

Hydrodynamics of Domain Size Equilibration in Monolayers

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Coexisting thermodynamic phases of lipid molecules at the air–water interface often exhibit microscopically observable domains with a variety of sizes and shapes. The size and shape equilibration of these domains generally involve fluid flow in the monolayer as well as in the aqueous subphase. The present work treats the problem of the rate of size equilibration of a circular solid domain surrounded by a liquid composed of the same substance. The pressure at large distances from the domain is maintained constant, so that there is monolayer flow toward or away from the central domain. The central domain accordingly increases or decreases in size until a state of stable or metastable equilibrium is reached. Calculated rates of domain size change are discussed in terms of different experimental conditions, including applied electric fields.

Introduction

Domains of coexisting phases in lipid monolayers at the air–water interface can be observed using epifluorescence or Brewster-angle microscopy.^{1,2} Although theories of the equilibrium sizes and shapes of these domains have been extensively developed, the understanding of the rates of size and shape equilibration has only been the subject of recent work. These rate problems, in general, involve monolayer and subphase fluid mechanics. For example, it has been shown that the kinetics of shape changes of liquid domains are governed by the hydrodynamic drag of the aqueous subphase.³ The times required for shape equilibration are relatively short, on the order of seconds or a few minutes. On the other hand, the times required for spontaneous domain size change are often found to be very long, calling into question whether these domains ever reach equilibrium sizes. In the present work, we consider the role that subphase flow plays in limiting the rate of domain size equilibration.

Previous work has described the rate of size equilibration of a circular lipid domain for the case of a two-component mixture in which the equilibration rate is limited by the interdiffusion of the two lipid molecules.⁴ This work used the simplifying assumption that the two molecular species have equal surface areas. In general, however, size equilibration of lipid domains involves hydrodynamic flow. That is, domain size change between two coexisting monolayer phases of different molar areas is accompanied by macroscopic hydrodynamic flow. The question is whether this macroscopic hydrodynamic flow determines the rates of domain size equilibration seen experimentally. As will be seen in the following discussion, the hydrodynamic problem treated here involves a mathematical singularity along the domain boundary. This is due to the area change in the monolayer arising from the phase change. Outside the domain boundary there is subphase flow just under the monolayer due to monolayer flow. Inside the boundary just under the central domain there is no subphase flow. This situation can potentially produce a special retardation of the monolayer flow. A related monolayer hydrodynamic problem has been treated in great detail by Jensen and Halpern.⁵ Their approach is applicable to the calculation of the rate of equilibration of the size of liquid- and gas-phase domains, where there is little retardation of the subphase flow immediately below the gas phase.⁶

The Model. Consider a single circular domain of a dense *black* phase surrounded by a less dense *white* background phase. Both phases are composed of the same chemical substance, for which the molar areas satisfy the condition $A_B < A_W$. Both phases are treated as incompressible. The two-dimensional monolayer pressure at a very large distance R from the black domain is maintained constant, equal to $p^m(R)$. This distance is very large compared to the radius R of the circular domain, $R \gg R$, see Figure 1. An imaginary device maintains this pressure constant by making small changes in the radius R . As discussed later, it is assumed that the pressure in the immediate vicinity of the circular domain is equal to the equilibrium pressure p_{eq}^m of a lipid domain of radius R . The model also assumes that the monolayer flow is slow and nearly steady state.

When $p^m(R) > p_{eq}^m$, there is flow in the white phase toward the black domain and the radius R of the domain increases. When $p^m(R) < p_{eq}^m$, the flow in the white phase is away from the black domain and the domain decreases in size. (The subscript eq refers to equilibrium.) Our problem is to calculate the rate of change of the domain radius under these conditions. The “pressure” p^m used here is an “equivalent pressure”. As discussed later, in the white phase this equivalent pressure is $p^m = p^{m*} - m_W E_z$ where p^{m*} is the true pressure, E_z is any electric field acting perpendicular to the monolayer, and m_W is the molecular dipole density in the white phase. This equivalent pressure terminology is used to keep the notation as simple as possible. For an incompressible liquid, this equivalent pressure is proportional to the chemical potential.

