The aqueous viscous drag of a contracting open surface

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A problem for fluid flow around an axisymmetric spherical surface with a hole is presented to characterize pore dynamics in liposomes. A rotational stream function for the contraction of a punctured plane region is obtained and is used in the perturbation expansion for a stream function in the case of a spherical surface with a hole of small radius compared to the spherical radius. The Rayleigh dissipation function is calculated and used to infer the aqueous friction induced by the contraction of the hole. The theoretical aqueous friction coefficient is compared with one derived from experimental data, and they are in agreement. © 2014 AIP Publishing LLC. [<http://dx.doi.org/10.1063/1.4864192>]

I. INTRODUCTION

Biological membranes consist of lipids and proteins. Membranes deform as a natural part of many biological processes, such as the changes in shape red blood cells undergo as they pass through capillaries, the merger of separate membranes in the release of neurotransmitters in the brain, and the engulfment of large extracellular molecules by cells. The deformation of membranes is hindered by the internal viscosity of the membrane and by the aqueous viscosity of the surrounding water.

A single bilayer can be arranged into a sphere that separates interior and exterior aqueous compartments. These liposomes can be large (20 μm), mimicking cell membranes, or small (100 nm), modeling membranes of intracellular granules. Pores more or less circular, form in membranes as a result of injury or osmotic bursting and the spherically shaped membrane surface becomes open to the extracellular solution. Pore dynamics has been experimentally modeled by osmotic swelling of liposomes, and it has been found that the pore grows until the internal pressure of the liposome, responsible for swelling, is relieved; the hole then shrinks, minimizing its circumference.

The standard theory that had been used to predict pore growth and shrinkage assumed that dissipation of the energy stored within the stretched bilayer is dominated by the viscosity of the bilayer itself.¹ This prior theory, however, did not correctly account for pore dynamics as a function of aqueous viscosity; the time course for growth and shrinkage of the pore is slowed as the aqueous viscosity is experimentally increased, and the prior theory ignored any contribution of aqueous viscosity to energy dissipation.^{1,2} More recently, we developed a theory that does properly describe the experimentally observed dependence. We further showed by dimensional analysis that aqueous viscosity, and not bilayer viscosity, is the leading term in the dissipation function.³ But this recent theory assumed that the bilayer was flat, whereas liposomes and cells are spherical. A drag friction coefficient accounting for the aqueous viscosity was obtained empirically by fitting this theory to experimental data of measured pore time courses.

In this note, we present a self-contained theoretical derivation for the viscous drag of the ambient fluid for spherical, rather than flat, open membranes. We will refer to the viscous drag as *aqueous friction*. We view a liposome with a pore as an axisymmetric, two-dimensional surface immersed in

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an incompressible, viscous, Newtonian fluid. We present a boundary value problem for the fluid flow around the surface. In the biological situation, the Reynolds number $\text{Re} = \rho UL/\mu \approx 10^{-5}$ is low; the velocity is obtained from a stream formulation for the equations of motion. We first study the case of a sphere with infinite radius and obtain a closed form solution for the stream function around a flat plane with a hole. We address the case of a sphere with finite radius by using the method of perturbation expansion assuming the ratio between the radius of the hole and the radius of the sphere is small. We then calculate the rate of mechanical energy dissipation in order to infer the following value of the aqueous friction coefficient:

$$\gamma(\epsilon) = 2\pi - 4\epsilon \ln \epsilon + \dots, \quad (1)$$

where ϵ is the non-dimensional ratio of hole radius to sphere radius. Equation (1) shows that the friction coefficient for a contracting, infinite, flat plane with a hole is precisely 2π . This coefficient increases as the plane is made spherical with a finite radius that is large when compared to the radius of the hole. We combine the value of $\gamma(\epsilon)$, which now depends on the liposome geometry, with the Raleigh dissipation equation to derive pore dynamics.

The analytical and numerical calculation of the interaction between fluid flows and bounding regions is in general a difficult problem that is further complicated by the domain geometry. The boundary integral,⁴⁻⁶ immersed boundary,^{7,8} and phase field⁹ methods are three important numerical methods capable of modeling these interactions. Exact expressions for the fluid flow, like those obtained by for the nonlinear flow over a spreading, flat surface,¹⁰ are rare. For the annular region, we consider in this note, the shear forces for unidirectional flow across the circular hole in a plane wall have been obtained.¹¹ Exact solutions for the Stokes flow and drag force for a spherical cap in a uniform far field flow have been derived.^{12,13} In these works, the steady streaming flow describes the rigid translation of a spherical cap in a viscous fluid. In contrast, in the present study the boundary velocity is tangential and the flow is time dependent because the hole contracts or expands axisymmetrically—there is no inertial frame of reference in which the hole appears at rest. The consequences of viscous drag on oscillating cantilevers used for atomic force microscopes has also been considered through a shape dependent hydrodynamic function.¹⁴ There has been significant work that has considered the retraction of viscous sheets that is controlled by energy dissipation internal to the bilayer itself, but ignoring any contributions caused by movement of the ambient viscous fluid.¹⁵⁻¹⁹ To our knowledge, a closed form expression for the stream function accounting for the interaction between a spreading surface that contains a circular hole with the viscous ambient medium has not been described before.

