

Drag force on a liquid domain moving inside a membrane sheet surrounded by aqueous medium

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We compute the drag on a circular and liquid microdomain diffusing in a two-dimensional fluid lipid bilayer membrane surrounded by a fluid above and below. Under the assumptions that the liquids are incompressible and the flow is of low Reynolds number, Stokes' equations describe the flow in the two-dimensional membrane as well as in the surrounding three-dimensional fluid. The expression for the drag force on the liquid domain involves Fredholm integral equations of the second kind, which we numerically solve using discrete collocation method based on Chebyshev polynomials. We observe that when the domain is more viscous than the surrounding membrane (including the rigid domain case), the drag force is almost independent of the viscosity contrast between the domain and the surrounding membrane, as also observed earlier in experiments by other researchers. The mobility also varies logarithmically with Boussinesq number β for large β . On the other hand, for a less viscous domain the dimensionless drag force reduces with increasing viscosity contrast, and a significant change in the drag force, from that when there is no viscosity contrast or when the domain is rigid, has been observed. Further, the logarithmic behaviour of the mobility no longer holds for less viscous domains. Our method of computing the drag force and diffusion coefficient is valid for arbitrary viscosity contrast between the domain and membrane and any domain size (subject to $\beta \geq 5$).

Key words: biological fluid dynamics, low-Reynolds-number flows, membranes

1. Introduction

Cell membranes consist of different lipid molecules and proteins and they form a heterogeneous two-dimensional surface (Singer *et al.* 1972; Engelman 2005). Sphingolipid and cholesterol-rich microdomains of the membrane, sometimes called rafts, diffuse on the membrane surface (Simons & Ikonen 1997). The important roles played by rafts in different cell biological processes have been the focus of many studies on membrane biology and biophysics in the past (Brown & London 1998; Ikonen 2001). Recent studies put the proposed mechanisms of emergence of raft domains under scrutiny; however, the fact that there are cholesterol-rich microdomains that play a crucial role in cell functions is still valid. Furthermore, the motion or

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diffusion of these heterogeneous submicrometre size domains in the surrounding membrane surface is crucial for the cell functionality.

The size of the microdomains in cell membranes is of the order of a tenth of a micrometre, which makes it difficult to observe them under the optical microscope in live conditions. On the other hand, giant unilamellar vesicles (GUVs) consisting of phase-separated liquid-ordered and disordered domains are simpler model systems for cell membranes (Dietrich *et al.* 2001). These GUVs have domains that are rich in saturated lipids and cholesterol, have sizes in micrometre range (so that they can be observed via optical microscope) and move in the membrane surface.

In his pioneering work, Saffman (1976) employed a hydrodynamic model to obtain the drag on a protein molecule moving in an incompressible lipid membrane sheet of viscosity η and thickness h . The protein was considered to be a rigid cylinder of height h . The space above and below the membrane was filled up with a liquid of viscosity μ_s that is less than the membrane viscosity η . For the case when the cylinder radius a is much smaller than the ratio $\eta h/\mu_s$, the translational diffusion coefficient of the cylinder obtained by Saffman (1976) is

$$D_{SDr} = \frac{k_B T}{4\pi\eta h} \left[\log \left(\frac{\eta h}{\mu_s a} \right) - \gamma \right], \quad (1.1)$$

where k_B is Boltzmann's constant, T is absolute temperature and γ is Euler's constant. Later the diffusion coefficient for a rigid cylindrical particle of an arbitrary size was computed by Hughes, Pailthorpe & White (1981) and Petrov & Schwille (2008). Evans & Sackmann (1988) obtained the diffusion constant of a rigid disk moving along a supported lipid bilayer. They considered the effect of the supporting fluid on the lipid bilayer with a momentum dissipation term proportional to the membrane fluid velocity in the momentum equation. In contrast, Stone & Ajdari (1998) obtained the diffusion coefficient for a rigid circular domain of the same thickness as that of a supported lipid bilayer by considering the viscous force of the supporting fluid on the lipid bilayer with a body force term in the corresponding momentum equation.

When the domain is rigid and its size is small compared to the hydrodynamic length scale ($a \ll \eta h/\mu_s$), the domain diffusion constant depends on the domain radius as $\ln(1/a)$ (Saffman & Delbrück 1975; Saffman 1976). This has been validated experimentally (Hughes *et al.* 1982; Peters & Cherry 1982; Lee & Petersen 2003; Cicuta, Keller & Veatch 2007). However, the experiments by Gambin *et al.* (2006) show that for a large range of proteins and protein clusters, the diffusion constant varies as $1/a$, in contrast to $\ln(1/a)$ as predicted by the theoretical results of Saffman & Delbrück (1975) and Saffman (1976). In support of the experimental results of Gambin *et al.* (2006), Naji, Levine & Pincus (2007) reported that the membrane deformation in the neighbourhood of the particle reduces the diffusion constant. By using mesoscopic simulations Guigas & Weiss (2006) reported that the domain diffusion varies as $\ln(1/a)$ for the smaller domains, and when the domain size is larger than the hydrodynamic length scale the domain diffusion constant depends on the domain size as $1/a^2$. However, the experimental results of Klingler & McConnell (1993) and Cicuta *et al.* (2007) support the prediction of Hughes *et al.* (1981) that the diffusion constant varies as $1/a$ when the domain radius is large compared to the hydrodynamic length scale.

In general, the liquid-ordered domains in vesicles or protein-rich microdomains in a cell membrane are large compared to the size of proteins; they are not rigid but rather fluid-like and their viscosity differs from the viscosity of the surrounding membrane.