Monolayer Hydrodynamics. Let dn moles of the white phase convert into black phase. The domain area grows by $A_B dn$. At the same time, the total amount of white phase shrinks by $A_W dn$. The net change in total area is therefore $(A_B - A_W)dn < 0$. This area change can only occur if there is a net inward flow of the white phase. Because of the circular symmetry, all the flow in the monolayer is radial, i.e., $u_{\theta m}(r, \theta) = 0$, $u_r^m(r, \theta) = u_r^m(r)$. At the domain edge

$$2\pi R U \, dt = (A_B - A_W)dn \quad (1)$$

where $U = u_r^m(R)$, the flow velocity of the white phase at this edge, $r = R$. Note that the flow is inward, $U = u_r^m(R) < 0$, if $A_B < A_W$. Since the area change of the black domain is related to the change of the domain radius

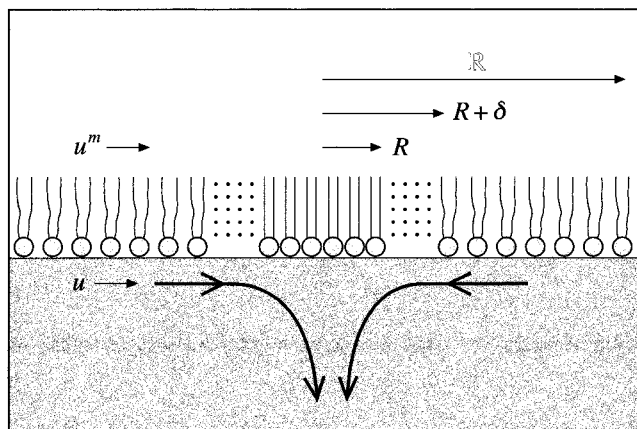


Figure 1. Schematic representation of monolayer and subphase fluid flow. Distances are such that $R \gg R \gg \delta$, where R is the radius of the (black) solid lipid phase domain and R is the radius of a hypothetical circular barrier of a monolayer trough. The barrier radius R gradually decreases or increases so as to cause the solid-phase domain to increase or decrease in radius. The associated fluid-flow velocities in the monolayer and subphase are denoted u^m and u . The parameter δ is a cutoff distance between R and $R + \delta$. This region surrounding the central domain is assumed to be of molecular dimensions in which macroscopic hydrodynamic equations are not applicable. It is further assumed that the two-dimensional pressure in the monolayer liquid at $R + \delta$ is equal to the equilibrium pressure p_{eq}^m of a domain of radius R , as given in eq 24c.

$$2\pi R \, dR = A_B \, dn \quad (2)$$

there is a relationship between the rate of change of the domain radius and the velocity of the white phase at the domain boundary, namely

$$\begin{aligned} \frac{dR(t)}{dt} &= U \frac{A_B}{A_B - A_W} \\ &= U(1 - \alpha)^{-1} \end{aligned} \quad (3)$$

with the ratio of the areas denoted by

$$\alpha = \frac{A_W}{A_B} \quad (4)$$

The flow velocity of the black phase inside the domain is zero due to symmetry and the assumed incompressibility. The flow velocity of the white phase at an arbitrary distance is determined by the flow at the domain edge, since in the incompressible outside phase the total radial flux is the same at any distance r from the center of the domain:

$$2\pi r u_r^m(r) = 2\pi R u_r^m(R) = 2\pi R U \quad (5)$$

The radial flow velocity is thus determined everywhere in the monolayer:

$$\begin{aligned} u_r^m(r) &= 0 & r < R \\ &= \frac{RU}{r} & r > R \end{aligned} \quad (6)$$