In Sec. II, we present the stream function formulation for axisymmetric Stokes flow and derive particular solution expansions of the stream equation. In Sec. III, we solve the flow problem for the contraction of a flat plane surface. In Sec. IV, we solve the analogous flow problem for a spherical surface using the method of perturbation expansions. The dissipation function and the friction coefficient given by Eq. (1) are calculated at the ends of Secs. III and IV. The results of these calculations are compared in Sec. V with the numerical value of the aqueous friction coefficient obtained by empirical means. An experiment that would explicitly test our theory is suggested.

II. NOTATION AND PRELIMINARIES

We treat the problem of determining the flow field in the aqueous region surrounding the membrane by the method of the Stokes' stream function. Consider an axisymmetric, open surface Σ_t with a single hole where the surface is moving with normal velocity v_n and tangential velocity v_s (Figure 1). The stream function ψ is a solution to the boundary value problem²⁰

$$D^2\psi - \frac{1}{v}(D\psi)_t = 0, \quad x \in \mathbb{R}^3 \setminus \Sigma_t, \quad (2)$$

$$\frac{1}{\varpi} \frac{\partial \psi}{\partial s} = -v_n, \quad x \in \Sigma_t, \quad (3)$$

FIG. 1. Cut-away portion of a rotationally symmetric open surface Σ_t representing a spherical liposome of radius R with a pore of radius $c(t)$ lying between the azimuthal angles $0 < \phi < \pi$. A viscous ambient fluid occupies the region bathing the surface. The pore contracts (expands) by decreasing (increasing) $c(t)$.

$$\frac{1}{\varpi} \frac{\partial \psi}{\partial n} = v_s, \quad x \in \Sigma_t, \quad (4)$$

$$\psi = 0, \quad \varpi = 0. \quad (5)$$

Here, D is the stream operator which, in cylindrical coordinates (ϖ, z) , reads

$$D = \frac{\partial^2}{\partial \varpi^2} - \frac{1}{\varpi} \frac{\partial}{\partial \varpi} + \frac{\partial^2}{\partial z^2}.$$

When $D\psi = 0$ the stream function ψ is said to be irrotational and when $D\psi \neq 0$ the stream function ψ is said to be rotational. Here, $\nu = \mu/\varrho$ is the kinematic viscosity where μ is the aqueous (dynamic) viscosity and ϱ the aqueous density. The surface tangent $\mathbf{e}_s$ is oriented away from the hole and the surface normal $\mathbf{e}_n$ is chosen so that $(\mathbf{e}_s, \mathbf{e}_n)$ form a right-handed orthonormal frame (Figure 1). In (3), the partial derivative of ψ is taken in the $\mathbf{e}_s$ direction with arc-length parameter s and in (4) the partial derivative of ψ is taken in the direction $\mathbf{e}_n$. Since Σ_t faces the fluid on two sides, we will distinguish the side of Σ_t lying in the direction $\mathbf{e}_n$ as positive and the side of Σ_t lying in the direction $-\mathbf{e}_n$ side as negative. Finally, (5) is the requirement that fluid flux be nonsingular on the axis of symmetry.

We will focus our attention on contractile motions of the Σ_t . As defined below, contraction is related to a dimensional parameter $c(t)$ —the hole radius. Lipid bilayers are generally homogeneous so we let the lipid density be spatially constant. Mass conservation then implies that $\text{div } \mathbf{v} = \frac{\partial \mathbf{v}}{\partial s} \cdot \mathbf{e}_s + \frac{1}{\varpi} \mathbf{v} \cdot \mathbf{e}_\varpi$ is independent of s , where $\mathbf{v} = v_s \mathbf{e}_s + v_n \mathbf{e}_n$ is the velocity of Σ_t , div is the surface divergence, and $\mathbf{e}_\varpi$ and $\mathbf{e}_z$ are the cylindrical basis vectors. If $v_n = 0$, then

$$v_s(s) = \frac{k_1}{\varpi} + \frac{k_2}{\varpi} \int_0^s \varpi \, du, \quad (6)$$

where k_1 and k_2 are integration constants determined by the rim and far field tangential velocities.

In classical calculations, the drag force that is imposed on obstacles in a Stokes flow generally shares the same direction as the far field flow. In the present problem, this identification is not possible because the shear forces caused by contraction are radial. Strictly speaking, the total shear force is a pseudo force. We calculate the rate of mechanical energy dissipation as a function of μ , $c(t)$, and pore velocity U to infer the friction coefficient. Once $\mathbf{v}$ has been specified and the stream

function ψ determined from (2)–(5), we calculate the Rayleigh dissipation function,²⁰

$$\Delta_a = -2\mu \int_{\Sigma_t} \frac{v_s}{\varpi} D\psi dA. \quad (7)$$

The dissipation function Δ_a is the rate at which internal energy is transferred from the bilayer into the aqueous surrounding by viscous losses. The coefficient 2 preceding the previous integral accounts for the dissipation on the positive and negative side of Σ_t . We have also chosen a sign convention making Δ_a nonnegative.

To illustrate how the friction coefficient is derived from the dissipation function and applied to the problem of pore dynamics, let $E(c, R)$ be the internal energy of a liposome as a function of the hole radius c and sphere radius R . For a liposome in which the internal pressure is zero, for example,

$$E(c, R) = T2\pi c + S \frac{(4\pi R_0^2 - 4\pi R^2 + \pi c^2)^2}{8\pi R_0^2}$$

is the sum of the edge energy and stretching energy where $T = 2.5 \text{ kT nm}^{-1}$ is edge tension of a hole in a bilayer and $S = 0.045 \text{ kT nm}^{-2}$ is the modulus for unfolding of the wrinkles in the bilayer. The Rayleigh dissipation equation permits us to determine an evolution equation for $c(t)$

$$\frac{1}{2} \frac{\partial \Delta}{\partial U} = - \frac{\partial E}{\partial c}, \quad (8)$$

where $\Delta = \Delta_a + \Delta_m$ and Δ_m is the rate of internal energy dissipation due to viscous losses within the membrane. The aqueous friction coefficient γ is defined by the relation $\mathcal{F}_a = 2\pi\mu c U \gamma$ where

$$\mathcal{F}_a = \frac{1}{2} \frac{\partial \Delta_a}{\partial U} \quad (9)$$

is the aqueous friction.