Towards this Ramachandran *et al.* (2010) modelled the microdomain as a circular liquid domain with zero thickness moving in a 2D liquid membrane sheet. They obtained the finite diffusion coefficient of the liquid domain by considering the effect of surrounding fluid above and below the membrane plane through a momentum decay term in the momentum equation. Also recently, Seki, Ramachandran & Komura (2011) obtained the diffusion coefficient of a liquid disk moving on a supported membrane sheet when the viscosities of the liquid disk and the membrane are the same. Seki, Mogre & Komura (2014) studied the diffusion of a circular liquid domain moving along one of the monolayers with viscosity identical to the domain viscosity while considering the frictional resistance between the monolayers of the lipid bilayer. When the viscosity contrast, defined as the ratio of the difference between the viscosities of the domain and the surrounding membrane and the domain viscosity, is either zero or small, Fujitani (2011, 2012, 2013) derived approximate analytical expressions for the drag force on the liquid domain and thus the diffusion coefficient. To compute values of the drag force, certain integrals had to be evaluated numerically or further approximations had to be made.

All the above studies suffer from the limitation that either the domains are rigid, or they are too small in comparison to the hydrodynamic length scale, or they have very little viscosity contrast with the surrounding membrane. In the actual experimental scenario of the domains moving in a vesicle, none of these holds. For example, the domains have sizes in the μm range, their viscosity is approximately five times that of the surrounding disordered membrane and certainly the domains are not rigid. Recently, Aliaskarsohi *et al.* (2010), have studied the diffusion of domains in a spherical vesicle surface and obtained an approximate series solution for the diffusion coefficient for a liquid domain. The authors observe that the diffusion of the domains is suppressed due to the confinement to the vesicle surface and the diffusion is dominated by the dissipation into the bulk fluid. The authors also mention the difficulty in applying their analysis to the case of a flat membrane as a large number of terms need to be retained in the series solution, leading to difficulty in numerical inversion of a matrix of extremely large size. The works of Aliaskarsohi *et al.* (2010), Fujitani (2011, 2012, 2013) and Seki *et al.* (2011, 2014) assumed the no-slip boundary condition at the membrane-surrounding fluid and the domain–membrane interfaces.

To understand the effect of different fluid viscosity on the domain diffusion in a lipid bilayer, Cicuta *et al.* (2007) recorded the diffusion of circular liquid domains on the surface of GUVs. They reported that the diffusion coefficient of the circular liquid domain varies with the domain size and it is independent of the membrane viscosity when the membrane viscosity is less than the domain viscosity. In contrast, when the domain viscosity is less than the membrane viscosity, they observed that the domain diffusion depends on the membrane viscosity and the domain size. The experimental and theoretical observations of Cicuta *et al.* (2007) and Aliaskarsohi *et al.* (2010) motivated us to study the motion of a circular liquid domain moving in a flat liquid membrane sheet of different viscosity.

In our study, the membrane sheet spans to infinity, and the domain and the membrane are assumed to have the same thickness, remain flat and be surrounded by liquid of a different viscosity that spans to infinity above and below the membrane sheet. All the liquids are incompressible and subject to low-Reynolds-number flow such that the motion is governed by Stokes' equation. The drag on the domain is obtained by solving Stokes' equation for the two-dimensional membrane as well as the surrounding three-dimensional fluid. The resulting expressions for the drag

force involve a set of dual integral equations, of Fredholm second kind. We employ a discrete collocation method (Atkinson 1997) with approximations based on Chebyshev polynomials to numerically solve the dual integral equations.

Our computation of the drag coefficient (and mobility) is valid for arbitrary viscosity contrast between the domain and membrane as well as the membrane and fluid subject to the condition that the surrounding membrane curvature can be neglected. The numerical solution procedure is valid for arbitrary size, in principle. However, in practice, we obtain high accuracy when the Boussinesq number is larger than five. Our computation agrees with the experimental observation that when the domains are more viscous than their surrounding, the diffusion coefficient is almost independent of the viscosity contrast. However, for negative viscosity contrast, the dimensionless mobility (or equivalently the diffusion constant) is larger than the mobility when the domains are more viscous, it is sensitive to the viscosity contrast, and it does not vary logarithmically with the Boussinesq number. In fact, the mobility varies non-monotonically with the Boussinesq number when the viscosity contrast is large and negative. This is unlike the behaviour observed when the domains are more viscous or rigid. To our knowledge, this is a new observation and experiments need to be conducted to demonstrate the behaviour observed here for negative viscosity contrast. Upon choosing a suitable composition from the ternary phase diagram of a saturated lipid, an unsaturated lipid and cholesterol, we can prepare GUVs with coexisting liquid-ordered and disordered phases in which domains consisting of ordered phase are embedded in the disordered surrounding (Veatch & Keller 2005). In this case the viscosity contrast is positive. Further, by selecting different compositions along the tie-line of the ternary phase diagram of Veatch & Keller (2005), we can make domains enriched with disordered phase in a surrounding consisting of ordered phase. In this scenario the viscosity contrast becomes negative and it is possible to prepare experimental systems in which the viscosity contrast is less than -5 (i.e. large in magnitude).

2. Problem formulation

A circular liquid domain of size a and viscosity η_d moves with velocity U along X -axis in a flat fluid membrane sheet of viscosity η_m . The space above and below the domain and membrane sheet is occupied by a liquid with viscosity μ_s . A schematic diagram of the system is shown in figure 1. All the fluids considered are incompressible and undergo low-Reynolds-number flow.

The governing equations for various domains are as follows. For the 3D fluid above ($z > 0$) and below ($z < h$) the membrane sheet, including the domain, we have

$$\mu_s \Delta \mathbf{v} = \nabla p \quad \text{and} \quad \nabla \cdot \mathbf{v} = 0, \tag{2.1a,b}$$

where $\mathbf{v}(r, \theta, z) = (v_r, v_\theta, v_z)$ and $p(r, \theta, z)$ are the velocity and pressure fields in the surrounding fluid, respectively. The Δ and ∇ are the Laplacian and the gradient operators, respectively. For the membrane and domain liquid ($-h \leq z \leq 0$), the variation of the quantities across the thickness direction is precluded due to its molecular structure. Further, because of the symmetry about the mid-plane of the membrane we assume that the velocity in the z direction is zero. Thus for the in-plane motion in the domain and the surrounding membrane we have (Saffman 1976)

$$\eta_d \Delta \mathbf{u} + 2\sigma/h = \nabla \Pi \quad (\text{for } r < a), \quad \eta_m \Delta \mathbf{u} + 2\sigma/h = \nabla \Pi \quad (\text{for } r > a) \quad \text{and} \quad \nabla \cdot \mathbf{u} = 0, \tag{2.2a-c}$$

