Growth kinetics of circular liquid domains on vesicles by diffusion-controlled coalescence

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Abstract
Motivated by recent experiments on multicomponent membranes, the growth kinetics of domains on vesicles are theoretically studied. It is known that the steady-state rate of coalescence cannot be obtained by taking the long-time limit of the coalescence rate when the membrane is regarded as an infinite two-dimensional (2D) system. The steady-state rate of coalescence is obtained by explicitly taking into account the spherical vesicle shape. Using the expression for the 2D diffusion coefficient obtained in the limit of small domain size, an analytical expression for domain growth kinetics is obtained when a circular shape is always maintained. For large domains, the growth kinetics are discussed by investigating the size dependence of the coalescence rate, using the expression for the diffusion coefficient of arbitrary domain size.

1. Introduction

Lipid bilayer membranes can be regarded as two-dimensional (2D) systems embedded in a three-dimensional (3D) solvent. The membranes are coupled to the solvent since the lipids composing the membrane interact with the solvent surrounding them and momentum can be exchanged between the membrane and the solvent [1–10]. In this sense, membranes can be regarded as quasi-2D systems. With recent advances in experiments, domains formed by phase separation in multicomponent membranes are visualized, and the lipid spatial organization and its dynamics have been studied [11–15]. The phase separation kinetics and coarsening are influenced by the dimensionality, the domain shapes and the hydrodynamics in the systems [16]. The phase separation in a multicomponent lipid bilayer exhibits rich dynamics, partly due to momentum dissipation to third dimensions while the motion is confined to 2D [7–9].

In recent experiments, the growth kinetics of circular domains on ternary fluid vesicles have been observed by fluorescence microscopy [11, 13, 14]. In these experiments, liquid domains are formed in giant vesicles by phase separation into the liquid-ordered phase and the liquid-disordered phase, on lowering the temperature from the one-phase region. Yanagisawa *et al* found two different types of domain coalescence kinetics [14]. In one of the coalescence processes, the domains grew by collision and coalescing while keeping their circular shape until the large domains of vesicle size appeared. These growth kinetics due to diffusion-controlled coalescence (DCC) were described by a power-law. In the other coalescence process, domain growth was suppressed by membrane-mediated repulsive inter-domain interactions. Recently, it was pointed out that domain coalescence could be prevented by the membrane-mediated interactions between liquid domains associated with deformations of the membrane [17–21]. When the liquid domain size exceeds a critical value, the boundary line energy

is reduced by budding, at the expense of some bending energy. The significant slowing down of domain growth can be observed for large budded domains [14, 21]. In the steady state, the domain patterns and the membrane shapes can be stabilized by coupling between the local membrane curvature and the line tension [12, 15, 22–24].

As briefly summarized above, the liquid domains coarsen under the influence of several competing processes. Even without budding, the observed growth kinetics were different from those obtained from the scaling hypothesis [13, 14]. Motivated by the experiments, we study theoretically the growth kinetics of domains on vesicles by DCC.

The study of domain growth on vesicle surfaces is still limited compared to that in 3D [16]. According to the scaling hypothesis, the domain growth exponent due to DCC in 2D is 1/2, in contrast to that in 3D given by 1/3 [25, 26]. However, it should be noted that, in the scaling hypothesis, the coalescence process is not explicitly taken into account. Moreover, it is known that a steady-state rate of coalescence cannot be obtained for an infinitely large 2D system [27, 28]. In contrast to diffusion in 3D space, in order to obtain the coalescence rate when diffusion is restricted in 2D, boundary conditions are crucial. This point is missing in the scaling hypothesis.

In addition to the above argument for pure 2D systems, the coalescence of liquid domains can be influenced by coupling between the membrane and the solvent. The diffusion of large domains is influenced more by coupling compared to that of small domains. As the domain grows, the influence of coupling between the membrane and the solvent increases. The domain growth kinetics have been studied by dissipative particle dynamics simulations and continuum simulations [7–9, 29]. The simulation results suggest the slowing down of domain growth by DCC due to the coupling [7].

