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Unexpected Dynamics in Shape Fluctuations of Bilayer Vesicles

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Abstract. — Fluid lipid bilayers are composed of two mono-molecular sheets held together by weak van der Waals forces. Except for viscous resistance, the monolayers are free to slide relative to one another — giving rise to a "hidden" degree of freedom within the composite structure. In this paper, important effects of interlayer coupling are demonstrated through their influence on the static and dynamic features of undulating bilayer vesicles. In particular, it is shown that the non-local bending elasticity can modulate mean square undulatory amplitudes with a long wavelength suppression similar to that of membrane tension; the two effects are indistinguishable on the basis of spectral analysis. With regard to conformational dynamics, we show that the two dissipative mechanisms — namely interlayer drag and conventional hydrodynamics — are important on different length scales. With the crossover length being a fraction of a μm, it is concluded that viscous resistance to conformational changes is dominated by interlayer dissipation in the mesoscopic regime.

1. Introduction

Lipid bilayers are molecularly-thin membranes that possess exceptional flexibility when the interior acyl chains are disordered (i.e., in the fluid state). Flaccid vesicles made of such bilayers can deform easily into bizarre shapes with highly curved contours; even weak thermal excitations can roughen the surfaces of these vesicles significantly. This unusual softness and other exotic features of bilayers have stimulated many theoretical developments over the past twenty years — beginning with simple elastic models [1,2] and shape predictions [3,4] followed by thermodynamic and dynamic analyses of fluctuations [5-9], studies of adhesion [10,11] and unbinding transitions [12,13], and, most recently, models for spontaneous shape changes in vesicles [14-16]. Nearly all of these theoretical developments have been based on the elastic behaviour for a unit membrane structure, i.e., as if the monolayers of a bilayer are chemically bonded at the midplane. In the simple case of a fluid bilayer surface, Hamiltonians proposed for collective excitations have coupled energy to deformation through single fields of surface density and curvature — with elastic moduli for area compressibility and bending rigidity appropriate to unit membranes. However, in reality, the monolayers of a bilayer are not chemically bonded; they are only weakly adherent — drawn together by van der Waals attraction between the aqueous spaces surrounding the bilayer. At equilibrium, these two leaflets can move relative to
one another laterally with no change in elastic energy provided the surface shape remains fixed. As such, bending a bilayer seems to merely involve curving two adjacent monolayers along a common form with little interaction between layers. On the other hand, rapid sliding between monolayers must produce viscous drag at the bilayer midplane; this dynamic coupling will cause the layers to behave as if connected. Consequently, when changes in shape of a bilayer vesicle create relative motions between monolayers, there is a “hidden” dynamic impedance superposed on the hydrodynamic resistance of the aqueous environment.

Examining the mechanical consequences of inter-monolayer coupling in membranes, we have recently shown that the action is non-local and, in many situations, interlayer dissipation intervenes on a length scale close to the macroscopic regime to overtake conventional hydrodynamic losses [1,18,19]. Further, for vesicles with closed-spherical topology, another global consequence of bilayer coupling is a non-local curvature elasticity that plays a role analogous to that of the spontaneous curvature in shape determination [1, 20]. These subtle features arise from local differences in density (differential dilations) between monolayers that define a new field on the bilayer surface. Here, we demonstrate the special consequences of this field on the amplitude spectrum and dynamics of thermal shape fluctuations in quasi-spherical vesicles. Because the dynamic response of vesicle shape to perturbative forces is completely overdamped — forces are swamped by viscous dissipation in the fluid environment — analyses of collective shape excitations follow two distinct conceptual approaches [6–8]: first, equilibrium thermodynamic theory is used to predict the mean-square amplitude spectrum for small harmonic deformations of the vesicle shape. Assuming long time averages can be taken over the random-uncorrelated modes, mean-square amplitudes are derived based on the equipartition of energy. Second, mechanical force balances are used to predict the relaxation behaviour of the thermally excited modes. Treating each mode as a transient departure from the equilibrium shape, dissipation of elastic forces through viscous actions leads to the continuous decay of amplitude. The essential ingredients in these analyses are the elastic energy (Hamiltonian) and mechanical fields (tensions and bending moments) for a fluid bilayer. Hence, we will first introduce modifications to previous bilayer descriptions that are needed here to represent inter-monolayer coupling (details are given in Ref. 19).

2. Surface Fields and Equilibrium Conditions

Bilayers are formed from diacyl lipids of chain lengths typically greater than 12 carbons (di-lauryl, dimyristoyl, etc.). Above the melting temperature for these hydrocarbon chains, monolayers of the bilayer structure are condensed surface fluids; the constituent molecules appear to remain confined in the monolayer plane with no detectable solubility in the adjacent aqueous medium [20]. Monolayers in such cohesive states can be treated as unist membrane structures. Here, we conceptualize the monolayers as two-dimensional surfaces represented by their neutral planes [18, 19]. Stresses within the monolayers are replaced by surface fields — namely the lateral tension and bending moment which are, respectively, the zeroth and first moments of the internal stress about the neutral plane. For a flat-stationary monolayer, lateral tension is an isotropic scalar field \( \tau \) that depends only on the fractional reduction in surface density (characterized by the dilational field \( \alpha = a/a_0 - 1 \) where \( a \) is the area per molecule) relative to a reference value (= 1/\( a_0 \)) at zero tension, i.e.,

\[
\frac{\sigma}{\tau} = K \alpha
\]

The constant of proportionality \( K \) is the elastic modulus for monolayer area compressibility. At the next higher level of accuracy, moments of chain stresses (i.e., bending torques) must be
Fig. 1. — Schematic diagram of an element of equivalent mechanical surface representing the bilayer composite. Cumulation of stresses within the membrane lead to lateral tensions $\tau_1, \tau_2$, shear force resultants $(Q_1, Q_2)$, and the isotropic bending moment $M$. Membrane curvatures $c_1$ and $c_2$ are simply reciprocals of the radii of curvature.

Included in the mechanical force description. For fluid monolayers, the bending moment $M$ is also an isotropic scalar field; it is proportional to local changes in total curvature as given by

$$M = k_c \left( c_1 + c_2 - c_0 \right) \quad (2)$$

where $k_c$ is the bending elastic modulus of the monolayer. $c_1$ and $c_2$ are the principal curvatures of the surface, and $c_0$ is a reference curvature that defines the state in which moments of stress in the monolayer are zero. For curved membranes, the lateral tensions have additional contributions due to the bending moment [19]. Because these contributions depend on local curvatures of the surface, the generalized tension fields are no longer isotropic when the surface is bent, i.e.,

$$\tau_1 = \frac{\partial}{\partial} + c_2 M \quad (3)$$
$$\tau_2 = \frac{\partial}{\partial} + c_1 M$$

The tension components $(\tau_1, \tau_2)$ correspond to the principal directions specified by the curvature tensor(2). Defining also the isotropic tension $\bar{\tau}$ and the mean curvature $\bar{c}$ as

$$\bar{\tau} = \frac{1}{2} (\tau_1 + \tau_2) \quad \bar{c} = c_1 + c_2$$

we have, for the monolayer, $\bar{\tau} = \frac{\partial}{\partial} + \frac{1}{2} \bar{c} M$.

Similar mechanical fields can be assigned to the bilayer, which is a stratified composite structure consisting of two unit membranes (the monolayers) loosely coupled together. With

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(1) For simplicity, we neglect the elastic term due to Gaussian curvature $c_1 \times c_2$.

(2) A schematic of this mechanical-surface representation is shown in Figure 1.
the bilayer midplane taken as the equivalent surface, the corresponding isotropic tension and bending moment are

\[ M = M(1) + M(2) + M_\pm \]
\[ \bar{\tau} = \bar{\tau}(1) + \bar{\tau}(2) + \frac{1}{2} \bar{\epsilon} M_\pm \]

Here, the outer and inner monolayers are identified by labels \( (2) \) and \( (1) \) respectively. Note that in addition to the sum of contributions from individual layers, the effective \( \bar{\tau} \) and \( M \) for the composite structure are augmented by coupling terms. In particular, the coupling moment \( M_\pm \) arises from mismatch in area dilation (and hence in the tension fields) between the monolayers; it has the form

\[ M_\pm = \bar{k}_c \alpha_\pm / h \]

where \( \alpha_\pm \equiv \alpha(2) - \alpha(1) \) is the differential dilation field and \( h \) is the thickness parameter that represents the distance between centres of force within each monolayer (called the neutral planes [19]). Clearly, \( h \) is less than the structural thickness of the bilayer and must be established by mechanical experiments. \( \bar{k}_c \) is the non-local bending stiffness given by \( \bar{k}_c = h^2 K/2 \). In the special case of a bilayer vesicle (i.e., one that forms a closed surface of spherical topology) at equilibrium, the coupling moment is proportional to the small global difference in surface area between the monolayers; it is a uniformly distributed quantity given by

\[ M_\pm = \bar{k}_c \left( \frac{1}{A_0} \int \bar{\epsilon} \, dA - \Gamma_0 \right) \]

\[ \Gamma_0 = \frac{\Delta A_0}{h A_0} \]

where \( \Delta A_0 \) is the area difference between the monolayers in their initial state of formation (established by the history of bilayer preparation and chemical composition) and \( A_0 \) is the surface area of the bilayer midplane. In contrast to relation (2), which expresses dependence of the bending moment on local curvatures, the coupling moment in a stratified composite at equilibrium depends on the global average of \( \bar{\epsilon} \); the elastic constant in such a situation is the non-local bending rigidity \( \bar{k}_c \).

