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Fluid membranes exchanging material with external reservoirs

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Abstract. We investigate the dynamics of a single component fluid bilayer, which exchanges material with the surrounding fluid. We derive covariant equations of motion taking into account solvent permeation, exchange of lipids between solvent and the membrane and discuss the sources of noise in these equations. Different lipid concentrations on both sides of the membrane lead to a non-equilibrium state. We discuss steady states as well as shape instabilities which occur at a critical osmotic-pressure difference.

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1 Introduction

Biological membranes play a crucial role in the compartmentalization of cells. They act as highly selective permeability barriers separating the cytosol from the extracellular environment as well as from different cell organelles. They participate also in a variety of biological processes, such as passive and active transport, cell locomotion, phagocytosis and endocytosis, etc. [1]. Biomembranes, despite their different functions, have a common structural basis: they are composed of lipid molecules that have a polar head group region and two hydrophobic hydrocarbon chains. Due to their amphiphilic character, when dissolved in an aqueous solvent these molecules aggregate spontaneously into two opposing monomolecular layers [2,3].

Single-component incompressible membranes have represented the fundamental model of biomembranes over thirty years. The elastic continuum description has been the starting point for studies of the thermodynamic and statistical properties of such membranes [4–6]. It is valid at length scales large compared to microscopic lengths such as the bilayer thickness and allows us to understand mesoscopic shapes and long-wavelength fluctuations [3,7,8]. However, in living cells, membranes contain many components such as several different species of lipids, anchored polymers or membrane proteins which can move within the two-dimensional liquid state of the membrane and perform diffusive motion. Many of these complexities have been addressed both theoretically and experimentally and are known to play a role in shape transformation [9–11], magnification of shape fluctuation [12,13], coalescence and budding processes [14]. Futhermore, inside an organism, the membranes are subject to exchanges of small transport vesicles containing different sorts of cargo molecules (*e.g.* lipids, enzymes, proteins, small intercalated particles, etc.). Thus, in order to obtain a more appropriate description of biological membranes, physicists have to learn how to deal with membranes exchanging material with their three-dimensional surrounding. The work we present here may be considered as a step in this direction. It follows and generalizes earlier work considering static properties [3], Rouse dynamics [15], or membrane interactions with a diffusion field as protein density [16].

We extend a covariant, reparametrization invariant theory for one-component membranes, proposed initially by Cai and Lubensky [17], by allowing for an exchange of material with the three-dimensional embedding fluid. The fluid is assumed to contain a fraction of membrane material either in the form of isolated molecules or of small vesicles, controlled by its chemical potential μ. In the case of vesicles dissolved in the three-dimensional fluid, the length scales considered in this manuscript must be large compared to the vesicle diameter. We assume the chemical potential difference between the membrane and each of the 3D compartments to be small enough to ensure the validity of an Onsager theory of the exchanges. This allows us to systematically construct a theory of membranes with sources and sinks of material. In order to illustrate our theory, we define the conditions under which a flat steady state may be reached, and derive the mode structure of the

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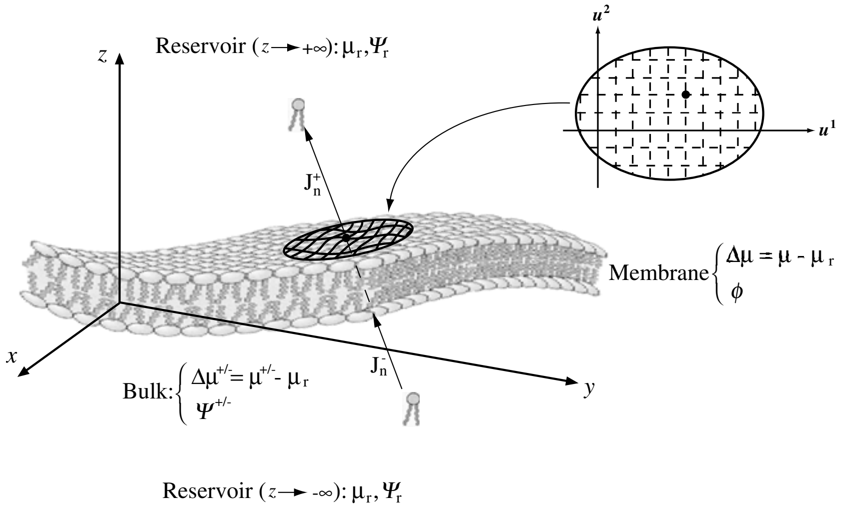

Fig. 1. Schematic representation of a fluid membrane which exchanges material with the solvent. The shape of the membrane in the three-dimensional embedding space is parameterized in terms of two internal coordinates u^a, $a = 1, 2$. Lipids in the membrane are characterized by the density $\phi(\check{u}, t)$ and the chemical potential $\mu(\check{u}, t)$. The membrane is located in the (x, y)-plane and exchanges material with the solvent via the currents $J_n^{\pm}$. The density and chemical potential of material above and below are denoted $\Psi^{\pm}$ and $\mu^{\pm}$. Reservoirs of membrane material far from the membrane at $z \rightarrow \pm\infty$ are characterized by the density Ψ_r and the chemical potential μ_r.

membrane under these conditions. In particular, we show the existence of an instability under certain conditions, and derive a simple criterion which gives us an insight into the physical basis of this shape instability.

