Hydrodynamic interaction between overlapping domains during recurrence of registration within planar lipid bilayer membranes

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I. INTRODUCTION

Lipid bilayer membranes are often idealized as simple two-dimensional (2D) liquid sheets which may contain compositional lipid domains or other inclusions, and which are embedded in a three-dimensional (3D) aqueous solvent. The internal structure of the bilayer and the couplings between the two leaflets (both thermodynamic and kinematic), however, affect many important equilibrium and dynamic membrane properties. For example, strong spatial correlations between compositional lipid domains residing within opposing leaflets are often observed [1–3], and in the case of membranes with an asymmetry in the lipid compositions across the leaflets, it has been demonstrated that domains within one “active” leaflet can induce the formation of domains in the opposing “passive” leaflet even when the phase diagram of the passive one would not support coexisting phases [2]. Furthermore, if the system is perturbed by displacing one domain relative to the other, diffusive and advective lipid fluxes are established to restore equilibrium and reestablish the thermodynamically favored domain overlap configuration [4,5]. Finally, a friction coefficient couples the hydrodynamic flow fields within the leaflets [6–8], thus affecting the motion of objects embedded within the leaflets.

Very recently, we have developed an analytical treatment of the dynamics of recurrence of registration of two compositional lipid domains residing within opposing leaflets of a planar bilayer membrane [5]. In particular, we derived a closed-form expression for the rate of approach, which explicitly incorporates both diffusive and advective lipid transport effects, and wherein the advective part is expressed in terms of a hydrodynamic drag coefficient $\lambda_T$, given by the ratio of the net force acting on one domain and its instantaneous speed. This drag coefficient in turn depends on both the domain radius $R$ as well as the separation between the domains $\Delta h$.

In the present work, we generalize the analysis to the case of liquid domains whose properties may differ from those of the matrix phase, and the results presented in our previous work are recovered as a special case by setting the viscosity of the liquid domains to infinity in the analytical expressions. Furthermore, we numerically explore the behavior of $\lambda_T$ as a function of $R$ and $\Delta h$ over a wide range of parameter values. These numerical results are in turn employed to develop simple, analytically tractable expressions for $\lambda_T$, which together with our analytical results from Ref. [5] provide a comprehensive means to quantify the compositional domain registration dynamics.

The rest of this manuscript is organized as follows. In Sec. II we outline the theoretical model employed in the analysis and numerical simulations, while Sec. III contains both the derivation of $\lambda_T$ for perfect overlap and presentation of numerical simulation results for $\lambda_T(R,\Delta h)$. Finally, a discussion of our results and concluding remarks are presented in Sec. IV, while some of the key steps in the derivation of $\lambda_T$ can be found in the Appendix.

II. THEORETICAL MODEL

In our approach, both leaflets of the planar bilayer membrane embedded within a 3D aqueous solvent support compositional lipid domains, as illustrated schematically in Fig. 1. The domains residing within opposing leaflets can be either solid or liquid, while the matrix phase is taken to be liquid. In order to account for the presence of these domains, two order parameters (OPs) are introduced, one for each leaflet.
FIG. 1. (Color online) Schematic of the recurrence of registration process in a planar bilayer. Initially, two circular domains of radius \( R \) (shown in blue) residing against opposing leaflets are displaced out of registry, and the domains subsequently slide back to registry driven by a thermodynamic interaction between the domains. The drag registry, and the domains subsequently slide back to registry driven (shown in blue) residing within opposing leaflets are displaced out of process in a planar bilayer. Initially, two circular domains of radius \( R \) are embedded, has been omitted from the schematic for clarity.

Physically, these OPs quantify the relative lipid compositions within each leaflet, and they satisfy the so-called advective Cahn-Hilliard equations [5,9],

\[
\frac{\partial \psi_I}{\partial t} + \mathbf{u}_{M_I} \cdot \nabla \psi_I = \nabla \cdot [M \nabla \mu_I],
\]

where the subscript \( I = 1 \) or 2 stands for the upper and lower leaflets, respectively, \( \mathbf{u}_{M_I} \) is the membrane velocity, \( M(\psi_I) \) denotes the mobility, and \( \mu_I \equiv \delta F/\delta \psi_I \) denotes the chemical potential, where \( F = \int d\mathbf{r}[W_I^1(\nabla \psi_I)^2/4 + W_I^2(\nabla \psi_I)^2/4 + A_1 f_I(\psi_I) + A_2 f_2(\psi_I) + \Lambda g(\psi_I, \psi_I)] \) denotes a Ginzburg-Landau free energy functional. Furthermore, \( W_1 \) and \( W_2 \) are constant coefficients, while \( A_1 f_I(\psi_I) \) denotes the bulk energy density with magnitude \( A_1 \). Finally, the term \( \Lambda g(\psi_I, \psi_I) \) incorporates a thermodynamic coupling between the leaflets with strength \( \Lambda \). For convenience, we choose the typical functional forms given by \( A_1 f_I(\psi_I) = -\frac{a}{2} \psi_I^2 + \frac{b}{4} \psi_I^4 \) with \( a = \text{const.} \), \( b = \text{const}, \) and \( W_1 = W_2 = W \), and the compositional coupling is the local coupling \( g(\psi_I, \psi_I) = (\psi_I - \psi_I^2) / \Delta \psi^2 \) [10,11], with \( \Delta \psi = 2 / \sqrt{\bar{\alpha} B} \).

Equation (1) explicitly incorporates both advective and diffusive transport mechanisms. For the advective part, we assume that the hydrodynamic flow fields within the two leaflets are incompressible and dominated by viscosity over inertial effects, such that the membrane velocity fields are governed by the creeping flow equations,

\[
\frac{\partial}{\partial \mathbf{x}} \left[ \eta_I(\psi_I) \left( \frac{\partial \mathbf{u}_{M,I}}{\partial \mathbf{x}_j} + \frac{\partial \mathbf{u}_{M,I}}{\partial \mathbf{x}_j} \right) + \frac{\partial p_{M,I}}{\partial \mathbf{x}_k} \delta_{jk} \right] + \Gamma(\psi_I, \psi_I)(\mathbf{u}_{M,I} - \mathbf{u}_{M,I}) + W_{I,j} = 0
\]

for \( j = x \) or \( y \), and

\[
\nabla \cdot \mathbf{u}_{M_I} = 0.
\]

In Eq. (2), summation over repeated indices is implied, and \( \delta_{jk} \) denotes the Kronecker delta. Furthermore, \( \eta_I(\psi_I) \) and \( p_{M,I} \) denote the phase-dependent viscosity and pressure, respectively, and \( \mathbf{u}_{M,I} \) denotes the membrane velocity field of the leaflet under consideration, while \( \mathbf{u}_{M,I} \) denotes that of the opposing leaflet. The term \( \Gamma(\psi_I, \psi_I)(\mathbf{u}_{M,I} - \mathbf{u}_{M,I}) \) in turn incorporates interleaflet friction forces acting on the flow fields within the two layers [6,7]. Finally, \( \mathbf{W}_J = \mu_J \nabla \psi_J \) accounts for the effects of compositional variations on the membrane pressure field [9].

