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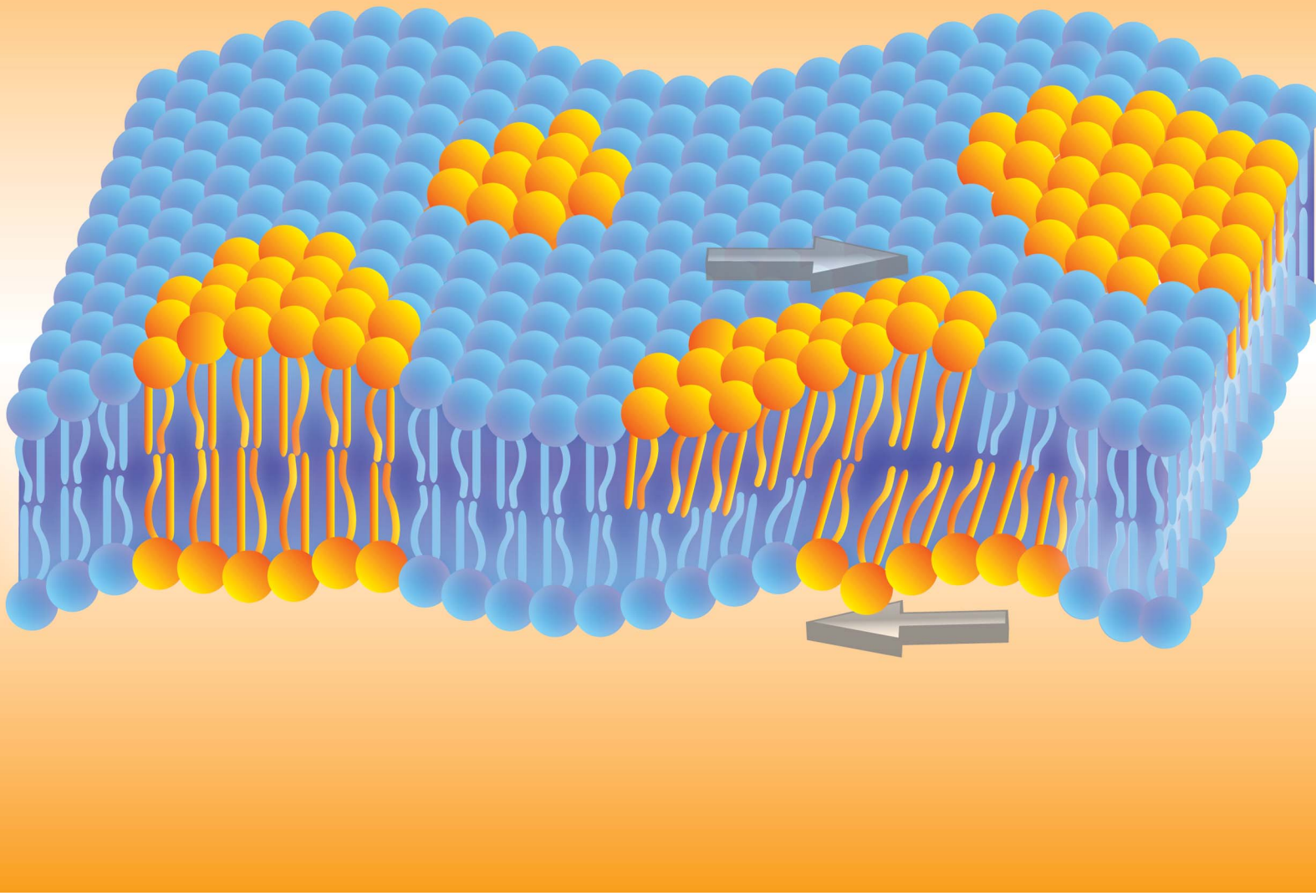

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Compositional domains within multicomponent lipid bilayer membranes are believed to facilitate many important cellular processes. In this work, we first derive the general equations that describe the dynamics of compositional domains within planar membranes with asymmetry in leaflet properties and in the presence of a thermodynamic coupling between the leaflets. These equations are then employed to develop analytical solutions for the dynamics of the recurrence of registration for circular domains in the case of weak coupling. In addition, a closed-form expression for the decay rate of interface fluctuations, when only one leaflet supports compositional domains, is derived.