2 Membrane description

For a theoretical description on length scales large compared to microscopic lengths, fluid membranes can be considered as two-dimensional fluctuating surfaces embedded in a three-dimensional Newtonian fluid. The membrane shape is described by a three-component vector field $\mathbf{R}(u^1, u^2)$ depending on two internal coordinates u^1 and u^2 of the membrane (see Fig. 1). We can locally define covariant tangent-plane vectors[1]:

$$\mathbf{R}_a = \partial_a \mathbf{R}, \quad \text{for } a = 1, 2, \tag{1}$$

from which we obtain the metric tensor $g_{ab} \equiv \mathbf{R}_a \cdot \mathbf{R}_b$. Its determinant, $g \equiv \det(g_{ab})$, yields the area element $\mathrm{d}\mathcal{A} = \mathrm{d}u^1 \mathrm{d}u^2 \sqrt{g}$. The inverse metric tensor g^{ab} satisfying $g^{ab} g_{bc} = \delta^a_c$ allows us to define contravariant tangent-plane vectors $\mathbf{R}^a = g^{ab} \mathbf{R}_b$ [2]. The tangent plane is completely defined and oriented by the local unit (outward) normal

$$\mathbf{n} = \frac{\mathbf{R}_1 \wedge \mathbf{R}_2}{|\mathbf{R}_1 \wedge \mathbf{R}_2|}.$$

The curvature tensor is given by $\mathrm{K}_{ab} = \mathbf{n} \cdot \partial_a \partial_b \mathbf{R}$ and permits us to construct two invariant scalars which are the mean curvature $H \equiv g^{ab} \mathrm{K}_{ab}/2$ and the Gaussian curvature $K \equiv \det(g^{ab} \mathrm{K}_{bc})$, where g^{ab} is the contravariant metric tensor [2].

In the classical curvature model, a membrane is characterized by the Helfrich-Canham Hamiltonian [4,5]

$$\mathcal{F}_{\mathrm{HC}} \equiv \frac{1}{2} \int \mathrm{d}^2 \check{u} \sqrt{g} \left[\kappa (2H - H_0)^2 + \kappa_{\mathrm{G}} K \right], \tag{2}$$

where κ is the bending rigidity, κ_{G} is the Gaussian curvature rigidity and H_0 is the spontaneous curvature which takes into account the possible asymmetry of either chemical or physical origin. If we exclude topological fluctuations, the Gauss-Bonnet theorem [2] allows us to omit the term controlled by the Gaussian rigidity, since it is merely a topological invariant.

Following Cai and Lubensky, we use a single continuous scalar variable $\phi(\check{u}, t)$ to describe the local density of phospholipids in the membrane. In order to include the lateral density in our description, let us introduce the local free energy density $f(\phi) - \Delta\widetilde{\mu}\phi$ corresponding to the replacement of the embedding fluid in the presence of its equilibrium solvated lipid density by the bilayer membrane without curvature terms. $\Delta\widetilde{\mu}$ is the difference between the membrane chemical potential and the equilibrium lipid chemical potential $\mu_r = \mu_e(T, P, \Psi_r)$ at the temperature T and pressure P of the experiment, and Ψ_r is the three-dimensional lipid density in the reservoir (see Fig. 1). The corresponding Ginzburg-Landau Hamiltonian then can be written as

$$\mathcal{F}_{\mathrm{GL}} = \int \mathrm{d}^2 \check{u} \sqrt{g} \left[f(\phi) - \Delta\widetilde{\mu}\phi \right]. \tag{3}$$

The equilibrium value ϕ_e in a flat membrane with imposed $\Delta\widetilde{\mu}$ is given by $\Delta\widetilde{\mu} = f'(\phi_e)$. For instance, for a membrane covering a small hole and when the equilibration time with the bulk embedding fluid is long enough the chemical potential is imposed by the Plateau borders

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[1] $\partial_a = \frac{\partial}{\partial u^a}$ denotes the partial derivative with respect to coordinate u^a.

which forces $\Delta\widetilde{\mu} \neq 0$ (see App. A). Under such circumstances, $f(\phi)$ can be expanded in a power series of the density deviation $\phi - \phi_e$:

$$f(\phi) = f(\phi_e) + \Delta\widetilde{\mu}(\phi - \phi_e) + \frac{\chi_e}{2}(\phi - \phi_e)^2 \quad (4)$$

with $\chi_e = f''(\phi_e)$. Equation (3) defines the equilibrium surface tension

$$\sigma = f(\phi_e) - \Delta\widetilde{\mu}\phi_e. \quad (5)$$

In a situation where the bulk embedding fluid and the membrane are at equilibrium, then $\Delta\widetilde{\mu} = 0$ and $\phi_e = \phi_0$ with $f(\phi_0) = 0$. As a consequence of relation (5), the tension σ also vanishes. For small deviations of ϕ from that value ϕ_0, equation (4) becomes

$$f(\phi) \simeq \frac{\chi}{2}(\phi - \phi_0)^2. \quad (6)$$

Here, $\chi = f''(\phi_0)$ is the compressibility modulus of the membrane. In general, there will also be stiffness terms depending on covariant derivatives of ϕ, as for example $|\mathcal{D}^2\phi|$ and $g^{ab}(\partial_a\phi)(\partial_b\phi)$, where $\mathcal{D}^2 = g^{-1/2}\partial_a g^{1/2} g^{ab}\partial_b$ denote the Laplace-Beltrami operator associated with the metric g_{ab}. They will, however, not concern us here since they introduce subdominant terms in the long length scale limit.