Subphase Hydrodynamics. The sublayer flow velocity u is found from solutions of Stokes equation

$$-\nabla p + \eta \nabla^2 u = 0 \quad (7)$$

together with the continuity equation, $\nabla \cdot u = 0$. These solutions

can be expressed in terms of Hankel transforms which have the following form for cylindrically symmetric flow

$$u_r(r, z) = \int_0^\infty dk \phi(k) (1 - kz) J_1(kr) e^{-kz} \quad (8)$$

$$u_\theta(r, z) = 0 \quad (9)$$

$$u_z(r, z) = - \int_0^\infty dk \phi(k) k z J_0(kr) e^{-kz} \quad (10)$$

$$p = -2\eta \int_0^\infty dk \phi(k) k J_0(kr) e^{-kz} \quad (11)$$

with $\phi(k)$, an unknown function of k , to be determined by the boundary condition at the monolayer interface. Bessel functions are denoted $J_0(kr)$ and $J_1(kr)$. At the interface, $z = 0$; this gives a radial component

$$u_r(r, 0) = \int_0^\infty dk \phi(k) J_1(kr) \quad (12)$$

This flow must equal the monolayer flow eq 6. It follows from the Weber–Schafheitlin integral

$$\int_0^\infty dk J_0(kR) J_1(kr) = \begin{cases} 0 & r < R \\ 1/r & r > R \end{cases} \quad (13)$$

that $\phi(k)$ is given by

$$\phi(k) = UR J_0(kR) \quad (14)$$

With this expression for $\phi(k)$, the flow field and pressure can, in principle, be calculated anywhere in the sublayer. The stream function, $\psi(r, z)$, which determines the streamlines through $\psi(r, z) = cst$ and the flow field through

$$\begin{aligned} u_r &= \frac{1}{r} \frac{\partial \psi}{\partial z} \\ u_z &= - \frac{1}{r} \frac{\partial \psi}{\partial r} \end{aligned} \quad (15)$$

is given by

$$\psi(r, z) = UR rz \int_0^\infty dk J_0(kR) J_1(kr) e^{-kz} \quad (16)$$

A streamline is given by $r = 0$. Along this streamline, the vertical flow is

$$\begin{aligned} u_z(r = 0, z) &= -UR \int_0^\infty dk k z J_0(kR) e^{-kz} \\ &= UR z \frac{d}{dz} \int_0^\infty dk J_0(kR) e^{-kz} \\ &= -U \frac{(z/R)^2}{(1 + (z/R))^{3/2}} \end{aligned} \quad (17)$$

and is downward when $U = u_r^m(R)$ is negative. With these solutions for the coupled monolayer and sublayer flows, one can determine the viscous forces between the monolayer and the sublayer, the amount of energy dissipated by the flow, and the distribution of pressures in the monolayer. The viscous force per unit volume acting on the monolayer at the monolayer–water interface is given by

$$f_r^{\text{visc}} = \left(\frac{\partial u_r}{\partial z} \right)_{z=0}$$

$$\begin{aligned}
&= -\frac{2\eta}{h} \int_0^\infty dk k \phi(k) J_1(kr) \\
&= -\frac{2\eta UR}{h} \int_0^\infty dk k J_0(kR) J_1(kr) \\
&= \frac{2\eta R}{h} \frac{d}{dr} \int_0^\infty dk k J_0(kR) J_0(kr) \\
&= \frac{2\eta UR}{h} \frac{d}{dr} \left(\frac{2}{\pi r} K\left(\frac{R}{r}\right) \right) \quad (18)
\end{aligned}$$