Multicomponent lipid bilayer membranes comprise an important class of soft biological materials. In mammalian cells, compositional lipid domains coined "rafts"[1] are believed to play a key role in several cellular processes, such as cell signaling and trafficking.[2] Experimentally, it has been shown that synthetic membranes whose overall compositions mimic those of the extracellular leaflet of the cell membrane can phase separate into distinct liquid phases,[3] while those mimicking the cytoplasmic leaflet are homogeneous.[4] Interestingly, when the two kinds of leaflets are combined to form asymmetric membranes, phase separation can either be induced[5,6] or suppressed altogether.[6] Furthermore, when both leaflets contain domains, they are often found in perfect registry,[5,7,8] although out-of-registry formation of nanoscale domains has also been observed in simulations.[9] These observations indicate that a significant thermodynamic coupling exists between the two leaflets.

Several physical mechanisms have been proposed to account for the coupling effect. Collins has suggested that the coupling strength is directly related to the line tension between the compositional domains within a single leaflet.[10] May in turn has compared three possible candidates, namely electrostatic coupling, cholesterol flip-flop, and dynamic chain interdigitation, and suggested that dynamic chain interdigitation likely provides the main contribution to the coupling,[11] while Putzel *et al.* have argued that the coupling results from a complex interplay between entropic and energetic effects.[12] In our work, the coupling is treated phenomenologically; interested readers are referred to the papers by Collins,[10] May,[11] and Putzel *et al.*[12] for a more detailed discussion of the possible coupling mechanisms.

While the effects of this thermodynamic coupling have been theoretically investigated with regard to the equilibrium behavior of asymmetric membranes,[11,13,14] its effects on the compositional domain dynamics have received less attention. Wagner *et al.*[13] employed lattice Boltzmann simulations to investigate phase separation processes within asymmetric bilayer membranes. Using the same technique, Ngamsaad *et al.*[15] studied the effects of dynamic asymmetry between the leaflets on phase separation kinetics, in addition to the thermodynamic coupling. Finally, Pantano *et al.*[16] employed coarse-grained molecular dynamics simulations to investigate the recurrence of registration, when domains across the two leaflets are initially displaced from the registry. While these studies have yielded important physical insights into the coupled dynamics of lipid domains, a physically based approach capable of providing quantitative predictions for such dynamics has been lacking.

To this end, in this work, starting from a coarse-grained diffuse-interface approach, we first derive the general equations that describe the dynamics of compositional domains within planar symmetric or asymmetric lipid bilayer membranes. The general equations are then employed to develop analytical solutions for the dynamics of the recurrence of registration for circular domains in the case of weak coupling. In addition, a closed-form expression for the decay rate of interface fluctuations, when only one leaflet supports compositional domains, is derived.

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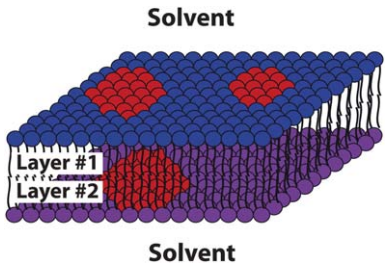

Fig. 1 Schematic of the lipid bilayer membrane model considered in this work. Compositionally segregated domains are indicated in red, and the matrix phase is indicated in blue or purple. Such domains can exist either within both leaflets or only one.

Theoretical approach

As illustrated in the schematic in Fig. 1, we will consider planar lipid bilayer membranes in contact with an aqueous solvent on both sides of the membrane. Compositional domains can exist either within both leaflets or only one, and they may be in or out of registry across the leaflets. In order to model the membrane dynamics within both leaflets, we will employ the so-called diffuse-interface method, which explicitly incorporates both advective and diffusive lipid transport processes within the two coupled leaflets of the 2D membrane,[17,18] and which also allows for asymmetry in terms of composition and thermodynamic behavior.