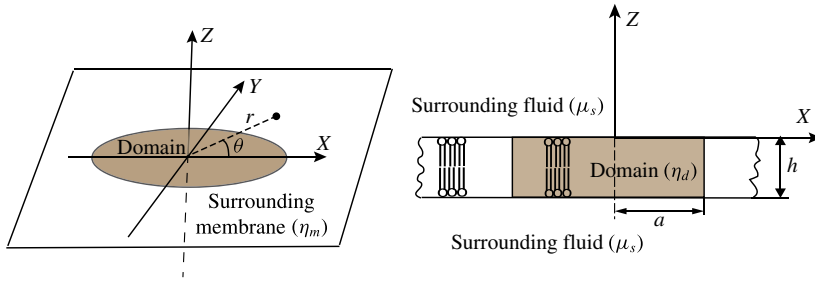


FIGURE 1. (Colour online) Schematic diagram of a circular liquid domain of size a and thickness h moving with velocity U along the X -axis in a membrane sheet of the same thickness. The viscosities of the domain, the surrounding membrane and the surrounding fluid are η_d , η_m and μ_s , respectively. The schematic diagram on the right is the sectional view in the x - z plane. Both the membrane and the surrounding fluid span to infinity in their respective directions.

where $\mathbf{u}(r, \theta) = (u_r, u_\theta, 0)$ and $\Pi(r, \theta)$ are the velocity and pressure fields, respectively, and σ is the traction (or drag) applied on the top and bottom surfaces of the membrane and domain by the surrounding fluid. No-slip boundary conditions at the membrane-surrounding liquid and domain-membrane interfaces are applied and the velocity decays to zero at infinity for both the membrane and the surrounding fluid. Note that the no-slip boundary condition at the membrane-surrounding liquid interface leads to the following relations between the velocity fields in the surrounding fluid and the domain/membrane:

$$u_r(r, \theta) = v_r(r, \theta, z=0) \quad \text{and} \quad u_\theta(r, \theta) = v_\theta(r, \theta, z=0). \quad (2.3a,b)$$

The incompressibility conditions for the surrounding and membrane fluids are separately imposed (see equation (2.8) of Saffman (1976) and equation (2.22) of Fujitani (2011)). However, it is worth mentioning that as both the domain and its surrounding are assumed to be incompressible fluids, the in-plane flow field must be divergence-free at the domain boundary. This condition has not been imposed in the present study.

Equations (2.1) and (2.2), along with the boundary conditions, can be solved analytically for the pressure and velocity fields by exploiting the rotational symmetry about the z -axis and use of Fourier and Hankel transforms (Saffman 1976; Fujitani 2011). The contributions to the drag force on the circular liquid domain moving with a steady velocity U come from the tangential components of the tractions applied to the domain by the surrounding membrane at the cylindrical interface (at $r = a$) and by the surrounding fluid at the top and bottom circular interfaces of radius a . The expression for the magnitude of the drag force is given by the integral

$$F = \lim_{\tilde{r} \rightarrow 1^+} \frac{\pi}{a} \int_0^\infty dz z A(z) J_2(z\tilde{r}), \quad (2.4)$$

where $\tilde{r} = r/a$ dimensionless radial distance and $A(z)$ is an as yet undetermined function. The details of the derivation of (2.4) have been omitted here to avoid repetition. They are available in Fujitani (2011). The quantity $A(z)$ is obtained, in principle, by solving the following two integral equations:

$$A(z) = \frac{2acU}{\pi z} J_1(z) + \epsilon \int_0^\infty dt \frac{t}{1 + \beta t} \frac{[zJ_0(t)J_1(z) - tJ_0(z)J_1(t)] A(t)}{z^2 - t^2} \quad (2.5)$$

and

$$2\mu_s Ua^2 = \int_0^\infty dt \frac{A(t)J_1(t)}{t(1 + \beta t)}, \tag{2.6}$$

where c is an unknown constant, $\beta = \eta_m/(2\mu_s a)$ is the Boussinesq number representing the ratio between the membrane drag and surrounding fluid drag, $\epsilon = (\eta_d - \eta_m)/\eta_d$ denotes the relative viscosity contrast between the domain and the surrounding membrane, and $J_i(z)$ is the Bessel function of i th order and first kind. Note that, typically, $0 \leq \epsilon \leq 1$, and $\epsilon = 0$ indicates that the domain and membrane have same viscosity while $\epsilon = 1$ implies that the domain is rigid or the membrane viscosity is very small in comparison to the domain viscosity. Further, for $\epsilon < 0$ the surrounding membrane has higher viscosity than the domain, which is not the case in general. However, it is possible to make two-phase lipid bilayer vesicles in the laboratory with appropriately chosen lipid composition such that the domain viscosity is smaller than the surrounding. A typical value of ϵ is $4/5$ and $0.2 < \beta < 1000$ (considering $10^{-9} < \eta_m < 10^{-6}$ N s m⁻¹ and $0.5 < a < 2.5$ μm (Brooks *et al.* 1999; Cicuta *et al.* 2007; Aliaskarisohi *et al.* 2010; Stanich *et al.* 2013)).