Here, h is the monolayer thickness and K is the complete elliptic integral. In the monolayer Stokes equation there is a simple relationship between this viscous force and the monolayer pressure. There are no viscous effects in the monolayer itself since the flow is radial and has zero vorticity. The monolayer Stokes equation is then

$$-\frac{\partial \pi^m}{\partial r} + f_r^{\text{visc}} = 0 \quad (19)$$

where π^m is the monolayer pressure expressed as a force per unit area. Thus

$$\pi^m = \frac{p^m}{h} \quad (20)$$

with p^m the pressure equal to the force per unit length used previously. The viscous force is related to the radial derivative of the monolayer pressure p^m :

$$f_r^{\text{visc}} = \frac{\partial p^m}{h \partial r} \quad (21)$$

From eqs 18 and 21 it follows that the pressure is

$$p^m(r) = \frac{4\eta UR}{\pi r} K\left(\frac{R}{r}\right) - \frac{4\eta UR}{\pi R} K\left(\frac{R}{R}\right) + p^m(R) \quad (22a)$$

$$\approx \frac{4\eta UR}{\pi r} K\left(\frac{R}{r}\right) + p^m(R) \quad (22b)$$

as long as $r > R$ and $R \gg \delta$. Note that the monolayer pressure diverges as $r \rightarrow R$. Thus, the macroscopic hydrodynamic model breaks down close to the domain boundary. We, therefore, always stay a distance δ away from the edge of the domain, i.e., $r \geq R + \delta$ in the monolayer, see Figure 1. The parameter δ is a cutoff and contributes a logarithmic divergence as $\delta \rightarrow 0$. For $R \gg \delta$, the elliptic integral can be approximated

$$K\left(\frac{R}{R+\delta}\right) \approx \frac{1}{2} \ln \frac{8R}{\delta} \quad (23)$$

Thermodynamics. In previous work it has been shown that if the monolayer fluid surrounding a circular solid domain is maintained at an equivalent pressure p^m , the solid domain must have a radius R_{eq} in order to be at equilibrium⁶

$$p^m = p_0^m + (\alpha - 1)^{-1} (m^2/R_{\text{eq}}) \ln(R_q/e^2 R_{\text{eq}}) \quad (24a)$$

This is the monolayer pressure measured at a large distance from the circular domain where there are no nonuniform electrical fields. Here, m is the difference in dipole density in the two phases and p_0^m is the equilibrium monolayer pressure of the domain if m were equal to zero. Alternatively, this is the equilibrium pressure for a domain of infinite radius. Except

for very small domains (see later), at the radius R_{eq} and pressure p^m the system is stable against small fluctuations in domain radius. The radius R_{eq} corresponds to stable or metastable equilibrium. In the special case when $R_{\text{eq}} = R_q$, the domain is stable against domain fission or fusion as well as fluctuations in domain radius. For an isolated domain, this radius of stable equilibrium is given by the equation

$$R_q = (e^3 \Delta / 8) \exp(\lambda / m^2) \quad (24b)$$

where λ is the line tension between liquid and (isotropic) solid phases. The parameter Δ is an electrostatic dipole–dipole cutoff distance, taken to be of the order of magnitude of nearest neighbor intermolecular distances. There is an infinite number of metastable equilibrium radii, $R_{\text{eq}} (\neq R_q)$, that are stable against small changes in domain size but are unstable with respect to domain fusion and fission.⁶ Domain fusion and fission are typically much slower than the equilibration rates considered here. *Hereinafter we refer to all stable and metastable domains as simply “stable”.*

Equation 24a defines the “equilibrium radius” R_{eq} . Alternatively, it is sometimes convenient to imagine a monolayer in which the circular domain is maintained so as to have a radius R so that the monolayer reaches equilibrium when the pressure at a large distance from the domain reaches the “equilibrium” pressure p_{eq}^m

$$p_{\text{eq}}^m = p_0^m + (\alpha - 1)^{-1} (m^2/R) \ln(R_q/e^2 R) \quad (24c)$$

Equations 24a and 24c make the same physical statement but serve as convenient definitions for the two equilibrium quantities.