Within the diffuse-interface formalism, two order parameters (OPs), $\psi_1(\boldsymbol{r}, t)$ and $\psi_2(\boldsymbol{r}, t)$, are employed to quantify the relative composition of matrix-enriched lipid components within the two leaflets. More specifically, the dynamic equations for the OPs, also known as advective Cahn–Hilliard equation,[19] are given by $\partial\psi_I/\partial t + \boldsymbol{u}_{MI} \cdot \nabla\psi_I = M_I\nabla^2\mu_I$, where the subscript $I = 1$ or 2 stands for monolayer 1 or 2, $\boldsymbol{u}_{MI}$ denotes the membrane velocity, M_I denotes mobility, and $\mu_I \equiv \delta F/\delta\psi_I$ denotes the chemical potential, where $F = \int d\boldsymbol{r}[W_1{}^2(\nabla\psi_1)^2/4 + W_2{}^2(\nabla\psi_2)^2/4 + A_1f_1(\psi_1) + A_2f_2(\psi_2) + \Lambda g(\psi_1,\psi_2)]$ denotes a Ginzburg–Landau free energy functional. Furthermore, W_1 and W_2 are constant coefficients, $A_If_I(\psi_I)$ denotes the bulk energy density with magnitude A_I, and the term $\Lambda g(\psi_1,\psi_2)$ incorporates a thermodynamic coupling between the leaflets with strength Λ.[11,13,14]

For the solvent and membrane hydrodynamic flow fields ($\boldsymbol{u}_S$ and $\boldsymbol{u}_M$, respectively), we make the common assumption that they both satisfy the overdamped linearized Navier–Stokes equations $\eta_{SI}\nabla^2\boldsymbol{u}_{SI} - \nabla p_{SI} = 0$, $\eta_{MI}\nabla^2\boldsymbol{u}_{MI} - \nabla p_{MI} + \boldsymbol{f}_{SI} + \Gamma(\boldsymbol{u}_{MII} - \boldsymbol{u}_{MI}) + \boldsymbol{W}_I = 0$ and incompressibility conditions $\nabla \cdot \boldsymbol{u}_{SI} = 0$, $\nabla \cdot \boldsymbol{u}_{MI} = 0$. Again, the subscript I, $II = 1$ or 2. Furthermore, η and p denote the viscosity and pressure, $\boldsymbol{f}_{SI} = \pm\eta_{SI}\partial\boldsymbol{u}_{SI}/\partial z|_{z=0}$ incorporates the coupling between solvent and membrane flow fields, while the term $\Gamma(\boldsymbol{u}_{MII} - \boldsymbol{u}_{MI})$ accounts for intermonolayer friction,[20,21] and $\boldsymbol{W}_I = \mu_I\nabla\psi_I$ accounts for the effects of compositional variations on the membrane pressure field.[19]

In thermodynamic equilibrium, the governing equations admit mean-field solutions for which the domains within each leaflet are delineated by interfaces with constant curvature, and the domains are either in perfect registry or out-of-registry across the two leaflets, depending on the sign of the thermodynamic coupling term. If the system is perturbed by introducing undulating interfaces or displacing the registered domains across the two leaflets apart, the system will relax back towards equilibrium *via* motion of compositional interfaces as driven by interfacial line tension and thermodynamic coupling. [Here we are explicitly assuming that the thermodynamic coupling favors the registered alignment. The analysis below, however, works for either attractive or repulsive interactions between the domains.] The goal is to extract these interface dynamics from the diffuse-interface description *via* the so-called sharp-interface (S-I) limit analysis.[18,22]

Sharp-interface limit equations

The basic qualitative idea of the S-I limit analysis is as follows. For each phase-separated leaflet, we consider solutions to governing equations in two distinct spatial regions, namely those in the vicinity of an interface ("inner region") and away from any interface ("outer region"). The governing equations in the outer region reduce to bulk transport equations, while matching the outer solutions to the inner ones provides the appropriate boundary conditions along the moving interface. Technically, this procedure is carried out by means of matched asymptotic expansions, where we treat the thermodynamic coupling and interface fluctuation as small perturbations.