In this paper, we study the growth of liquid domains immersed in a 2D membrane using an analytical theory which goes beyond the scaling hypothesis. We note that a steady-state rate of coalescence can be obtained by taking into account explicitly the vesicle shape [30, 31]. Using the diffusion coefficient for domains obtained by taking into account coupling between the membrane and the solvent [1–6, 10], we show that the coalescence rate is independent of domain size in the limit of small domain size. For such a case, it is known that the size distribution is described by the Smoluchowski theory of coalescence processes [32]. By further assuming that the circular shape of liquid domains is always maintained, the time evolution equation of the mean domain size is obtained from the size distribution using the conservation of domain area upon coalescence. The mean domain growth is expressed by a single function for the whole time regime, starting from the initial induction period of coalescence to the final asymptotic regime given by the power-law. When the domain size is large, we discuss the influence of coupling between the membrane and the solvent on domain growth by analyzing the size dependence of the coalescence rate.

In section 2, we present the results obtained from the scaling hypothesis. In section 3, the results from the

Smoluchowski theory in pure 3D and 2D infinite systems are reviewed. In section 4, the coalescence rate is obtained by taking into account the vesicle shape. In section 5, an analytical expression representing the growth of mean domain size is obtained when the circular shape and the area of the liquid domains are kept the same before and after coalescence. The size dependence of the coalescence rate is investigated using an analytical expression for the diffusion coefficient for the liquid domain of arbitrary size in section 6. In section 7, the theoretical results are discussed in relation to those obtained by recent experiments [14].

2. Scaling theory

In this section, we summarize the results obtained from scaling theory. Scaling theory is the simplest way to derive the power-law growth of domain size. Obviously, one cannot obtain both the transient growth leading to asymptotic power-law kinetics and the magnitude of the power-law growth.

Scaling theory is based on the hypothesis that the mean domain radius $\langle a(t) \rangle$ in d-dimension is related to time t by

$$\langle a(t) \rangle^2 \sim D_d t, \tag{1}$$

where D_d is the diffusion coefficient and subscript d denotes the dimensionality. In 3D, the diffusion coefficient for the domain is inversely proportional to $\langle a(t) \rangle$ from the Stokes–Einstein relation, $D_3 \sim 1/\langle a(t) \rangle$. Substituting this relation in the scaling relation, we obtain $\langle a(t) \rangle \sim t^{1/3}$ [16, 25, 26]. For 2D, we have $D_2 \sim k_B T/\eta$ from the dimensional argument, where k_B is the Boltzmann constant, T the temperature, and η the 2D membrane viscosity surrounding the domain. Using the above expression for D_2, the scaling hypothesis leads to $\langle a(t) \rangle \sim t^{1/2}$ [16, 25, 26]. It should be pointed out that a logarithmically time-dependent diffusion coefficient has been derived in pure 2D by hydrodynamic theory [2]. When the membrane couples to the solvent, a constant diffusion coefficient is derived, and D_2 depends logarithmically on the domain size in the weak coupling limit [1, 2]. The logarithmic size dependence and the numerical factors are ignored in the dimensional argument.

We also note that the time given by $\langle a(t) \rangle^2 / D_d$ is not equal to the coalescence time for the domain of size $\langle a(t) \rangle$. The coalescence time should be given by the mean first time that domains coalesce by diffusion from a random initial distribution. Below, we show that the latter time is different from the one given by $\langle a(t) \rangle^2 / D_d$.

The scaling hypothesis merely relates a single length scale given by the mean domain size at time t with the diffusion coefficient as shown in equation (1) and it should be justified. In subsequent sections, we point out that the results for the scaling hypothesis cannot be obtained for domain growth by diffusion coalescence in 2D infinite systems. We show then that the scaling hypothesis is consistent with domain growth kinetics via diffusion coalescence when the available diffusion area is finite in 2D. The whole kinetics, including transient growth and the final power-law growth, can be obtained by taking into account the diffusion-coalescent process and the vesicle shape explicitly.

3. Smoluchowski theory in infinite systems

In Smoluchowski theory, domain motion is assumed to be independent of others and coalescence between a pair of domains is considered. When both domains can move, it is difficult to solve the problem analytically. We assume that one of the domains is fixed and the other diffuses with a mutual diffusion coefficient D_d, which is the sum of the diffusion coefficients for two spherical domains of equal size [33]. Coalescence takes place immediately when two domains come in contact at the encounter distance, which is the sum of the radii of the two domains. In the theoretical formulation, the spatial distribution of domains satisfies the diffusion equation and the spatial domain density should vanish at the encounter distance. The domain size increases immediately after coalescence and the spatial distribution of the new domain size should be zero at the encounter distance for the increased domain size.

