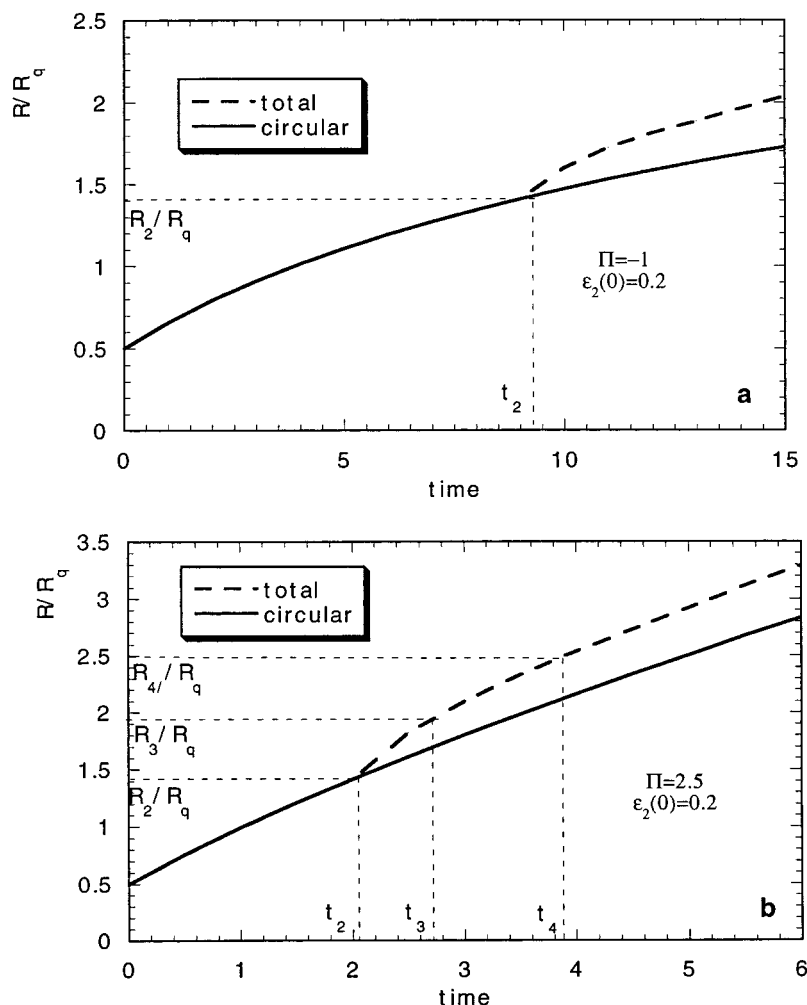
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Figure 6. Time evolution of the radius of a circular domain $R(t)/R_q$ and of the total distance $D(t)/R_q$ from the center of the domain to the point of maximum possible distortion. The radius R_n/R_q for the evolution of the nth mode is defined as $R_n/R_q = (1 + \epsilon_n(t) \cos n\phi) \exp(x_n)$ where $\epsilon_n(t)$ is a small perturbation and $\phi = 0$ for the direction of maximal elongation. In a, $\Pi = -1$ and initial condition $R(0)/R_q = 0.5$. As the radius of the circular domain increases, it reaches the condition $R(t)/R_q = R_2/R_q$ and the mode $n = 2$ superposes on the circular domain. In 6b, $\Pi = 2.5$ and the initial condition is $R(0)/R_q = 0.5$. The radius of the circular domain increases rapidly. The system overcomes the threshold value $R(t)/R_q = R_2/R_q$ and develops a 3-fold distortion at $R(t)/R_q = R_3/R_q$.

to the 2-fold instability. The increase in area of the dogbones and their mutual repulsions ultimately leads to the formation of a stripe phase.

The normalized monolayer pressures used in the above calculations shown are very small, and correspond to experimental monolayer pressure differences of the order of 10^{-5} dyne/cm. Under these circumstances the 2-fold symmetry distortion is dominant, leading ultimately to the stripe phase on continuing increase of domain size. Many published experiments dealing with lipid domains have not been carried out at such low pressure differentials; rather a much higher pressure differential is applied for a limited time, resulting in the formation of domains having many branches, corresponding to the initiation of the higher harmonic modes.[1,2] However, it is seen that in principle domains with a given *n*-fold distortion might be prepared experimentally by a sequence of pressure changes that prepare a domain with a specific radius before the harmonic shape changes are able to develop.

The change of shape discussed here can be considered to be a bifurcation, but in an extended sense. The patterns of the *n*-fold harmonic distortion appear when the circular domains become unstable with respect to small fluctuations, as in standard bifurcation analysis.[12] But the values of *R* at which the instability begins to grow are not stationary solutions of the dynamic

equation (eq 3). The transition described here depends on an *indirect* bifurcation parameter, the normalized excess pressure Π. Indeed, the circular domains are unstable with respect to small perturbations, but the bifurcation to a new shape depends on the value of the applied pressure, which controls the size of the circular domain. So in principle, a sequence of applied pressures can be used to produce domains of different shapes.