Upon generalizing the analysis developed for symmetric membranes,[18] the following set of S-I limit equations are obtained.[23] First, away from compositional interfaces, the OP dynamics reduce to advection–diffusion equations given by

$$\frac{\partial\psi_I}{\partial t} + \boldsymbol{u}_{MI} \cdot \nabla\psi_I = M_I\nabla^2\mu_I. \tag{1}$$

The two boundary conditions along the compositional interfaces are given by the kinematic one and the modified Gibbs–Thomson boundary conditions, which are

$$v_{In}|_{int} = u_{MIn}|_{int} + \frac{M_I}{\Delta\psi_I}\left[\frac{\partial\mu_I}{\partial u}\right]_+^-; \tag{2}$$

$$\mu_I|_{int} = \mu_{I;eq} - \frac{\kappa_I\sigma_I}{\Delta\psi_I} + \frac{\Lambda}{\Delta\psi_I}\int_{-\infty}^{+\infty} du\frac{d\psi_{I0}}{du}\frac{\partial[g(\psi_{I0},\psi_{II0})]}{\partial\psi_{I0}}. \tag{3}$$

Finally, compositional interfaces give rise to forces acting upon the membrane as given by

$$\boldsymbol{W}_I = \left[-\kappa_I\sigma_I + \Lambda\int_{-\infty}^{+\infty} du\frac{d\psi_{I0}}{du}\frac{\partial[g(\psi_{I0},\psi_{II0})]}{\partial\psi_{I0}}\right]\delta(\boldsymbol{r} - \boldsymbol{r}_{Is})\hat{\boldsymbol{n}}(\boldsymbol{r}_{Is}). \tag{4}$$

Here, $v_{In}|_{int}$ and $u_{MIn}|_{int}$ are the normal components of interface velocity and membrane velocity at the interface, respectively, u and s denote the coordinate normal and tangential to the interface, while $\Delta\psi_I \equiv \psi_I^+ - \psi_I^-$ denotes the order parameter difference between two bulk phases at equilibrium. Furthermore, $[X]_+^- \equiv X(0^-) - X(0^+)$ denotes the jump in the quantity "X" across the interface, $\mu_I|_{int}$ and $\mu_{I,eq}$ are the chemical potentials at interface and at equilibrium respectively, while κ_I and σ_I denote the interfacial curvature and line tension, respectively. Finally, $\psi_{I0}[u - h_I]$ and $\psi_{II0}[u - h_{II}]$ denote the one-dimensional equilibrium solutions corresponding to planar interfaces displaced by h_I and h_{II} in the absence of thermodynamic coupling and curvature effects within the two leaflets, $\delta(\boldsymbol{r} - \boldsymbol{r}_{Is})$

denotes the delta function, $\boldsymbol{r}_{Is}$ denotes the instantaneous position of the interface, and $\hat{\boldsymbol{n}}$ denotes the normal to the interface.

The interpretation of eqn (1)–(4), the derivation of which constitutes the central result of this manuscript, is straightforward. First, eqn (1) states that lipids undergo both diffusive and advective dynamics as dictated by the local thermodynamic driving forces and membrane flow field. Second, eqn (2) implies that interfaces can move by both lipids diffusing to/away from it and by advection. Third, the local chemical potential along the interfaces is affected by both the local interface curvature and thermodynamic coupling as given by eqn (3). Finally, eqn (4) expresses the fact that interfaces, which are either (a) curved or (b) planar but displaced away from equilibrium across the leaflets, give rise to the effective body forces acting upon the fluid membrane. [We note that in cases where one of the leaflets remains homogeneous, the term involving Λ in eqn (3) contributes a constant which can be ignored, while the corresponding term in eqn (4) no longer appears.[23]]