In principle, one should also explicitly account for the effects of the 3D viscous solvent on membrane hydrodynamics in Eq. (2), especially in light of the fact that the hydrodynamic properties of the solvent control many important dynamic processes on membranes, such as diffusion of large solid or liquid domains [12], compositional interface fluctuations at long wavelengths [13–15], and asymptotic decay of critical fluctuations [16,17]. As is well known by now, in membranes suspended in an infinite solvent, the effects of the solvent begin to dominate when the characteristic domain size exceeds the so-called hydrodynamic length \( l_H \equiv \eta_M / \eta_S \), where \( \eta_S \) denotes the viscosity of the 3D solvent within which the membrane is embedded [12,18,19]. In the particular case of interest in the present work, however, domains within opposing leaflets slide towards each other as driven by the thermodynamic coupling, and interleaflet friction plays a key role. More specifically, a length scale \( R_c = \sqrt{\eta_M / (2 \Gamma)} \) emerges from the analysis in Sec. III, and for typical parameter values (\( \eta_M = 10^{-3} \text{ Pa s}, \) \( \eta_S = 10^{-3} \text{ Pa s}, \) and \( \Gamma = 10^8 \text{ Pa s/m}) \), \( R_c \approx 2 \text{ nm} \). When \( R > R_c \), \( \lambda_T \sim \Gamma R^2 \), while the corresponding drag from the solvent phase estimated from the Hughes-Pailthorpe-White model [12] is given by \( \lambda_{TPW} \sim \eta_S R \), implying that \( \lambda_T / \lambda_{TPW} \sim \Gamma R / \eta_S \gg 1 \) for all physically reasonable domain sizes \( R \), that is, the drag from the solvent is but a minor perturbation, and can be safely neglected. Physically, this results from the fact that the presence of the thermodynamic coupling \( \Lambda \) induces an internal force distribution with overall dipolar character within the membrane, and the creeping flow equations in Eq. (2) admit nonsingular solutions even in the absence of the solvent; of course, the effect of the solvent cannot be neglected when evaluating the overall drag coefficient of a tightly bound pair of domains residing in opposing leaflets under an external force.

III. HYDRODYNAMIC INTERACTION BETWEEN TWO APPROACHING DOMAINS RESIDING WITHIN OPPOSING LEAFLETS

Having formulated the governing continuum equations, the behavior of the hydrodynamic drag coefficient, which quantifies the hydrodynamic interaction between two domains residing within opposing leaflets and moving in opposite directions, will be considered next. First, an analytic derivation for the drag coefficient for the special case of two perfectly overlapping domains will be presented. Then, its behavior is explored numerically over a wide range of domain separations \( \Delta h \) and other physical parameters.

A. Analytical derivation for perfectly overlapping domains

Due to the complexity of the hydrodynamic interaction when \( \Delta h \neq 0 \), a closed-form expression for \( \lambda_T \) has eluded us. However, an explicit expression can be obtained for the special case of perfect overlap (\( \Delta h = 0 \)) where the domains move in opposite directions with velocity \( \mathbf{v}_0 \) by exploiting a symmetry of the problem, as will be discussed next.
To facilitate the analysis, we will assume that the domain radius $R \gg \xi$, where $\xi$ denotes the width of the compositional interface delineating the domain and the matrix phase. In this limit, the governing equations—Eqs. (1) and (2)—can be analyzed in the so-called sharp interface limit [5,13,20,21], wherein the driving force $\mathbf{W}$ due to the thermodynamic coupling acts only along the domain boundaries. In the calculation, the domains are taken to be circular disks of radius $R$, and given the instantaneous velocity of each domain in the laboratory frame ($\mathbf{v}_0$), the drag force on each domain will be computed.

For the analytical part here, we will consider the general case, in which the viscosity and friction coefficient can be different between the domains and the matrix phase. From the sharp-interface limit analysis, it can be shown [5,21] that in the matrix phase (that is, for $r \gg R$), the hydrodynamic equations simplify to

$$\eta \nabla^2 \mathbf{u}_{M1} - \nabla p_{M1} + \Gamma (\mathbf{u}_{M1} - \mathbf{u}_{M2}) = 0 \quad \text{and} \quad \nabla \cdot \mathbf{u}_{M1} = 0,$$

where $\eta$ is the viscosity, and $\Gamma$ denotes the friction coefficient between matrix phases on two layers. Within the domains (i.e., for $r < R$), Eq. (4) still holds, with $\eta$ and $\Gamma$ replaced by $\eta'$ and $\Gamma'$, respectively. Furthermore, the appropriate boundary conditions can be written,

$$\tau_{\theta \theta}(r \rightarrow R, ., \theta) = \tau_{\theta \theta}^\prime(r \rightarrow R - ., \theta);$$

$$\mathbf{u}_{M1}(r \rightarrow R, ., \theta) = \mathbf{u}_{M1}(r \rightarrow R - ., \theta);$$

$$\int_0^R \int_0^{2\pi} \mathbf{u}_{M1,2}(r, \theta) r d \theta dr = \pm \mathbf{v}_0 \pi R^2;$$

$$\mathbf{u}_{M1,2} \rightarrow \mathbf{0} \quad \text{when} \ r \rightarrow \infty,$$

where $\tau_{\theta \theta}$ is the shear stress. While Eqs. (5), (6), and (8) are standard and express the continuity of shear stress and velocity field across the domain boundary within both leaflets as well as enforce that the fluids are quiescent at infinity, Eq. (7) warrants further discussion. Along the domain boundary, the normal stress undergoes a jump discontinuity whose magnitude is given by $\alpha \kappa(s)$, where $\alpha$ denotes the line tension (taken constant here) while $\kappa(s)$ denotes the interface curvature. Since the shape of the domain is unknown a priori, the discontinuity in the normal stress turns the problem into a fully nonlinear one. Assuming that the domain shape remains circular (that is, the effective capillary number $Ca \equiv \eta \nabla u_M R / \sigma \ll 1$), we relax this discontinuity boundary condition and replace it with a physically based one in Eq. (7), which simply states that the spatial averages of the flow fields within the domains are given by $\pm \mathbf{v}_0$. We note that this boundary condition is also physically based in the case of a solid domain for which $\mathbf{u}_{M1,2} = \pm \mathbf{v}_0 \mathbf{x}$ within the domain, corresponding to rigid body motion.