The density of the mobile domain around the immobile domain satisfies the diffusion equation

$$\frac{\partial}{\partial t}\rho_d(r,t) = D_d \nabla^2 \rho_d(r,t), \tag{2}$$

where r is the distance to the center of the immobile domain. We assume a random initial condition, given by

$$\rho_d(r, t=0) = 1. \tag{3}$$

The boundary condition applied at the encounter distance σ is given by

$$\rho_d(r=\sigma, t) = 0. \tag{4}$$

We should set another boundary condition such that the density at infinite separation is unity, i.e.,

$$\lim_{r\to\infty} \rho_d(r,t) = 1. \tag{5}$$

3.1. Three dimensions (3D)

Before investigating domain growth on the 2D spherical surface, we shall briefly present the known results for 3D infinite systems and show that the corresponding results do not hold for 2D cases.

For 3D infinite systems, the density profile which satisfies both of the boundary conditions is $\rho_3(r) = 1 - (\sigma/r)$ [33]. The mean coalescence rate is given by the inward flow of domains across the surface at σ

$$k_3 = 4\pi\sigma^2 D_3 \left(\frac{\mathrm{d}\rho_3(r)}{\mathrm{d}r}\right)_{r=\sigma} = 4\pi\sigma D_3. \tag{6}$$

In a 3D fluid of viscosity η_s, the diffusion coefficient is inversely proportional to the size of the diffusing object, $D_3 = k_B T / 3\pi\eta_s\sigma$. Using this Stokes–Einstein relation, the mean coalescence rate can be expressed by $k_3 = 4k_B T/3\eta_s$. Notice that $\sigma/2$ is the radius of the spherical domain [32].

3.2. Two dimensions (2D)

Applying the boundary condition at σ, we obtain

$$\rho_2(r) = C \ln(\sigma/r), \tag{7}$$

where C is a constant determined from the other boundary condition at $r \to \infty$. However, it is impossible to fix C because $\rho_2(r)$ diverges for $r \to \infty$ as long as C is finite. Unlike 3D infinite systems, the density cannot satisfy both boundary conditions, equations (4) and (5), simultaneously.

4. Smoluchowski theory in spherical surface

The difficulty mentioned in the previous section for 2D can be overcome if the available diffusion area is finite. The density profile depends crucially on the shape of the 2D region. In earlier experiments [14], DCC of circular domains was observed on the vesicle surfaces. In principle, the coalescence rate can be obtained by modifying the method shown in the previous section to the spherical region, but the calculation is rather complicated. In this paper, we employ an alternative method.

Here, we investigate the life time of the density of mobile domains which survive from collision with the immobile domain. In a confined region, the density decay can be well approximated by a single exponential. The time constant of the exponential decay can be reasonably obtained from the mean first-passage time of a mobile domain to the periphery of the immobile domain assuming uniform distribution for the starting point. For coalescence, the mean first-passage time is the mean coalescence time corresponding to the encounter time between two domains. When the initial position of the mobile reactant is $z = \cos\theta$ (see figure 1 for the geometry), the mean coalescence time $\tau(z)$ satisfies the following equation (see the appendix for the derivation) [30]

$$\frac{D_2}{R^2}\frac{\partial}{\partial z}(1-z^2)\frac{\partial}{\partial z}\tau(z) = -1. \tag{8}$$

The boundary conditions are

$$\tau(z = -\cos\alpha) = 0, \qquad \left(\frac{\partial \tau(z)}{\partial z}\right)_{z=1} = 0, \tag{9}$$

where α is the angle between domain centers at collision (see figure 1). Notice that a simple geometric argument gives $\sin(\alpha/2) = \sigma/(2R)$ and $\cos\alpha = 1 - \sigma^2/(2R^2)$ [30]. Equations (8) and (9) can be easily solved, and we obtain

$$\tau(z) = \frac{R^2}{D_2} \ln\left[\frac{2R^2}{\sigma^2}(1+z)\right]. \tag{10}$$

Averaging over the random initial distribution, we obtain [30]

$$\begin{aligned}\tau_{\text{av}} &= \frac{\int_{-\cos\alpha}^{1} \mathrm{d}z\, \tau(z)}{2 - \sigma^2/(2R^2)} \\ &= \frac{R^2}{D_2}\left[\frac{2}{1-(\sigma/2R)^2}\ln\left(\frac{2R}{\sigma}\right) - 1\right].\end{aligned} \tag{11}$$