Before we apply the above S-I limit equations to two representative examples of compositional interface dynamics, namely (1) recurrence of interface registration within symmetric membranes and (2) compositional interface fluctuations within asymmetric membranes, a few pertinent remarks are in order. First, although eqn (2)–(4) explicitly depend on ψ_{I0}, once a specific coupling term g is chosen, the resulting expressions can be written solely in terms of physical parameters, as will be demonstrated below. Second, in deriving eqn (1)–(4), we have treated the thermodynamic coupling as a weak perturbation. In the case of strong coupling, which induces significant compositional variations and additional interfaces within the displaced domains, these equations can still be applied within each "sub-domain", once the parameters σ_I and fields ψ_{I0} (which now depend on Λ) appearing in the expressions have been evaluated numerically.

Recurrence of interface registration in symmetric membranes

When initially registered domains are displaced relative to each other, recurrence of interface registration takes place. Since in experiments, circular domain morphology has been most often observed,[3,5,7] we will study the dynamics of this process for circular domains, which admit explicit analytical solutions in the case of weak thermodynamic coupling.

Here we consider only one domain on each layer and ignore the solvent effect for simplicity (see Fig. 2A for a schematic). We assume that the domains maintain a circular shape with radius R throughout the relaxation process. Initially, one of the registered domains is displaced relative to the other by $\Delta h(0)$ in the x-direction. In order to derive an equation of motion for $\Delta h(t)$, we will consider contributions from advective and diffusive lipid transport separately. For the advection part, we first evaluate the net force on one of the domains for a given configuration from eqn (4), which is

$$F_x = R\int_0^{2\pi}\int_-^+ W_x \,\mathrm{d}u\,\mathrm{d}\theta = \Lambda R\int_0^{2\pi}\left(\int_{-\infty}^{+\infty}\mathrm{d}u\,\frac{\mathrm{d}\psi_{I0}}{du}\frac{\partial g}{\partial\psi_{I0}}\right)\cos\theta\,\mathrm{d}\theta,$$

where $\int_-^+$ denotes an integration across the compositional interface. Then, by introducing a hydrodynamic drag coefficient $\lambda_T(R, \Delta h)$, which depends on both domain radius R and distance between

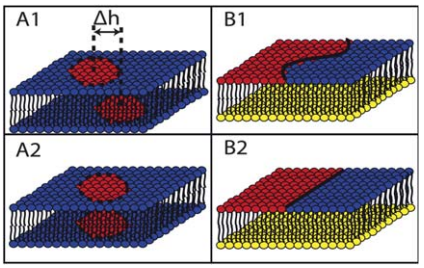

Fig. 2 Schematic of different compositional interface problems considered in this work. In the case of recurrence of interface registration of domains (A), the compositional domains are initially displaced by an amount Δh, and migrate back towards the registry due to the thermodynamic coupling between the leaflets. For the interface fluctuation problem in (B), domains form only within one of the leaflets, while the other remains homogeneous. Here, a curved interface will relax towards a planar one due to line tension.

