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Fluctuation-magnification of non-equilibrium membranes near a wall

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Abstract. Membranes in thermal equilibrium are well known to exhibit Brownian motion type shape fluctuations. Membranes containing active force centers — such as chemically active membrane proteins — suffer additional non-equilibrium shape fluctuations due to the activity of these force centers. We demonstrate, using scaling arguments, that non-equilibrium shape fluctuations are in general greatly amplified by the presence of a nearby wall or membrane due to the absence of a fluctuation-dissipation theorem. For adhesive membranes, this fluctuation magnification effect may facilitate the establishment of bonding. For non-adhesive membranes, fluctuation magnification produces a long-range repulsive pressure which can exceed the well known Helfrich repulsion due to purely thermal fluctuations.

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1 Introduction

Membranes are flexible bilayers of surfactant molecules embedded in an (usually) aqueous medium. In biology they play a key role as partitioning walls of cells [1], but membranes have also been investigated extensively in the physics literature [2], mostly in the form of pure, single-component bilayers. Membranes of biological interest differ from single-component bilayers in a number of ways. From the view-point of statistical physics, the most fundamental difference lies in the fact that biomembranes in general contain large numbers of *chemically active* centers ("force centers") which dissipate energy. Examples are membrane proteins like ion channels, ion pumps, or photo-active membrane proteins. Biomembranes can also be attached to actin-myosin fibers which exert localized forces. The chemical activity dissipates energy provided by ATP to ADP conversion, concentration gradients, or an external light source. The equilibrium thermodynamic properties of the single-component membrane are well explained on the basis of an effective elastic free energy: the Helfrich Hamiltonian [3]. One of the most striking predictions of this theory involves the role played by thermal fluctuations when membranes interact with each other or with hard walls [4]. A membrane that is not under tension and in between a pair of walls feels a repulsive pressure $P(d)$ due to the loss of configurational entropy suffered by the confinement of the membrane. It is of the order of

$$P(d) \cong \frac{(k_{\mathrm{B}}T)^2}{\kappa d^3} \tag{1.1}$$

with κ the bending modulus of the membrane, and d the spacing between the walls. Because of the power-law dependence, this "entropic" interaction dominates — for dilute systems — over short-range membrane forces like the screened Coulomb interaction. Detailed X-ray synchrotron studies [5] of aligned stacks of surfactant bilayers ("L_α" phase) have confirmed equation (1.1) for dilute systems. Membranes adhering to a wall through an attractive force — like the van der Waals interaction — are normally under tension. Entropic repulsion between a wall and a tense membrane is not long ranged and decays exponentially as

$$P(d) \cong \exp\left(-\alpha \frac{\gamma d^2}{k_{\mathrm{B}}T}\right) \tag{1.2}$$

with α a numerical constant and γ the membrane tension.

An intuitively appealing way of arriving at equations (1.1, 1.2) is by introducing the concept of membrane-wall "collisions" [6,7]. Every time a membrane is in contact with a wall, it loses of order $k_{\mathrm{B}}T$ in entropic free energy. The free-energy increase per unit area $V(d)$, due to the confinement between the plates, is then:

$$V(d) \propto \frac{k_{\mathrm{B}}T}{L_{\mathrm{c}}^2(d)} \tag{1.3}$$

with $L_{\mathrm{c}}^{-2}(d)$ the area concentration of the collisions. The collision length L_{c}, *i.e.* the mean spacing between collisions, is then found by computing the mean square $\langle u^2(L)\rangle$

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of membrane height fluctuations of an L by L patch of *unconfined* membrane:

$$\langle u^2(L)\rangle \propto \begin{cases} \left(\frac{k_{\rm B}T}{\kappa}\right) L^2 & \gamma = 0 \\ \left(\frac{k_{\rm B}T}{\gamma}\right) \ln(L/a) & \gamma \neq 0 \end{cases} \quad (1.4)$$

where a is a microscopic length scale. The collision length is now the patch size for which $\langle u^2(L_{\rm c})\rangle \approx d^2$ since beyond that length the patch senses the presence of the wall. This argument gives:

$$L_{\rm c}(d) \propto \begin{cases} \sqrt{\frac{\kappa}{k_{\rm B}T}} d & \gamma = 0 \\ a \exp(\text{const.}\gamma d^2/k_{\rm B}T) & \gamma \neq 0. \end{cases} \quad (1.5)$$

Note that we are implicitly assuming in equation (1.4) that the height correlation function is not affected by the wall for length scales less than the collision length. Using equations (1.4) and (1.5) in equation (1.3) leads to equations (1.1, 1.2). Equation (1.1) also can be derived by minimization of the free energy of confinement [4].