If we now define $\mathbf{v}_a \equiv \mathbf{u}_{M1} - \mathbf{u}_{M2}$, $p_a \equiv p_{M1} - p_{M2}$, $\mathbf{v}_b \equiv \mathbf{u}_{M1} + \mathbf{u}_{M2}$, and $p_b \equiv p_{M1} + p_{M2}$, the hydrodynamic equations above reduce to

$$\eta \nabla^2 \mathbf{v}_a - \nabla p_a = 2\Gamma \mathbf{v}_a \quad \text{and} \quad \nabla \cdot \mathbf{v}_a = 0 \quad \text{when} \ r \geq R;$$

$$\eta \nabla^2 \mathbf{v}_b - \nabla p_b = 2\Gamma' \mathbf{v}_b \quad \text{and} \quad \nabla \cdot \mathbf{v}_b = 0 \quad \text{when} \ r < R,$$

with

$$\mathbf{v}_a = \mathbf{0} \quad \text{at} \ r = \infty,$$

and

$$\eta \nabla^2 \mathbf{v}_b - \nabla p_b = 0 \quad \text{and} \quad \nabla \cdot \mathbf{v}_b = 0 \quad \text{when} \ r \geq R;$$

$$\eta' \nabla^2 \mathbf{v}_b - \nabla p_b = 0 \quad \text{and} \quad \nabla \cdot \mathbf{v}_b = 0 \quad \text{when} \ r < R,$$

with

$$\mathbf{v}_b = \mathbf{0} \quad \text{at} \ r = \infty.$$

Now, Eqs. (9) and (10), together with the boundary conditions expressed in Eq. (11), have already been studied by Ramachandran et al. [22] in a different context, while Eqs. (12)–(14) admit a trivial solution $\mathbf{v}_b = \mathbf{0}$. By following the procedure outlined in Ref. [22], we can readily solve the governing equations above and obtain the total drag force. For completeness, the solution procedure for obtaining $\mathbf{v}_a$ and forces acting on the domain is outlined in the Appendix, with the result that the total drag force on one of the domains is given by

$$F_T = \pi \mathbf{v}_0 \left\{ \epsilon^2 \eta + \epsilon^2 \eta' + \frac{4\epsilon K_0}{4 + \epsilon^2} [(4 + \epsilon^2) I_1 - 2\epsilon' I_0 + 2(\epsilon' I_0 - 2I_1)] \right\},$$

where $\epsilon = R/Rc \equiv \sqrt{\frac{\eta}{\eta'}}$, $\epsilon' = R/Rc' \equiv \sqrt{\frac{\eta}{\eta'}}$, $E \equiv \eta/\eta'$, and where $I_1 = I_1(\epsilon')$ and $K_i = K_i(\epsilon)$ denote modified Bessel functions of the first and second kind, order $i$, respectively. Hence, the drag coefficient $\lambda_{T0} \equiv \lambda_T (R, \Delta h = 0)$ for perfectly overlapping liquid domains residing within opposing leaflets moving in opposite directions with velocity $\mathbf{v}_0$ is explicitly given by

$$\lambda_{T0} = \frac{F_T}{\mathbf{v}_0} = \frac{\pi}{\epsilon^2 \eta + \epsilon^2 \eta'} \left\{ \frac{4\epsilon K_0}{4 + \epsilon^2} [(4 + \epsilon^2) I_1 - 2\epsilon' I_0 + 2(\epsilon' I_0 - 2I_1)] \right\}.$$
where the domain and the matrix have identical viscosities and friction coefficients (that is, \( \eta = \eta' = \eta_M \) and \( \Gamma = \Gamma' \)), which will be studied numerically below, the expression above simplifies to
\[
\lambda_{T0} = \frac{2\pi \eta_M \epsilon^3 (I_1 K_0 + I_0 K_1)}{\epsilon (I_1 K_0 + I_0 K_1) - 2 I_1 K_1}. 
\] (17)

We note that there are two contributions to \( \lambda_{T0} \) in Eq. (17). The first term originates from the interleaflet friction effect and pressure variations within each leaflet, while the second one accounts for dissipative flow within each leaflet. The relative importance between these two contributions to \( \lambda_{T0} \) is controlled by the dimensionless parameter \( \epsilon \). In the limit \( \epsilon \ll 1 \) (\( R \ll R_s \)), membrane viscosity dominates, and \( \lambda_{T0} \approx 4\pi \eta_M / [\ln(2R_s/R) - \gamma + 1/4] \), where \( \gamma = 0.577 \ldots \) denotes the Euler’s constant. In the opposite limit \( \epsilon \gg 1 \) (\( R \gg R_s \)), on the other hand, interleaflet friction dominates, and \( \lambda_{T0} \approx 4\pi \Gamma R^2 \). Crossover from viscosity-dominated to friction-dominated behavior occurs for \( \epsilon \sim 1 \) or \( R \sim R_s \approx 2 \text{ nm} \) for typical parameter values. Thus, for all practical cases of interest in lipid membranes, \( \lambda_{T0} \) is always dominated by interleaflet friction, such that \( \lambda_{T0} \approx 4\pi \Gamma R^2 \).