This work is restricted to small harmonic distortions. It is known experimentally in the case of liquid lipid domains that after these early distortions the domains assume quite complex shapes.[8] However these complex shapes often have a topology that permits one to identify a single initial harmonic symmetry number. Some previous computer simulations already include calculations of the energy state of domains in lipid monolayers with finite distortions from circular symmetry.[10,13] Related phenomena are well-known in the case of films of ferrofluids and superconductors[14−16] where the theory of these more complex shapes is well developed. In the case of monolayers, however, extension of the theory to the fully nonlinear regime is likely to be difficult because of the involvement of the subphase hydrodynamics.
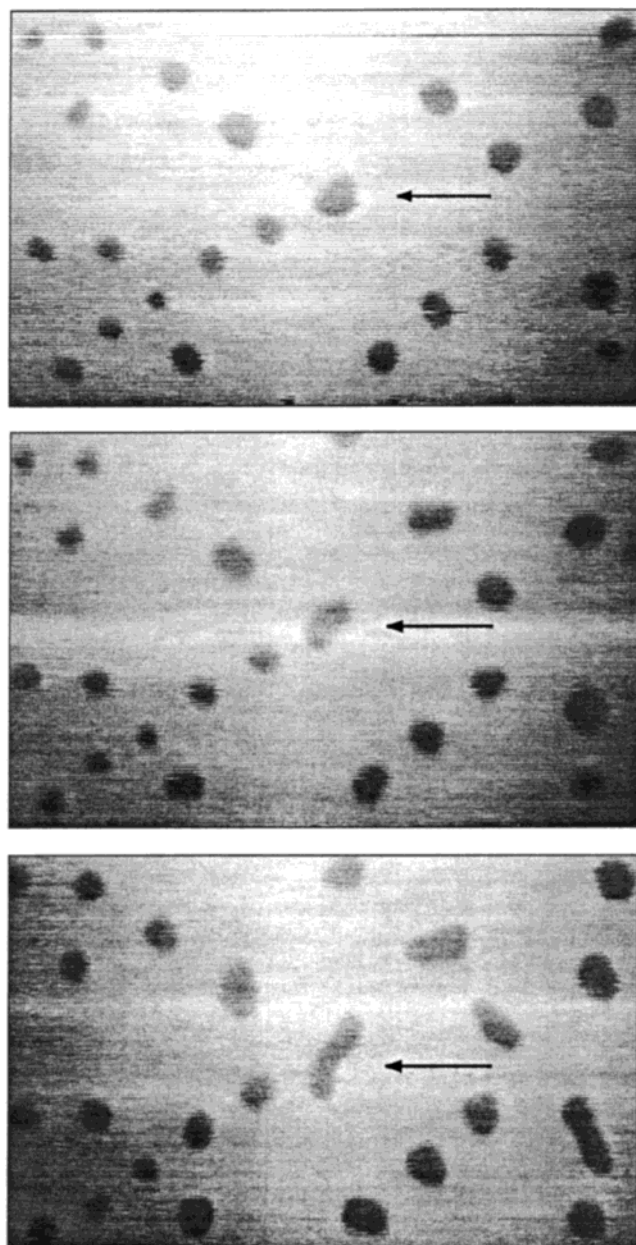
Figure 7. Gas domains (black) in a liquid monolayer (white) of dimyristoyl phosphatidyl−choline containing 10 mol % gramacidin. The three micrographs are taken at successive times (time interval is 10 s). It is seen that small circular domains expand (arrow in top figure), show large thermal fluctuations and finally shape transitions to dogbone shapes (arrow in bottom figure). First-order transitions are sometimes observed in the same experiment by apparent jumps in domain shape, from largely circular to dogbone (lower righthand side of the figure). The gramacidin reduces the line tension and enables the shape changes to be seen when the area fraction of gas phase is relatively small. The arrows correspond to approximately 30 microns.

S.L. Keller for helpful discussions concerning the experiments.

It is a pleasure to acknowledge that the unpublished data shown in Figure 7 were obtained by K.Y.E. Lee and Jurgen Klingler in this laboratory in 1992.

Appendix

Due to typographical errors, the section on gas phase domains in McConnell and De Koker[5] is garbled. A simple abbreviated treatment of the problem is given below.

Since the density of lipid molecules in a gas phase domain is doubtless very small, the dipole density of the gas phase domain is essentially the same as that of the air−water interface, and is thus constant and substantially independent of any variations of gas phase pressure or domain size. The surrounding liquid phase is assumed incompressible, and its dipole density is likewise constant. The discussion of the equilibrium and hydrodynamic properties of the gas phase domain can then be simplified by adding a constant, hypothetical uniform dipole density over the entire system so that the dipole density in the surrounding liquid phase is canceled, and the only remaining dipole density is that in the gas phase region, where the dipole density is the dipole density difference m. Since the dipole density in the liquid phase is thus effectively zero, at equilibrium there is no effect of a pressure gradient in the liquid phase. The equilibrium pressure for a domain of radius R is

$$p^m = p_0^m + (\alpha - 1)^{-1}(m^2/R)\ln(R/e^2 R_{eq}) \qquad (13)$$

Here R is the equilibrium radius of a domain when the pressure is p^m. Due to the low density of the gas phase, $\alpha \approx 0$. In using the hydrodynamic calculation of De Koker and McConnell[4] it is assumed that the pressure in the vicinity of the domain boundary is the equilibrium pressure. (p_0^m is thus the equilibrium vapor pressure of a domain of infinite radius.)

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