We make the ad hoc assumption that the pressure at $r = R + \delta$ is equal to the equilibrium pressure p_{eq}^m for a domain of radius R (eq 24c). That is, we assume local thermodynamic equilibrium in the immediate vicinity of the domain boundary. With this assumption eq 22 becomes

$$p_{\text{eq}}^m = \frac{4\eta UR}{\pi(R+\delta)} K\left(\frac{R}{R+\delta}\right) + p^m(R) \quad (25)$$

It is interesting to note that this result can be obtained in another way. One neglects the energy of viscous dissipation due to flow between R and $R + \delta$ and equates the energy of viscous dissipation between $R + \delta$ and R to the change of the self-energy of the domain plus the external work done on the system. The resulting relation between these quantities also leads to eq 25.

Electric Field Effects. It is pointed out above that these calculations use an “equivalent” monolayer pressure p^m . In the white liquid phase, this equivalent pressure is related to the true pressure p^{m*} by the equation

$$p^m(r) = p^{m*}(r) - m_w E_z(r) \quad (26a)$$

The chemical potential of the white incompressible liquid phase is a linear function of the right-hand side of this equation, so that under equilibrium conditions, both $p^m(r)$ and $p^{m*}(r) - m_w E_z(r)$ are constant, independent of r . Thus

$$p_{\text{eq}}^m(R) = p_{\text{eq}}^{m*}(R) - m_w E_z(R) \quad (26b)$$

$$p_{\text{eq}}^m(\infty) = p_{\text{eq}}^{m*}(\infty)$$

It is this equilibrium pressure $p_{\text{eq}}^{m*}(\infty)$ at infinity ($r = R \approx \infty$)

that is given in eq 24c.

$$p_{\text{eq}}^{m*}(\infty) = p_0^m + (\alpha - 1)^{-1}(m^2/R) \ln(R_q/e^2 R) \quad (27)$$

One can now generalize these results to include the effects of externally applied uniform or nonuniform electric fields that have circular symmetry, $E_z^{\text{app}}(r)$. In previous work,⁶ it is shown that

$$p_{\text{eq}}^{m*}(\infty) = p_0^m + (\alpha - 1)^{-1}(\lambda/R - mE_z(R)) \quad (28)$$

Here, $E_z(R)$ is the electric field at the domain boundary. When this field is the “edge field” due to molecular dipoles in the monolayer, one obtains eq 27. In the presence of an externally applied field E_z^{app} , eq 27 needs to be generalized

$$p_{\text{eq}}^{m*}(\infty) = p_0^m + (\alpha - 1)^{-1}[(m^2/R) \ln(R_q/e^2 R) - mE_z^{\text{app}}(R)] \quad (29)$$

This equation then replaces eq 24c.

Domain Growth Rate. By combining eqs 22, 23, and 24, one obtains the velocity U for the domain size change (assuming no externally applied field):

$$U = \pi m^2 [R^{-1} \ln(R_q/e^2 R) - R_{\text{eq}}^{-1} \ln(R_q/R_{\text{eq}})] / 2(\alpha - 1)\eta \ln(8R/\delta) \quad (30)$$

It is convenient to rewrite this equation in terms of a relative rate and inverse relaxation time

$$(1/R)dR/dt = \tau_R^{-1} \quad (31)$$

$$\tau_R^{-1} = \tau_0^{-1}(R_q/R) \left[\frac{(R_q/R) \ln(R_q/e^2 R) - (R_q/R_{\text{eq}}) \ln(R_q/e^2 R_{\text{eq}})}{\ln(R/R_q) + \ln(8R_q/\delta)} \right] \quad (32)$$

$$\tau_0^{-1} = \frac{\pi m^2}{2(\alpha - 1)\eta R_q^2} \quad (33)$$

For small variations of the radius R around the equilibrium radius R_{eq} , the relative growth rate can be written

$$\tau_R^{-1} = -\tau_0^{-1} \left(1 - \frac{R}{R_{\text{eq}}} \right) [R_q/R_{\text{eq}}]^2 \frac{\ln(R_q/e R_{\text{eq}})}{\ln(8R_{\text{eq}}/\delta)} \quad (34)$$