The conditions of mechanical equilibrium for a fluid membrane — whether it is the monolayer or the bilayer composite — are given by the following expressions.

\[ \sigma_n = \left[ \bar{\tau} \tilde{\epsilon} - \nabla_s^2 M - 2M \left( \frac{1}{4} \tilde{c}^2 - c_1 c_2 \right) \right] \mathbf{n} \]
\[ -\sigma_s = \nabla_s \bar{\tau} + \frac{1}{2} (\tilde{\epsilon} \nabla_s M - M \nabla_s \tilde{\epsilon}) \]

Here, \( \sigma_n \) and \( \sigma_s \) are the normal and tangential tractions (external force/unit area) on the membrane. \( \mathbf{n} \) is the unit vector normal to the membrane surface, and \( \nabla_s \) denotes the surface gradient operator. Equations (7) represent force-balances in directions normal and tangent to the membrane surface with no restriction on the origins of the stresses. As such, these equations are applicable to either elastic or dissipative materials.

3. Conformational Energetics for Bilayer Vesicles

Because stretching a bilayer is energetically much more costly than bending it, static conformations of a non-spherical vesicle are governed by the curvature energy and subject to the auxiliary condition that the bilayer surface area remains unchanged. Based on the above
elastic relations, the general curvature energy $E_{\text{curv}}$ can be divided into its local and global parts [10,19]; i.e.,

$$E_{\text{curv}} = E_{\text{local}} + E_{\text{global}}$$

(8)

The first contribution is due to local changes in membrane curvature. For a symmetric bilayer with vanishing $c_0$ (spontaneous curvatures of the two monolayers cancel), the local curvature energy has the form [1]

$$E_{\text{local}} = \frac{1}{2} (2k_c) \int \int \bar{\varepsilon}^2 \, dA$$

(9)

Recall $k_c$ is the bending rigidity of each monolayer. As pointed out in the introduction, the local elastic energy has been established many years ago and used extensively to model mechanical behaviours of bilayer vesicles. However, such a description is only appropriate for unit liquid-crystalline membranes. For bilayer vesicles, an additional resistance to curvature changes arises that is due to the differential dilation between monolayers as the membrane is bent. This is reflected in the coupling moment $M_{\pm}$ as given in equation (7); the corresponding work required for bending is the global curvature energy $E_{\text{global}}$:

$$E_{\text{global}} = \frac{1}{2} k_c A_0 \left( \frac{1}{A_0} \int \int \bar{\varepsilon} \, dA - \Gamma_0 \right)^2$$

(10)

Incorporating the constraint of constant area, the appropriate Hamiltonian for the bilayer vesicle is

$$\mathcal{H} = E_{\text{curv}} + \tau_0 \int \int dA$$

(11)

$\tau_0$ in the above expression acts as a surface field conjugate to the requirement of constant surface density. The Hamiltonian specified by equation (11) defines equilibrium shapes of fluid bilayer vesicles and governs collective excursions from these shapes driven by thermal excitations. It can be shown that minimization of $\mathcal{H}$ indeed leads to the correct conditions for mechanical equilibrium

4. Dynamic fields

The dynamic response of a bilayer vesicle to external forces is retarded by viscous dissipation from three principal sources: hydrodynamic movements of water, mean surface flow of the bilayer (as a unit structure), and differential flow (sliding) between monolayers. Constitutive descriptions for the first two contributions are given by classical proportionalities of stresses to gradients of velocity that are well known for Newtonian fluids. Since we can neglect fluid inertia, divergence of the stress field is sufficient to establish equations of motion for the surrounding aqueous fluid. These creeping flow equations are deceptively simple in form where the velocity field $\mathbf{v}$ is specified by solution to

$$\nabla^2 \mathbf{v} = \left( \frac{1}{\eta_w} \right) \nabla p$$

$$\nabla \cdot \mathbf{v} = 0 \quad \text{(incompressibility)}$$

(12)

Here, $\eta_w$ is the viscosity of the aqueous surrounding and $p$ is the hydrostatic pressure field conjugate to the incompressibility requirement that maintains constant fluid density. For the bilayer, the important consequence is the set of tractions on its surface created by the normal and tangential stress components of the hydrodynamic flow field. These are given symbolically
by

\[ \sigma_n = -p + 2\eta_w \frac{\partial v_n}{\partial x_n} \]
\[ \sigma_s = \eta_w \left( \frac{\partial v_s}{\partial x_n} + \frac{\partial v_n}{\partial x_s} \right) \]

\( x_n \) and \( x_s \) are the coordinates local to the membrane surface along the normal and tangent directions respectively, while \( v_n \) and \( v_s \) are the corresponding components of fluid velocity.

As for the bulk fluid, there is viscous impedance to the 2-D coherent flow of the membrane as a unit surface. Bilayer flow represents convection of the surface that can be viewed as a superposition of shear and dilational flows. Dilations of lipid bilayers are always extremely small so surface flows can be approximated as incompressible with the deviatoric stresses modeled by 2-D Newtonian relations [20]; that is,

\[ \tau_1 - \tau_2 = 4(\eta_l \ h) V_S \]

where \( V_S \) is the surface shear rate. The surface viscosity is expressed as the product of an apparent 3-D viscosity \( \eta_l \) and the bilayer thickness \( h \) — as if the bilayer were a homogeneous liquid film\(^{(3)}\). Comparing surface flow stresses with the hydrodynamic stresses imparted to the bilayer by movement through the aqueous environment, a crossover length \( \delta_0 \sim \eta_l h/\eta_w \) is found above which dissipation in the environment is expected to dominate over viscous losses in the bilayer due to mean surface convection [19]. For typical lipid bilayers, this length is of order 100 h (\( \sim 0.1 \) \( \mu \)m) or less. However, in nearly all deformations of vesicles, viscous dissipation in surface flow is overwhelmed by interlayer (sliding) drag. Thus, we will neglect viscous shear contributions to monolayer tensions and assume that the tensions are determined only by local surface density.

Because of the proportionality to thickness, viscous contributions to bilayer tensions from mean surface flow are small. On the other hand, the viscous drag between monolayers scales as the reciprocal of membrane thickness, i.e.,

\[ \sigma_s \equiv b v_s^\pm \sim (\eta_l/h) v_s^\pm \]

so this resistance can be enormous if the relative velocity \( v_s^\pm = v_s(2) - v_s(1) \) becomes significant. Phenomenologically, the interlayer shear stress \( \sigma_s \) can be modeled to first order by a simple drag coefficient \( b \) since momentum transport occurs over a dimension well below the continuum scale for hydrodynamics. In fact, the apparent length scale for momentum exchange between monolayers of lipid bilayers is on the order of \( \text{atomic dimensions} \ [18, 19] \). Interlayer drag produces gradients of the tension difference \( \Delta \sigma \) between layers and, thereby, of the differential dilation field \( \alpha^\pm \). From the force-balance relation \( 2\sigma_s = \nabla_s(\Delta \sigma) \), we derive,

\[ v_s^\pm = D \nabla_s \alpha^\pm , \quad D \equiv \frac{K}{2b} \]  \hspace{1cm} (13)

where the quantity \( D \) is an elastically driven "diffusivity". By interpreting \( v_s^\pm \) as the flux of the differential strain field \( \alpha^\pm \), equation (13) can be considered a "Fick's law" that models