The effective Hamiltonian of symmetric membranes has the following structure:

$$\mathcal{F}[\mathbf{R}, \phi] = \int \mathrm{d}^2\breve{u}\sqrt{g}\left[\frac{\kappa}{2}(2H)^2 + \frac{\chi}{2}(\phi - \phi_0)^2\right]. \quad (7)$$

In the case when the chemical potential is imposed by Plateau borders, and for small deviations from ϕ_e, then

$$\mathcal{F}[\mathbf{R}, \phi] = \int \mathrm{d}^2\breve{u}\sqrt{g}\left[\sigma + \frac{\kappa}{2}(2H)^2 + \frac{\chi_e}{2}(\phi - \phi_e)^2\right], \quad (8)$$

in which σ is defined by equation (5).

3 Membrane dynamics

For the mesoscopic length scales of membrane systems, the hydrodynamic flow is usually in the low-Reynolds-number creeping flow regime ($\mathrm{Re} = \rho_s V_s L/\eta \simeq 10^{-3}$ for a typical lateral size L of order micrometers and a solvent velocity V_s of few millimeters per second). In this case, the embedding incompressible fluid dynamics is governed by the 3D Stokes equation [18]:

$$\begin{aligned}\eta\Delta\mathbf{v}_s(\mathbf{r},t) = \boldsymbol{\nabla}P(\mathbf{r},t) &+ \int \mathrm{d}^2\breve{u}\,\delta(\mathbf{r} - \mathbf{R})\left.\frac{\delta\mathcal{F}}{\delta\mathbf{R}}\right|_{\sqrt{g}\phi} \\ &+ \boldsymbol{\zeta}_h(\mathbf{r},t), \\ \boldsymbol{\nabla}\cdot\mathbf{v}_s(\mathbf{r},t) = 0,&\end{aligned} \quad (9)$$

in which $\mathbf{v}_s$, P and η are the embedding fluid velocity, pressure and viscosity. The force density acting on the solvent $\delta\mathcal{F}/\sqrt{g}\delta\mathbf{R}$ is obtained at constant areal density projected onto the tangent plane $\sqrt{g}\phi$:

$$\begin{aligned}\frac{1}{\sqrt{g}}\left.\frac{\delta\mathcal{F}}{\delta\mathbf{R}}\right|_{\sqrt{g}\phi} =& \Big[\kappa(2\mathcal{D}^2H + 4H^3 - 4HK) \\ &+ 2p(\phi)H\Big]\mathbf{n} + \partial_a p\,\mathbf{R}^a\end{aligned} \quad (10)$$

with $p(\phi)$ the two-dimensional membrane pressure: $p(\phi) \simeq \chi\phi_0(\phi - \phi_0)$. The last term in equation (9), $\boldsymbol{\zeta}_h$, represents the fluctuating force exerted on the solvent due to equilibrium thermal fluctuations and has the correlation:

$$\begin{aligned}\langle\boldsymbol{\zeta}_h(\mathbf{r},t)\rangle =& \mathbf{0}, \\ \langle\zeta_{h_i}(\mathbf{r},t)\zeta^*_{h_j}(\mathbf{r}',t')\rangle =& 2\mathrm{kT}\eta(-\delta_{ij}\nabla^2 + \partial_i\partial_j) \\ &\times\delta(\mathbf{r} - \mathbf{r}')\delta(t - t'),\end{aligned} \quad (11)$$

where the star symbol denotes complex conjugate. A special solution of the noiseless Stokes equation for the velocity field generated is given by

$$\mathbf{v}_s(\mathbf{r},t) = \int \mathrm{d}^2\breve{u}\sqrt{g}\,\boldsymbol{\mathcal{O}}(\mathbf{r},\mathbf{R})\frac{1}{\sqrt{g}}\left.\frac{\delta\mathcal{F}}{\delta\mathbf{R}}\right|_{\sqrt{g}\phi}, \quad (12)$$

where the Oseen tensor $\boldsymbol{\mathcal{O}}(\mathbf{r},\mathbf{r}')$ has Cartesian matrix elements [19]:

$$\mathcal{O}_{ij}(\mathbf{r},\mathbf{r}') \equiv \frac{1}{8\pi\eta|\mathbf{r} - \mathbf{r}'|}\left[\delta_{ij} + \frac{(r_i - r'_i)(r_j - r'_j)}{|\mathbf{r} - \mathbf{r}'|^2}\right]. \quad (13)$$

Thus, as already well known, hydrodynamics mediates a long-range interaction ($\sim 1/|\mathbf{r} - \mathbf{r}'|$) through the velocity field.