The arguments used to compute the wall force crucially depend on the applicability of equilibrium statistical mechanics. However, we are not allowed to assume that an active membrane, *i.e.* a membrane containing active centers, evolves spontaneously to a state which minimizes the free energy, so there is no variational principle available any longer and we should not expect equation (1.1) or (1.2) to be valid. In this article, we examine the interaction between an active membrane and a wall in the following special case: the active membrane is in *steady-state*. We thus assume that the average shape and structure of the membrane are not evolving in time. This assumption allows us to study the equal-time correlation function $\langle u^2(L)\rangle$ of active membranes, which played such an important role for the equilibrium behavior of membranes. However, as shown in an earlier paper [8], the height correlation function $\langle u^2(L)\rangle$ is no longer given by equation (1.4) but, in general, depends on kinetic parameters like the solvent viscosity, the membrane permeability, the diffusion constant and the autocorrelation time of the force centers.

Of particular importance for the following is the role of *hydrodynamic interaction*. For a membrane in thermal equilibrium, we are guaranteed by the fluctuation-dissipation theorem that we do not need to be concerned about membrane-wall interaction mediated by the solvent, since the equal-time correlation functions cannot depend on the solvent viscosity. For a non-equilibrium membrane, the fluctuation-dissipation theorem does not apply and, in general, we cannot neglect long-range hydrodynamic interactions mediated by the solvent: a non-equilibrium membrane can interact hydrodynamically with a wall. Hydrodynamic coupling between a membrane and a wall puts the concept of sharp membrane-wall collision into question: the interaction between a membrane immersed in solvent and a wall is obviously "spread-out" rather than localized to a small region of contact.

A direct calculation of the hydrodynamic interaction between a membrane and a wall is a rather complex problem: the Helfrich wall force is qualitatively similar to osmotic pressure, and a kinetic (*i.e.* hydrodynamic) derivation of the equilibrium osmotic pressure of solutions (van't Hoff's Law) remains a long- standing unsolved problem [9]. Instead, we propose in this paper a scaling description of the equal-time correlation function and of the wall force for steady-state active membranes in embedding solvents. In the infinite medium limit, this scaling procedure reproduces the known results for membranes in thermal equilibrium, while for active membranes it reproduces the results of [8]. For a membrane fluctuating near a wall, our procedure predicts that the non-equilibrium height correlation function $\langle u^2(L)\rangle$ is amplified. The amplification factor depends on the nature of the noise and on whether or not the membrane is under tension:

	Tense	Tensionless
Shot-noise	$(L/d)^3$	$(L/d)^3$
Concentration Fluctuations	$(L/d)^6$	$(L/d)^3$

(concentration fluctuations are force fluctuations exerted on the membrane due to fluctuations in the concentration of active force centers). Fluctuation amplification is a direct consequence of the absence of a fluctuation-dissipation theorem. The amplitude of non-equilibrium force fluctuations is not directly affected by the wall. However, a nearby wall is well known to greatly decrease the relaxation rate of membranes. The net effect is an amplification of the membrane shape fluctuations. For equilibrium membranes, the fluctuation-dissipation theorem guarantees that reduced relaxation rates are off-set by reduced effective thermal noise amplitudes.

Fluctuation amplification can have different consequences depending on whether the membrane interacts with the wall (or another membrane) *via* repulsive (non-adhesive membrane) or attractive (adhesive membrane) interactions. For non-adhesive membranes, the amplification effect produces a new wall force:

$$P(d) \propto P_0 \left(\frac{\delta}{d}\right)^{\alpha} \quad (1.6)$$

	Tense	Tensionless
Shot-noise	$\alpha = 6$	$\alpha = 7/2$
Concentration Fluctuations	$\alpha = 4/3$	$\alpha = 1$

with P_0 local pressures and δ length scales to be specified later (validity restrictions on these results are given