It is also straightforward to extract the behavior of \( \lambda_{T0} \) in the case of a solid domain by setting \( \eta' \to \infty \) and \( \eta = \eta_M \) in Eq. (16), resulting in a simpler expression,
\[
\lambda_{T0,\text{solid}} = 4\pi \left[ R^2 \left( \frac{\Gamma + \Gamma'}{2} \right) + \frac{\epsilon K_1(\epsilon) \eta_M}{K_0(\epsilon)} \right]. 
\] (18)

It is noteworthy that the expression above has been derived previously by Evans and Sackmann [23] in the context of a cylindrical membrane inclusion coupled to a substrate via a frictional force. As in the case of \( \lambda_{T0} \) for liquid domains, the expression for \( \lambda_{T0,\text{solid}} \) in Eq. (18) displays simple limiting behavior. In particular, when interleaflet friction dominates (\( \epsilon \gg 1 \)), \( \lambda_{T0,\text{solid}} \approx 2\pi (\Gamma + \Gamma')R^2 \), which is identical to the liquid domain case when \( \Gamma = \Gamma' \). On the other hand, when membrane viscosity dominates (\( \epsilon \ll 1 \)), \( \lambda_{T0,\text{solid}} \approx 4\pi \eta_M / [\ln(2R_s/R) - \gamma] \), which differs from the corresponding expression for liquid domains by a constant 1/4 in the denominator.

**B. Numerical simulations**

The derivation above exploited the presence of a convenient symmetry in the case of perfect overlap (\( \Delta h = 0 \)), while the drag coefficient is expected to explicitly depend on \( \Delta h \). To extract this dependence, we will numerically simulate the registration process of two compositional liquid domains embedded in opposing leaflets, and from the dynamics determine the \( \Delta h \)-dependent drag coefficient. In the simulations reported below, the viscosities and friction coefficients are taken to be phase independent.

To facilitate the numerical solution to the governing equations, namely Eqs. (1) and (2), we will first convert them into dimensionless form. To this end, we will rescale spatial coordinates by the correlation length \( \xi \), time by the diffusion time within the correlation length \( t_d = \xi^2 / D \), where \( D \) denotes the lipid diffusivity (taken to be phase independent in this work), all velocities by \( \xi / t_d \), and chemical potential by \( \mu_0 \). These rescalings lead to the dimensionless advective-diffusion equation,
\[
\frac{\partial \psi}{\partial t} + \tilde{u}_M \cdot \nabla \psi = \frac{M \mu_0}{D} \nabla^2 \tilde{\mu}, 
\] (19)

where \( \tilde{X} \) denotes a dimensionless form for variable \( X \). The hydrodynamic equations in turn can be expressed in dimensionless form as
\[
\tilde{\eta}_M \nabla^2 \tilde{u}_M = -\frac{p_0}{\mu_0} \nabla \tilde{p}_M + \tilde{\Gamma} (\tilde{u}_M - \tilde{u}_M) + \tilde{\mu} \nabla \psi = 0, 
\] (20)

and
\[
\tilde{\nabla} \cdot \tilde{u}_M = 0, 
\] (21)

where \( \tilde{\eta}_M \equiv \eta_M D / \mu_0^2 \), and \( \tilde{\Gamma} \equiv \Gamma D / \mu_0^2 \), and \( p_0 \) denotes the dimensional pressure. For the chemical potential, we have
\[
\tilde{\mu}_I = \frac{\delta F}{\delta \psi_I} = -\frac{W_2}{2} \nabla^2 \psi_I - a \psi_I + b \psi_I^2 + \frac{2 \tilde{\Lambda}}{\Delta \psi^2} (\psi_I - \psi_{1I}), 
\] (22)

which can be written in dimensionless form as
\[
\tilde{\mu}_I = \frac{W_2}{\xi^2 \mu_0} \left( -\frac{1}{2} \nabla^2 \psi_I \right) - a \psi_I + b \psi_I^2 + \frac{2 \tilde{\Lambda}}{\Delta \psi^2} (\psi_I - \psi_{1I}), 
\] (23)

where \( \tilde{\Lambda} \equiv \Lambda / \mu_0 \). Next, we choose \( \mu_0 = \lambda_0 = a = b \), and exploit the S-1 limit results \( \xi = \sqrt{W^2 / a}, D = M a \), and \( \sigma = a \sqrt{a W^2 / b} = \sqrt{a W^2} \), where \( \sigma \) denotes the line tension between the domain and the matrix phase [13,20]. Substituting these relations into the above equations leads to a set of dimensionless equations in final form as
\[
\frac{\partial \psi_I}{\partial t} + \tilde{u}_M \cdot \tilde{\nabla} \psi_I = \tilde{\nabla}^2 \tilde{\mu}_I, 
\] (24)

\[
\tilde{\eta}_M \tilde{\nabla}^2 \tilde{u}_M - \tilde{\nabla} \tilde{p}_M + \tilde{\Gamma} (\tilde{u}_M - \tilde{u}_M) + \tilde{\mu} \tilde{\nabla} \psi = 0, 
\] (25)

and
\[
\tilde{\mu}_I = -\frac{1}{2} \tilde{\nabla}^2 \psi_I - \psi_I + \psi_I^2 + \frac{2 \tilde{\Lambda}}{\Delta \psi^2} (\psi_I - \psi_{1I}), 
\] (27)

where \( \tilde{\eta}_M \equiv \eta_M D / \sigma \xi, \tilde{\Lambda} \equiv \Lambda \xi / \sigma, \) and \( \tilde{\Gamma} \equiv \Gamma D \xi / \sigma \). We note that for a typical membrane system, \( \xi \sim 10^{-9} \text{ m} \), \( \sigma \sim 10^{-12} \text{ N}, D \sim 10^{-12} \text{ m}^2 / \text{s}, \) \( \Lambda \sim 10^{5} \sim 10^{-3} \) \text{ J/m}^2, \( \eta_M \sim 10^{-9} \) \text{ Pa s }, and \( \Gamma \sim 10^9 \) \text{ Pa s/nm}, which imply that \( \tilde{\Lambda} = O(10^{-2}-1), \tilde{\eta}_M \sim 1, \) and \( \tilde{\Gamma} \sim 0.1 \). As the goal of the present work, however, is to quantify the behavior of the drag coefficient, we will employ much smaller values for \( \tilde{\eta}_M \) and \( \tilde{\Gamma} \) in the numerical simulations to enhance the contribution of advective lipid transport over the diffusive one to the domain registration kinetics. In the remainder of this section, for notational clarity and ease, we will drop the bars indicating dimensionless variables with the understanding that all variables discussed below refer to dimensionless ones.
FIG. 2. (Color online) Representative order parameter configurations taken at times $t = 0$ (top left), 5 (top right), 10 (bottom left), and 18 (bottom right) during the recurrence of registration process for the interleaflet-friction-dominated case. The parameter values employed in this simulation were set to $R = 15$, $\Gamma = 0.001$, and $\eta_M = 0.001$. Black indicates overlapping regions between the domains in opposing leaflets, while the lighter shades correspond to nonoverlapping regions of the domains within the upper (blue) and lower (red) leaflet. White arrows correspond to the instantaneous membrane velocity field in the upper leaflet.