The probability that the mobile domain has not reached the immobile domain up to time t is given by $\exp(-t/\tau_{\text{av}})$ when
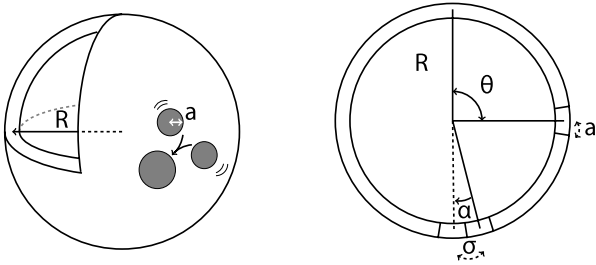
Figure 1. A schematic picture of the liquid domains embedded in a fluid vesicle (left). The radius of the liquid domains is a while the vesicle radius is R. Liquid domains undergo Brownian motion on the vesicle surface. Shown on the right is the geometrical parametrization. θ denotes the azimuthal angle and α is the angle between domain centers at collision. σ represents the encounter distance.

domains are initially distributed uniformly in the spherical surface. The same probability can be expressed using the bulk bimolecular rate as $\exp(-k_d t/A)$, where the surface area available for diffusion is $A = 2\pi R^2 [2 - \sigma^2/(2R^2)]$. Comparing these expressions, we find that the bulk bimolecular rate can be calculated from the mean coalescence time by $k_2 = A/\tau_{\mathrm{av}}$ [30, 31, 34].

Using the bimolecular rate, the mean coalescence rate is obtained as [30, 31, 34]

$$k_2 = \frac{4\pi[1 - (a/R)^2]D_2(a)}{2\ln(R/a) - 1 + (a/R)^2} \quad (12)$$

$$\simeq \frac{4\pi D_2(a)}{2\ln(R/a) - 1}, \quad (13)$$

where $a \ll R$ is used to obtain the second equality. The mutual diffusion coefficient is now expressed by $D_2(a)$ since it depends on the domain radius a as shown below.

Unfortunately, the full size dependence of the diffusion coefficient is not known for spherical vesicles. However, an analytical expression is known for a circular liquid domain which has the same viscosity as the outside of the domain for 2D flat membranes. For this case, the mutual diffusion coefficient was obtained by De Koker as [3]

$$D_2(a) = \frac{2k_B T}{\pi\eta} \int_0^\infty \mathrm{d}z \, \frac{J_1^2(z)}{z^2(z + \nu a)}, \quad (14)$$

when the two circular domains have the same radius a. In the above, $J_1(z)$ is the Bessel function of the first kind, η is the 2D membrane viscosity, and $\nu = 2\eta_s/\eta$ with η_s being the viscosity of the outer fluids. Here we have assumed that the viscosities of the liquid inside and outside the vesicle are the same. The analytical expression after the integration can be expressed using Meijer G-functions [5, 6]. For the case of $\nu a \ll 1$, the above expression reduces to [5, 6]

$$D_2(a) \approx \frac{k_B T}{\pi\eta} \left[\ln\left(\frac{2}{\nu a}\right) - \gamma + \frac{1}{4} \right], \quad (15)$$

where $\gamma = 0.5772 \cdots$ is Euler's constant. Equation (15) is slightly larger than the mutual diffusion coefficient of Saffman–Delbrück (SD) theory derived for solid domains

under the condition of $\nu a \ll 1$. Strictly speaking, the SD result was also obtained for 2D flat membranes. Recently, it was shown that the SD result was applicable for spherical vesicles when $a < R < 1/\nu$ [36].

Substituting equation (15) into equation (13), we obtain

$$k_2 \approx \frac{k_B T}{\eta}, \quad (16)$$

when $a/R \ll 1$. The coalescence rate is independent of a in this limit. $k_2 t$ then approximately represents the area explored by a diffusive object of radius σ during time t [34, 35]. Hence $k_2 t$ is given by $D_2(a) t$ times the effective collision cross-section. The size independence is the result of the two opposing effects; with increasing domain size, the diffusion coefficient decreases while the effective collision cross-section given by $4\pi/[2\ln(R/a) - 1]$ in equation (13) increases.