Equations 32–34 are useful in discussing the rate of approach to equilibrium when the stable or metastable equilibrium radius is known or can be estimated. In considering different experimental situations, it is sometimes convenient to express eq 32 in terms of other variables. For example,

$$\frac{1}{\tau_R} = \frac{\pi[p^m(R) - p^m(R + \delta)]}{2(\alpha - 1)\eta R \ln \frac{8(R + \delta)}{\delta}} \quad (35a)$$

Here, the equilibration rate is expressed in terms of the applied pressure $p^m(R)$ and the local pressure at $r = R + \delta$, assumed equal to p_{eq}^m . Thus

$$\frac{1}{\tau_R} = \frac{\pi[p^m(R) - p_{\text{eq}}^m]}{2(\alpha - 1)\eta R \ln \frac{8(R + \delta)}{\delta}} \quad (35b)$$

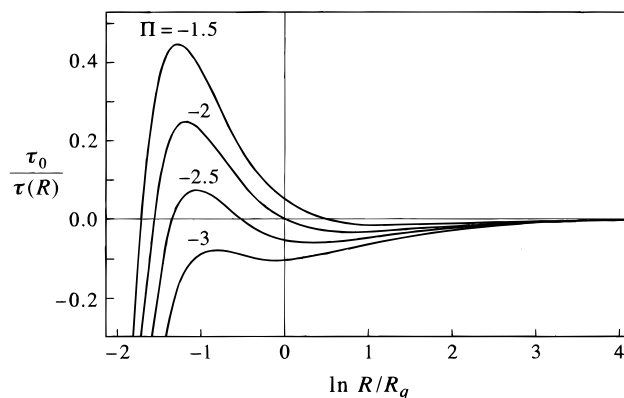


Figure 2. Domain growth rate as a function of domain radius and applied pressure. The domain growth rate $\tau(R)^{-1}$ is measured relative to a rate parameter τ_0^{-1} defined in eq 33. The domain radius R is scaled relative to the (stable) equilibrium radius R_q given in eq 24b. The scaled pressure Π is proportional to the difference between the applied monolayer pressure $p^m(R)$ and the equilibrium pressure p_0^m and is defined in eq 37. For some plots the domain growth rates are equal to zero for two values of $\ln R/R_q$. At this zero growth rate the smaller values of $\ln R/R_q$ correspond to points of unstable equilibrium, whereas the larger values of $\ln R/R_q$ correspond to states of metastable equilibrium, except for $\ln R/R_q = 0$, which is a state of stable equilibrium.

Still another equation equivalent to eq 32 is

$$\tau_0/\tau(R) = \frac{\Pi - \frac{R_q}{R} \ln \frac{R_q}{e^2 R}}{\frac{R}{R_q} \left[\ln \frac{R}{R_q} + \ln \frac{8R_q}{\delta} \right]} \quad (36)$$

where the normalized excess pressure Π is

$$\Pi = \frac{[p^m(R) - p_0^m](\alpha - 1)R_q}{m^2} \quad (37)$$

Equations 36 and 37 give the equilibration rate in terms of the applied pressure and the equilibrium pressure of a domain of very large radius ($R \rightarrow \infty$). Plots of the normalized growth rate from eq 36 are given in Figure 2 for different values of the domain radius R and normalized relative pressure Π . Note that the radius R and Π are independent variables. The calculations make the assumption that $\ln(8R_q/\delta) = 0$, where δ is of the order of a nearest neighbor intermolecular distance. This assumption sets the magnitude of the membrane flow.