domains Δh, we obtain the advective contribution to the velocity of approach as $v_{adv} = F_x/\lambda_T(R, \Delta h)$. Next, for the diffusion part, we solve $\nabla^2\mu_I = 0$ for an isolated circular domain embedded within an infinite matrix, subject to the boundary conditions from eqn (3). In particular, it can be shown that $\mu_I = A_0 + \sum_{n=1}^{\infty}A_n\left(\frac{r}{R}\right)^n\cos(n\theta)$ when $r \le R$ and $\mu_I = A_0 + \sum_{n=1}^{\infty}A_n\left(\frac{R}{r}\right)^n\cos(n\theta)$ when $r \ge R$, where $A_0 = \frac{1}{2\pi}\int_0^{2\pi}\mu_I|_{\mathrm{int}}\mathrm{d}\theta$ and $A_n = \frac{1}{\pi}\int_0^{2\pi}\mu_I|_{\mathrm{int}}\cos(n\theta)\mathrm{d}\theta$. By using the boundary conditions $v_{\mathrm{In}}^{\mathrm{diff}}(\theta) = \frac{M_I}{\Delta\psi_I}\left[\frac{\partial\mu_I}{\partial u}\right]_+^-$ from eqn (2) and the relationship $v_{\mathrm{diff}} = \pi^{-1}\int_0^{2\pi}v_{\mathrm{In}}^{\mathrm{diff}}(\theta)\cos\theta\mathrm{d}\theta$, we obtain $v_{\mathrm{diff}} = \frac{2M_I\Lambda}{\pi R(\Delta\psi_I)^2}\int_0^{2\pi}\left(\int_{-\infty}^{+\infty}\mathrm{d}u\frac{\mathrm{d}\psi_{I0}}{\mathrm{d}u}\frac{\partial g}{\partial\psi_{I0}}\right)\cos\theta\mathrm{d}\theta$ due to diffusion alone.[23] Finally, combining the advective and diffusive contributions, we obtain

$$\frac{\mathrm{d}\Delta h}{\mathrm{d}t} = -\frac{2\Lambda}{\pi R}\left[\frac{\pi R^2}{\lambda_T(R,\Delta h)} + \frac{2d_0D}{\sigma}\right]\int_0^{2\pi}\left(\int_{-\infty}^{+\infty}\mathrm{d}u\frac{\mathrm{d}\psi_{I0}}{\mathrm{d}u}\frac{\partial g}{\partial\psi_{I0}}\right)\cos\theta\mathrm{d}\theta, \tag{5}$$

in which we have used the relationship $M\sigma = d_0D(\Delta\psi)^2$,[18] where d_0 and D denote the capillary length and lipid diffusion coefficient, respectively. Note that the thermodynamic coupling term implicitly depends on Δh, thus making eqn (5) in general a non-linear equation.

To make further progress, we will employ a commonly used form for g, namely a local interaction of the form $g(\psi_{I0},\psi_{II0}) = (\psi_{I0} - \psi_{II0})^2/\Delta\psi_0{}^2$.[11,13] In the S-I limit, where we can approximate ψ_{I0} and ψ_{II0} as step functions, it is straightforward to simplify eqn (5) to yield

$$\frac{\mathrm{d}|\Delta h|}{\mathrm{d}t} = -\frac{2\Lambda}{\pi R}\left[\frac{4\pi R^2}{\lambda_T(R,\Delta h)} + \frac{8d_0D}{\sigma}\right]\sqrt{1-\left(\frac{\Delta h}{2R}\right)^2}\times\Theta(|\Delta h|), \tag{6}$$

where $\Theta(x)$ denotes the unit step function such that $\Theta = 1$ for $x > 0$ and zero otherwise, and $\Delta h(0) < 2R$ to guarantee non-zero initial overlap. Due to the hydrodynamic interaction between the domains, we have been unable to derive a closed-form expression for λ_T with an arbitrary Δh. However, an explicit expression can be derived for

the case of perfect overlap (*i.e.*, $\Delta h = 0$). By following the approach in ref. 24, we can explicitly solve the hydrodynamic equations to yield $\lambda_T(R,0) \equiv \hat{\lambda}_T = 4\pi\eta_M\left(\frac{1}{2}\nu^2 + \frac{\nu K_1(\nu)}{K_0(\nu)}\right)$, where $\nu \equiv R\sqrt{2\Gamma/\eta_M}$, and K_0 and K_1 denote the modified Bessel functions of the second kind of orders zero and one, respectively.[23] Note that in the limit $R \ll R_c$, where $R_c \equiv \sqrt{\eta_M/2\Gamma}$, $\hat{\lambda}_T \approx 4\pi\eta_M/[\ln(2R_c/R) - \gamma]$, where $\gamma = 0.577\ldots$ denotes the Euler's constant, while in the opposite limit $R \gg R_c$, $\hat{\lambda}_T \approx 4\pi\Gamma R^2$.