\( \text{(3)} \) In general, the dynamic stresses produced by viscous dissipation within the monolayer structure will be non-uniform along the chains and lead to dynamic moments. However, these moments can be neglected since the stresses due to mean surface flow are themselves very small as a consequence of the dependence of the surface viscosity on membrane thickness.
the transport of $\alpha_{\pm}$ on the bilayer surface. Examining the kinematics of relative flow between surfaces separated by $\pm h/2$ from a central interface, we find that dynamic changes in differential dilation between layers are dispersed by divergence of the relative velocity field $v^\pm_s$ over the surface and arise from dynamic changes in local curvature, i.e.\(^{(4)}\),

$$\frac{d\alpha_{\pm}}{dt} = \nabla_s \cdot v_{\pm}^s + \hbar \frac{d\varepsilon}{dt} \tag{14}$$

Combining equations (13) and (14), we establish a conservation equation that describes the dynamics of the differential dilation field:

$$\frac{\partial \alpha_{\pm}}{\partial t} + \bar{v}_{s} \frac{\partial \alpha_{\pm}}{\partial s} = D \nabla_{s}^{2} \alpha_{\pm} + \hbar \left( \frac{\partial \varepsilon}{\partial t} + \bar{v}_{s} \frac{\partial \varepsilon}{\partial s} \right)$$

where $\nabla_{s}^{2}$ denotes the surface Laplacian operator. Interestingly, gradients of differential density in the bilayer relax by a non-local diffusion-like process over the surface and are driven by either rapid local changes in curvature or convection of bilayer between regions of high and low curvatures. The diffusivity $D$, as defined in equation (13), represents dissipation of elastic energy through viscous drag at the monolayer–monolayer interface\(^{(5)}\). Evolution of the differential dilation field also describes the dynamics of force coupling between monolayers as given by equation (5). Multiplying the above equation by the factor $\bar{k}_{c}/\hbar$ yields

$$\frac{\partial M_{\pm}}{\partial t} + \bar{v}_{s} \frac{\partial M_{\pm}}{\partial s} = D \nabla_{s}^{2} M_{\pm} + \bar{k}_{c} \left( \frac{\partial \varepsilon}{\partial t} + \bar{v}_{s} \frac{\partial \varepsilon}{\partial s} \right) \tag{15}$$

We see that the coupling field $M_{\pm}$ acts through curvature to impede the viscous response of the shape to external fields. This dynamic equation must be satisfied along with the classical hydrodynamic equations of motion for the surrounding aqueous fluid subject to appropriate mechanical boundary conditions at the bilayer surface. The dissipative action of intermonolayer drag has been directly demonstrated in experiments where nanoscale tubes of highly curved bilayer were pulled rapidly from macroscale vesicles \([18,19]\). Here, to demonstrate the non-local features of interlayer coupling and to establish the dimension scale where dynamic coupling is important, we will apply these equations of motion to the relaxation of shape fluctuations in nearly spherical vesicles.

5. Thermal Shape Fluctuations of Nearly Spherical Vesicles

As noted in the introduction, collective thermal excitations of vesicles have been analyzed and observed experimentally for over a decade with excellent optical techniques \([6–9]\). Here, we revisit this problem because recognition of the dynamic coupling internal to the bilayer exposes new physics absent from the previous perspective of a \textit{unit} membrane. This subtle behaviour was not detected in previous studies of shape fluctuations because, typically, interlayer coupling becomes dominant just below the resolution of optical measurements. However, very recent tests of nanotube extrusion from large vesicles \([17–19]\) and mesoscale neutron scattering experiments \([21]\) have clearly demonstrated the importance of interlayer effects in bilayers.

\(^{(4)}\) $d(\cdot)/dt$ includes both the changes in time observed from a fixed spatial reference and the convective contribution; i.e., $d(\cdot)/dt = \partial(\cdot)/\partial t + \bar{v}_{s} \cdot \partial(\cdot)/\partial s$ where $\bar{v}_{s}$ represents the average of $v_{\delta_{1}}(1) \text{ and } v_{\delta_{2}}(2)$.

\(^{(5)}\) In practical situations, there could also be relaxation of the differential density through exchange or permeation of molecules between the layers \([19]\). Such an effect (lipid “flip-flop”) is considered to be extremely slow in bilayers and will be neglected here.
Because of the small size of vesicles (even visible sizes), response to mechanical deformation is always overdamped and described by low Reynolds number hydrodynamic relations for inertialess flows. Hence, following thermal perturbation, transient excited states simply dissipate elastic energy through viscous processes with no inertial propagation. As a consequence of the stiff condensed state of the bilayer, random excursions from the preferred (minimum energy) shape show up as collective bending undulations. These "wiggles" become optically visible only when lateral tension falls to ultralow levels ($< 10^{-4}$ mN/m), which can be achieved by slight osmotic dehydration of a spherical vesicle as shown in Figure 2a. On the other hand, when the tension is increased by osmotic pressurization ($\geq 10^{-6}$ Atm!), the vesicle appears to be a smooth sphere even though we know that the wiggles persist on a dimension scale below this "capillary cutoff". Two wavelength-dependent features of surface wiggles can be readily analyzed: i) the mean square amplitudes of displacements normal to the surface averaged over long times; and ii) the characteristic "lifetimes" for relaxation of transient harmonic excitations. The spectrum of mean square amplitudes follows from equilibrium thermodynamics through equipartition of energy amongst the ensemble of normal modes. By comparison, the lifetimes of the modes are derived from the dynamic relaxation of the vesicle shape following deformations by random forces. Details of these analyses are tedious and involve extensive manipulations of formulae that have been well described in the past [6-8]. Hence, we will only highlight conceptual steps required in these analyses; more complicated technical aspects are placed in the Appendix.

We start with a description of the time dependence of vesicle conformation. For small deviations of the surface from a mean spherical shape, it is sufficient to consider only displacements normal to the surface where the radial position $R(\Omega, t)$ described in spherical coordinates ($\Omega$ represents the polar and azimuthal angles $\theta, \phi$) is given by

$$R(\Omega, t) = R_0 \left[ 1 + u(\Omega, t) \right]$$
$R_0$ is the mean radius and $u(\Omega, t)$ is the dimensionless amplitude of radial displacements\(^6\). Because the bilayer strongly resists area dilation, it is necessary to have a small amount of excess area above the value $4\pi R_0^2$ to allow for fluctuations; this can be provided by a reduction in volume. Fluctuations in the quasi-spherical shape are expanded in terms of spherical harmonics with time-dependent amplitudes $u_{lm}(t)$:

$$u(\Omega, t) = \sum_{l,m} u_{lm}(t) Y_{lm}(\Omega)$$

Assuming the surface excitations are random and that the harmonic modes are uncorrelated, statistical averages can be used to characterize the mean square amplitudes of independent modes as follows:

$$\langle u_{lm}^2 \rangle \equiv \langle u_{lm}(0) u_{lm}(0) \rangle$$

where $\langle \cdots \rangle$ symbolizes ensemble averages. The corresponding dynamics of shape recovery are expressed in terms of relaxation functions $f_{lm}(t)$ as

$$u_{lm}(t) = u_{lm}(0) f_{lm}(t)$$

where $u_{lm}(0)$ represents an instantaneous perturbation in shape. The relaxation functions $f_{lm}(t)$ is derived deterministically. Equations (17) and (18) are, respectively, static and dynamic descriptions of the thermal undulations of quasi-spherical vesicles.

5.1. Mean Square Amplitudes of Shape Fluctuations. — Here, the elastic energy for collective excitations of the bilayer is expanded to quadratic order in the normal displacements. Mean square amplitudes of the independent modes of deformation (assumed to be the angular harmonics themselves) are described by Gaussian statistics in accordance with equilibrium thermodynamics; that is, an average energy of $k_B T/2$ is assigned to each independent mode as required by the equipartition theorem. Using the Hamiltonian specified by equation (11) and guided by earlier analyses [7], we have derived the following excess energies (above the equilibrium value) for small random perturbations in shape (see Ref. [18] for the detailed derivation). Derived from equation (11) for constant volume vesicles, the excess free energy is

$$\Delta H = \Delta E_{\text{local}} + \Delta E_{\text{global}} + \tau_0 \Delta A,$$

where

$$\Delta E_{\text{local}} = k_c \sum_{l > 1} l(l + 1)(l + 2)(l - 1) u_{lm}^2$$

$$\Delta E_{\text{global}} = \tilde{k}_c' \sum_{l > 1} l(l + 2)(l - 1) u_{lm}^2$$

$$\tau_0 \Delta A = \frac{1}{2} \tau_0 R_0^2 \sum_{l > 1} (l + 2)(l - 1) u_{lm}^2$$