Now, in order to numerically solve Eq. (24), we employ a spectral method and integrate the equation in Fourier space. By using the incompressibility condition and carrying out a spatial Fourier transformation, we arrive at

$$\frac{\partial \hat{\psi}_I}{\partial t} + iq_x (\hat{u}_{MIx} \hat{\psi}_I) + iq_y (\hat{u}_{MIy} \hat{\psi}_I) = -(\hat{q}_x^2 + \hat{q}_y^2) \hat{\mu}_I,$$

(28)

where $q_x$ and $q_y$ denote the wave vectors, and the notation $\hat{f}$ implies the Fourier transform of $f$. The chemical potentials $\mu_I$ are first evaluated in real space, then Fourier transformed to yield $\hat{\mu}_I$. By exploiting the linearity of the governing equations, the membrane flow fields $\hat{u}_{MI}$ are first readily computed in Fourier representation and then transformed back to real space. The products $\hat{u}_{MI} \hat{\psi}_I$ are subsequently first evaluated in real space and then transformed to Fourier space in order to evolve the OPs as per Eq. (28) using an explicit Euler method. Periodic boundary conditions are employed in the simulation. We set the numerical grid spacing to be $\Delta x = \Delta y = 0.5$. In order to keep the domains as circular as possible during the registration process, a relatively weak thermodynamic coupling is employed ($\Lambda = 0.04 \ll 1$).

The system is initialized by introducing two circular domains of radius $R$ (one in each leaflet) and displacing their centers by an amount $\Delta h_0$. Since we are considering a local thermodynamic coupling of the form $g(\psi_1, \psi_2) = (\psi_1 - \psi_2)^2 / \Delta \psi^2$ [10,11], with $\Delta \psi = 2\sqrt{a/b} = 2$, the initial separation is restricted to values $\Delta h_0 \leq 2R$ so as to guarantee a nonzero initial domain overlap. In particular, in the absence of any domain overlap, the thermodynamic coupling does not induce advective flow processes in incompressible systems with nonoverlapping circular domains due to radial symmetry [24]. Of course, introducing a sufficiently long-ranged attractive interaction between the domains will drive them towards registry even in the absence of initial overlap. In addition, the nonoverlapping domains still continue to interact indirectly through hydrodynamic interactions, such that the motion of one affects that of the other, while chemical potential gradients.
within the same leaflet between a compositional domain and a thermodynamic coupling-induced “image” domain will facilitate the recurrence of a registration process via long-ranged, purely diffusive mass transport processes [21], rather than the advective ones studied in the present work. Once complete registration is achieved, on the other hand, the driving force and relative velocity of the domains vanish (courtesy of overdamped dynamics), and the system reaches equilibrium.

In the simulations, we first evaluate the net force \( F(\Delta h) \) acting on either one of the domains as well as the instantaneous domain velocity in the laboratory frame, \( v(\Delta h) \), and the separation-dependent drag coefficient \( \lambda_T \) is then obtained from \( \lambda_T(\Delta h) = F/v \). In the following, by choosing different values for the domain radius \( R \), membrane viscosity \( \eta_M \) and interleaflet friction strength \( \Gamma \), the relative contributions from interleaflet friction and viscosity to the drag coefficient can be tuned. In particular, in this parametric study, we focus on systems where either interleaflet friction or membrane viscosity dominates.

1. Interleaflet-friction-dominated systems

We will first consider the case where the interleaflet friction dominates. To this end, we choose a system size \( N_x = N_y = 512 \), and employ a set of parameter values for \( R \), \( \Gamma \), and \( \eta_M \) such that \( R \gg R_c = \sqrt{\eta_M/(2\Gamma)} \). Typical configurations during the registration process are shown in Fig. 2. It can be seen that the domains maintain an almost circular shape during the process, which can be rationalized by considering the effective capillary number \( \text{Ca} \equiv \eta_M \nabla u_M R/\sigma \). In particular, \( \text{Ca} \) quantifies the relative importance of viscous vs surface tension forces acting on the liquid domain, such that when \( \text{Ca} \rightarrow 0 \), surface tension forces dominate and maintain a circular domain shape; for this system, \( \text{Ca} \sim 10^{-3} \). The corresponding data for the numerically computed \( \lambda_T \) vs \( \Delta h \) are in turn presented in Fig. 3. It can be seen that when \( \Delta h \rightarrow 0 \), the numerically extracted \( \lambda_T \) values agree very well with the analytical predictions \( \lambda_{T0} \) from Eq. (17). This is further demonstrated in Fig. 4, which explicitly compares the analytical predictions with the numerically extracted \( \lambda_T \) values at complete overlap. A direct comparison is compounded by the fact that we are using a diffuse-interface model, and hence the physical domain radius can only be determined within a range \( (R - \xi/2, R + \xi/2) \), where \( \xi \) denotes the interface width [20]. For each nominal domain radius \( R \) within this range, a corresponding range of \( \lambda_{T0} \) values is computed from Eq. (17) and plotted together with the numerically extracted one. As can be seen, in all cases studied, the numerically obtained \( \lambda_{T0} \) is within the expected range based on the range of physical domain sizes, confirming the validity of the analytical result.

Turning now to the \( \Delta h \) dependence of \( \lambda_T \), we observe that the data is well approximated by a simple linear function of \( \Delta h \), with a slope that depends on the product \( R \Gamma \), as demonstrated in Fig. 5. In particular, \( d\lambda_T/d\Delta h \approx -5.4R\Gamma \), such that an...
empirical formula for $\lambda_T$ when $0 \leq \Delta h \leq 2R$ can be written as

$$
\lambda_T(R, \Delta h) = \lambda_T(R, 0) \left( 1 - \frac{\Delta h}{L_c} \right) \approx 4\pi \Gamma^2 R^2 \left( 1 - \frac{5.4\Delta h}{4\pi R} \right),
$$

where the characteristic length $L_c = \lambda_T(R, 0)/5.4\Gamma^2 \approx 4\pi R/5.4$. This formula is validated by the corresponding scaling collapse of all the simulation data shown in Fig. 6.