We first study the stream function for the planar surface

$$\Sigma_t^0 = \{(\varpi, z, \phi) : \varpi > c(t), z = 0, 0 \leq \phi < 2\pi\}$$

formed by an infinite, flat plane punctured by a hole of radius $c(t)$ centered on the axis of symmetry. Here, ϕ is the azimuthal angle. We then study the stream function for the spherical surface using Σ_t^0 as an approximation of the surface Σ_t^ϵ depicted in Figure 1, in the cases when the sphere radius R is large compared to the hole radius $c(t)$. Here, the stream function ψ^ϵ will be developed by the method of perturbation expansion²¹ where we tentatively assume

$$\psi^\epsilon = \psi^0 + \epsilon \psi^1 + \dots \quad (10)$$

and $\epsilon = c(t)/R$ is a small, non-dimensional perturbation parameter. The stream functions in (10) are solutions to auxiliary boundary value problems on $\mathbb{R}^3 \setminus \Sigma_t^0$. The boundary data for $\psi^0, \psi^1, \dots$ are supplied by the surface velocity, the coordinate changes associated with the approximation of Σ_t^ϵ by Σ_t^0 , and by any preceding terms in the expansion. We will restrict our attention to the first two terms in the expansion (10), although it is in principle possible to pursue terms of arbitrarily high order.

Stream functions are presented in oblate spheroidal coordinates²²

$$z + i\varpi = c \sinh(\xi + i\eta).$$

The contours $\xi = \text{const.}$ and $\eta = \text{const.}$ form an orthogonal family of planetary spheroids and hyperboloids, respectively. The succeeding expressions will be simplified by working with the coordinates

$$p = \cos \eta, \quad q = \sinh \xi$$

for which

$$\varpi = c\sqrt{1-p^2}\sqrt{1+q^2}, \quad z = cpq. \quad (11)$$

In this way, the infinite cylinder $\{(p, q, \phi): 0 < p < 1, -\infty < q < \infty, 0 \leq \phi < 2\pi\}$ is identified with the region $\mathbb{R}^3 \setminus \Sigma_t^0$. In these coordinates, the stream operator is

$$D = \frac{1}{c^2(p^2 + q^2)} \left((1 - p^2) \frac{\partial^2}{\partial p^2} + (1 + q^2) \frac{\partial^2}{\partial q^2} \right).$$

Later in this note, rotational stream functions of the form

$$\psi_0 = qf(p), \quad \psi_1 = pg(p), \quad (12)$$

will arise for which $D^2\psi_0 = D^2\psi_1 = 0$ provided f and g are quadratic. Further solutions of the equation $D^2\psi = 0$ are obtained by the decomposition²³

$$\psi = \psi_{\text{irr}} + \psi_{\text{rot}}, \quad D\psi_{\text{irr}} = 0, \quad D\psi_{\text{rot}} = \omega, \quad D\omega = 0,$$

where ψ_{irr} and ω are expressed in terms of Gegenbauer polynomials. Specifically,

$$\psi_{\text{irr},0} = 1, \quad \psi_{\text{irr},1} = p, \quad \psi_{\text{irr},2} = q, \quad \psi_{\text{irr},3} = pq, \quad \psi_{\text{irr},4} = \frac{1}{4}(p^2 - 1)(q^2 + 1), \dots \quad (13)$$

satisfy $D\psi_{\text{irr},n} = 0$ for $n = 0, 1, 2, \dots$, and

$$\begin{aligned} \psi_{\text{rot},0} &= \frac{1}{2}(q^2 - p^2 + 2), \quad \psi_{\text{rot},1} = \frac{1}{2}q \left(\frac{1}{3}q^2 - p^2 \right), \quad \psi_{\text{rot},2} = \frac{1}{2}p \left(q^2 - \frac{1}{3}p^2 \right), \\ \psi_{\text{rot},3} &= \frac{1}{6}(pq^3 - p^3q + 2pq), \dots \end{aligned} \quad (14)$$

satisfy $D\psi_{\text{rot},n} = \psi_{\text{irr},n}$ for $n = 0, 1, 2, \dots$. The mathematical details of the derivation of (13) and (14) are provided in the Appendix. We will determine the solution ψ to boundary value problems by setting

$$\psi = B\psi_0 + B'\psi_1 + \sum_{n=0}^{\infty} A_n\psi_{\text{irr},n} + \sum_{n=0}^{\infty} B_n\psi_{\text{rot},n}, \quad (15)$$

where the value of the coefficients $B, B', A_0, A_1, \dots$, and $B_0, B_1, \dots$ are chosen to satisfy the boundary conditions (3)–(5). Prior investigators²³ have obtained more general expansions for the stream function in oblate spheroidal coordinates.