Strictly speaking, the coalescence rate depends on the domain size if the coalescence occurs between domains of different sizes. However, such a size dependence is small for 2D because of the weak logarithmic dependence in equations (13) and (15), and will be ignored hereafter. In fact, the size dependence was not taken into account, even to study the coalescence processes in 3D [32].

Equation (12) is valid even if the condition $a/R \ll 1$ is not satisfied. The full size dependence of the coalescence rate will be studied by substituting equation (14) into equation (12) as we shall discuss in section 6.

5. Growth kinetics of liquid domains

Now we consider the formation of m-fold domains from initial domains of the same size. When the coalescence rate is independent of the domain size as discussed above, the number density of an m-fold domain $n_m(t)$ at time t is given by [32]

$$\frac{n_m(t)}{n_1} = \frac{(t/\tau)^{m-1}}{(1 + t/\tau)^m}, \quad (17)$$

where

$$\tau = \frac{1}{k_d n_1}, \quad (18)$$

n_1 is the initial number density of the primary domains, and k_d is the coalescence rate in d-dimensional space.

In general, if aggregates of large size are in the solid state, there are many possible shapes for them. Shape characterization and size distribution have been studied in the conventional theory of Brownian coagulation. Here, we study Brownian coalescence of liquid domains under the condition that a circular shape is always maintained. For comparison, we also consider Brownian coalescence of liquid domains in 3D infinite systems, where a spherical shape is always maintained. Under this assumption, the time evolution of the domain size can be obtained analytically.

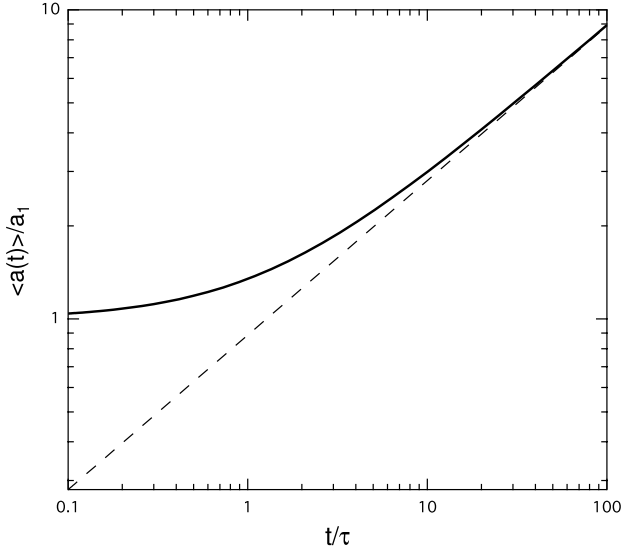Assuming that the domain shape is immediately restored after coalescence, the radius of the m-fold domain a_m

Figure 2. The average domain size $\langle a(t)\rangle/a_1$ as a function of dimensionless time t/τ when domains are confined in the spherical surface. The solid line is obtained from equation (20) and the dashed line represents the asymptotic behavior given by equation (22).

Figure 3. $k_2\eta/(k_BT)$ as a function of the dimensionless domain size νa. The solid line is obtained from equation (12) using an expression for the diffusion coefficient of a circular liquid domain which has the same viscosity as the outside of the domain. $R\nu = 5$, 10 and 50 from top to bottom, respectively. The dashed lines are obtained by substituting equation (15) into equation (12). The dots are obtained by substituting equation (24) into equation (12).

is determined by the area ($d = 2$) or volume ($d = 3$) conservation relation,

$$a_m^d = m a_1^d. \quad (19)$$

Averaging a_m over the distribution of m-fold aggregates (see equation (17)), the mean domain radius $\langle a(t)\rangle$ at time t is obtained as

$$\frac{\langle a(t)\rangle}{a_1} = \sum_{m=1}^{\infty} m^{1/d}\frac{n_m(t)}{n_1} = \frac{\tau}{t}\mathrm{Li}_{-1/d}\left(\frac{t/\tau}{1+t/\tau}\right). \quad (20)$$