$\Delta E_{\text{global}}$ is a stretch energy contribution that arises from mean square fluctuations in differential area dilation $\langle A_{2l}^2 \rangle / A^2$; it is scaled by a modified non-local bending elasticity $\tilde{k}_c'$ given by

$$\tilde{k}_c' \equiv k_c \left(1 - \frac{R_0 \Gamma_0}{2}\right)^2$$

\(^6\) Tangential displacements produce second order contributions that can be neglected for small excitations.
Note that there is no term linear in the displacement amplitudes since, by definition, the energy is minimum with respect to first order variations. As is well known, at large wave numbers (small wavelengths), the local bending energy increases as \( l^4 \) whereas the tension term varies as \( l^2 \). Here, the tension \( \tau_0 \) is regarded as a chemical potential conjugate to the area of the vesicle; it is determined by the excess area which in turn is controlled through osmotic dehydration or other mechanical means. Because the monolayers are coupled globally in the closed spherical topology, the non-local bending elasticity leads to a tension-like contribution that also acts to suppress long wavelength excitations. This consequence of interlayer coupling manifests itself as a positive tension threshold in the vesicle surface. Applying equipartition to the quadratic expansion of \( \Delta H \) as given above, we arrive at the spectrum of mean square amplitudes for collective bending excitations:

\[
\langle u_{lm}^2 \rangle = \frac{k_B T}{(l+2)(l-1)} \left[ l(l+1) \frac{2k_c}{2k_c' + R_0^2} + \frac{2k_c'}{R_0^2} + \tau_0 \right] R_0^2
\]

(20)

Based on this spectrum of displacement amplitudes, the following expression relates the average tension to vesicle excess area \( \Delta A/A_0 \) :

\[
\Delta A/A_0 = \frac{1}{8\pi} \sum_{l>1} \frac{(2l+1)k_B T}{l(l+1)} \frac{2k_c}{2k_c' + R_0^2} + \tau_0
\]

(21)

where \( l_c \) is the wave number corresponding to molecular cutoff.

5.2. Dynamics of Shape Fluctuations. — Because the system is highly overdamped, dynamic features of a fluctuating vesicle are characterized by the relaxation behaviour of the excited modes. For small displacements, the dynamic equations are linear and, thus, surface undulations can be considered a superposition of many simultaneous shape relaxations that result from random perturbations of the equilibrium shape (i.e., the sphere). Mechanically, relaxation of a mode is represented by equation (18):

\[
u_{lm}(t) = u_{lm}(0) f_{lm}(t)
\]

where \( f_{lm}(t) \) is a deterministic function with the obvious boundary values:

\[
f_{lm}(0) = 1 \quad \lim_{t \to \infty} f_{lm}(t) = 0
\]

Time dependence of \( f_{lm}(t) \) reflects the interplay between elastic forces within a bilayer that drive shape recovery, and the viscous forces that limit the rate of such a process. The elastic restoring forces arise from the local and non-local bending rigidities as discussed in the previous Section and the dynamic resistance to shape recovery involves two mechanisms: intermonolayer viscous drag and the surrounding hydrodynamic stresses. To calculate \( f_{lm}(t) \), we need to consider the problem of bilayer deformation in a viscous medium; the two systems are coupled by matching kinematic and stress boundary conditions at the bilayer-fluid interface. Other workers have analysed the problem of a fluctuating unit membrane vesicle suspended in water [6]. In their analysis, all dynamical variables are expanded to linear powers in the displacement field \( u(\Omega, t) \) — resulting in a lowest order perturbative solution about the spherical shape. Here, we will extend the original work to include coupling effects which give rise to non-local elasticity and interlayer dissipation.

We begin with the equilibrium conditions on a fluid bilayer membrane. Keeping only terms that are first order in displacements, the force-balance equations (Eqs. (7)) simplify to

\[
\sigma_n = \left( \tau \mathbf{c} - \nabla_s^2 M \right) \mathbf{n}
\]

\[
-\sigma_s = \nabla_s \mathbf{t}
\]

(22)
The bending moment $M$ that appears in the first of equations (22) embodies interlayer effects. In general, this quantity can be written as (see Eqs. (4))

$$M = 2 k_c \bar{c} + M_\pm$$

(23)

where the coupling term $M_\pm$ has dynamic properties given by equation (15). In the case of small-amplitude undulations, the lateral surface velocity $\bar{c}_s$ is negligible; we can therefore omit the convective terms in equation (15). The resulting dynamic equation for the coupling moment is

$$\frac{\partial M_\pm}{\partial t} = D \nabla^2 M_\pm + \bar{k}_c \frac{\partial \bar{c}}{\partial t}$$

(24)

In specifying initial conditions for $M_\pm$, we make the assumption that the shape-perturbing impulses imparted to the vesicle have durations that are much shorter than the characteristic relaxation times of $\alpha_-^\pm$ (the latter time scale is given roughly by $b R_0^2 / K$, which, for typical values of $R_0 \sim 10 \mu m$, $b \sim 10^8$ N s/m$^2$ and $K \sim 10^2$ mN/m, is of order 0.1 s). Consequently, at the end of each impulse, the $\alpha_-^\pm$ field is completely determined by the perturbed geometry; i.e., $\alpha_-^\pm(\Omega, 0) = (h/a) \bar{c}(\Omega, 0)$. Relaxation of this field (via lateral redistribution of lipid molecules) is assumed to begin after this instant. Using equation (5), the initial condition for $M_\pm(\Omega, t)$ is

$$M_\pm(\Omega, 0) = \bar{k}_c \bar{c}(\Omega, 0)$$

(25)

Equations (23–25) define a bilayer membrane whose bending moment exhibits both elastic and dissipative character; the latter arises, of course, from interlayer viscous drag. This history-dependent bending moment can be conveniently expressed in terms of a convolution integral with the mean curvature as follows:

$$M(\Omega, t) = \mu(t) \bar{c}(\Omega, 0) + \int_0^t \mu(t - t') \frac{\partial \bar{c}}{\partial t'}(\Omega, t') dt'$$

(26)

where the response function has modal components given by

$$\mu_l(t) = 2 k_c + \bar{k}_c e^{-\omega_D t}$$

(27)

with $\omega_D = \ell (\ell + 1) D / R_0^2$.

The bilayer membrane must now be mechanically coupled to the surrounding aqueous fluid. In addition to matching velocity components at the bilayer-water interface, membrane surface tractions ($\sigma_n$ and $\sigma_s$ in Eqs. (22)) must also balance the adjacent hydrodynamic stresses. On length scales of micrometers, all inertial effects within the aqueous fluid are negligible in comparison to viscous forces, the resulting flow fields are governed by the creeping motion equations as given by equation (12). General solutions to these equations — along with boundary conditions tailored for slightly deformed spheres — have been established in the past [22]. In the Appendix, it is shown how these relations are used to satisfy the above boundary conditions (at the bilayer-water interface) and eventually lead to the solution of the relaxation function. With the intermediate steps appended, the final form of $f_{1m}(t)$ is given below.

We first introduce three intrinsic relaxation rates. $\omega_D$ is a rate associated with the diffusivity of $\alpha_-^\pm$ on the bilayer plane; it is defined as

$$\omega_D \equiv \ell (\ell + 1) D / R_0^2$$

(28)

This relaxation is driven by the area elasticity of the bilayer and limited by interlayer drag ($D \sim K / b$). The other two rates are associated with the relaxation of bilayer conformations
— or equivalently, of the curvature field. These rates are driven by curvature elastic moduli and membrane tension (through different scalings with the wave number) and are retarded by the viscosity of water; they have the forms

\[ \omega_c = \frac{l(l + 1)(2k_c + \bar{k}_c) + \tau_0 R_0^2}{4 \eta_w R_0^3 \zeta} \]

\[ \omega_u = \frac{l(l + 1)2k_c + \tau_0 R_0^2}{4 \eta_w R_0^3 \zeta} \]

where \( \tau_0 \) is the membrane tension and the numerical factor \( \zeta(l) \) is given by

\[ \zeta(l) = \frac{1}{4} \frac{(2l + 1)(2l^2 + 2l - 1)}{l(l + 1)(l + 2)(l - 1)} \]

For large wave numbers, \( \zeta \approx l^{-1} \).