III. AN INFINITE, FLAT PLANE WITH HOLE

As the base case, we consider the planar surface Σ_t^0 moving with tangential velocity

$$v_s(\varpi) = U \frac{c(t)}{\varpi} \quad (16)$$

and normal velocity

$$v_n(\varpi) = 0.$$

With this velocity, the rim of the hole contracts with rate U and the area density is independent of position and t . This velocity is sometimes referred to as radial plug flow. It is immediately verified that v_s satisfies the continuity equation (6). Consider the associated boundary value problem

$$D^2\psi^0 - \frac{1}{\nu}(D\psi^0)_t = 0, \quad x \in \mathbb{R}^3 \setminus \Sigma_t^0, \quad (17)$$

$$\frac{1}{\varpi} \frac{\partial \psi^0}{\partial \varpi} = 0, \quad x \in \Sigma_t^0, \quad (18)$$

$$\frac{1}{\varpi} \frac{\partial \psi^0}{\partial z} = U \frac{c}{\varpi}, \quad x \in \Sigma_t^0, \quad (19)$$

$$\psi^0 = 0, \quad \varpi = 0. \quad (20)$$

With the help of (11), one verifies that the boundary conditions (18)–(20) imply

$$\psi^0(1, q) = 0, \quad \frac{\partial \psi^0}{\partial q}(0, q) = 0, \quad \frac{\partial \psi^0}{\partial p}(0, q) = Uc^2q, \quad -\infty < q < \infty. \quad (21)$$

We therefore guess a solution of the form $\psi^0 = qf(p)$ given in (12). We require that $f(1) = 0$, $f(0) = 0$, and $f'(0) = Uc^2$. This is achieved by setting $f(p) = Uc^2p(1 - p)$ and therefore

$$\psi^0(p, q, t) = Uc^2(t)qp(1 - p). \quad (22)$$

Note that ψ^0 is now also a solution of (17) because $D^2\psi^0 = 0$ and

$$D\psi^0 = \frac{-2Uq(1 - p^2)}{p^2 + q^2} \quad (23)$$

is independent of t , once terminal velocity U is reached. The function ψ^0 is an exact solution to the unsteady Stokes flow problem for an incompressible plane region shrinking with constant speed around a circular hole.

The pressure P can be integrated yielding²⁰

$$P(p, q, t) = -\frac{2\mu Up}{c(t)(p^2 + q^2)}. \quad (24)$$

Although the pressure P is singular on the leading edge of the hole ($q = 0, p \rightarrow 0$), the dissipation of mechanical energy due to pressure vanishes. This occurs because the pressure is symmetric on opposite sides of Σ_t^0 . Contours of the pressure and ψ^0 are provided by Figure 2. Although the velocity is an exact solution of the Stokes equation, it is not a solution to the full Navier-Stokes equations ($\nabla\psi^0 \times \nabla(\varpi^{-1}D\psi^0) \neq 0$). However, the very low Reynolds number implies that the velocity fails to solve the full Navier-Stokes equation by a residual on the same order as the residual found in numerical approximations;²⁴ the linear Stokes flow is thus indistinguishable from the nonlinear flow in practical, biological applications.

The pressure field (24) in the vicinity of the pore edge is locally the same as the pressure field induced by the steady, two-dimensional flow past a semi-infinite plate. Taking h to be the distance from a point in the plane with the surface, setting $q = 0$ in (24) and using (11), yields $P \sim -2U\mu/c\sqrt{h}$. The expression $\tilde{\xi}\tilde{\eta}^2$ for the stream function in parabolic coordinates ($\tilde{\eta}, \tilde{\xi}$) holds at the leading edge of a flat plate.²⁵ By integrating the equations of motion, the pressure P_{plate} on the leading edge of a flat plate is then proportional to $\tilde{\eta}/(\tilde{\eta}^2 + \tilde{\xi}^2)$. Evaluating in the region adjacent to

FIG. 2. The contour lines of the stream function ψ^0/U and values (panel (a)) and the contour lines of the pressure $P/2\mu U$ and values (panel (b)) when $c = 1$. The surface Σ_t^0 , depicted by the thick curve, represents a planar bilayer with a circular hole.

the edge gives P_{plate} proportional to $1/\sqrt{h}$ which is locally of the same form as the pressure near the pore edge. A similar comparison holds for the flat plate and axisymmetric uniform flow past the leading edge of a hemispherical cup.¹²

The fact that the location of the pressure singularity $(\varpi, z) = (c(t), 0)$ and coordinate transformation (11) varies with t illustrates the time dependence of the velocity and pressure derived from ψ^0 . To evaluate the dissipation function, we set $p = 0$ in (11), (16), and (23), to find

$$\Delta_a = -2\mu \int_{\Sigma_t^0} \frac{v_s}{\varpi} D\psi dA = 8\pi\mu c U^2 \int_0^\infty \frac{1}{1+q^2} dq = 4\pi^2\mu c U^2 \quad (25)$$

from which we infer

$$\mathcal{F}_a = 4\pi^2\mu c U, \quad \gamma = 2\pi. \quad (26)$$

Here, $\gamma = 2\pi$ is the leading term in the expansion (1). The succeeding terms in the expansion are calculated in Sec. IV.