Equations (2.4)–(2.6) complete the description to obtain the drag force on the domain, and subsequently the diffusion coefficient or mobility of the domain. However, the main difficulty lies in solving the dual integral equations (2.5) and (2.6), particularly when the viscosity contrast is neither zero nor unity. For $\epsilon = 0$, the solution to the integral equation (2.5) is exact and is given by $A(z) = 2acU J_1(z)/\pi z$, and through the subsequent use of (2.6) the constant c can be evaluated. For $\epsilon \ll 1$, Fujitani (2011) obtained a semi-analytical solution to (2.5). However, when ϵ is not very small, the dual integral equations (2.5) and (2.6) are not analytically tractable. To our knowledge, no numerical solution is available either. We develop a simple algorithm to obtain a numerical solution to (2.5) and (2.6) using the discrete collocation method (Atkinson 1997) and Chebyshev polynomials. We first introduce a new variable $B(z) = zA(z)$ and rewrite (2.5) and (2.6) as

$$B(z) = \frac{2acU}{\pi} J_1(z) + \epsilon \int_0^\infty dt M(z, t)B(t) \tag{2.7}$$

and

$$2\mu_s Ua^2 = \int_0^\infty dt \frac{B(t)J_1(t)}{t^2(1 + \beta t)}, \tag{2.8}$$

where

$$M(z, t) = \frac{z}{(1 + \beta t)} \frac{[zJ_0(t)J_1(z) - tJ_0(z)J_1(t)]}{(z^2 - t^2)}. \tag{2.9}$$

Equation (2.7) is in the form of a Fredholm equation of second kind. The drag force in terms of the new variable $B(z)$ is

$$F = \lim_{\tilde{r} \rightarrow 1^+} \frac{\pi}{a} \int_0^\infty dz B(z)J_2(z\tilde{r}). \tag{2.10}$$

The expression (2.10) for the drag force in terms of the new variable $B(z)$ eliminates the possibility of the integrand taking prohibitively large values when z is large, making the numerical computation of the integral easier. In the following, we describe the numerical solution procedure for (2.7) and (2.8).

3. Numerical solution of Fredholm integral equation

To solve (2.7), we need to map the infinite domain $[0, \infty)$ to a finite domain (see Collocation Theorem 2.6.2 of Zemyan (2012)). To achieve this, we define the change of variable $z = \tan[(X + 1)\pi/4]$, and rewrite (2.7) and (2.8) as

$$B(X) = \frac{2acU}{\pi} J_1(z(X)) + \epsilon \frac{\pi}{4} \int_{-1}^1 dY \sec^2[(Y + 1)\pi/4] M(X, Y) B(Y) \quad (3.1)$$

and

$$2\mu_s U a^2 = \frac{\pi}{4} \int_{-1}^1 dY \frac{\sec^2[(Y + 1)\pi/4] B(Y) J_1(t(Y))}{t(Y)^2(1 + \beta t(Y))}, \quad (3.2)$$

respectively. In the above $t(Y) = \tan[(Y + 1)\pi/4]$ and the values of X and Y lie in the finite domain $[-1, 1]$.

Now we can approximate $B(X)$ using a set of n linearly independent functions that are continuous in $[-1, 1]$ (Zemyan 2012). We choose Chebyshev polynomials for this purpose:

$$B(X) \approx \sum_{i=1}^n B_i T_{i-1}(X), \quad (3.3)$$

where $T_i(X)$ is the Chebyshev polynomial of first kind with degree i . Note that the number of collocation points is same as the number of Chebyshev polynomials used to approximate $B(X)$. By substituting (3.3) into (3.1), we obtain

$$\sum_{i=1}^n B_i \left[T_{i-1}(X) - \epsilon \frac{\pi}{4} \int_{-1}^1 dY \sec^2[(Y + 1)\pi/4] M(X, Y) T_{i-1}(Y) \right] = \frac{2acU}{\pi} J_1(z). \quad (3.4)$$

The most convenient choice of the collocation points for (3.4) are the zeros of the n th degree Chebyshev polynomial, and with this choice we obtain a system of n linear equations with n unknown Chebyshev coefficients:

$$\left[\bar{\mathbf{T}} - \epsilon \frac{\pi}{4} \bar{\mathbf{V}} \right] \mathbf{b} = \mathbf{R}, \quad (3.5)$$

where $\bar{\mathbf{V}}$ and $\bar{\mathbf{T}}$ are $n \times n$ matrices with elements $v_{i,j} = \int_{-1}^1 dY \sec^2[(Y + 1)\pi/4] M(z_j, t) \times T_{i-1}(Y)$ and $t_{i,j} = T_{i-1}(X_j)$, respectively, and X_j are the collocation points. The elements of the $n \times 1$ array \mathbf{b} of Chebyshev coefficients are $b_i = B_i \pi / 2acU$, and $r_j = J_1(z_j)$ are the elements of the $n \times 1$ array \mathbf{R} .

We use the Gauss–Chebyshev quadrature method (Mason & Handscomb 2010) to compute the elements $v_{i,j}$:

$$v_{i,j} \approx \frac{\pi}{n} \sum_{k=1}^n \left[\sqrt{1 - Y_k^2} \sec^2 \left[(Y_k + 1) \frac{\pi}{4} \right] M(z_j, t_k) T_{i-1}(Y_k) \right], \quad (3.6)$$

where the Y_k are the zeros of the n th degree Chebyshev polynomial. Substituting the expression $v_{i,j}$ obtained from (3.6) into (3.5) and solving for \mathbf{b} , we obtain the Chebyshev coefficients B_i in terms of the unknown constant c . To calculate c , we

substitute the Chebyshev polynomial approximation of function $B(X)$, given by (3.3), into (3.2) and obtain

$$c = 4\mu_s a \left/ \left\{ \frac{\pi}{n} \sum_{i=1}^n \sum_{k=1}^n \left[\frac{\sqrt{1 - Y_k^2} \sec^2 \left[(Y_k + 1) \frac{\pi}{4} \right] b_i T_{i-1}(Y_k) J_1(Y_k)}{t_k^2 (1 + \beta t_k)} \right] \right\} \right. \quad (3.7)$$

Note that we use the Gauss–Chebyshev quadrature method to compute the integral appearing in (3.2). Using the results of (3.5) and (3.7), and substituting (3.3) into (2.10), we obtain the approximation to the drag force F on the circular liquid domain of radius a as

$$F \approx \lim_{\tilde{r} \rightarrow 1^+} \frac{\pi}{a} \sum_{i=1}^n \int_0^\infty dz B_i T_{i-1}(X) J_2(z\tilde{r}). \quad (3.8)$$