Following standard procedures in irreversible thermodynamics [20], we can postulate linear constitutive relations between the fluxes (the relative flow of the solvent through the membrane and the particle currents $J_n^{\pm}$ between each half-space and the membrane) and the associated forces (hydrostatic- minus osmotic-pressure discontinuity across the membrane, chemical potential difference between positive (respectively, negative) half-space and membrane. According to Onsager's reciprocal relations [21], the constitutive flux-force relations in the linear regime can be expressed in the form

$$\begin{aligned}&\begin{pmatrix}(\mathbf{v}(\breve{u},t) - \mathbf{v}_s(\mathbf{R},t))\cdot\mathbf{n} \\ J_n^+ \\ J_n^-\end{pmatrix} = \\ &\mathbf{L}\begin{pmatrix}\Delta P(\breve{u},t) - \Delta\Pi \\ \Delta\mu(\breve{u},t) - \Delta\mu^+(\mathbf{R}(\breve{u}),t) \\ \Delta\mu^-(\mathbf{R}(\breve{u}),t) - \Delta\mu(\breve{u},t)\end{pmatrix} + \boldsymbol{\mathcal{N}}(\breve{u},t),\end{aligned} \quad (14)$$

where we define the Onsager matrix by

$$\mathbf{L} = \begin{pmatrix}\lambda_p & -\Lambda\Psi_r & -\Lambda\Psi_r \\ -\Lambda\Psi_r & \lambda\Psi_r^2 & 0 \\ -\Lambda\Psi_r & 0 & \lambda\Psi_r^2\end{pmatrix}. \quad (15)$$

The membrane velocity $\mathbf{v}(\breve{u},t)$ will be defined below. $\Delta P(\breve{u},t)$ is the hydrostatic-pressure difference across the membrane, $\Delta\Pi$ the osmotic-pressure difference, $\Delta\mu(\check{u},t)$ the chemical potential of lipids in the membrane defined by

$$\Delta\mu(\check{u},t)=\frac{1}{\sqrt{g}}\frac{\delta\mathcal{F}}{\delta\phi}\Big|_{\mathbf{R}}=\chi(\phi-\phi_0), \tag{16}$$

or more generally $\Delta\mu=\chi_e(\phi-\phi_e)+\Delta\tilde{\mu}$ and $\Delta\mu^{\pm}(\mathbf{r},t)$ denote the chemical potentials in the $+/-$ half-spaces which, in the dilute solution case, can be written as

$$\Delta\mu^{\pm}(\mathbf{r},t)=\mu^{\pm}(\mathbf{r},t)-\mu_r=\mathrm{kT}\ln(\Psi^{\pm}(\mathbf{r},t)/\Psi_r). \tag{17}$$

The kinetic coefficients λ_p (the membrane permeability), λ and Λ are entirely determined by the internal structure of the membrane, independently of the constraints applied on the system, and do not depend on Ψ_r for small Ψ_r. They are dependent, however, on the state variables such as temperature, pressure and the density ϕ_0 or ϕ_e. Stability conditions imply that all diagonal elements (λ_p and λ) are positive, whereas the off-diagonal elements must satisfy the condition $\lambda_p\lambda-2\Lambda^2>0$. In principle all fluxes should depend linearly on all forces, and the Onsager matrix $\mathbf{L}$ should not have any vanishing element. However, the particle current between the membrane and the lower half-plane driven by the chemical potential difference between the upper half-plane and the membrane is very small, and reciprocally. Thus, for the sake of simplicity, we set the corresponding coefficients to zero.

In order to describe long-wavelength fluctuations, we further introduce thermal noise sources $\boldsymbol{\mathcal{N}}=(\zeta_n;\varsigma^+;\varsigma^-)$ in the dynamical equations. The first contribution of noise, ζ_n, is the Brownian noise corresponding to the dissipation of energy in the permeation process. The contributions, $\varsigma^{\pm}$, represent the thermal noise due to particle flow perpendicular to the membrane. The fluctuation-dissipation theorem requires

$$\begin{aligned}&\langle\mathcal{N}_\alpha(\check{u},t)\rangle=0,\\&\langle\mathcal{N}_\alpha(\check{u},t)\mathcal{N}^*_\beta(\check{u}',t')\rangle=2\mathrm{kT}\mathrm{L}_{\alpha\beta}\frac{\delta(\check{u}-\check{u}')}{\sqrt{g}}\delta(t-t').\end{aligned} \tag{18}$$

We now write down the equation of conservation of the membrane molecule density. They exhibit a conserved part which corresponds to molecule motion within the membrane, and a source term which is nothing else than the flux difference $J_n^- - J_n^+$:

$$\mathcal{D}_t\phi+\mathcal{D}_a j^a(\phi)=J_n^- - J_n^+\,, \tag{19}$$

where $\mathcal{D}_t=g^{-1/2}\partial_t g^{1/2}$ and $\mathcal{D}_a=g^{-1/2}\partial_a g^{1/2}$ is the covariant derivative. A detailed discussion of the current $j_a(\phi)=g_{ab}j^b(\phi)$ can be found in reference [17]:

$$j_a(\phi)=\sum_i\frac{\mathrm{d}u_a^{(i)}}{\mathrm{d}t}\frac{\delta(\check{u}-\check{u}_i)}{\sqrt{g}}, \tag{20}$$

where the summation i is over all molecules defining the membrane and $\mathrm{d}u_a^{(i)}/\mathrm{d}t$ is the covariant component of the molecule velocity, tangential to the membrane. Thus, the membrane velocity is defined by:

$$\mathbf{v}=\frac{j_a(\phi)\mathbf{R}^a}{\phi}+\partial_t\mathbf{R}. \tag{21}$$

The source and sink terms, which are not included in reference [17], generate a new physics which needs to be investigated. If we denote the friction coefficient γ of the membrane with the solvent, the in-plane membrane dynamics obeys the following equation:

$$-\partial_a p-\gamma\big[\mathbf{v}(\check{u},t)-\mathbf{v}_s(\mathbf{R}(\check{u}),t)\big]\cdot\mathbf{R}_a+\zeta_a(\check{u},t)=0, \tag{22}$$

where we have ignored other sources of dissipation, for example, due to intra-membrane viscosity, since that is subdominant compared to the friction with the surrounding fluid [22]. The function $\zeta_a(\check{u},t)$ is a Gaussian white noise source with correlations:

$$\begin{aligned}&\langle\zeta_a(\check{u},t)\rangle=0,\\&\langle\zeta_a(\check{u},t)\zeta^*_b(\check{u}',t')\rangle=2\mathrm{kT}\gamma g_{ab}\frac{\delta(\check{u}-\check{u}')}{\sqrt{g}}\delta(t-t').\end{aligned} \tag{23}$$