In terms of these quantities, time dependence of the relaxation function, as expressed in equation (18), embodies two exponential relaxations:

\[ f_j(t) = a_1 e^{-\Omega_1 t} + a_2 e^{-\Omega_2 t} \]

where the amplitudes of the decaying exponentials are

\[ a_1 = \frac{\omega_D - \Omega_1}{\Omega_2 - \Omega_1} \quad ; \quad a_2 = -\frac{\omega_D - \Omega_2}{\Omega_2 - \Omega_1} \]

Note that dependence on the azimuthal wave number \( m \) is omitted in the relaxation function due to degeneracy. The two "mixed" rates in the above expressions are given by

\[ \Omega_1 = \left( \frac{\omega_D + \omega_c}{2} \right) \left[ 1 - \sqrt{1 - \frac{4 \omega_D \omega_u}{(\omega_D + \omega_c)^2}} \right] \]

\[ \Omega_2 = \left( \frac{\omega_D + \omega_c}{2} \right) \left[ 1 + \sqrt{1 - \frac{4 \omega_D \omega_u}{(\omega_D + \omega_c)^2}} \right] \]

Thus, we see that the shape relaxation of a bilayer involves two time constants, namely \( \Omega_1^{-1} \) and \( \Omega_2^{-1} \), which are in turn determined by the three intrinsic recovery rates \( \omega_D \), \( \omega_u \) and \( \omega_c \). Since the relaxation process is overdamped, \( \Omega_1 \) and \( \Omega_2 \) are always real positive quantities.

6. Discussion

This work exposes the often-overlooked effects of interlayer coupling on the thermal undulations of bilayer vesicles. In the first part of our analysis, the spectrum of mean square amplitudes is predicted to have the form (see Eq.(20))

\[ \langle u_{lm}^2 \rangle \sim \frac{k_B T}{2 k_c l^4 + (2 k_c^2 / R_0^2 + \tau_0) R_0^2 l^2} \]

It is seen that local and non-local bending effects suppress the undulation amplitudes through different powers of the wave number \( l \). More importantly, because of the global elastic coupling
between monolayers (embodied in \( \tilde{k}_e \)), thermal fluctuations lead to a small renormalization of the bare bilayer tension \( \tau_0 \). Even when the bare mechanical tension vanishes, non-local elasticity continues to give rise to a positive tension-like quantity that is set by the radius of the vesicle which is of order \( \tilde{k}_e/R_0^2 \). Recall \( \tilde{k}_e \) is the non-local bending modulus scaled by a factor that reflects the area difference between monolayers in their initial stress-free states (Eq.(19)). Thus, the history of vesicle formation (from planar multilamellar arrays) determines the magnitude of this effect, i.e.,

\[
\tilde{k}_e = k_e \left( 1 - \frac{R_0}{2h} \frac{\Delta A_0}{A_0} \right)^2
\]

where \( R_0/h \) is of order \( 10^3 \) for cell-size vesicles. For finite initial area differences of typically 0.1% to 1% [18], the scaled non-local rigidity can give rise to effective "tensions" of order \( 10^{-5} \) to \( 10^{-4} \) mN/m. It is interesting that in previous attempts to correlate experimentally-measured amplitude spectra with conventional theories in which stratification effects are absent, a small positive tension of the same magnitude is always required to achieve good fits to the data [6,8,9]. Specifically in reference [8], the authors evaluated carefully the apparent levels of tension in vesicles and obtained values that grouped between \( 10^{-6} \) to \( 10^{-4} \) mN/m.

With regard to dynamics, time-dependent recovery of a nearly spherical vesicle has been analysed in the past with the bilayer treated as a single-layered structure [6,7]. The resulting relaxation function \( f(t) \) is a single decaying exponential with the recovery rate given by

\[
\Omega_{\text{single}} = \frac{l(l+1)k_{bl} + \tau_0 R_0^2}{4 \eta_w R_0^2 \zeta}
\]

where \( k_{bl} \) is the bilayer's bending modulus. Such a recovery process involves relaxation of the curvature field and is identified as bending relaxation. Assuming the tension term can be neglected, recovery rates of bending modes scale as \( l^3 (\zeta \sim l^{-1}) \). Despite of stratification in real bilayers, there are instances when the composite structure can be treated collectively as a single-layered membrane: they are the limiting cases when the two monolayers are either coupled together rigidly (e.g., as \( b \to \infty \)) or are completely free to slide past one another (e.g., as \( b \to 0 \)). In such situations, the bilayer has bending rigidities

\[
k_{bl} = \begin{cases} 
2k_c + \tilde{k}_e & \text{for rigidly coupled monolayers} \\
2k_c & \text{for uncoupled monolayers}
\end{cases}
\]

From definitions (29) and (30), we see that \( \omega_c \) and \( \omega_u \) are precisely the recovery rates in these two limits, corresponding respectively to the bending modes of coupled and uncoupled monolayers.

For situations intermediate between the above extremes, relaxation dynamics of a bilayer involve energy dissipation by lateral redistribution of lipid molecules through interlayer slip. The rate of this slipping process is \( \omega_D \) as defined in equation (28); it is characterized by an \( l^2 \) dependence. As seen from equations (31–33), the general relaxation function involves a mixture of the two mechanisms, i.e., \( f(t) \) is a function of \( \omega_c, \omega_u \) and \( \omega_D \). It is of interest to compare the magnitudes of these intrinsic rates. Introducing the dimensionless parameters

\[
\tilde{\omega}_0 \equiv \frac{\omega_u}{\omega_c} ; \quad \tilde{\omega} \equiv \frac{\omega_D}{\omega_c}
\]

it is noted that, given \( k_c \) and \( \tilde{k}_e \) are comparable in magnitude, \( \tilde{\omega}_0 \) is effectively a constant of order unity. The more interesting parameter is \( \tilde{\omega} \), which measures the relative rates of
relaxation by bending and by slipping. Unlike \( \tilde{\omega}_0 \), this parameter has an \( l^{-1} \) dependence on the wave number.

We now examine changes in the overall relaxation behaviour as the parameter \( \tilde{\omega} \) is varied. As \( \tilde{\omega} \) approaches 0 and \( \infty \), the two decay rates \( \Omega_1 \) and \( \Omega_2 \) of the relaxation function have limiting values given by

\[
\lim_{\tilde{\omega} \to 0} \begin{cases} 
\Omega_1 = \tilde{\omega}_0 \omega_D \left( \sim l^2 \right) \\
\Omega_2 = \omega_c \left( \sim l^3 \right)
\end{cases}
\]

\[
\lim_{\tilde{\omega} \to \infty} \begin{cases} 
\Omega_1 = \omega_u \left( \sim l^3 \right) \\
\Omega_2 = \omega_D \left( \sim l^2 \right)
\end{cases}
\]  

(35)

Thus, the first response function in equation (31) evolves from slipping at \( \tilde{\omega} = 0 \) (large \( l \)) to bending as \( \tilde{\omega} \) approaches \( \infty \) (small \( l \)); intermediate stages are characterized by a mixture of both mechanisms. The reverse is true for the second response function: as \( \tilde{\omega} \) increases from 0 to \( \infty \), the solution changes from coupled bending to slipping. Relations similar to (35) were first published by Seifert and Langer [23] for undulating planar bilayers. These authors examined the consequences of viscous coupling between monolayers on dispersion relations for bending excitations of flat bilayers.

It is also important to evaluate the “weighting” assigned to each response function at different stages. Figure 3 shows the amplitudes \( a_1 \) and \( a_2 \), as defined in equation (31), plotted against the parameter \( \tilde{\omega} \). As shown clearly, the first exponential relaxation completely dominates the second one at large values of \( \tilde{\omega} \) (small \( l \)) while the converse is true for small \( \tilde{\omega} \) (large \( l \)). Limiting behaviours of the relaxation function are therefore

\[
\lim_{\tilde{\omega} \to 0} f_1(t) = e^{-\omega_c t}
\]

\[
\lim_{\tilde{\omega} \to \infty} f_1(t) = e^{-\omega_u t}
\]

(36)

Interestingly, both limits are associated with local bending modes. As discussed earlier, these limiting forms represent, respectively, the situations of negligible resistance to interlayer sliding at small wave numbers and the dominance of such forces at large \( l \). The intermediate point at which bending and slipping modes are “equally mixed” can be estimated by setting \( \tilde{\omega} = 1 \). As originally described in Bloom et al. [25] and by Seifert and Langer [23], such a condition leads to a crossover wavelength \( \lambda_\infty \) given by

\[
\lambda_\infty = \frac{(2k_c + \tilde{k}_c) b}{2 \eta_w K}
\]

(37)

With this definition, the dimensionless parameter \( \tilde{\omega} \) can alternatively be interpreted as the ratio of the undulatory wavelength to the crossover value; i.e., \( \tilde{\omega} = \lambda / \lambda_\infty \) where \( \lambda \) is roughly \( R_0 / l \).