In the above, we have used the polylogarithm function defined by [37]

$$\mathrm{Li}_s(x) = \sum_{k=1}^{\infty}\frac{x^k}{k^s}. \quad (21)$$

In the asymptotic limit of $t/\tau \gg 1$, equation (20) reduces to either

$$\frac{\langle a(t)\rangle}{a_1} \approx \frac{\sqrt{\pi}}{2}\left(\frac{t}{\tau}\right)^{1/2} \quad (22)$$

for coalescence in 2D spherical surfaces, or

$$\frac{\langle a(t)\rangle}{a_1} \approx \Gamma\left(\frac{4}{3}\right)\left(\frac{t}{\tau}\right)^{1/3} \quad (23)$$

for coalescence in 3D infinite systems. Here $\Gamma(x)$ is the gamma function. The time evolution of $\langle a(t)\rangle/a_1$ is shown in figure 2 for domain coalescence on the vesicle. The asymptotic time dependence is well approximated by equation (22) when $t/\tau \gg 1$. We can see the induction period of coalescence when $t/\tau < 1$. The induction period is characterized by the inverse of the apparent coalescence rate given by the coalescence rate times the initial number density for the primary domains, equation (18). Taking into
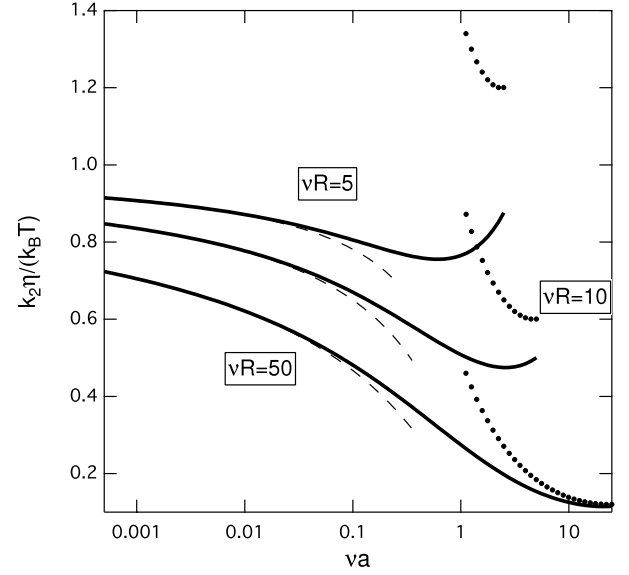
account explicitly the vesicle shape, the finite coalescence rate is obtained from Smoluchowski theory and the results indicate the induction period before asymptotic growth.

6. Size dependence of the coalescence rate

In the previous section, growth kinetics for the circular liquid domain via diffusion coalescence are obtained when the coalescence rate is independent of the size of the liquid domain. The result for domain growth on the vesicle is obtained in the limit of $\nu a \ll 1$. Below, we study the size dependence of the coalescence rate using equations (12) and (14). The diffusion coefficient, equation (14), is obtained for a circular liquid domain of arbitrary size. In the limit of $\nu a \ll 1$, the domain size dependence of the diffusion coefficient is logarithmic, as shown by equation (15). The coalescence rate is given by k_BT/η, independent of the domain size because of the cancellation of the logarithmic domain size dependence both in equations (12) and (15). For the opposite limit of $\nu a \gg 1$, the diffusion coefficient is obtained as [5, 6]

$$D_2(a) \approx \frac{8k_BT}{3\pi^2\eta_s a}, \quad (24)$$

which is inversely proportional to the domain radius a.

The coalescence rate obtained by substituting equation (14) into equation (12) is indicated by the solid lines in figure 3. For a relatively small vesicle, say $\nu R = 5$, the coalescence rate is almost independent of the domain size and is approximately given by k_BT/η. The situation is very different for large vesicles. When $\nu R \geq 10$, the size dependence of the coalescence rate can be ignored only when

$va < 0.1$. In the same figure, we indicate the results obtained by substituting equation (15) into equation (12) by dashed lines. As long as the domain size dependence of the diffusion coefficient can be approximated by equation (15), the size dependence of the coalescence rate is weak.

When $vR = 5$, the size dependence is weak, even beyond the regime given by $va \ll 1$. However, when $vR \geq 10$ and $va > 0.1$ the coalescence rate decreases with increasing domain size. In the figure, we indicate the results obtained by substituting equation (24) into equation (12) by dots. The coalescence rates with a full size dependence of the diffusion coefficients (equation (14)) approach the results indicated by dots as the size increases. The dots rapidly decrease with increasing domain size because of the power-law dependence of the domain size in equation (24). When $vR \geq 10$ and $va > 0.1$, the coalescence rate decreases with increasing domain size due to the strong size dependence of the diffusion coefficient. If the coalescence rate decreases with increasing size, the growth kinetics of the domain size should be suppressed. The growth law given by equation (20) and the result shown in figure 2 can be applicable when $vR = 5$, but should be applicable only when $va \ll 1$ if the vesicle radius is large, such as $vR \geq 10$.