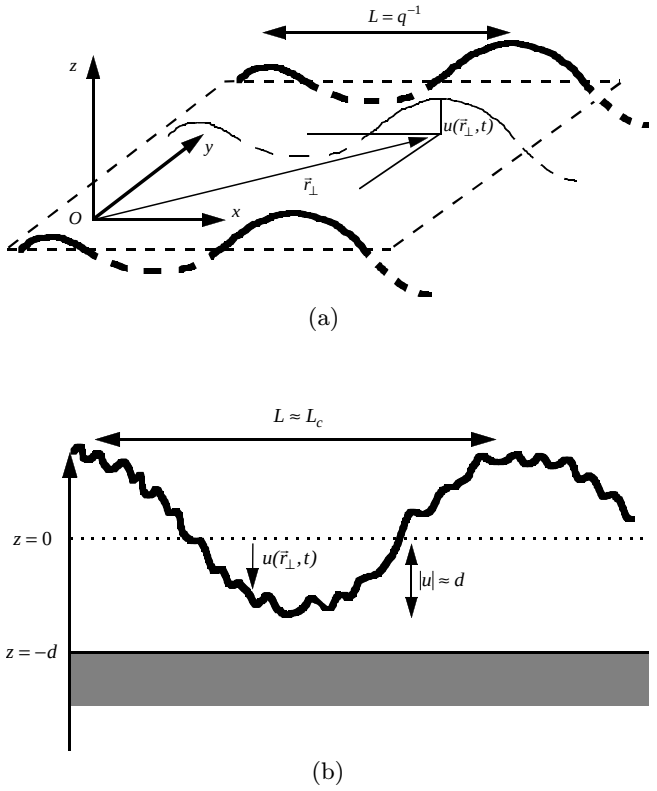

Fig. 1. Definition of the notations used in the text: (a) without wall, (b) with wall: note that the "collision" length L_c does not correspond to real physical collisions.

in Sect. 4). The non-equilibrium contribution to the wall force exceeds the Helfrich force in the large d limit for the case of concentration fluctuations.

For adhesive membranes, fluctuation magnification should have a surprising effect: two adhesive membranes approaching each other should first increase their fluctuation amplitude, as if they were "searching" for each other. The increased fluctuation amplitude could then produce contact followed by establishment of an adhesive link between the two membranes. Fluctuation enhancement could thus play an important role in cell-cell interaction.

2 Membrane dynamics

2.1 Equation of motion

We characterize the geometrical shape of a fluctuating membrane by the time-dependent displacement $u(\mathbf{r}_\perp, t)$ of the membrane above a surface (the $x-y$ plane) along the normal (z-direction), with $\mathbf{r}_\perp$ the position vector in the $x-y$ plane (Fig. 1a). The membrane is embedded in a solvent which is able to permeate the membrane. We assume that the solvent does not contain any impermeable solute molecules and we do not consider any osmotic pressure differences across the membrane. The solvent of viscosity η is supposed to be incompressible. The solvent flow is characterized by the hydrodynamic flow velocity field $\mathbf{v}(\mathbf{r}, t)$. To the lowest order in $u(\mathbf{r}_\perp, t)$ (and its gradients), the elastic free energy of the membrane is given by:

$$F_{\mathrm{H}} = \int \mathrm{d}^2 r_\perp \left\{ \frac{1}{2}\gamma(\nabla_\perp u)^2 + \frac{1}{2}\kappa(\nabla_\perp^2 u)^2 \right\} \tag{2.1}$$

with γ the tension and κ the Helfrich bending energy. The linearized hydrodynamic equations of motion of the membrane and solvent are:

$$\frac{\partial u(\mathbf{r}_\perp, t)}{\partial t} - v_z(\mathbf{r}_\perp, z=0, t) = \lambda_{\mathrm{p}}\{\delta P(\mathbf{r}_\perp, t) + f_{\mathrm{p}}(\mathbf{r}_\perp, t) + f_{\mathrm{a}}(\mathbf{r}_\perp, t)\} \tag{2.2a}$$

$$\eta\nabla^2 \mathbf{v}(\mathbf{r}, t) = \boldsymbol{\nabla} P(\mathbf{r}, t) + \frac{\delta F_{\mathrm{H}}}{\delta u(\mathbf{r}, t)}\delta(z)\hat{\mathbf{z}} + \mathbf{f}_{\mathrm{h}}(\mathbf{r}, t) \tag{2.2b}$$