IV. A LARGE SPHERE WITH HOLE

We can avoid the mixed boundary value problem for the sphere with a hole by forming a perturbation expansion in the coordinates for the punctured plane. The solution derived in Sec. III is the base case for this expansion. The spherical surface with radius R is parametrized by

$$z = R - \rho \cos \theta, \quad \varpi = \rho \sin \theta. \quad (27)$$

Let

$$R \gg c(t), \quad \epsilon = \frac{c(t)}{R}, \quad \sin \theta_0 = \epsilon$$

and set

$$\Sigma_t^\epsilon = \{(\varpi, z, \phi) : \rho = R, \theta_0 < \theta < \pi, 0 \leq \phi < 2\pi\}.$$

Then Σ_t^ϵ is the surface formed by a sphere of radius R centered at $z = R$ on the axis of symmetry with a hole of radius $c(t)$. In order to allow the sphere to approach the punctured planar surface Σ_t^0 in the limit $\epsilon \rightarrow 0$, we identify a given point $(\varpi(\theta, R), z(\theta, R), \phi)$ on Σ_t^ϵ with a reference point $(s, 0, \phi)$ on Σ_t^0 whose distance s from the axis of symmetry is identical to the arc length $R\theta$ of the circular arc connecting the point $(\varpi(\theta, R), z(\theta, R), \phi)$ to the origin. This is done by fixing the product

$$R\theta = s \quad (28)$$

in the limit $R \rightarrow \infty$. Also, the set of points $\{(\varpi(\rho, \theta), z(\rho, \theta)) : 0 < \rho < \infty\}$ form a family of radial lines orthogonal to the section of Σ_t^ϵ , as depicted in Figure 3. This gives a convenient way to compute the normal derivative needed shortly.

Define the tangential velocity

$$v_s^\epsilon(s) = \frac{U}{\cos \theta_0} \frac{1 + \cos \theta}{1 + \cos \theta_0} \frac{\sin \theta_0}{\sin \theta}, \quad (s = R\theta) \quad (29)$$

and normal velocity

$$v_n^\epsilon(s) = 0.$$

With this velocity, the rim of the hole contracts with rate U and the area density of the surface is independent of position (but not time). A short calculation verifies that $v_s^\epsilon(R\pi) = 0$, $v_s^\epsilon(R\theta_0) = \frac{U}{\cos \theta_0}$, and that v_s is a solution to (6).

The Reynolds number $\text{Re} \approx 10^{-5}$ for pore dynamics in liposomes is very small and solutions to the unsteady equations (2)–(5) are suitably approximated by solutions of the creeping motion equations associated with the bounding region Σ_t^ϵ ,

$$D^2\psi^\epsilon = 0, \quad x \in \mathbb{R}^3 \setminus \Sigma_t^\epsilon, \quad (30)$$

FIG. 3. Coordinates parametrizing a large sphere Σ_t^ϵ with a hole of radius c . The ρ -contours form spheres centered at $z = R$. The cone formed by the points $(w(\rho), z(\rho))$ is orthogonal to the sphere. The pore rim and intersection with the axis of symmetry are parametrized by the limits $\theta = \theta_0$ and $\theta = \pi$, respectively.

$$\frac{1}{w} \frac{\partial \psi^\epsilon}{\partial s} = 0, \quad x \in \Sigma_t^\epsilon, \quad (31)$$

$$\frac{1}{w} \frac{\partial \psi^\epsilon}{\partial n} = v_s, \quad x \in \Sigma_t^\epsilon, \quad (32)$$

$$\psi^\epsilon = 0, \quad w = 0. \quad (33)$$

To solve the boundary value problem (30)–(33) by the method of perturbation expansion, we tentatively assume that a perturbation expansion

$$\psi^\epsilon(p, q, t) = \psi^0(p, q, t) + \epsilon \psi^1(p, q, t) + \dots \quad (34)$$

holds in a neighborhood of $\epsilon = 0$ and where p and q are the oblate spheroidal coordinates. The general strategy is to substitute this expansion into Eqs. (30)–(33). Equating like powers in ϵ allows a determination of ψ^0 and ψ^1 as solutions to auxiliary boundary value problems. Noting that $\psi^\epsilon = 0$ on the intersection of Σ_t^ϵ with the axis of symmetry, (31) implies that

$$\psi^0 + \epsilon \psi^1 + \dots = 0, \quad x \in \Sigma_t^\epsilon. \quad (35)$$

Here, p and q depend implicitly on ϵ , necessitating an expansion of ψ^0 and ψ^1 before equating like powers. Expanding (35) into a Taylor series in ϵ ,

$$\psi^0 + \epsilon \left(\psi^1 + \frac{1}{2} \left(q + \frac{1}{q} \right) \psi_p^0 \right) + \dots = 0, \quad x \in \Sigma_t^0, \quad (36)$$

where we have used the chain rule with (11), (27), and (28), to derive $q_\epsilon = 0$ and $p_\epsilon = \frac{1}{2} \left(q + \frac{1}{q} \right)$. Subscripts p , q , and ϵ refer to their respective partial derivatives evaluated at $\epsilon = 0$.