This approximate linear dependence of $\lambda_T(R, \Delta h)$ on $\Delta h$ can be rationalized as follows. The area of geometric overlap between two circular domains of radius $R$ and separation $\Delta h$ is given by $S = 2(\theta R^2 - R\Delta h \sin \theta/2)$, where $\sin \theta = \sqrt{1 - (\Delta h/2R)^2}$. The frictional drag associated with the direct contact between the domains is roughly given by $\lambda_1 = 2 S\lambda$, which in the limit $\Delta h/R \ll 1$ becomes $\lambda_1 \approx 2 \Gamma (\pi R^2 - R\Delta h)$. Now, the membrane flow around the domain, which is mainly due to the pressure gradient, also provides an additional contribution to the total drag. For the special case $\Delta h = 0$, this contribution has exactly the same magnitude as the direct contact friction term, as discussed in the Appendix. Thus, we assume that the flow around the domain continues to contribute 1/2 of the total drag when $\Delta h/R \ll 1$, which implies that the total drag coefficient can be approximated by $\lambda_T \approx 2\lambda_1 = 4\pi \Gamma^2 [1 - \Delta h/(\pi R)]$. This simple argument thus suggests that $d\lambda_T/d\Delta h \approx -4\Gamma^2$ when $\Delta h/R \ll 1$, which is in reasonable agreement with the numerical result $d\lambda_T/d\Delta h \approx -5.4\Gamma^2$.

2. Membrane-viscosity-dominated systems

Next we will consider the membrane viscosity dominated case. This time, we employ a set of parameter values for $R$, $\Gamma$, and $\eta_M$ such that $R \ll R_c$. To properly account for...
FIG. 7. (Color online) Representative order parameter configurations taken at times $t = 0$ (top left), 0.22 (top right), 0.48 (bottom left), and 0.74 (bottom right) during the recurrence of registration process for the membrane-viscosity-dominated case. The parameter values employed in this simulation were set to $R = 15$, $\Gamma = 0.000002$, and $\eta_M = 0.01$. Black indicates overlapping regions between the domains in opposing leaflets, while the lighter shades correspond to nonoverlapping regions of the domains within the upper (blue) and lower (red) leaflet. White arrows correspond to the instantaneous membrane velocity field in the upper leaflet.

dissipation taking place in the matrix phase, a large system size ($N_x = N_y = 1000$) is employed in the simulations.

Typical order parameter configurations are shown in Fig. 7. It can be seen that the domains display a significant deformation during the process, which again can be rationalized by considering the effective capillary number $Ca \sim 0.1$ for this system. The numerically extracted data for $\lambda_T$ vs $\Delta h$ are in turn shown in Fig. 8. In contrast to the friction-dominated case, $\lambda_T$ is nearly a constant over the whole range of examined $\Delta h$ values, and its value at $\Delta h = 0$ agrees well with the analytical prediction $\lambda_{T0} \approx 4\pi \eta_M/[\ln(2/\epsilon) - \gamma + 1/4]$. It is not difficult to understand why the drag coefficient remains practically constant as $\Delta h$ varies in this case, as letting $\Gamma \to 0$ effectively decouples the two leaflets kinematically. Therefore, based on the agreement between analytical prediction and numerical simulation, the analytical formula at $\Delta h = 0$ can be employed to approximate $\lambda_T(R, \Delta h)$ over the whole range $0 \leq \Delta h \leq 2R$ in the membrane-viscosity-dominated case.

IV. DISCUSSION AND CONCLUDING REMARKS

In this work, we have investigated the hydrodynamic interaction between compositional lipid domains, confined within opposing leaflets of a bilayer membrane and moving in opposite directions, in order to develop a quantitative understanding of the registration kinetics. In general, when the system is perturbed by displacing one domain relative to the other, diffusive and advective lipid fluxes are established to restore equilibrium and reestablish domain overlap. In this work, we have focused on the advective part of the process. In particular, by exploiting a symmetry in the governing equations, we have presented a derivation of the hydrodynamic drag coefficient, which quantifies this interaction, between two perfectly overlapping domains. The result, expressed in Eq. (16), incorporates both membrane viscosity and interleaflet friction effects. The relative importance between the two effects is determined by the relation of domain radius $R$ versus the characteristic length $R_c = \sqrt{\eta_M/2\Gamma}$, where $\Gamma$ and $\eta_M$ denote the friction coefficient and membrane viscosity,
respectively. For typical values of $\Gamma$ and $\eta_M$, $R_c \sim 2$ nm, and hence frictional effects dominate for all practical cases of interest.

When the domains overlap only partially, we resorted to numerical simulations to extract the separation-dependent drag coefficient $\lambda_T$. In particular, $\lambda_T$ was obtained for both friction-dominated and membrane-viscosity-dominated cases as a function of the separation $\Delta h$. As expected, the numerical data were in very good quantitative agreement with analytical predictions when $\Delta h \to 0$. For finite $\Delta h$, on the other hand, $\lambda_T$ data display a linear dependence of $\Delta h$ in the friction-dominated case, while $\lambda_T(R, \Delta h) \approx \lambda_{T0} \approx 4\pi \eta_M/[(\ln(2R/\rho) - \gamma + 1/4]$ for the membrane-viscosity-dominated case. A simple argument was employed to rationalize the linear dependence in the former case.

In our previous work, an explicit result was derived for the recurrence of registration dynamics [Eq. (6) in Ref. [5]], which we reproduce here for convenience:

$$\frac{d|\Delta h|}{dt} = -\frac{2\Delta}{\pi R} \left[ \frac{4\pi R^2}{\lambda_T(R, \Delta h)} + \frac{8\xi D}{\sigma} \right] \times \sqrt{1 - \left( \frac{\Delta h}{2R} \right)^2} \times \Theta(|\Delta h|),$$

where $\xi$, $D$, and $\sigma$ denote the interface width, lipid diffusivity, and line tension, respectively, while $\Theta(x)$ denotes the unit step function such that $\Theta = 1$ for $x > 0$ and zero otherwise, and $\Delta h(0) < 2R$ to guarantee nonzero initial overlap for a local interaction. In conjunction with the approximation for the drag coefficient $\lambda_T(R, \Delta h)$ developed in this work for the practically relevant case where interleaflet friction dominates, namely

$$\lambda_T(R, \Delta h) = \lambda_{T0} \left( 1 - \frac{\Delta h}{L_c} \right),$$