The dynamics of the lipid density Ψ in the 3D solvent is described by a convection-diffusion equation in the membrane frame of reference:

$$\partial_t\Psi+\mathbf{v}_s(\mathbf{r},t)\cdot\boldsymbol{\nabla}\Psi=D\Delta\Psi+\boldsymbol{\nabla}\cdot\boldsymbol{\zeta}_\Psi, \tag{24}$$

where D is a diffusion coefficient and $\boldsymbol{\zeta}_\Psi$ is random source of diffusion related to dissipation in bulk through the generalized fluctuation-dissipation theorem:

$$\begin{aligned}&\langle\boldsymbol{\zeta}_\Psi(\mathbf{r},t)\rangle=\mathbf{0},\\&\langle\zeta_{\Psi i}(\mathbf{r},t)\,\zeta^*_{\Psi j}(\mathbf{r}',t')\rangle=2\Psi_r D\delta_{ij}\delta(\mathbf{r}-\mathbf{r}')\delta(t-t').\end{aligned} \tag{25}$$

Eventually, the lipid currents at the membrane verify the continuity conditions $J_n^{\pm}=(\Psi^{\pm}\mathbf{v}_s-D\boldsymbol{\nabla}\Psi^{\pm})\cdot\mathbf{n}\big|_{\mathbf{r}=\mathbf{R}(\check{u})}$, which express the coupling between the bulk and the membrane. Equations (7) to (25) constitute a complete set, which can in principle allow us to describe any dynamical behavior of a membrane submitted to specific initial and boundary conditions.

As an example, we consider the stationary behavior of a membrane, driven out of equilibrium by an osmotic-pressure difference $\Delta\Pi^0$. The pressure and chemical potential are kept identical on both sides of the membrane ($\Delta P=0$; $\Delta\mu^{\pm}(z\to\pm\infty,T,P,\Psi_r)=0$). If $\Delta\Pi^0=0$, the system evolves toward equilibrium with $\sigma=0$ and $\phi=\phi_0$. If $\Delta\Pi^0=0$ and the chemical potential in the membrane is determined by the chemical potential of the phospholipids in the Plateau borders and consequently $\Delta\tilde{\mu}\neq 0$, the membrane density evolves quickly towards ϕ_e and $\sigma\neq 0$ is determined by equation (5). When $\Delta\Pi^0\neq 0$, there is no bulk lipid flux, in the fluid reference frame. However, in the membrane reference frame, both a hydrodynamic flow and a lipid flow are generated. From the continuity relations, we obtain a lipid flow

$$J_n^-=J_n^+=\Psi_r v_{sz}(z=0). \tag{26}$$

Note that in the fluid reference frame, the membrane moves with a velocity $v_m=-v_{sz}(z=0)$. The lipid concentration $\Psi(z)$ is constant on the downstream side and exhibits an exponential variation over a length scale

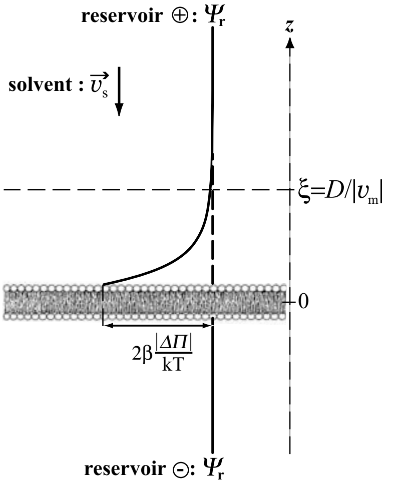

Fig. 2. Schematic 3D density profile of the flat membrane with a hydrodynamic flow $v_{s\,z} = -v_m$. The particles density of section ($z > 0$) changes on a characteristic length $\xi = |D/v_m|$.

$\xi = |D/v_m|$ on the upstream side, as shown in Figure 2. For instance for $v_m > 0$, the stationary state is given by $\Psi^+(z) = \Psi_r - (2\beta\Delta\Pi/\mathrm{kT})\exp(-v_m z/D)$ and $\Psi^-(z) = \Psi_r$, with $\beta = (\lambda_p - \Lambda)/(\lambda - 2\Lambda)$. Therefore, the difference in lipid concentration on each side of the membrane contributes to the osmotic pressure $\Delta\Pi = \Delta\Pi^0/(1+2\beta)$. Using the expression (26) of the lipid flow in equation (14) and adding the two last lines of this equation system, we obtain a fluid flow through the membrane given by

$$v_{s\,z}(z=0) = \lambda_p^e \Delta\Pi^0\,, \quad \text{with } \lambda_p^e = \frac{\lambda_p\lambda - 2\Lambda^2}{2\lambda_p + \lambda - 4\Lambda}. \tag{27}$$