We decompose the domain of integration appearing in (3.8) into two parts:

$$F \approx \lim_{\tilde{r} \rightarrow 1^+} \frac{\pi}{a} \sum_{i=1}^n \left[\int_0^{U_L} dz B_i T_{i-1}(X) J_2(z\tilde{r}) + \int_{U_L}^\infty dz B_i T_{i-1}(X) J_2(z\tilde{r}) \right]. \quad (3.9)$$

Exploiting the boundedness of $T_i(\cdot)$ and the exponentially decaying behaviour $J_2(z\tilde{r})$ for large z , we choose a $U_L < \infty$ such that the second integral in (3.9) is small and can be neglected in comparison with the first integral. Finally, the expression for the drag force becomes

$$F \approx \lim_{\tilde{r} \rightarrow 1^+} \frac{\pi}{a} \sum_{i=1}^n \int_0^{U_L} dz B_i T_{i-1}(X) J_2(z\tilde{r}). \quad (3.10)$$

The above integral is evaluated using Simpson’s rule.

4. Results and discussion

To compute the drag force F using (3.10), we need to choose the number of Chebyshev polynomials (or collocation points) n , the upper limit of integration U_L , and the step size h in Simpson’s rule. Furthermore, we need to choose an appropriate value of \tilde{r} larger than but close to unity to replace the limit $\tilde{r} \rightarrow 1^+$. We carry out convergence studies for the drag force F with respect to the parameters. Further, we compute the error in the drag force for two limiting cases in which the analytical solution is available. They are $\epsilon = 0$ (viscosity of domain and membrane are the same (Fujitani 2011)) and $\epsilon = 1$ (the domain is rigid (Hughes *et al.* 1981; Petrov & Schuille 2008)).

4.1. Validation of the numerical method for a domain with the same viscosity as the surrounding membrane ($\epsilon = 0$) and a rigid domain ($\epsilon = 1$)

For $\epsilon = 0$ the viscosities of the domain and the surrounding membrane are the same. In this case, from (2.7) we obtain $B(X) = 2acU J_1(X)/\pi$ and the drag force on the liquid domain given by (Fujitani 2011)

$$F = 2cU \lim_{\tilde{r} \rightarrow 1^+} \int_0^\infty dz J_1(z) J_2(\tilde{r}z) = 2cU, \quad (4.1)$$

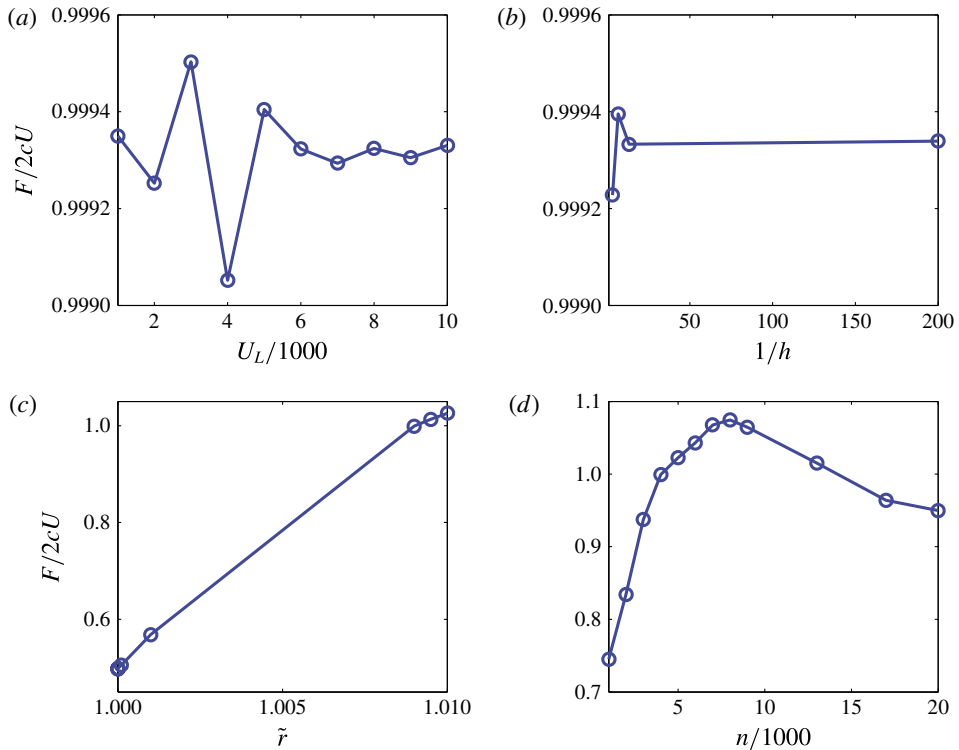


FIGURE 2. (Colour online) Variation of $F/2cU$ for $\epsilon = 0$ (a) with U_L for $\tilde{r} = 1.009$, $n = 4000$, $h = 0.05$, (b) with $1/h$ for $\tilde{r} = 1.009$, $n = 4000$, $U_L = 6000$, (c) with \tilde{r} for $n = 4000$, $U_L = 6000$, $h = 0.05$ and (d) with n for $\tilde{r} = 1.009$, $U_L = 6000$, $h = 0.05$.

where

$$c = \frac{\pi\mu_s a}{\int_0^\infty dz \frac{J_1^2(z)}{(z^2 + \beta z^3)}}. \quad (4.2)$$

In figure 2 we present the variation in the ratio $F/2cU$ computed numerically using (3.10) with respect to the parameters U_L , $1/h$, \tilde{r} and n . Note that the integral $\lim_{\tilde{r} \rightarrow 1^+} \int_0^\infty dz J_1(z) J_2(\tilde{r}z) = 1$, and consequently the ratio $F/2cU$ is unity and independent of β . Upon observing the convergence and the closeness of the ratio to unity we find the following parameter values: $n = 12000$, $\tilde{r} = 1.009$, $U_L = 6000$, $h = 0.05$. However, we also find from figure 2(d) that the ratio is closest to unity for $n = 4000$ as well. Thus to save computational time we finally choose $n = 4000$, $\tilde{r} = 1.009$, $U_L = 6000$ and $h = 0.05$ for calculating the drag force.