We also note that the coalescence rate increases with increasing domain size if the domain size approaches close to the vesicle radius. This dependence originates from the denominator of equation (12) and can be interpreted as the finite size effect of the domains confined in the spherical surface.

The diffusion coefficient, equation (14), shows a logarithmic size dependence (equation (15)) and a power-law size dependence (equation (24)) as va is varied. The dimensionless quantity va characterizes the coupling between the embedded bulk fluid and the membrane for a given size. The coupling is small when $va \ll 1$. The domain growth and its asymptotic limit given by equations (20) and (22), respectively, are obtained in the weak coupling limit. In the strong coupling limit $va \gg 1$, domain growth is suppressed as a result of the small coalescence rate compared to that in the weak coupling limit, as shown in figure 3. The results are consistent with the simulation results that the growth law is suppressed with increasing hydrodynamic coupling when the governing mechanism is DCC in 2D [7, 8].

The above conclusion is not altered if we use the diffusion coefficient for the solid domains instead of equation (14). Recently, the diffusion coefficient for the solid domain in the 2D flat membrane has been approximated by a closed-form empirical expression [10]. The interpolation formula for the diffusion coefficient reproduces the logarithmic size dependence obtained from SD theory when $va \ll 1$. When the interpolation formula is introduced, the coalescence rate equation (12) is slightly smaller but the overall size dependence is similar to that obtained using equation (14). The coalescence rate decreases with decreasing diffusion coefficient for the solid domain compared to that for the liquid domain of the same size. In general, the diffusion coefficient for the solid domain is smaller than that for the liquid domain of the same size since the friction between the membrane and

the solid edge is larger than that between the membrane and the liquid domain.

As shown above, the coalescence rate is constant in time when domains are confined on a spherical vesicle. The finite coalescence rate constant can also be calculated by considering a circular flat sheet of radius L and setting the absorbing boundary condition at $r = a$ and the reflecting boundary condition at $r = L$ ($a < L$). When a circular domain of radius a is placed at the center of a circular flat sheet, the coalescence rate is given by equation (13), by replacing R with L [38]. Within this substitution, the domain size dependence of the coalescence rate is the same as that in a spherical vesicle. The diffusion coefficient of a domain placed at the center of a circular sheet of radius L was obtained, taking into account the viscosity of a circular flat membrane [1]. However, the result was limited for $a \ll L$ and obtained by ignoring the hydrodynamic coupling between the membrane and the solvent.

7. Discussion and conclusion

We discuss the relevant length scales in the recent experiment on domain growth kinetics by diffusion coalescence [14]. In the experiments, giant vesicles with a diameter of about 20 μm undergo phase separation at 30 °C after a temperature drop from the one-phase region (42–43 °C). Circular domains were observed when the size exceeded an optical resolution of the microscope (roughly 0.8 μm). In one of the coalescence processes, the large domains of vesicle size appeared within several minutes. Domain growth by collision and coalescence was observed. In the other coalescence process, domain growth was suppressed for several tens of minutes. The former process can be theoretically studied by assuming DCC.

The value for $v = 2\eta_s/\eta$ can be estimated using typical values of $\eta_s = 10^{-3}$ Pa s, with η given by 0.1 Pa s times the membrane thickness 5 nm as $v = 4.0 \times 10^6$ m^{-1}. We estimate $vR \approx 40$ by introducing a typical radius for the vesicles of 10 μm. When $vR = 50$, the coalescence rate is almost independent of the domain size as long as $a < 25$ nm, obtained from the condition $va < 0.1$. The domain size is much smaller than the optical resolution of the microscope, typically 0.8 μm. Therefore, when the domain size grows and reaches the optical resolution, the coalescence rate decreases with increasing domain size and domain growth can be suppressed compared to that given by equation (22). According to figure 3, the coalescence rate is almost constant over the wide range of the domain size when $vR = 5$. This value corresponds to a vesicle radius close to 1 μm, which may be the maximum vesicle radius at which to observe the power-law growth given by equation (22).

It should be remembered that the full size dependence of the diffusion coefficient for spherical vesicles is not known. In this paper, the size dependence of the coalescence rate has been discussed by substituting the known expression for the diffusion coefficient for 2D flat membranes. The full size dependence of the diffusion coefficient for the spherical vesicle is needed to further develop the coagulation theory for large domains within the current limit of optical resolutions.