Relation (27) expresses the fact that the lipid flux modifies the fluid flow through the membrane. The effective permeation coefficient λ_p^e is always positive since $\lambda_p\lambda - 2\Lambda^2 > 0$ and $2\lambda_p + \lambda - 4\Lambda > 0$, both inequalities being required by the stability condition of the Onsager matrix. The difference between λ_p and λ_p^e in lipid systems has not been measured, to our knowledge. The experimentally measured quantity is λ_p^e. According to equation (27), it is always smaller than λ_p. If the rate of lipid uptake is large ($\lambda \gg \lambda_p,\ \Lambda$), the lipid exchange does not perturb the fluid flow through the membrane and $\lambda_p^e \simeq \lambda_p$. If the rate of lipid uptake is very slow ($\lambda_p \gg \lambda,\ \Lambda$), the osmotic-pressure difference across the membrane $\Delta\Pi$ is strongly reduced compared to $\Delta\Pi^0$, and $\lambda_p^e \simeq \lambda/2 \ll \lambda_p$. The experimental value of λ_p^e (10^{-13}–$10^{-12}\,\mathrm{m^3/N\cdot s}$ in [23]) is extremely small. This could be due to such an effect but there is currently no proof that this is the case. For $\Delta\tilde{\mu} = 0$, this solution corresponds to a true steady state. For conditions where chemical potentials are buffered by Plateau borders, $\Delta\tilde{\mu} \neq 0$, it correctly describes the short-time behaviour ($t < \tau = \eta L/\sigma$).

We can remark that there is no bulk lipid flux although there is exchange of lipids between the membrane and the 3D embedding fluid. From the relations (14) and (27), the stationary condition imposes that the 2D density attains a uniform value given by

$$\phi_{\mathrm{stat}} = \phi_0 + \frac{\beta}{\chi\Psi_r(1+2\beta)}|\Delta\Pi^0|. \tag{28}$$

The fact that the change in membrane density is non-analytic in $\Delta\Pi^0$ may look surprising at first sight. It results from the fact that irrespective of the sign of $\Delta\Pi^0$, there is an increase of the three-dimensional concentration Ψ on one side of the membrane.

For nearly flat surfaces, we can describe the membrane fluctuations in the Monge representation by the height $h(\mathbf{x})$ of the surface above a Euclidean base plane[2]. It is convenient to perform a Fourier transformation parallel to the membrane plane defined by $f_q(t) = \int \mathrm{d}^2\mathbf{x}\,\mathrm{e}^{i\mathbf{q}\cdot\mathbf{x}} f(\mathbf{x},t)$ with $q = \sqrt{q_x^2 + q_y^2}$. After assuming an e^{st} time dependence of the height and density variables, we obtain, in momentum space, the following noiseless linear dynamics:

$$s\begin{pmatrix} h_q \\ \delta\phi_q \end{pmatrix} = \boldsymbol{\mathcal{M}}(s,q)\begin{pmatrix} h_q \\ \delta\phi_q \end{pmatrix} \tag{29}$$

in which $\delta\phi = \phi - \phi_{\mathrm{stat}}$. The dynamical matrix $\boldsymbol{\mathcal{M}}(s,q) = (m_{ij})$ is defined by its components:

$$\begin{cases} m_{11} \simeq \left(2\bar{\Lambda}A^+(s,q) - 1\right)\dfrac{\sigma^e q + \kappa q^3}{4\eta}, \\ m_{12} = 2\chi\Lambda\Psi_r A^-(s,q), \\ m_{21} = 2\Psi_r A^-(s,q)\left(\Lambda + \dfrac{1}{4\eta q}\right)(\sigma^e q^2 + \kappa q^4) - \phi_0 v_m q^2, \\ m_{22} = -2\chi\lambda\Psi_r^2\left(1 - A^+(s,q)\right) - \chi\phi_0\dfrac{q}{4\eta}, \end{cases} \tag{30}$$

where we have taken advantage of the fact that $1/4\eta q \gg \lambda_p^e, \Lambda, 1/\gamma$ in the range of validity of the theory. We have defined

$$\begin{cases} A^\pm(s,q) = \frac{1}{2}\left(\frac{1}{1+B^+(s,q)} \pm \frac{1}{1-B^-(s,q)}\right), \\ B^\pm(s,q) = v_m(-1 \pm \sqrt{1 + 4\xi^2(s/D + q^2)})/2v_1, \\ \quad v_1 \quad = \mathrm{kT}\lambda\Psi_r, \\ \quad \sigma^e \quad = \sigma - \phi_0\beta|\Delta\Pi|/\Psi_r, \\ \quad \bar{\Lambda} \quad = \Lambda/\lambda. \end{cases} \tag{31}$$

For the slowest mode at vanishingly small q, we find

$$s_1 \simeq -\sigma^e q/4\eta^e, \text{ with } \eta^e = \eta/(1 - 2\bar{\Lambda}). \tag{32}$$

It describes membrane undulations in the tension controlled regime. Similar results are obtained in Langmuir films [24,25] and conserved membrane dynamics [17]. The effective viscosity is always larger than the fluid viscosity. It arises since the couplings described by equation (15) introduce extra dissipation. This mode becomes unstable

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[2] In this case, $\tilde{u} \equiv \mathbf{x} = (x,y)$ and $\mathbf{R}(\mathbf{x}) = (\mathbf{x}, h(\mathbf{x}))$.