Similarly, the condition (32) implies that

$$\frac{\partial \psi^0}{\partial n} + \epsilon \frac{\partial \psi^1}{\partial n} + \dots = w v_s^\epsilon, \quad x \in \Sigma_t^\epsilon. \quad (37)$$

To equate like powers, we rewrite the normal derivative in terms of the partial derivatives in p and q and then expand each term appearing in the chain rule in terms of ϵ . We find, after some calculation,

$$\begin{aligned}\frac{\partial \psi^0}{\partial n} &= \frac{1}{cq} \psi_p^0 + \epsilon \left(\frac{1}{2cq} \left(q + \frac{1}{q} \right) \psi_{pp}^0 + \frac{1-q^4}{2cq^3} \psi_q^0 \right) + \dots, \\ \frac{\partial \psi^1}{\partial n} &= \frac{1}{cq} \psi_p^1 + \dots, \quad \varpi v_s^\epsilon = cU + \dots,\end{aligned}\tag{38}$$

where we have used the chain rule with (11), (27), (28), and $\frac{\partial}{\partial n} = -\frac{\partial}{\partial \rho}$ to derive $p_\rho = \frac{1}{cq}$, $q_\rho = 0$, and $p_{\rho\epsilon} = 0$, and $q_{\rho\epsilon} = \frac{1-q^4}{2cq^3}$. With the help of (38), expanding (37) in powers of ϵ gives

$$\frac{1}{cq} \psi_p^0 + \epsilon \left(\frac{1}{cq} \psi_p^1 + \frac{1}{2cq} \left(q + \frac{1}{q} \right) \psi_{pp}^0 + \frac{1-q^4}{2cq^3} \psi_q^0 \right) + \dots = cU.\tag{39}$$

Consolidating the results from (36) and (39) yields

$$\psi^0(1, q) = 0, \quad \psi^0(0, q) = 0, \quad \psi_p^0(0, q) = Uc^2q, \quad -\infty < q < \infty,$$

and

$$\psi^1(1, q) = 0, \quad \psi^1(0, q) = -\frac{1}{2} \left(q + \frac{1}{q} \right) \psi_p^0, \quad \psi_p^1(0, q) = -\frac{1}{2} \left(q + \frac{1}{q} \right) \psi_{pp}^0 - \frac{1-q^4}{2q^2} \psi_q^0$$

for $-\infty < q < \infty$. As expected, the first three of the previous six equations are the same as (21) that appeared for the stream function on the infinite, flat plane in Sec. III. We identify $\psi^0 = Uc^2qp(1-p)$ as before. Plugging the known value of ψ^0 into the boundary values for ψ^1 now gives

$$\psi^1(1, q) = 0, \quad \psi^1(0, q) = -\frac{1}{2} Uc^2(q^2 + 1), \quad \psi_p^1(0, q) = Uc^2(q^2 + 1), \quad -\infty < q < \infty.$$

Equating these boundary values with the decomposition (15) (with $\psi_0 = qp^2$ and $\psi_1 = pq^2$) gives the system of equations

$$\begin{aligned}\frac{B_1}{6} q^3 + \left(B' + \frac{B_2}{2} + \frac{B_0}{2} \right) q^2 + \left(A_3 + B_1 + B - \frac{B_1}{2} \right) q + A_0 + A_1 - \frac{B_2}{6} + \frac{B_0}{2} &= 0, \\ \frac{B_1}{6} q^3 + \left(\frac{B_0}{2} - \frac{A_4}{4} \right) q^2 + B_1 q + B_0 + A_0 - \frac{A_4}{4} &= -\frac{1}{2} Uc^2(q^2 + 1), \\ \left(B' + \frac{B_2}{2} \right) q^2 + A_3 q + A_1 &= Uc^2(q^2 + 1).\end{aligned}$$

This system has the solution $B': A_1: B_2: A_0: A_4: B_0 = (-2: 1: 6: 1: -2: -2)Uc^2$ and all other coefficients zero. In this way,

$$\begin{aligned}\psi^\epsilon &= \psi^0 + \epsilon \psi^1 + \dots \\ &= Uc^2 [qp(1-p) + \epsilon (-2\psi_1 + \psi_{\text{irr},1} + 6\psi_{\text{rot},2} + \psi_{\text{irr},0} - 2\psi_{\text{irr},4} - 2\psi_{\text{rot},0})] + \dots.\end{aligned}\tag{40}$$

Recalling that D applied to the irrotational components of ψ^1 gives zero, we find

$$D\psi^\epsilon = U \left[\frac{-2q(1-p^2)}{p^2 + q^2} + \epsilon \left(\frac{-4p(1+q^2)}{p^2 + q^2} + 6p - 2 \right) \right] + \dots.\tag{41}$$

We evaluate (7) for the perturbation solution (40). The only technical difficulty presented by this perturbation expansion is that the integrand of order ϵ must be integrated over Σ_t^ϵ before taking the limit $\epsilon \rightarrow 0$ to avoid a divergent integral. From (40) and (41) and with $s = R\theta$ and $dA = 2\pi \varpi ds$,

we have

$$\begin{aligned}\Delta_a &= -2\mu \int_{\Sigma_t^\epsilon} \frac{v_s}{\varpi} D\psi^\epsilon dA = -4\pi\mu \int_{R\theta_0}^{R\pi} \frac{U}{\cos\theta_0} \frac{1+\cos\theta}{1+\cos\theta_0} \frac{\sin\theta_0}{\sin\theta} D\psi^\epsilon ds \\ &= 2\pi\mu c U^2 \left(\int_1^\infty \frac{4}{s\sqrt{s^2-1}} ds + 4\epsilon \int_{R\theta_0}^{R\pi} \frac{1}{s} ds + \dots \right) \\ &= 2\pi\mu c U^2 \left(2\pi + 4\epsilon \ln \frac{\pi}{\theta_0} + \dots \right).\end{aligned}$$

Finally, using the asymptotic relationship $\theta_0 \sim \epsilon$ yields the aqueous friction and dissipation terms for a sphere with $R \gg c$,

$$\Delta_a = 2\pi\mu c U^2 \left(2\pi - 4\epsilon \ln \frac{\epsilon}{\pi} + \dots \right), \quad \mathcal{F}_a = 2\pi\mu c U \gamma(\epsilon), \quad \gamma(\epsilon) = 2\pi - 4\epsilon \ln \frac{\epsilon}{\pi} + \dots \quad (42)$$

Absorbing $4\epsilon \ln \pi$ into the terms of order ϵ and higher then gives (1).