In original work by Yanagisawa *et al*, the best fitted exponent 2/3 was obtained for power-law domain growth [14]. However, the mechanism which leads to this large exponent is not well understood. An attractive interaction between domains seems to be present due to hydrodynamic flow around the domains, which would accelerate domain growth [39].

The power-law growth of circular domains can be induced by transport of molecules from one domain to another through the medium [16, 40–42]. The growth of large domains is associated with evaporation of small domains, which is known as Ostwald ripening. According to the Lifshitz–Slyozov–Wagner theory of Ostwald ripening, the power-law exponent is 1/3 [40]. In this paper, we studied domain growth using the DCC mechanism and did not consider the evaporation and condensation mechanism in 2D. We just remark that the exponent 1/3 is independent of the dimensionality and holds also in 2D [8, 41, 42].

In conclusion, we have investigated the DCC mechanism for the growth kinetics of liquid domains on fluid vesicles. Applying bimolecular reaction theory in the spherical surface and using a 2D diffusion coefficient, the 2D coalescence rate is found to be independent of the liquid domain size if it is small enough. As a result, the domain size distribution is given by classical Smoluchowski theory. When a circular shape is always maintained, we have obtained the mean domain size for the whole time range (equation (20)) using the domain size distribution and the area conservation relation. In the asymptotic long-time limit, we expect a power-law behavior with the exponent 1/2 (equation (22)).

Domain growth kinetics have been derived under the condition that the 2D coalescence rate is independent of the domain size. This condition is investigated using a recently obtained analytical expression for the diffusion coefficient of arbitrary domain size. When the vesicle radius is small, the coalescence rate can be approximated well as a constant over the wide range of the domain size. When the vesicle radius is large, the coalescence rate becomes independent of the domain size only in the limit of small domain size. In general, the coalescence rate decreases with increasing domain size up to a certain size where the finite size effect dominates. The results are discussed in relation to the recent experimental observations of DCC in vesicles.

Acknowledgments

Appendix. The mean coalescence time

In this appendix, we briefly present the derivation of equation (8) when the density satisfies equations (2)–(5). The density can be expressed using the probability of finding a pair of domains at a relative position r at time t if their initial relative position was r_i and this was uniformly distributed

$$\rho_d(r, t) = \int dr_i \, p_d(r, t|r_i, 0). \tag{A.1}$$

We introduce the survival probability that the pair has not coalesced up to time t if their initial relative position was r

$$w_d(r, t) = \int dr_f \, p_d(r_f, t|r, 0). \tag{A.2}$$

Because $p_d(r_f, 0|r, -t)$ satisfies the backward Kolmogorov equation and hence $p_d(r_f, t|r, 0) = p_d(r_f, 0|r, -t)$, we obtain [43–45]

$$\frac{\partial}{\partial t} w_d(r, t) = D_d \nabla^2 w_d(r, t), \tag{A.3}$$

with the initial condition

$$w_d(r, t = 0) = 1, \tag{A.4}$$

and the boundary conditions

$$w_d(r = \sigma, t) = 0, \qquad \lim_{r \to \infty} w_d(r, t) = 1. \tag{A.5}$$

Since $1 - w_d(r, t)$ is the probability that the pair coalesce at time t, the mean coalescence time $\tau(r)$ is given by

$$\tau(r) = \int_0^\infty dt \, t \frac{\partial}{\partial t} [1 - w_d(r, t)] = \int_0^\infty dt \, w_d(r, t). \tag{A.6}$$

In general, the mean coalescence time is called the mean first-passage time. Integrating equation (A.3) over time and using equation (A.4), we find that the mean coalescence time satisfies equation (8) when domains are confined in the spherical surface. Note that in equation (A.3), the diffusion equation in the spherical surface can be written assuming azimuthal symmetry such that

$$D_2 \nabla^2 w_2 = D_2 \frac{1}{R^2 \sin\theta} \frac{\partial}{\partial \theta} \left(\sin\theta \frac{\partial w_2}{\partial \theta} \right)$$
$$= \frac{D_2}{R^2} \frac{\partial}{\partial z} (1 - z^2) \frac{\partial w_2}{\partial z}, \tag{A.7}$$

where $z = \cos\theta$.

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