when σ^e changes sign that is in the Plateau border case at a critical osmotic-pressure difference:

$$|\Delta\Pi_c^0| = (1+2\beta)\sigma\Psi_r/\beta\phi_0 \,. \tag{33}$$

The corresponding instability in Langmuir films due to a direct compression of the film is called "buckling" instability in analogy with the buckling of beams. In the absence of Plateau borders, the mode is always unstable since then $\Delta\Pi_c^0$ vanishes. Keeping higher order terms in q, up to third order leads to

$$s_1 \simeq -(\sigma^e q + \kappa q^3)/4\eta^e + O((\Delta\Pi^0)^2). \tag{34}$$

Terms quadratic in q do exist. Their prefactor is linear in $\Delta\Pi^0$; anticipating $q \sim (\Delta\Pi^0)^{1/2}$ (see below), we find that this term contribute to s_1 as $(\Delta\Pi^0)^2$, small compared to the other terms which scale as $(\Delta\Pi^0)^{3/2}$.

In the unstable case, the fastest growing mode will appear with wave vector $q_g = \sqrt{-\sigma^e/3\kappa}$, on a time scale $\tau = s_1^{-1}(q_g) = \eta^e\kappa^{1/2}/(-\sigma^e/3)^{3/2}$. At threshold $\sigma^e = 0$, and the mode is controlled like in the buckling instability by lateral boundary conditions. However, it is very likely that $(-\sigma^e)$ keeps on growing to significantly non-vanishing values. We leave a more detailed analysis for further developments. All modes can be directly calculated from the equation $\det(\boldsymbol{\mathcal{M}}(s,q) - s\mathbb{1}_2) = 0$. After subtracting s_1, power counting allows to infer that there are four additional modes $s_i(q)$, $i \in [2,5]$ which have all a non-vanishing value at $q = 0$. It is possible to obtain analytical solutions in the latter case, but they are not very illuminating. They can be either complex or real depending on parameters, but in all cases their real part is negative. For non-zero q and real $s_i(q)$, it is possible to show analytically that $s_i(q)$ is always negative. In the complex case numerical analysis suggests that the real part of $s(q)$ is always negative. We thus conclude that these four modes are always stable. They correspond to exchanges of lipid between the membrane and the embedding fluid on both sides, and permeation flow. The assumption of exponential time dependance requires particular z distributions of the Ψ fluctuations on both sides of the membrane. The time dependance could be more complex for general types of Ψ fluctuations but there is not more physics to be learned from the general case.

Taking into account the influence of thermal noise in the dynamic equations, we can calculate the equal-time height fluctuations about this homogenous steady states. To that end, we first Fourier transform the variables in space and time, and integrate the correlator with respect to frequency ω to obtain

$$\langle h_q(t)h_q^*(t)\rangle \simeq \frac{\mathrm{kT}\left(1+\frac{\Lambda^2 v_1}{\lambda_p\lambda(v_1+v_m)}\right)}{\frac{\lambda-\Lambda}{\lambda-2\Lambda}\left(1-\frac{\Lambda^2}{\lambda\lambda_p}\right)\sigma^e q^2}. \tag{35}$$

The fluctuation spectrum does not reduce to the usual $1/q^4$ spectrum of a passive membrane but the exchanges of particles with the surrounding fluid induces a tension σ_{ind} proportional to kinetic parameters and the osmotic-pressure difference:

$$\sigma_{\mathrm{ind}} = \frac{(\lambda-\Lambda)\left(1-\Lambda^2/\lambda\lambda_p\right)}{(\lambda-2\Lambda)\left(1+\Lambda^2 v_1/\lambda_p\lambda(v_1+v_m)\right)}\sigma^e. \tag{36}$$

The fact that the induced tension is dependent on kinetic parameter shows that the fluctuation-dissipation theorem is not verified and that non-equilibrium fluctuations are produced by exchange phenomena. We can also notice that if both the osmotic-pressure difference and the linkage parameter vanish ($\Delta\Pi^0 = 0$ and $\Lambda = 0$), then the variance of height fluctuations approaches that of a tense membrane, *i.e.* $\langle |h_q(t)|^2\rangle \simeq \mathrm{kT}/\sigma q^2$ at small q.

Following the same steps, we find the following correlation function for the density difference field:

$$\langle \delta\phi_q(t)\delta\phi_q^*(t)\rangle \simeq \frac{\mathrm{kT}}{\chi}\left(1+\frac{3v_1}{2(v_m+v_1)}\right). \tag{37}$$

4 Discussion

The equations we have introduced in this work involve only two new parameters as compared to earlier one-component membrane descriptions, namely the rate at which phospholipids may be incorporated in the membrane, and the associated fluid flow. It would be highly interesting to measure these parameters. A conceptually simple experiment would be to work with a membrane without Plateau borders, and maintained at constant tension. Such an experiment is currently being set [26]. The area increase as a function of time, under conditions in which the chemical potential difference between the membrane and the bulk are controlled, would provide a direct measure of λ. The measurement of the off-diagonal coefficient would be more tricky. The best is certainly to extract the effective viscosity η^e from the study of the membrane undulation mode according to equations (32, 34) and compare it to the fluid viscosity η. The values of the permeation coefficients we have to date are effective permeation coefficients as defined by equation (27): this is enough to obtain a complete set of measurements for λ, Λ and λ_p. We would then be in a position to deal in a fully quantitative way with situations in which membranes are exchanging material with the bulk. As an example we have looked at the mode structure of a membrane submitted to an osmotic-pressure difference only. In practice, this could be done by maintaining salt concentration differences between the two sides of the membrane: ions are highly insoluble in phospholipid membranes and should not interfere with the membrane state, thus defining $\Delta\Pi^0$ only. We have assumed that the hydrostatic-pressure difference was kept small over the time scales of the experiment. This is clearly possible when the fluid reservoirs have a free surface. We show in Appendix A that this timescale is of the order of $t \simeq (S/S_m)/\rho g\lambda_p^e$ where S and S_m are, respectively, the area of the bulk fluid free surface and of the membrane, ρ the fluid density and g the gravitational acceleration. Since $1/\rho g\lambda_p^e \simeq 10^8$ s under most practical circumstances the pressure difference is indeed negligeable.