The two dissipative mechanisms relevant to bilayer shape changes, namely the viscosity of water and inter-monolayer drag, are important on different length scales separated by the crossover value \( \lambda_\infty \); i.e., interlayer viscous effects overtake the hydrodynamic forces on length scales below this crossover point. Using typical values of \( (2k_c + \tilde{k}_c) \sim 5 \times 10^{-19} \) J, \( \eta_w \sim 10^{-3} \) N s/m², \( K \sim 10^2 \) mN/m and \( b \sim 10^8 \) N s/m³ [18,19], the crossover length is estimated to be 0.2 \( \mu \)m. Thus, interlayer effects account for most of the energy dissipation on mesoscopic length scales.
Fig. 3. — Amplitudes \( (a_1, a_2) \) of the two relaxation functions, as defined in equation (33), plotted against the dimensionless parameter \( \tilde{\omega} \) which can be interpreted as the ratio of the undulatory wavelength relative to a crossover value (given by Eq. (39)). Also shown along these curves are limiting dispersive behaviours of the corresponding decay rates \( \Omega_1 \) and \( \Omega_2 \). Decay rates varying as \( t^3 \) imply relaxation through bending, while an \( t^2 \) dependence suggests relaxation via lateral redistribution of lipid molecules within their monolayer planes (i.e., slipping).

According to Figure 3, relaxation rates of bilayer vesicles are expected to vary as \( t^3 \) for wavelengths much larger or much smaller than 0.2 \( \mu m \). Unfortunately, data collected on length scales of 0.5 to 10 \( \mu m \) (\( \tilde{\omega} \gg 1 \)) using light microscopy — although abundant — have not been definitive on the relaxation dynamics of bilayer membranes [6, 8, 9, 24]. Likewise, for wavelengths much shorter than \( \lambda_\Theta \) (\( \lambda \approx 10 \) nm, \( \tilde{\omega} \ll 1 \)), neutron spin echo studies on partially hydrated bilayer stacks are consistent with the crossover behaviour described here but the results do not expose the wavelength dependence of the relaxation [21]. The dispersion behaviour predicted in this present work needs to be tested over the intermediate range of wavelengths from 50 to 500 nm.

7. Conclusion

Coupling between monolayers has introduced a new level of complexity to the physics of fluid bilayer membranes. Important consequences such as the global curvature energy and intermonolayer dissipation are direct results of the membrane’s stratified structure. In this paper, we have demonstrated the importance of such effects on the undulatory characteristics of bilayer vesicles. New interpretations of previous experimental results may be called for. For example, we have shown that the minute tensions needed to correlate experimentally-measured amplitude spectra may in fact be due to non-local bending. Dynamic stresses resulting from sliding between monolayers (i.e., viscous drag between hydrocarbon brushes) also give rise to a dissipative mechanism that has been widely overlooked. In considering conformational dynamics of bilayers, the relative importance between interlayer dissipation and conventional hydrodynamics depends on the length scale in question. We have estimated the crossover length for a typical bilayer to be a fraction of a \( \mu m \); below this value, hydrodynamic stresses become unimportant. Thus, it appears that interlayer drag is the dominant source of impedance to shape changes in a bilayer just as the relevant dimensions become invisible to light microscopy.
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Appendix A

The goal here is to obtain the response behaviour of a slightly perturbed sphere. Such a process is driven by curvature elastic forces with the recovery rate limited by: a) the bilayer's internal dissipation (i.e., interlayer drag), and b) the surrounding hydrodynamics. The elastic restoring forces arise from the vesicle's departure from spherical geometry. To lowest order, these forces are expanded to first powers in the perturbative displacements; they will then be balanced against the viscous stresses. This analysis is an extension of the work by Schneider et al. [6].

A.1. Bilayer Shell

A.1.1. Geometry. — Bilayer surface is described by

$$\mathbf{r}(\theta, \phi; t) = R_0 \mathbf{e}_r + R_0 \mathbf{e}(\theta, \phi; t) \quad |\varepsilon| \ll 1$$

The dimensionless displacement field $\varepsilon$ can be written quite generally as

$$\varepsilon = u \mathbf{e}_r + \alpha \mathbf{e}_\theta + \beta \sin \theta \mathbf{e}_\phi$$  \hspace{1cm} (A.1)

where $(\mathbf{e}_r, \mathbf{e}_\theta, \mathbf{e}_\phi)$ are unit vectors corresponding to spherical polar coordinates and the components $u$, $\alpha$ and $\beta$ are functions of $(\theta, \phi; t)$. By scaling all lengths by $R_0$ ($R_0 \equiv 1$), the vesicle surface is described by

$$\mathbf{r} = \mathbf{e}_r + \varepsilon$$  \hspace{1cm} (A.2)

Using methods of differential geometry, it is straightforward to derive the following relations [6]: To first order, the unit normal vector is

$$\mathbf{n} = \mathbf{e}_r + \left( \alpha - \frac{\partial u}{\partial \theta} \right) \mathbf{e}_\theta + \left( \beta \sin \theta - \frac{1}{\sin \theta} \frac{\partial u}{\partial \phi} \right) \mathbf{e}_\phi$$  \hspace{1cm} (A.3)

The condition of area incompressibility is given by the expression

$$\nabla \cdot \varepsilon = 2u + \frac{\partial \alpha}{\partial \theta} + \frac{\alpha}{\tan \theta} + \frac{\partial \beta}{\partial \phi} = 0$$  \hspace{1cm} (A.4)

where $\nabla$ is the usual three dimensional gradient operator. Likewise, the local mean curvature is given by

$$\bar{c} = 2 - \nabla^2 u - 2u$$  \hspace{1cm} (A.5)

Note that the tangential displacements $\alpha$ and $\beta$ drop out of this first order expansion. They will, however, appear as higher order terms.

A.1.2. Kinematics. — Let $\mathbf{V}(\theta, \phi)$ be the velocity field on the vesicle surface:

$$\mathbf{V}(\theta, \phi) = \frac{\partial}{\partial t} \varepsilon(\theta, \phi)$$

$$= \frac{\partial u}{\partial t} \mathbf{e}_r + \frac{\partial \alpha}{\partial t} \mathbf{e}_\theta + \frac{\partial \beta}{\partial t} \sin \theta \mathbf{e}_\phi$$
Velocity of the bulk fluid adjacent to the membrane must equal \( \mathbf{V} \) (no-slip condition). The three components of \( \mathbf{V} \) can therefore be velocity boundary conditions for the hydrodynamic problem. However, it is more convenient, for reasons that will become clear, to choose a slightly different set of boundary conditions as follows:

\[
\mathbf{n} \cdot \mathbf{V} = \frac{\partial u}{\partial t} \\
\nabla \cdot \mathbf{V} = \frac{\partial}{\partial t} (\nabla \cdot \mathbf{\epsilon}) = 0 \\
\mathbf{n} \cdot (\nabla \times \mathbf{V}) = \frac{1}{\sin \theta} \left[ \frac{\partial}{\partial \theta} \left( \sin^2 \theta \beta \right) - \frac{\partial \alpha}{\partial \phi} \right] ; \quad \cdot = \frac{\partial}{\partial t}
\]

The first condition is simply the normal velocity component. The second is a measure of surface dilatation, while the last condition represents in-plane shearing. Note that the tangential displacements \( \alpha \) and \( \beta \) only appear in the last condition.

**A.1.3. Forces.** — Equilibrium equations for the bilayer are, from equations (24)

\[
\sigma_n = \left( \tilde{\tau} \tilde{\epsilon} - \nabla^2 M \right) \mathbf{n} \\
\sigma_s = -\nabla \tilde{\tau}
\]

where \( \sigma_n \) and \( \sigma_s \) are the normal and tangential traction (force/unit area) on the membrane surface. \( \tilde{\tau} \) is the isotropic tension field. The moment resultant \( M \) embodies the elastic restoring forces and the bilayer's internal dissipation due to interlayer drag. Its viscoelastic behaviour is expressed, quite generally, in terms of a relaxation function \( \mu(t) \) (equation (28)):

\[
M(\Omega, t) = \mu(t) \tilde{\epsilon}(\Omega, 0) + \int_0^t \mu(t - t') \frac{\partial \tilde{\epsilon}}{\partial t'}(\Omega, t') \, dt'
\]

The total traction is simply

\[
\mathbf{\sigma} = \sigma_n + \sigma_s = \left( \tilde{\tau} \tilde{\epsilon} - \nabla^2 M \right) \mathbf{n} - \nabla \tilde{\tau}
\]

The quantities \( \tilde{\tau}, M, \mathbf{n} \) and \( \tilde{\epsilon} \) can be written as sums of a lead term plus a first order perturbation:

\[
\tilde{\tau} = \tau_0 + \tau ; \quad \tau/\tau_0 \ll 1 \\
M = m_0 + m ; \quad m/m_0 \ll 1 \\
\tilde{\epsilon} = 2 - \nabla^2 u - 2u ; \quad u \ll 1 \\
\mathbf{n} = \mathbf{e}_r + \left( \alpha - \frac{\partial u}{\partial \theta} \right) \mathbf{e}_\theta + \left( \beta \sin \theta - \frac{1}{\sin \theta \frac{\partial u}{\partial \phi}} \right) \mathbf{e}_\phi ; \quad u, \alpha, \beta \ll 1
\]