After fixing these parameters, we compute the constant c using (3.7) and compare it with the exact solution (4.2) for different β . The integral in (4.2) is evaluated using the software Mathematica. In figure 3(a,b), we present the variation in the error in c and percentage error in $F/\mu_s a U$ with β . We observe that up to $\beta = 10^7$ the error in c is small and the percentage error in F is below 0.05%. Thus we claim that our method can approximate the drag force on the liquid domain accurately.

For the case of a rigid domain, Petrov & Schuille (2008) derived a simple analytical expression for the drag force for the solution developed by Hughes *et al.* (1981).

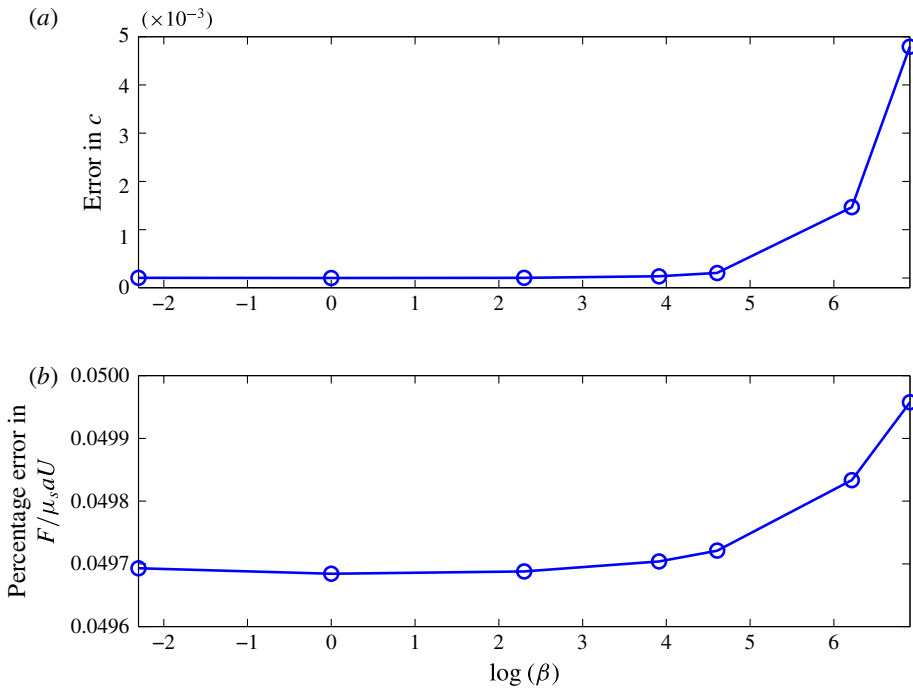


FIGURE 3. (Colour online) Error in calculation of constant c versus $\log \beta$ for $\epsilon = 0$. The parameters are $n = 4000$, $U_L = 6000$ and $h = 0.05$.

In figure 4 we present the variation of the error in dimensionless drag force ($F/\mu_s aU$) for $\beta = 10$ calculated using (3.10) with respect to the parameters U_L , $1/h$, \tilde{r} and n . The drag force computed by Petrov & Schuille (2008) has been taken as the benchmark. We observe that the error is minimum when $\tilde{r} = 1.014$, $n = 4000$, $h = 0.06$ and $U_L = 6000$ and we choose these parameter values for computing the drag force on the domain. The variation of the error and the percentage error in the dimensionless drag force $F/\mu_s aU$ with respect to β have been presented in figure 5(a,b), respectively. The error initially decreases with β and then increases almost linearly. However, the percentage error asymptotically reaches a constant value of around 2.5% (see inset of figure 5b). Further, the percentage error is large for β less than 5, and is around 5% or below for β larger than 5. Thus we say that our method is accurate for larger values of β when ϵ is unity.

For ϵ other than zero or unity, we do not have any analytical or existing results to compare. We carry out convergence studies for the drag force with respect to the parameters U_L , h , \tilde{r} and n for a few values of ϵ and β and obtain the same parameter values at convergence. The values of ϵ and β selected for convergence studies lie in a large range. Thus for subsequent studies we select $n = 4000$, $\tilde{r} = 1.014$, $U_L = 6000$, $h = 0.06$.

4.2. Drag on the domain for arbitrary ϵ

In figure 6(a,b) we present the variation of the dimensionless drag force with the Boussinesq number β for several values of the viscosity contrast ϵ between the domain and surrounding membrane. The values of ϵ are chosen such that the domain