with $L_c \approx \lambda_{T0}/5.4R\Gamma \approx 4\pi R/5.4$, Eqs. (30) and (31) provide a quantitative means to analyze and predict the recurrence of registration kinetics for compositional lipid domains. In principle, one can introduce a stochastic noise term in Eq. (30) to study out-of-registry fluctuations of the domains near equilibrium. In this case, $\lambda_T(R, \Delta h)$ would contribute to the configuration-dependent inverse mobility of a “particle” undergoing confined Brownian motion in a potential energy well. Of course, if the domains lose overlap (and hence no longer experience a net force driving hydrodynamic motion) as a result of the fluctuations and drift far away from each other, the mobility of each domain would be affected by the solvent, whose effect has been ignored in the present work. As is well known, for composite objects embedded within the membrane, not accounting for the dissipation within the 3D solvent results in a logarithmically diverging drag coefficient [12,18,19]. In contrast, in the case of interest here, the presence of the local thermodynamic coupling $\Lambda$ induces an internal force distribution with dipolar character within the membrane for finite domain overlap, and the creeping flow equations in Eq. (2) admit nonsingular solutions even in the absence of the solvent. Furthermore, it is important to
note that in systems where domain overlap is lost altogether, chemical potential gradients within the same leaflet between a compositional domain and a thermodynamic coupling-induced “image” domain are expected to facilitate the recurrence of registration process via long-ranged, purely diffusive mass transport processes [21], rather than advective ones of interest in the present work, as nonoverlapping circular domains do not induce hydrodynamic flow fields due to symmetry [24].

It should also be noted that the analytical derivations presented in this manuscript for \( \lambda_{T0} \) explicitly assume that the domains remain perfectly circular as the system evolves towards thermodynamic equilibrium, which implies that the effective capillary number \( Ca = \eta M \nu / \ell \rightarrow 0 \). With the aid of Eq. (30), \( Ca \) can be expressed as \( Ca \sim \eta M \Lambda / (\sigma \Gamma R) \), and employing typical values for the parameters in this expression in the case of lipid bilayer membranes leads to the estimate \( 10^{-10} m / R \lesssim Ca \lesssim 10^{-8} m / R \) for \( 10^{-5} \text{ J/m}^2 \lesssim \Lambda \lesssim 10^{-3} \text{ J/m}^2 \). Thus, for domains larger than \( \approx 1 \mu \text{m} \), \( Ca \approx O(10^{-2}) \), and the shape deformation is expected to be negligible. On the other hand, for very small domains (\( R \approx 10 \) nm) interacting via a large thermodynamic coupling (\( \Lambda \approx 10^{-3} \text{ J/m}^2 \)), \( Ca = O(1) \), and shape deformations can become significant. Nevertheless, we expect that most physically relevant cases fall into the \( Ca \ll 1 \) category, and the results presented in this manuscript should be directly applicable.

Finally, in the present work, we have focused on the hydrodynamic interaction between an isolated pair of domains. Such interactions between multiple objects within the same bilayer [25–30] or different bilayers [30] have received a plethora of attention over the years. In particular, analytical expressions for the particle mobility tensors in the case of particle pairs have been derived both for close particle contact [25] and for well-separated pairs [25,28–30]. It would be interesting to extend these approaches to the case of recurrence of registration process via long-ranged, purely diffusive mass transport processes [21], rather than advective ones of interest in the present work, as nonoverlapping circular domains do not induce hydrodynamic flow fields due to symmetry [24].

In closing, our hope is that the work presented here will inspire new theoretical and experimental investigations into strongly coupled compositional lipid domain formation processes in lipid membranes, both natural and synthetic.

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APPENDIX: HYDRODYNAMIC DRAG COEFFICIENT FOR TWO PERFECTLY OVERLAPPING COMPOSITIONAL DOMAINS

The starting point of the analysis is given by Eqs. (9)–(14) for \( \nu_a = u_{M1r} - u_{M2r} \) and \( \nu_b = p_{M1} - p_{M2} \), which we reproduce here for convenience:

\[ \eta \nabla^2 \nu_a - \nabla p_a = 2 \Gamma \nu_a \quad \text{and} \quad \nabla \cdot \nu_a = 0 \quad \text{when} \quad r \geq R; \]

\[ \eta' \nabla^2 \nu_b - \nabla p_b = 2 \Gamma' \nu_b \quad \text{and} \quad \nabla \cdot \nu_b = 0 \quad \text{when} \quad r < R, \]

with

\[ \nu_a = 0 \quad \text{at} \quad r = \infty, \]

and

\[ \eta \nabla^2 \nu_b - \nabla p_b = 0 \quad \text{and} \quad \nabla \cdot \nu_b = 0 \quad \text{when} \quad r \geq R; \]

\[ \eta' \nabla^2 \nu_b - \nabla p_b = 0 \quad \text{and} \quad \nabla \cdot \nu_b = 0 \quad \text{when} \quad r < R, \]

with

\[ \nu_b = 0 \quad \text{at} \quad r = \infty. \]

For \( \nu_b \), we can immediately write down the trivial solution \( \nu_b = 0 \) and \( p_b = \text{const.} = 0 \). On the other hand, for \( \nu_a \), the system of equations is exactly the one analyzed by Ramachandran and coworkers [22]. By following their solution procedure, we can readily solve the equations for \( \nu_a \) and \( p_a \). In particular, for \( r \geq R \) we obtain

\[ u_{M1r} = \frac{v_{a,r}}{2} = \frac{1}{2} \left[ C_1 + C_2 \frac{K_1(\kappa r)}{r} \right] \cos \theta; \]

\[ u_{M1\theta} = \frac{v_{a,\theta}}{2} = \frac{1}{2} \left[ C_1 + C_2 \frac{K_0(\kappa r)}{r} \right] \sin \theta; \]

\[ p_{M1} = \frac{p_a}{r} = \frac{\Gamma C_1 \cos \theta}{r}, \]

while for \( r < R \),

\[ u_{M1r} = \frac{v_{a,r}}{2} = \frac{1}{2} \left[ -C_1 + C_2 \frac{I_1(\kappa' r)}{r} \right] \cos \theta; \]

\[ u_{M1\theta} = \frac{v_{a,\theta}}{2} = \frac{1}{2} \left[ C_1' - C_2' \frac{I_0(\kappa' r)}{r} + C_2' \frac{I_1(\kappa' r)}{r} \right] \sin \theta; \]

\[ p_{M1} = \frac{p_a}{r} = \Gamma' C_1' \kappa' \cos \theta, \]