\( \tau_0 \) represents a time-averaged tension. To first order in the perturbations, the surface traction vector is

\[
\mathbf{\sigma} = \left[ 2\tau_0 + 2\tau - \tau_0 \left( \nabla^2 u + 2u \right) - \nabla^2 m \right] \mathbf{e}_r \\
+ 2\tau_0 \left[ \left( \alpha - \frac{\partial u}{\partial \theta} \right) \mathbf{e}_\theta + \left( \beta \sin \theta - \frac{1}{\sin \theta \frac{\partial u}{\partial \phi}} \right) \mathbf{e}_\phi \right] - \nabla \tau
\]

Components of \( \mathbf{\sigma} \) can become boundary conditions for the adjacent fluid. However, we again choose to represent the stress boundary conditions in a manner similar to the kinematic forms.
After some algebra, one arrives at the following:

\[ \mathbf{n} \cdot \sigma = 2\tau_0 + 2\tau - \tau_0 (\nabla^2 u + 2u) - \nabla^2 m \]
\[ \nabla \cdot \sigma = 2\tau_0 \bar{c} - \nabla^2 \tau + 4\tau - 2\tau_0 (\nabla^2 u + 2u) - 2 \nabla^2 m \]  
\[ \mathbf{n} \cdot (\nabla \times \sigma) = \frac{2\tau_0}{\sin \theta} \frac{\partial}{\partial \theta} \left( \beta \sin^2 \theta - \frac{\partial \alpha}{\partial \phi} \right) \]  

(A.8)

In arriving at the second boundary condition (divergence of \( \sigma \)), equations (A.4) and (A.5) are used. Here, we see again that the tangential displacements \( \alpha \) and \( \beta \) only appear in the last equation. In general, boundary conditions that involve in-plane motions can be separated out (analogous to the separation of variables in solving PDE’s) and will be ignored in the present analysis.

A.1.4. Modal Expansion. — We will proceed now to expand the boundary conditions into harmonic modes. Let

\[ u(\Omega, t) = \sum_{l > 1} u_{lm} Y_{lm}(\Omega) f_{lm}(t) ; \quad f_{lm}(0) \equiv 1 \]  

(A.9)

where \( f_{lm}(t) \) is an undetermined time dependence; it is our goal to solve for this function. The above sum starts from \( l = 2 \) since the \( l = 0 \) mode violates volume constraint and \( l = 1 \) modes correspond to rigid body translations. We also let the perturbative tension be

\[ \tau(\Omega, t) = \sum_{l > 1} \tau_{lm} Y_{lm}(\Omega) f_{lm}(t) \]  

(A.10)

with the same time dependence. From equation (A.5)

\[ \nabla^2 \varepsilon(\Omega, t) = - \sum_{l > 1} l(l + 1)(l + 2)(l - 1) u_{lm} Y_{lm}(\Omega) f_{lm}(t) \]

The Laplacian of equation (A.7) can also be expanded in modal components as follows:

\[ \nabla^2 M(\Omega, t) = \nabla^2 m(\Omega, t) = \mu(t) \nabla^2 \varepsilon(\Omega, 0) + \int_0^t \mu(t - t') \frac{\partial}{\partial t'} \left[ \nabla^2 \varepsilon(\Omega, t') \right] dt' \]
\[ = - \sum_{l > 1} l(l + 1)(l + 2)(l - 1) u_{lm} g_{lm}(t) Y_{lm}(\Omega) \]  

(A.11)

where

\[ g_{lm}(t) = \mu(t) f_{lm}(0) + \int_0^t \mu(t - t') \frac{df_{lm}(t')}{dt'} dt' \]  

(A.12)

Using these relations, the first two kinematic boundary conditions (Eqs. (A.6)) are

\[ \mathbf{n} \cdot \mathbf{V} = \sum_{l > 1} u_{lm} Y_{lm} \frac{df_{lm}}{dt} \]  

(A.13)

\[ \nabla \cdot \mathbf{V} = 0 \]

and from equations (A.9), (A.10) and (A.11), the first two stress boundary conditions (Eqs. (A.8)) are

\[ \mathbf{n} \cdot \sigma = 2\tau_0 + \sum_{l > 1} \{ 2 \tau_{lm} f_{lm} \]
\[ + u_{lm} \left[ \tau_0 (l+2)(l-1) f_{im} + l(l+1)(l+2)(l-1) g_{im} \right] \] \( Y_{im} \) 

\[
\nabla \cdot \sigma = 2\tau_0 \varepsilon + \sum_{l>1} \left\{ (l^2 + l + 4) \tau_{lm} f_{lm} \right. \\
+ u_{lm} \left[ 2\tau_0 (l+2)(l-1) f_{lm} + 2l(l+1)(l+2)(l-1) g_{lm} \right] \] \( Y_{lm} \) 

(A.14)

A.2. HYDRODYNAMICS. — The low Reynolds’s number velocity field is given by equation (12):

\[
\nabla^2 \mathbf{v} = \frac{1}{\eta_w} \nabla p \\
\nabla \cdot \mathbf{v} = 0 \quad \text{(incompressibility)}
\]

where \( \eta_w \) is the shear viscosity, \( \mathbf{v} \) the velocity field, and \( p \) the pressure. The general solution to these equations is given in terms of three independent sets of solid spherical harmonics with coefficients \( p_{im} \), \( \psi_{im} \) and \( \chi_{im} \). Based on these general solutions, kinematic and stress boundary conditions are formulated on a spherical surface \([22]\). By letting \( \mathbf{v}^i \) be velocity field inside a unit sphere, the boundary conditions on its surface are

\[
\mathbf{n} \cdot \mathbf{v}^i = \sum_{l>1} \left[ \frac{l}{2(2l+3)\eta_w} p_{im}^l + l \psi_{im}^l \right] Y_{im}(\Omega) f_{im}(t) \quad \text{(A.15)}
\]

\[
\nabla \cdot \mathbf{v}^i = -\sum_{l>1} \left[ \frac{l(l+1)}{2(2l+3)\eta_w} p_{im}^l + l(l-1) \psi_{im}^l \right] Y_{im}(\Omega) f_{im}(t)
\]

\[
\mathbf{n} \cdot (\nabla \times \mathbf{v}^i) = \text{function of } \chi_{im} \text{ only}
\]

Note that, again, the same time dependence is used. Corresponding boundary conditions for fluid outside the sphere are obtained by substituting \(-(l+1)\) for \( l \), \( p_{im}^l \) for \( p_{im}^l \) and \( \psi_{im}^l \) for \( \psi_{im}^l \).

Let \( \mathbf{P}_r^i \) be the stress vector on a surface of the interior fluid whose normal is in the \( r \) direction. The associated boundary conditions on the unit sphere are \([22]\)

\[
\mathbf{n} \cdot \mathbf{P}_r^i = -p^i \\
+ \eta_w \sum_{l>1} \left[ \frac{(l^2 - l - 3)}{(2l+3)\eta_w} p_{im}^l + 2l(l-1) \psi_{im}^l \right] Y_{im}(\Omega) f_{im}(t) \quad \text{(A.16)}
\]

\[
\nabla \cdot \mathbf{P}_r^i = -p^i \varepsilon \\
- \eta_w \sum_{l>1} \left[ \frac{(l^2 + 2l + 6)}{(2l+3)\eta_w} p_{im}^l + 2l(l-1)^2 \psi_{im}^l \right] Y_{im}(\Omega) f_{im}(t)
\]

\[
\mathbf{n} \cdot (\nabla \times \mathbf{P}_r^i) = \text{function of } \chi_{im} \text{ only}
\]

Here, \( p^i \) denotes the hydrostatic pressure inside the vesicle. Corresponding conditions for fluid outside the vesicle are obtained by substituting \(-(l+1)\) for \( l \), \( p_{im}^l \) for \( p_{im}^l \), \( \psi_{im}^l \) for \( \psi_{im}^l \), and \( p^o \) for \( p^i \). The coefficients \( \chi_{im} \) represent spheroidal harmonics associated with tangential motions on the vesicle surface and can therefore be ignored for our purposes. They are, however, necessary for the complete solution of the flow field.