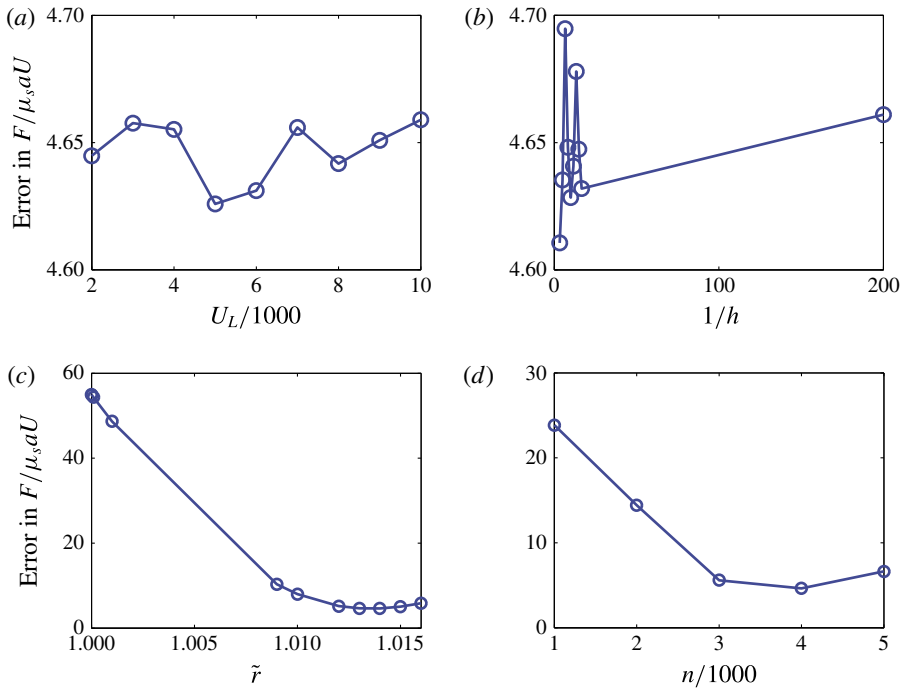


FIGURE 4. (Colour online) Variation of the error in $F/\mu_s aU$ (a) with U_L for $\tilde{r} = 1.014$, $n = 4000$, $h = 0.06$, (b) with $1/h$ for $\tilde{r} = 1.014$, $n = 4000$, $U_L = 6000$, (c) with \tilde{r} for $n = 4000$, $U_L = 6000$, $h = 0.06$ and (d) with n for $\tilde{r} = 1.014$, $U_L = 6000$, $h = 0.06$. In all the above cases $\beta = 10$ and $\epsilon = 1$.

characteristic varies from highly viscous to one having very low viscosity with respect to the surrounding membrane. For example, $\epsilon = 0.8$ implies $\eta_d/\eta_m = 5$, and for $\epsilon = -20$ we obtain $\eta_d/\eta_m = 1/21$. We have chosen β to vary between 5 and 1000, for most cases, as this lies within the range of its possible values. Further, we obtained accuracy of 95% or more in the computation of the drag force above $\beta = 5$ in the previous subsection. From figure 6, we observe that, for any specified ϵ , the dimensionless drag force increases with β . An increasing β implies increasing surrounding membrane viscosity η_m for fixed surrounding fluid viscosity and domain radius. Thus the drag force should increase with β in this scenario.

We observe from figure 6(a) that for positive ϵ the dimensionless drag force does not change significantly with ϵ . The same is true for $-1 \leq \epsilon \leq 1$. Note that when ϵ changes from 0 to unity the domain behaviour changes from having the same viscosity as the surrounding membrane to near rigid. During this drastic change in the domain behaviour the diffusion coefficient does not change. In this scenario, the domains diffuse in a membrane of low viscosity. A similar observation was also made by Cicutta *et al.* (2007) in their experimental study.

For large and negative ϵ the domain viscosity is much smaller than that of the surrounding membrane. In this scenario, we observe a significant drop in the drag force for all β (see figure 6b). From figure 7(a), we also observe that the ratio between the drag forces on the rigid and liquid domains increases with β initially and then decreases. The drop is most significant in the intermediate range of β , between approximately 10 and 100. Again, from figure 7(a) we observe that the drag

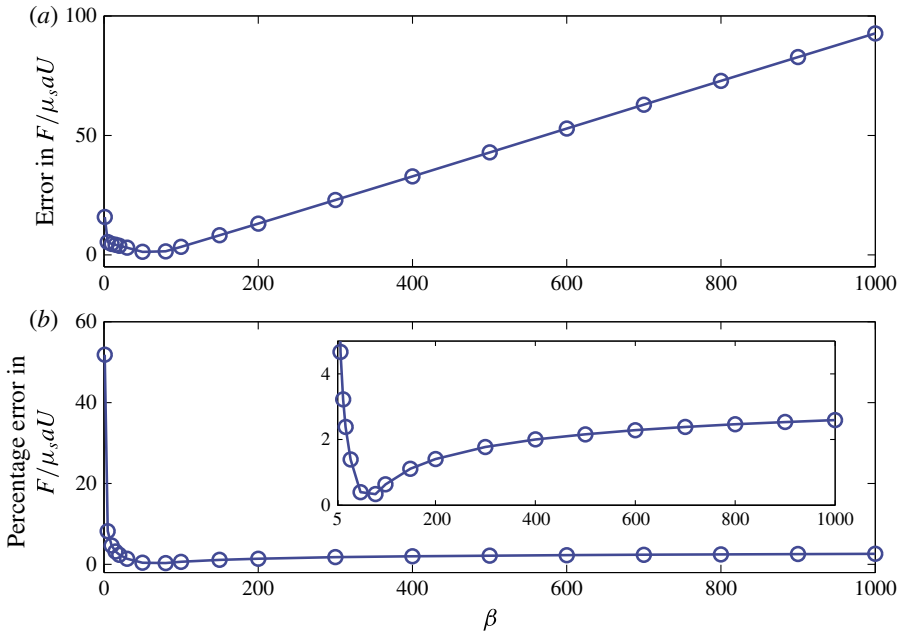


FIGURE 5. (Colour online) Variation of the error and percentage error in $F/\mu_s aU$ versus β for $\epsilon = 1$. The parameters are $n = 4000$, $\tilde{r} = 1.014$, $U_L = 6000$, $h = 0.06$.