As a conceptual matter, the functional dependence of the friction coefficient can be further characterized by dimensional analysis. In order to do so, let Ψ^ϵ be the reference stream function for solving the creeping motion boundary value problem (30)–(33), where we substitute the bounding region Σ_t^ϵ by a reference bounding region Σ_t^{ref} formed by a sphere of radius 1 with a hole of radius $\epsilon(t)$. For the boundary data v_s^{ref} , we take the spherical plug flow given by (29) and normalize U to 1. It is straightforward to verify that

$$\psi^\epsilon(x, t) = U R^2 \Psi^\epsilon(R^{-1}x, t).$$

Here, Ψ^ϵ depends implicitly on ϵ through the dimensions of the time varying bounding region. The change of variables formula shows that

$$\Delta_a = -2\mu \int_{\Sigma_t} \frac{v_s}{\varpi} D\psi^\epsilon dA = -2\mu U^2 R \int_{\Sigma_t^{\text{ref}}} \frac{v_s^{\text{ref}}}{\varpi} D\Psi^\epsilon dA =: -\mu U^2 R F(\epsilon),$$

where we have identified that the dissipation function for the reference stream function is now a function of ϵ . The friction coefficient can then be computed from the dissipation equation

$$\gamma = \frac{1}{2\pi\mu c U} \frac{1}{2} \frac{\partial \Delta_a}{\partial U} = -\frac{1}{2\pi} \frac{F(\epsilon)}{\epsilon}.$$

This equation implies the exact value $\lim_{\epsilon \rightarrow 0} F(\epsilon)/\epsilon = -4\pi^2$ as obtained from (42) and that the exact value of the friction coefficient depends only on the ratio $\epsilon = c/R$ and not on any other combinations of the parameters c and R . In Sec. V, we make a comparison between pore dynamics using the value $\gamma(\epsilon)$ and the experimental record for spherical liposomes.

V. EXPERIMENTAL VALIDATION

We now compare the drag coefficient $\gamma(\epsilon)$ derived by theoretical reasoning with the drag coefficient C derived from experimental data,³ which assumed that C was independent of liposome radius and hole size. Curve fitting the data with a friction term of the form $C\mu c c'$ yielded $C = 8.16$. In the experiments, the smallest measured hole radius was $2 \mu\text{m}$ and the widest measured radius was $10 \mu\text{m}$, placing $c(t)$ in the range from one tenth to one half of the liposome radius, $R = 19.7 \text{ nm}$. For this range of values of ϵ , the friction coefficient $\gamma(\epsilon)$ in (42) takes values between 7.6 and 9.9. Thus, the experimental fit is in accord with the present theoretical determinations. We now use the theoretically derived coefficient $\gamma(\epsilon)$ instead of the value of the coefficient C , previously derived by curve fitting experimental data, to calculate the expected pore dynamics predicted by the theory.³ The agreement between the theory and experimental data is excellent (Figure 4).

To further validate (26) by experimental means, a single planar bilayer with diameter greater than a millimeter, could be used. For planar bilayers, surface tension σ is constant (and maintained by the supporting circular Gibbs-Plateau border of radius c_B), and the radial plug flow profile is undisturbed by the far field conditions. The bilayer can be punctured (e.g., by electroporation²⁷) and

FIG. 4. Comparison of the theoretically derived coefficient $\gamma(\epsilon)$ (solid lines), the experimentally inferred coefficient $C = 8.16$ (dashed lines), and the experimental record (crosses) for pore dynamics.³ (a) For the simulation, we used $\mu_0 = 32$ cP, $R = 19.7$, $\mu_l = 1$ P, $T = 12.5$ pN, and $S = 0.045$ kT nm⁻², the values reported for the experimental records.^{1,26} (b) For this experimental record,² aqueous viscosity was smaller $\mu_0 = 1.13$ cP than in the record of panel (a) and pore dynamics is faster, underscoring the importance of aqueous viscosity. We calculated the expected pore dynamics by using the values of the physical parameters given in the experimental study: $R = 21.1$, $\mu_l = 1$ P, $T = 14$ pN, and $S = 0.045$ kT nm⁻². As a practical matter, the curve fit value of $C = 8.16$ gives virtually the same curve as that using $\gamma(\epsilon)$ derived from first principles.

the expansion of the hole's radius $c(t)$ measured as a function of time. The energy of the bilayer is $E = \sigma\pi(c_B^2 - c^2)$ while the aqueous dissipation of energy, according to (25), is $\Delta_a = 4\pi^2\mu_c U^2$. The dissipation due to bilayer friction is $\Delta_m = 4\pi\mu_l h U^2$ where h is the thickness of the bilayer (3–4 nm) and μ_l is the viscosity of lipid.¹ Note that the aqueous dissipation, which is volumetric, is proportional to pore radius while the membrane dissipation, accounted for only in the membrane surface, is independent of this radius.