Discussion

With typical order-of-magnitudes in cgs-esu units, $m \approx 10^{-4}$, $(\alpha - 1) \approx 1$, $\eta \approx 0.01$, and $R_q \approx 10^{-3}$, it is seen that the time constant τ_0 is about 1 s. In the limiting case corresponding to eq 34, one has exponential growth or decay of the domain radius depending on the relative size of the instantaneous and equilibrium radii. The important result is that this equilibration time is short.

It is seen in Figure 2 that for some values of the pressure the growth rate is equal to zero for two finite values of R . The larger values of R correspond to states of (meta)stable equilibrium, whereas the smaller values of R correspond to states of unstable equilibrium. In the latter case, a small fluctuation in domain size will result in a domain that disappears or grows until it achieves a radius where the growth rate is again zero. In previous work,⁶ it was shown that in an ensemble of domains,

the domains can only be stable when $R/R_q > 1/e$. This result can be seen in terms of Figure 2 by noting that as the radii of stability become smaller and smaller with decreasing Π , the growth rate finally becomes always negative when $\ln R/R_q < -1$. That is, these smaller domains "evaporate". This occurs for domains of all sizes when $\Pi < -e$. It will also be seen that depending on the pressure, the stable domains may have radii larger or smaller than R_q .⁷

The calculations are meant to simulate two experimental situations. In one case, the outer boundary of the monolayer trough is maintained at constant pressure $p^m(R)$ and the area gradually increases or decreases. In general, the more this applied pressure deviates from the equilibrium pressure for a domain of a given size, the more rapid is the equilibration rate. From eq 35 one sees that for excess pressures of the order of 0.1 dyn/cm, relative growth rates of hundreds of seconds are achieved. This calculated result is consistent with the observation that domain sizes do change rapidly in response to typical experimental monolayer pressure changes. On the other hand, in the absence of externally applied pressure gradients, pressure differences within monolayers arising from domains with different sizes can only be of magnitude $p^m(R) - p_0^m$. For typical experimental situations this is of the order of $m^2/R \approx 10^{-4}$ dyn/cm. Thus, experimentally applied pressure gradients easily overwhelm intrinsic domain equilibrium pressure differences arising from domains of different sizes.

The second, common, experimental situation^{1,2,4} is one in which a small domain is electrostatically trapped within a large doughnut-shaped domain of inner radius R . In this case, we take the equivalent equilibrium pressure of the large domain equal to p_0^m , the equivalent pressure for a domain of very large radius (see eq 24c and let $R \rightarrow \infty$). Then for the small domain we proceed as in the above calculations and let $p^m(R) = p_0^m$. Thus, the relative pressure Π in eq 36 is negligible and

electrostatically trapped domains are estimated to grow rapidly ($\tau_0 \approx 1 \text{ s}^{-1}$) when their radii are of the order of magnitude R_q . Small electrostatically trapped liquid domains are commonly observed in certain binary mixtures of lipids, and they do *not* grow rapidly. Their slow growth has been previously attributed to the required interdiffusion of the two chemical components in the special case where the two components have equal molecular areas.⁴ The present work implies that even if the two components have different molecular areas, the macroscopic hydrodynamic drag should not be limiting.

Like externally applied pressure gradients, externally applied nonuniform electric fields can produce rapid changes in domain sizes.^{1,6} Applied fields are known to produce rapid domain size changes in binary mixtures of lipids, and it is possible that subphase hydrodynamic drag limits the rates of these changes.⁶

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References and Notes

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- (7) When $\ln R/R_q \geq 1/3$, a circular domain is unstable with respect to a 2-fold distortion. It is shown in Figure 2 that this condition is reached when the normalized relative pressure is $\Pi = -1.5$. At larger values of $\ln R/R_q$, the circular domain becomes unstable with respect to higher harmonic distortions, see ref 3. Starting with a small, growing circular domain, the symmetry number of the first observed distortion will likely depend on the value of Π as this should determine the rate of domain size change relative to the rate of shape change.