$$\nabla \cdot \mathbf{v}(\mathbf{r}, t) = 0. \tag{2.2c}$$

Equation (2.2a) represents Darcy's law for the permeation of the solvent through the membrane. The left-hand side is the relative flow velocity between the membrane and the solvent. It measures the solvent volume flow per unit area permeating the membrane, which, according to Darcy's law, must be proportional to the force per unit area exerted on the membrane. The proportionality constant, λ_{p}, is the membrane permeability. The quantity in brackets on the right-hand side is the force per unit area. The first term, δP, is the discontinuity of the hydrodynamic pressure $P(\mathbf{r}, t)$ across the membrane (recall that we are excluding osmotic pressure discontinuities). The second contribution, f_{p}, represents the contribution to the force per unit area due to equilibrium thermal fluctuations. According to the fluctuation-dissipation theorem:

$$\langle f_{\mathrm{p}}(\mathbf{r}_\perp, t)\rangle = 0 \tag{2.3a}$$

$$\langle f_{\mathrm{p}}(\mathbf{r}_\perp, t) f_{\mathrm{p}}(\mathbf{r}'_\perp, t')\rangle = 2k_{\mathrm{B}}T\lambda_{\mathrm{p}}^{-1}\delta(\mathbf{r}_\perp - \mathbf{r}'_\perp)\delta(t-t'). \tag{2.3b}$$

The final contribution, f_{a}, is the force due to the active centers and will be specified below.

Equation (2.2b) is the Stokes equation for an incompressible solvent at low Reynolds number. The quantity on the right-hand side of equation (2.2b) is the force per unit volume exerted on the solvent. The first term is the usual hydrodynamic pressure gradient. To understand the second term, note that $\frac{\delta F_{\mathrm{H}}}{\delta u(\mathbf{r},t)}$ is the (elastic) force per unit area exerted by the membrane on the solvent along the membrane normal (z-direction) since F_{H} is the membrane free energy per unit area. The last term in brackets, $\mathbf{f}_{\mathrm{h}}$, is the force density exerted on the solvent due to equilibrium thermal fluctuations. From the fluctuation-dissipation theorem it follows that:

$$\langle \mathbf{f}_{\mathrm{h}}(\mathbf{r}, t)\rangle = 0 \tag{2.4a}$$

$$\langle \mathbf{f}_{\mathrm{h}}(\mathbf{r}, t)_i \mathbf{f}_{\mathrm{h}}(\mathbf{r}', t')_j\rangle = -2k_{\mathrm{B}}T\eta\{-\delta_{ij}\nabla^2 + \partial_i\partial_j\} \times \delta(\mathbf{r}-\mathbf{r}')\delta(t-t'). \tag{2.4b}$$

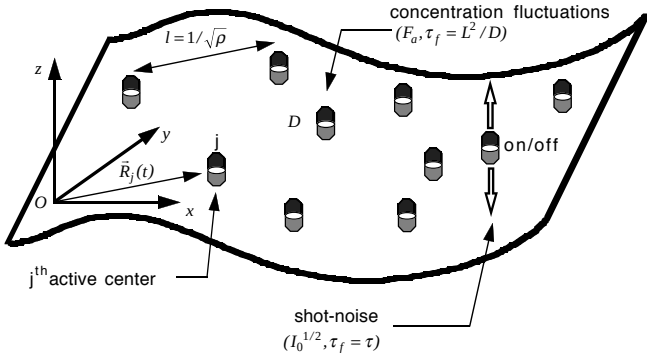

Fig. 2. Schematic representation of a membrane with active force centers.

There is no non-equilibrium contribution to the force density in the Stokes equation, because we are considering here only intrinsic active centers, such as membrane-associated proteins or embedded proteins not attached to the cytoskeleton. By Newton's Third law, intrinsic active centers cannot exert a net force on the solvent (although there is a zero-average localized area force profile surrounding an active membrane protein, which we are not including). If the cytoskeleton was exerting a force on the membrane then its contribution would appear in the right-hand side of equation (2.2b). Finally, note that if we integrate equation (2.2b) along the z-direction across a thin slab containing the membrane we find for the pressure discontinuity:

$$\delta P(\mathbf{r}_\perp, t) \cong -\frac{\delta F_{\rm H}}{\delta u\left((\mathbf{r}_\perp, t)\right)} = \gamma \nabla_\perp^2 u - \kappa \nabla_\perp^4 u \tag{2.5}$$

which simply states that the membrane is in local mechanical equilibrium (for tensionless membranes, $\gamma = 0$ in Eq. (2.5)).