Upon employing the approximation $\lambda_T(R,\Delta h) \approx \hat{\lambda}_T$, eqn (6) can be now explicitly solved to yield $\frac{\Delta h(t)}{2R} = \sin\left[\arcsin\left(\frac{\Delta h(0)}{2R}\right)\left(1 - \frac{t}{\tau_r}\right)\right]$, where $\tau_r \equiv \arcsin\left(\frac{\Delta h(0)}{2R}\right) \Big/ \left[\Lambda\left(\frac{4}{\hat{\lambda}_T} + \frac{8d_0D}{\pi R^2\sigma}\right)\right]$ denotes the time it takes for the shifted domains to return to the registry. By employing representative values for the parameters appearing in τ_r, namely $\Delta h(0) = R$, $\Gamma = 10^8$ Pa s m^{-1}, $\eta_M = 10^{-9}$ Pa s m, $d_0 = 10^{-9}$ m, $D = 10^{-12}$ m^2 s^{-1}, $\sigma = 10^{-12}$ N, and $\Lambda = 10^{-4}$ J m^{-2}, we obtain $\tau_r \sim 10^{-4}$ s for $R = 10$ nm and $\tau_r \sim 10^2$ s for $R = 10$ μm. It is interesting to note that the sliding of the two leaflets and diffusion within each leaflet give rise to comparable contributions to τ_r above in the case of liquid domains.

Interestingly, Pantano *et al.* have recently studied the dynamics of domain registration *via* coarse-grained MD simulations.[16] In their work, simulations were employed to evaluate the effective coupling strength Λ. By employing the values $\Lambda \approx 10^{-2}$ J m^{-2} and $\tau_r \approx 3.3 \times 10^{-7}$ s for domains of size $R = 4$ nm as reported by Pantano *et al.*, we can employ our expression to compute the frictional coupling strength between the leaflets (which was not reported) to be $\Gamma \approx 10^8$ Pa s m^{-1}, which falls right into the reasonable range of experimental measurements.[20,21] Perhaps more importantly, by experimentally measuring the registration kinetics of initially displaced circular domains, one can quantify the magnitude of the coupling coefficient Λ by employing eqn (6), once the other relevant physical parameters (D, σ, d_0, η_M, and Γ) have been determined independently. Of course, one can in principle experimentally measure Λ by quantifying the out-of-registry fluctuations between the domains, as discussed by Putzel *et al.*;[12] however, fluctuations are expected to be very small in magnitude (~1 nm), which poses significant experimental challenges.

Compositional interface fluctuations in asymmetric membranes

Finally, to further highlight the generality of the S-I limit equations [*i.e.*, eqn (1)–(4)], we discuss the case of interface fluctuation within asymmetric membranes as the second example. Here, we will consider one experimentally observed case (see, *e.g.*, ref. 5), where one of the leaflets remains homogeneous while the other one contains compositional domains, as illustrated in Fig. 2B.

Starting from a gently undulating interface, the fluctuation amplitude decays to zero driven by line tension. Assuming a sinusoidal form $h = h_0 \exp(i\omega_k t + ikx)$ for the interface fluctuation, the goal is to compute the decay rate $i\omega_k$ *versus* wave number k. Following the procedure outlined previously,[18] by solving the coupled hydrodynamic equations for the two leaflets and solvent as well as eqn (1)–(4), we obtain

$$i\omega_k = -\frac{\sigma k^3}{2\pi}\int_{-\infty}^{+\infty}\frac{a_2}{(a_1a_2 - \Gamma^2)}\frac{d\tilde{q}}{(1+\tilde{q}^2)} - 2Dd_0k^3, \qquad (7)$$

where $a_n \equiv \eta_{Mn}k^2(1+\tilde{q}^2) + \eta_{Sn}k\sqrt{1+\tilde{q}^2} + \Gamma$.[23] To illustrate the new physics contained in eqn (7), we will consider the case in which the homogeneous layer is effectively immobile (for example, due to a solid support) and choose $\eta_{M2} = \infty$ correspondingly. In this case,

$$i\omega_k \approx -\left(\frac{\sigma}{2\Gamma} + 2Dd_0\right)k^3 \text{ when } k \to 0. \qquad (8)$$

Thus, both lipid diffusion and sliding of the two leaflets relative to each other contribute $\sim k^3$ terms to the decay rate. This behavior should be readily observable in supported membranes.