A.3. MATCHING BOUNDARY CONDITIONS

A.3.1. Laplace Transform. — It is convenient to transform the convoluted time dependencies into frequency space. By letting \( L \) be the Laplace transform operator and using the “hat”
notation ('\cdot') to denote a transformed variable, we have
\begin{align*}
\mathcal{L}[f_{lm}(t)] &= \hat{f}_{lm}(\omega) \\
\mathcal{L}[\mu(t)] &= \hat{\mu}(\omega)
\end{align*}

and from equation (A.12),
\begin{align*}
\mathcal{L}[g_{lm}(t)] &= \hat{\mu}(\omega) f_{lm}(0) + \hat{\mu}(\omega) \left[ \omega \hat{f}_{lm}(\omega) - f_{lm}(0) \right] \\
&= \omega \hat{\mu}(\omega) \hat{f}_{lm}(\omega) \quad \text{(A.17)}
\end{align*}

We now transform boundary conditions on the shell. Using the relation \( f_{lm}(0) = 1 \), the two kinematic conditions (Eqs. (A.13)) are
\begin{align*}
\mathcal{L}(\mathbf{n} \cdot \mathbf{V}) &= \sum_{l>1} u_{lm} \left( \omega - \hat{f}_{lm}^{-1} \right) Y_{lm}(\Omega) \hat{f}_{lm}(\omega) \quad \text{(A.18)} \\
\mathcal{L}(\nabla \cdot \mathbf{V}) &= 0
\end{align*}

Similarly, using equation (A.17), the transformed stress boundary conditions (Eqs. (A.14)) are
\begin{align*}
\mathcal{L}(\mathbf{n} \cdot \sigma) &= \mathcal{L}(2 \tau_0) + \sum_{l>1} \{ 2 \tau_{lm} \\
&\quad + u_{lm} \left[ \tau_0 (l+2)(l-1) + \omega \hat{\mu} l (l+1)(l+2)(l-1) \right] \} Y_{lm}(\Omega) \hat{f}_{lm}(\omega) \\
\mathcal{L}(\nabla \cdot \sigma) &= \mathcal{L}(2 \tau_0 \tilde{c}) + \sum_{l>1} \{ (l^2 + l + 4) \tau_{lm} \\
&\quad + u_{lm} \left[ 2\tau_0 (l+2)(l-1) + \omega \hat{\mu} 2l (l+1)(l+2)(l-1) \right] \} Y_{lm}(\Omega) \hat{f}_{lm}(\omega) \quad \text{(A.19)}
\end{align*}

A.3.2. Matching Kinematic Boundary Conditions: No-Slip. — No-slip condition at the shell-interior fluid interface is expressed by the following equations:
\begin{align*}
\mathcal{L}(\mathbf{n} \cdot \mathbf{V}) &= \mathcal{L}(\mathbf{n} \cdot \mathbf{v}^i) \\
\mathcal{L}(\nabla \cdot \mathbf{V}) &= \mathcal{L}(\nabla \cdot \mathbf{v}^i)
\end{align*}

Equating (A 18) to the transforms of equation (A.15) leads to the following two equations:
\begin{align*}
\frac{l}{2(2l+3)\eta_w} p_{lm} + l \psi_{lm} &= u_{lm} \left( \omega - \hat{f}_{lm}^{-1} \right) \\
\frac{l(l+1)}{2(2l+3)\eta_w} p_{lm} + l (l-1) \psi_{lm} &= 0
\end{align*}

The solutions are
\begin{align*}
p_{lm} &= -\frac{\eta_w (2l+3)(l-1)}{l} u_{lm} \left( \omega - \hat{f}_{lm}^{-1} \right) \quad \text{(A.20)} \\
\psi_{lm} &= \frac{(l+1)}{2l} u_{lm} \left( \omega - \hat{f}_{lm}^{-1} \right)
\end{align*}
Matching Stress Boundary Conditions: Force Balance. — Substituting equations (A.20) into the transforms of equation (A.16), we obtain stress boundary conditions on the interior fluid with no-slip condition implicitly satisfied to first order:

\[
\mathcal{L}(n \cdot P_r^i) = -\mathcal{L}(p^i) + \eta_w \sum_{l > 1} \frac{(l-1)(2l+3)}{l} \left( \omega - \hat{f}_{im}^{-1} \right) u_{lm}(\Omega) \hat{f}_{im}(\omega)
\]

\[
\mathcal{L}(\nabla \cdot P_r^i) = -\mathcal{L}(p^i \hat{c}) + \eta_w \sum_{l > 1} \frac{3(l+2)(l-1)}{l} \left( \omega - \hat{f}_{im}^{-1} \right) u_{lm}(\Omega) \hat{f}_{im}(\omega)
\]

Similar stress boundary conditions are obtained for the exterior fluid by replacing \(l\) by \(-(l+1)\):

\[
\mathcal{L}(n \cdot P_r^0) = -\mathcal{L}(p^0) - \eta_w \sum_{l > 1} \frac{(l+2)(2l-1)}{l+1} \left( \omega - \hat{f}_{im}^{-1} \right) u_{lm}(\Omega) \hat{f}_{im}(\omega)
\]

\[
\mathcal{L}(\nabla \cdot P_r^0) = -\mathcal{L}(p^0 \hat{c}) - \eta_w \sum_{l > 1} \frac{3(l-1)(l+2)}{l+1} \left( \omega - \hat{f}_{im}^{-1} \right) u_{lm}(\Omega) \hat{f}_{im}(\omega)
\]

Defining the quantities \(\Delta P_r = P_r^i - P_r^0\) and \(\Delta p = p^i - p^0\), we have

\[
\mathcal{L}(n \cdot \Delta P_r) = -\mathcal{L}(\Delta p)
\]

\[
+ \eta_w \sum_{l > 1} \left[ \frac{(2l+1)(2l^2+2l-3)}{l(l+1)} \left( \omega - \hat{f}_{im}^{-1} \right) \right] u_{lm}(\Omega) \hat{f}_{im}(\omega)
\]

\[
\mathcal{L}(\nabla \cdot \Delta P_r) = -\mathcal{L}(\Delta p \hat{c})
\]

\[
+ 3\eta_w \sum_{l > 1} \left[ \frac{(l-1)(l+2)(2l+1)}{l(l+1)} \left( \omega - \hat{f}_{im}^{-1} \right) \right] u_{lm}(\Omega) \hat{f}_{im}(\omega)
\]

The equilibrium condition at the shell-fluid interface is \(\sigma + \Delta P_r = 0\). Components of this relation in the transformed space are

\[
\mathcal{L}(n \cdot \sigma) + \mathcal{L}(n \cdot \Delta P_r) = 0
\]

\[
\mathcal{L}(\nabla \cdot \sigma) + \mathcal{L}(\nabla \cdot \Delta P_r) = 0
\]

Expressions from equations (A.19) and (A.21) are substituted into the above equations. Recognizing that \(\Delta p = 2\tau_0\) (on unit sphere), we have the following set of homogeneous equations for each mode:

\[
c_{11} \tau_{lm} + c_{12} u_{lm} = 0
\]

\[
c_{21} \tau_{lm} + c_{22} u_{lm} = 0
\]

where

\[
c_{11} = 2
\]

\[
c_{12} = \tau_0 (l+2)(l-1) + \omega \hat{\mu} l(l+1)(l+2)(l-1)
\]

\[
+ \eta_w \frac{(2l+1)(2l^2+2l-3)}{l(l+1)} \left( \omega - \hat{f}_{im}^{-1} \right)
\]

\[
c_{21} = l^2 + l + 4
\]

\[
c_{22} = 2\tau_0 (l+2)(l-1) + \omega \hat{\mu} 2l(l+1)(l+2)(l-1)
\]

\[
+ 3\eta_w \frac{(l-1)(l+2)(2l+1)}{l(l+1)} \left( \omega - \hat{f}_{im}^{-1} \right)
\]
For non-trivial solution, the determinant $|c_{ij}|$ is set to zero. It follows from this that

$$
\hat{f}_{m}(\omega) = \frac{4 \eta_{w} \zeta}{4 \eta_{w} \zeta \omega + \ell(\ell + 1) \omega \bar{\mu}(\omega) + \tau_{0}}
$$

where

$$
\zeta(\ell) = \frac{1}{4} \frac{(2\ell + 1)(2\ell^{2} + 2\ell - 1)}{\ell(\ell + 1)(\ell + 2)(\ell - 1)}
$$

Finally, from equation (29), the transform of $\mu(t)$ is

$$
\bar{\mu}(\omega) = \frac{2 k_{c}}{\omega} + \frac{\bar{k}_{c}}{\omega + \omega_{D}}
$$

Substituting into equation (A.22) and evaluating the inverse transform, the final form of $f_{m}(t)$ is as given by equations (33–35).

References