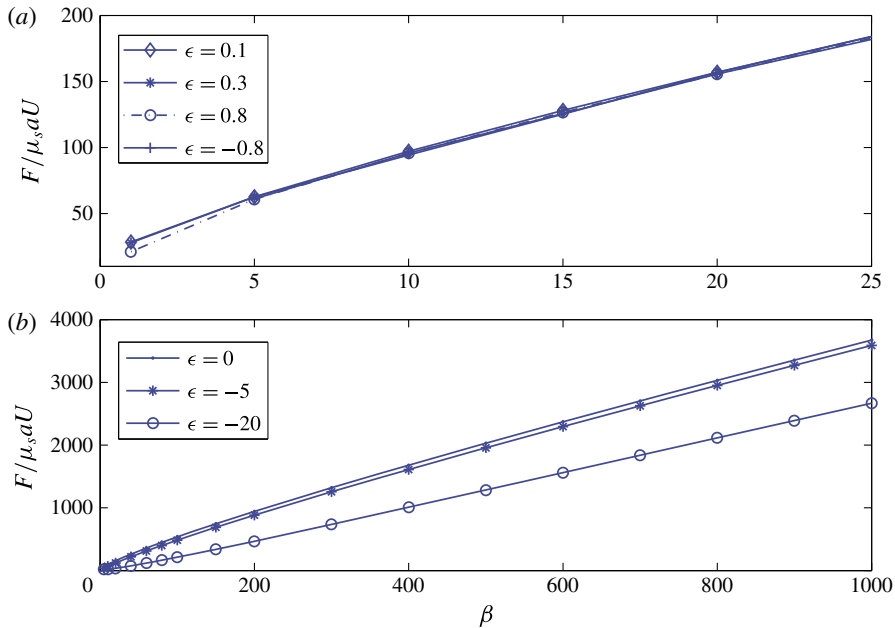


FIGURE 6. (Colour online) Variation of $F/\mu_s aU$ with the Boussinesq number β for different viscosity contrast ϵ . The parameters chosen are $n = 4000$, $\tilde{r} = 1.014$, $U_L = 6000$, $h = 0.06$.

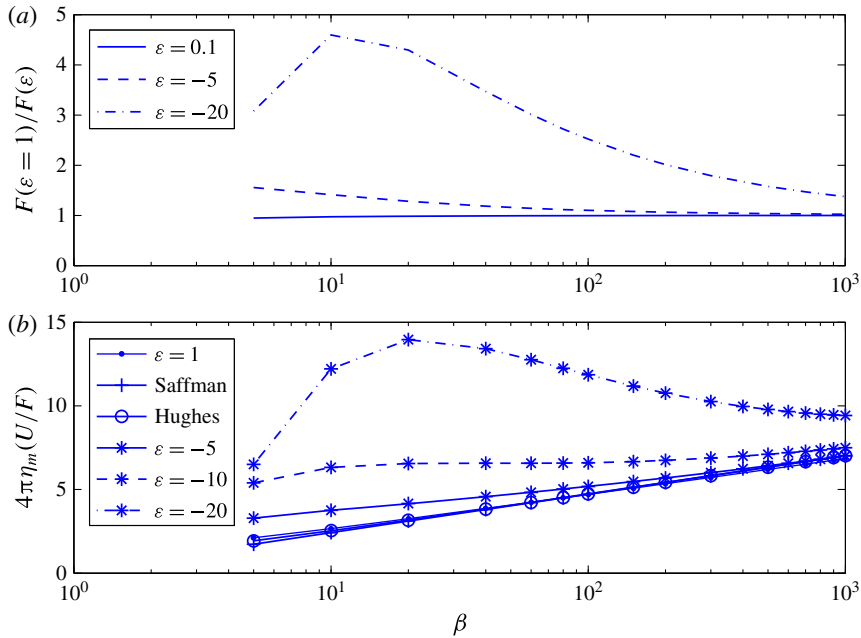


FIGURE 7. (Colour online) (a) Variation of drag force on the liquid domain, relative to the drag force on a rigid domain of the same size, with the Boussinesq number β for three different values of viscosity contrast ϵ . (b) Mobility with respect to β for $\beta \geq 5$ and comparison with the results of Saffman (1976) and Hughes *et al.* (1981). For large and negative ϵ , significant departure from the logarithmic behaviour is observed.

forces on the rigid and the liquid domains are almost the same $-1 \leq \epsilon \leq 1$ (data for $\epsilon = -1$ not presented).

Hughes *et al.* (1981) have predicted that mobility varies linearly with β for small β . Due to the large percentage error in our results for $\beta \leq 5$, we do not attempt a quantitative comparison of mobility with the asymptotic behaviour predicted by Hughes *et al.* (1981). However, we do observe that the absolute error is less for $\beta \ll 1$ and the mobility varies linearly with β in this regime (not shown). Finally, in figure 7(b), we present the dimensionless mobility variation with β for different ϵ . For a rigid domain ($\epsilon = 1$) our results agree with the logarithmic behaviour ($U/F \approx \ln(2\beta)$) predicted by Saffman (1976) and Hughes *et al.* (1981). When the domain is not rigid, but the viscosity contrast ϵ is less than unity in magnitude, the mobility for the liquid domain is close to that for the rigid domain. However, for large and negative ϵ , that is when the surrounding membrane is significantly more viscous than the domain, the mobility is significantly different and does not vary as $\ln(2\beta)$. The dimensionless mobility initially increases with β and subsequently decreases but is always larger than the mobility for the rigid domain. To the best of our knowledge, such a behaviour has not been predicted previously. It is possible to design experiments by choosing a ternary lipid mixture of ordered and disordered lipids and cholesterol of suitable composition to obtain domains of significantly lower viscosity than the surrounding. Ternary phase diagrams presented in figures 8–10 of Veatch & Keller (2005) can provide guidance to choosing such compositions.

5. Conclusions

In this paper, we develop a simple numerical solution procedure involving the discrete collocation method and Chebyshev polynomials for the dual integral equations, of Fredholm second kind, that compute the drag force (and the diffusion coefficient) on a liquid microdomain diffusing in a two-dimensional lipid bilayer membrane. We first validate our method with the existing results for the cases when either the domain is rigid or the domain and the surrounding membrane have the same viscosity. For the general case of arbitrary viscosity contrast between the domain and surrounding membrane, the drag force is almost independent of the viscosity contrast between the domain and the surrounding membrane for a more viscous domain, whereas it varies significantly with the viscosity contrast for a less viscous domain. Further, unlike the rigid domain, the mobility of the domain does not vary logarithmically with the Boussinesq number for larger values of the latter. The mobility initially increases with the Boussinesq number and then decreases but is always larger than that for the rigid domain. In our solution of the dual integral equations, we do not make any assumptions. Accordingly, unlike the earlier studies, our methodology of computing the drag force and diffusion coefficient is valid for arbitrary viscosity contrast between the domain and membrane and for any domain size subject to the condition that the Boussinesq number should be larger than 5 for good accuracy. A study of the diffusion behaviour and drag on a microdomain for such a large range of viscosity contrast between the domain and the surrounding membrane is now possible.

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