Conclusion

In this work, starting from a diffuse-interface approach, we have derived the general equations that describe the dynamics of compositional domains within symmetric or asymmetric lipid bilayer membranes in the presence of a thermodynamic coupling between the leaflets. The general equations were then employed to quantify the dynamics of the recurrence of registration for circular domains in the case of weak coupling. It was shown that experimentally measuring these dynamics would enable one to determine the strength of the thermodynamic coupling between the leaflets. A closed-form expression for the decay rate of interface fluctuations, in the case in which only one leaflet supports compositional domains, was also derived.

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References

1 K. Simons and E. Ikonen, *Nature*, 1997, **387**, 569.
2 D. A. Brown and E. London, *Annu. Rev. Cell Dev. Biol.*, 1998, **14**, 111.
3 S. L. Veatch and S. L. Keller, *Biochim. Biophys. Acta*, 2005, **1746**, 172.
4 T.-Y. Wang and J. R. Silvius, *Biophys. J.*, 2001, **81**, 2762.
5 S. Garg, J. Rühe, K. Lüdtke, R. Jordan and C. A. Naumann, *Biophys. J.*, 2007, **92**, 1263.
6 M. D. Collins and S. L. Keller, *Proc. Natl. Acad. Sci. U. S. A.*, 2008, **105**, 124.
7 V. Kiessling, C. Wan and L. K. Tamm, *Biochim. Biophys. Acta*, 2009, **1788**, 64.
8 S. J. Marrink, J. Risselada and A. E. Mark, *Chem. Phys. Lipids*, 2005, **135**, 223.
9 S. V. Bennun, M. L. Longo and R. Faller, *Langmuir*, 2007, **23**, 12465.
10 M. D. Collins, *Biophys. J.*, 2008, **94**, L32.

11 S. May, *Soft Matter*, 2009, **5**, 3148.
12 G. G. Putzel, M. J. Uline, I. Szleifer and M. Schick, *Biophys. J.*, 2011, **100**, 996.
13 A. J. Wagner, S. Loew and S. May, *Biophys. J.*, 2007, **93**, 4268.
14 G. G. Putzel and M. Schick, *Biophys. J.*, 2008, **94**, 869.
15 W. Ngamsaad, S. May, A. J. Wagner and W. Triampo, *Soft Matter*, 2011, **7**, 2848.
16 D. A. Pantano, P. B. Moore, M. L. Klein and D. E. Discher, *Soft Matter*, 2011, **7**, 8182.
17 J. Fan, T. Han and M. Haataja, *J. Chem. Phys.*, 2010, **133**, 235101.
18 T. Han and M. Haataja, *Phys. Rev. E: Stat., Nonlinear, Soft Matter Phys.*, 2011, **84**, 051903.
19 P. C. Hohenberg and B. I. Halperin, *Rev. Mod. Phys.*, 1977, **49**, 435.
20 R. Merkel, E. Sackmann and E. Evans, *J. Phys. (Paris)*, 1989, **50**, 1535.
21 T. Pott and P. Méléard, *Europhys. Lett.*, 2002, **59**, 87.
22 K. R. Elder, M. Grant, N. Provatas and J. M. Kosterlitz, *Phys. Rev. E: Stat., Nonlinear, Soft Matter Phys.*, 2001, **64**, 021604.
23 T. Han and M. Haataja, 2012, manuscript in preparation.
24 E. Evans and E. Sackmann, *J. Fluid Mech.*, 1988, **194**, 553.