Using the Rayleigh dissipation equation, the evolution equation for the expansion of the hole's radius in terms of the sum of the aqueous ($\gamma(0) = 2\pi$) and membrane friction is

$$\frac{\mathcal{F}_a + \mathcal{F}_m}{2\pi} = (2\pi\mu_c + 2h\mu_l)U = \sigma c.$$

For moderate values of lipid viscosity ($\mu_l = 1$ P) and c in the μm range, the aqueous component of friction is dominant. In this case, we predict that the terminal velocity will be

$$U = \frac{\sigma}{2\pi\mu}.$$

If, however, the contribution of the lipid viscosity μ_l to energy dissipation is high ($\mu_l \gg 1$ P), then $c(t)$ will not grow linearly but satisfy

$$2\pi\mu(c - c_0) + 2h\mu_l \ln \frac{c}{c_0} = \sigma t,$$

where $c_0 = c(0)$ is the radius directly after pore formation. Because the functional forms of aqueous and lipid viscosity to the time course of pore size are quite different from each other, the relative contributions of each can be determined. Prior investigators^{15,17} have established the functional form of pore growth in the extreme case of a lipid film suspended in air. Because aqueous friction is zero in this case, pore dynamics is affected by membrane friction alone.

VI. CONCLUSION

Experiments that measure the expansion and contraction of holes in liposomes motivated us to formulate a boundary value problem to determine the motion of an incompressible, viscous fluid surrounding a spherical surface of zero thickness when a hole in the surface expands or contracts with a prescribed velocity. The analogue of radial plug flow for a spherical shape was derived under the assumption that the surface density is spatially constant. This allowed us to derive a stream function using a perturbation expansion and then calculate the dissipation function for the flow field.

The method of complementary integral representation used for the translational motion of a spherical cap¹² can potentially be adapted to the tangential flow problem addressed in this paper. The zeroth order term in the stream function perturbation expansion is an exact solution to the Stokes system. One can take advantage of the closed form expression by considering other perturbation problems where the limiting shape is similar to the plane region studied here. Alternatively, since the surface velocity is known, the flow field can be determined from the Green's function representation used by the boundary integral method. Although mathematically more complicated, not only could the velocity expressions be derived, but the error of the perturbation solution as a function of the perturbation parameter could be estimated.

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APPENDIX: COMPONENTS IN OBLATE SPHEROIDAL COORDINATES

By performing a separation of variables to the equation $D\psi = 0$, we express the irrotational stream functions in terms of the solution set $I_n(p)$ and $G_n(p)$ for

$$(1 - p^2)P'' + n(n - 1)P = 0,$$

and the solution set $J_n(q)$ and $H_n(q)$ for

$$(1 + q^2)Q'' - n(n - 1)Q = 0,$$

where $n = 0, 1, 2, \dots$. The Gegenbauer functions I_n and G_n satisfy²²

$$I_n(p) = \frac{1}{(n - 1)!} \left(\frac{d}{dp} \right)^{n-2} \left(\frac{p^2 - 1}{2} \right)^{n-1}, \quad n = 2, 3, \dots,$$

$$G_n(p) = \frac{1}{2} I_n(p) \ln \frac{p + 1}{p - 1} - K_n(p), \quad n = 2, 3, \dots,$$

where $K_n(p)$ are polynomial. For the exceptional cases $n = 0$ and $n = 1$, we define $I_0(p) = -1$, $G_0(p) = p$, $I_1(p) = p$, and $G_1(p) = -1$ and set $I_m(p) = G_m(p) = 0$ for $m = -2, -1$. The functions $J_n(q)$ and $H_n(q)$ are obtained by setting

$$i^n J_n(q) = I_n(iq), \quad i^{n+1} H_n(q) = G_n(iq), \quad n = -2, -1, 0, \dots$$

The functions $I_n(p)$ and $J_n(q)$ are polynomials. For $n = 2, 3, \dots$, the functions $G_n(p)$ are singular at $p = 1$ and the functions $H_n(q)$ are discontinuous at $q = 0$. For this reason, we retain only G_0 , G_1 , H_0 , H_1 , and I_n and J_n for $n = 0, 1, 2, \dots$ in the series expansion of physically realizable stream functions and deem the functions G_n and H_n for $n = 2, 3, \dots$ unphysical. The functions (13) are obtained by forming the products of $\psi_{\text{irr},0} = I_0 J_0$, $\psi_{\text{irr},1} = -G_0 J_0$, $\psi_{\text{irr},2} = -I_0 H_0$, and $\psi_{\text{irr},n+2} = I_n J_n$ for $n = 1, 2, \dots$. With the help of the recurrence identity²²

$$p^2 I_n = \frac{(n + 1)(n + 2)}{(2n - 1)(2n + 1)} I_{n+2} + \frac{2n^2 - 2n - 3}{(2n + 1)(2n - 3)} I_n + \frac{(n - 2)(n - 3)}{(2n - 1)(2n - 3)} I_{n-2},$$

for $n = 0, 1, 2, \dots$, the rotational components (14) are now found by setting $\psi_{\text{rot},0} = \frac{1}{2}(q^2 - p^2 + 2)$, $\psi_{\text{rot},1} = \frac{1}{2}q(\frac{1}{3}q^2 - p^2)$, $\psi_{\text{rot},2} = \frac{1}{2}p(q^2 - \frac{1}{3}p^2)$, and

$$\psi_{\text{rot},n+2} = \frac{(n + 1)(n + 2)(I_n J_{n+2} - I_{n+2} J_n)}{2(2n - 1)(2n + 1)^2} + \frac{(n - 2)(n - 3)(I_{n-2} J_n - I_n J_{n-2})}{2(2n - 1)(2n - 3)^2}$$

for $n = 1, 2, \dots$.

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