where \( I_i \) and \( K_i \) denote modified Bessel functions of the first and second kind, order \( i \), respectively, while \( \kappa = \sqrt{\frac{2 \eta}{\eta'}} \) and \( \kappa' = \sqrt{\frac{2 \eta'}{\eta}} \), and \( C_1, C_2, C_1', C_2' \) are constants to be determined. Now, by employing the boundary conditions in Eqs. (5)–(7), we explicitly obtain

\[ C_1 = 2 R^2 v_0 \left[ 1 + \frac{2 K_1}{\epsilon K_0} + 2 K_1' \frac{(-2 I_1 + I_0 \epsilon)}{K_0 M} \right]; \]

\[ C_2 = 4 R v_0 \left[ -\frac{1}{\epsilon K_0} + \frac{K_1 (2 I_1 - I_0 \epsilon)}{K_0 M} \right]; \]

\[ C_1' = v_0 \left[ -2 + \frac{4 K_1 \epsilon}{M} \right]; \]

\[ C_2' = \frac{4 K_1 \epsilon R \eta v_0}{M}, \]
where $M = (2K_0 + K_1 \epsilon)(2I_1 - I_0 \epsilon') \eta - K_0(4I_1 - 2I_0 \epsilon' + I_1 \epsilon'^2) \eta'$ and $\epsilon \equiv \kappa R = R / R_c$, $\epsilon' \equiv \kappa' R = R / R_c$. For the components of the stress tensor, we obtain, for $r \gg R$,

$$\tau_{rr} = 2\eta \frac{\partial u_{M1r}}{\partial r}$$

$$= -\eta \left[ \frac{2C_1}{r^3} + \frac{2C_2}{r^2} K_1(\kappa r) + \frac{C_2 \kappa}{r} K_0(\kappa r) \right] \cos \theta;$$

(A17)

$$\tau_{\theta \theta} = \eta \left[ r \frac{\partial}{\partial r} \left( \frac{u_{M1\theta}}{r} \right) + \frac{1}{r} \frac{\partial u_{M1r}}{\partial \theta} \right]$$

$$= -\eta \left[ \frac{2C_1}{r^3} + \frac{C_2 \kappa}{r} K_0(\kappa r) + 2 \left( \frac{\kappa^2}{2} + \frac{2}{r^2} \right) K_1(\kappa r) \right] \sin \theta.$$

(A18)

Therefore, the drag force contribution from the membrane flow field around the domain is given by

$$F_D = 2R \int_0^\pi [(\rho_{M1} - \tau_{rr}) \cos \theta + \tau_{\theta \theta} \sin \theta]|_{r=R} d\theta.$$  

(A19)

For the drag force contribution from direct contact between two domains, on the other hand, we obtain

$$F_p = 2 \int_A \Gamma' u_{M1r} dA$$

$$= 2\Gamma' \int_0^R \int_0^{2\pi} (u_{M1r} \cos \theta - u_{M10} \sin \theta) r d\theta dr,$$

(A20)

where we have taken the relative motion of the two domains to take place in the $x$ direction. Therefore, the total drag force is

$$F_T = F_D + F_p = \pi v_0 \left\{ \epsilon^2 \eta + \epsilon'^2 \eta' + \frac{4\epsilon K_1 \eta}{K_0} \left[ (4 + \epsilon^2)I_1 - 2\epsilon' I_0 + 2E(2K_0 + \epsilon K_1)(\epsilon' I_0 - 2I_1) \right] \right\},$$

(A21)

and the drag coefficient at perfect overlap is thus given by

$$\lambda_{T0} = \frac{F_T}{v_0} = \pi \left\{ \frac{\epsilon^2 \eta + \epsilon'^2 \eta'}{E} + \frac{4\epsilon K_1 \eta}{K_0} \left[ (4 + \epsilon^2)I_1 - 2\epsilon' I_0 + 2E(2K_0 + \epsilon K_1)(\epsilon' I_0 - 2I_1) \right] \right\},$$

(A22)

where $E \equiv \eta / \eta'$.

For the special case $\eta = \eta' = \eta_M$ and $\Gamma = \Gamma'$ (implying $\epsilon = \epsilon'$ and $E = 1$), the expression for $\lambda_{T0}$ simplifies to

$$\lambda_{T0} = \frac{2\pi \eta_M \epsilon^3 (I_1 K_0 + I_0 K_1)}{\epsilon (I_1 K_0 + I_0 K_1) - 2I_1 K_1}.$$

(A23)

Now, in the limit $\epsilon \to 0$ [31],

$$K_0(\epsilon) = \ln \left( \frac{2}{\epsilon} \right) - \gamma + \frac{1}{4} \left\{ 1 + \ln \left( \frac{2}{\epsilon} \right) - \gamma \right\} \epsilon^2 + \cdots;$$

(A24)

$$K_1(\epsilon) = \frac{1}{\epsilon} - \frac{1}{2} \left\{ 1 + \ln \left( \frac{2}{\epsilon} \right) - \gamma \right\} \epsilon + \cdots;$$

(A25)

$$I_0(\epsilon) = 1 + \frac{\epsilon^2}{4} + \cdots;$$

(A26)

$$I_1(\epsilon) = \frac{\epsilon^3}{16} + \cdots.$$

(A27)

and the expression for $\lambda_{T0}$ reduces to

$$\lambda_{T0} \approx \frac{4\pi \eta_M}{\ln \left( \frac{2}{\epsilon} \right) - \gamma + \frac{1}{4}};$$

(A28)

which corresponds to the case when viscosity effects dominate. On the other hand, in the opposite limit $\epsilon \to \infty$, we have

$$K_0(\epsilon) \approx \sqrt{\frac{\pi}{2\epsilon}} e^{-\epsilon};$$

(A29)

$$I_0(\epsilon) \approx \frac{\epsilon^3}{\sqrt{2\pi \epsilon}},$$

(A30)

and the expression for $\lambda_{T0}$ in turn reduces to

$$\lambda_T \approx 2\pi \eta_M \epsilon^2 = 4\pi \Gamma R^2;$$

(A31)

which corresponds to the case when interlayer friction effect dominates. It is interesting to note that in the limit where friction dominates ($\epsilon \to \infty$), pressure variations along the domain perimeter and direct frictional contact between the domains contribute an equal amount to the total drag coefficient, as can be easily verified by employing Eqs. (A9) and (A19) and the definition of $C_i$.