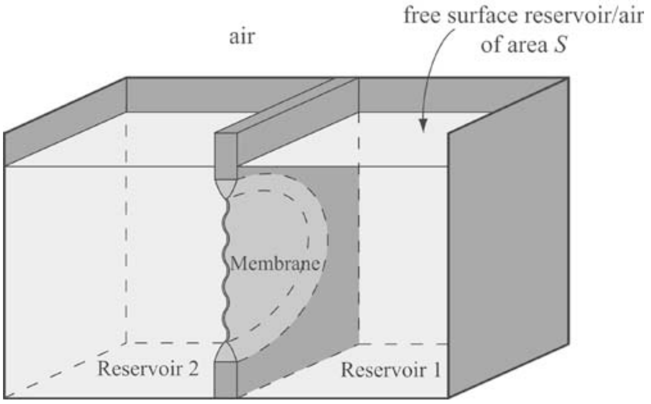

Fig. 3. Schematic section of a membrane which covers a small hole and separates two bulk reservoirs in contact with air.

It is useful to check if the critical osmotic-pressure difference can be reached experimentally when the membrane chemical potential is set by the Plateau borders. The lamellar structure of the Plateau border with interlayer distance d provides an estimate of the tension σ_{imp} imposed on the membrane: $\sigma_{\mathrm{imp}} \simeq \mathrm{kT}/d^2$. Introducing the average distance ℓ_b between phospholipids in the bulk such that $\Psi_r = 1/\ell_b^3$, and the average lateral distance between phospholipids in the membrane ℓ_m such that $\phi_0 = 1/\ell_m^2$, we get

$$|\Delta\Pi_c^0| \simeq \left(\frac{\mathrm{kT}}{\ell_b^3}\right)\left(\frac{\ell_m}{d}\right)^2 \ll \left(\frac{\mathrm{kT}}{\ell_b^3}\right) = \Pi \qquad (38)$$

since $\ell_m \ll d$. Π is the osmotic pressure due to phospholipids in the fluid. It is thus clear that the critical value for triggering the instability is easily accessible to experiment.

One may wonder why we do not find in our analysis an other instability reminiscent of the one described by Rao *et al.* [15]. This instability arises from a coupling between membrane local velocity and curvature. If we express the first line of equation (14), we find

$$\mathbf{v}(\check{u},t) - \mathbf{v}_s(\mathbf{R},t) = -\lambda_p \Delta\Pi + \Lambda\Psi_r(\Delta\mu^+ - \Delta\mu^-) \qquad (39)$$

any reference to the curvature state, which is contained in the membrane chemical potential $\Delta\mu(\check{u},t)$ disappears from the equations because of the symmetry of membrane at rest. However, in steady state the two sides of the membrane are not equivalent since they experience different phospholipid concentrations. The off-diagonal components should really read $\Lambda(\Psi_r + \beta\Delta\Pi/\mathrm{kT})$ on the plus side, and $\Lambda\Psi_r$ on the minus side (keeping the same conventions as before). Then, relation (39) reads

$$\begin{aligned}\mathbf{v}(\check{u},t) - \mathbf{v}_s(\mathbf{R},t) = &- \lambda_p \Delta\Pi + \Lambda\Psi_r(\Delta\mu^+ - \Delta\mu^-) \\ &- \Lambda\frac{\beta}{\mathrm{kT}}\Delta\Pi(\Delta\mu(\check{u},t) - \Delta\mu^+),\end{aligned} \qquad (40)$$

in which $\Delta\mu$ does depend on curvature. In the logic of equation (14), the expansion must be linear in the fields $\Delta\Pi$, $\Delta\mu$, etc..., and the last term of equation (40) must be omitted. However, in any extension to higher powers of $\Delta\Pi$, such a term should be retained and provided Λ has the appropriate sign it would be an instability source. One should however point out that many other non-linearities would have to be retained in order to set up a fully consistent analysis.

At last, conditions under which the chemical potentials $\Delta\mu^\pm$ are set different far from the membrane could be worked out as well. They cannot lead to steady-state situations, and we postpone their study for future work.

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Appendix A. Experimental application

Consider an experimental case in which a membrane separates two bulk reservoirs in contact with air via a free surface, each of area S (see Fig. 3). At the free surface the hydrostatic pressure is continuous and any hydrostatic-pressure discontinuity at the membrane translates in a height difference δh of the free surfaces. The hydrostatic-pressure difference will cancel the osmotic-pressure difference when $\rho g \delta h = \Delta\Pi^0$. this requires a volume flow $\delta h S$ through the membrane. Knowing that the rate of volume flow is given by $v_{sz}S_m$, where S_m is the membrane area, we get immediately: $t \simeq (S/S_m)/\rho g \lambda_p^{\mathrm{e}}$.

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