Equation (2.2c) is the usual mass conservation equation for an incompressible flow.

We have now to specify the nature of the active force centers. The linearized hydrodynamic equations of motion described above followed from an application of general hydrodynamic principles to membranes, and are valid at long length and time scales under the conditions stated (provided we can neglect non-linear terms). However, we are forced to make more specific assumptions concerning the nature of the force centers. We assume that the membrane patch contains $n_{\rm f}$ active centers localized at positions $\mathbf{r}_\perp = \mathbf{R}_j(t)$ with $j = 1, 2, ..., n_{\rm f}$ (Fig. 2). Each center exerts a force $F_j(t)$, the "firing sequence", with

$$\begin{aligned} \langle F_j(t) \rangle &= F_{\rm a} \\ \langle F_j(t) F_{j'}(t') \rangle &= F_{\rm a}^2 + \delta_{j,j'} I(t - t') \end{aligned} \tag{2.6}$$

where $F_{\rm a}$ is the time-averaged mean force per center, and $I(t)$ the autocorrelation function of the firing sequence (the mean force $F_{\rm a}$ is non zero because the activity of membrane proteins is usually asymmetric across the lipid bilayer). We assume that there is no correlation in the firing sequences of different centers. If the firing of the force centers occurs with a certain random probability over a certain time interval, then:

$$I(t) = I_0 {\rm e}^{-t/\tau} \tag{2.7}$$

with τ the autocorrelation time. (For ion channels the above set of assumptions is known as the Stevens' model). Finally, we also assume that the force centers freely diffuse inside the membrane. The area force density $f_{\rm a}$ on the membrane due to the $n_{\rm f}$ active centers is then given by:

$$f_{\rm a}(\mathbf{r}_\perp, t) = \sum_{j=1}^{n_{\rm f}} F_j(t) \delta(\mathbf{r}_\perp - \mathbf{R}_j(t)) \tag{2.8}$$

and has the following correlation function:

$$\begin{aligned} &\langle f_{\rm a}(\mathbf{r}_\perp, t) \rangle = \rho F_{\rm a} \\ &\langle \tilde{f}_{\rm a}(\mathbf{r}_\perp, t) \tilde{f}_{\rm a}(\mathbf{r}'_\perp, t') \rangle = F_{\rm a}^2 G_{\rm c}(\mathbf{r}_\perp - \mathbf{r}'_\perp, t - t') \\ &\qquad + I(t - t') G_{\rm sp}(\mathbf{r}_\perp - \mathbf{r}'_\perp, t - t') \end{aligned} \tag{2.9}$$

where, ρ is the area density of the force centers, $\tilde{f}_{\rm a}(\mathbf{r}_\perp, t) = f_{\rm a}(\mathbf{r}_\perp, t) - \langle f_{\rm a}(\mathbf{r}_\perp, t) \rangle$, while $G_{\rm c}$ and $G_{\rm sp}$ are the collective and single-particle density correlation functions of the centers respectively. The first term on the right-hand side of equation (2.9) arises from area density fluctuations of the force centers (concentration noise), while the second term is due to the firing-noise of individual force centers (shot-noise). Assuming simple diffusion for the motion of the force centers gives:

$$G_{\rm c}(\mathbf{r}_\perp, t) \propto \frac{\rho}{Dt} {\rm e}^{-\mathbf{r}_\perp^2 / Dt} \tag{2.10}$$

with D the (collective) diffusion constant of the active centers. A similar formula applies to the single-particle correlation function.

2.2 Membrane Langevin equation: no wall

First consider the case of a membrane in an infinite embedding medium. A net force is applied to the membrane, such that the membrane would drift along the z-direction with a velocity $V = \lambda_{\rm p} \rho F_{\rm a}$. We assume that this net force is canceled by an external force and that the drift velocity is zero. This could be for instance achieved by maintaining a suitable pressure difference across the membrane. To find the steady-state shape fluctuations, we solve the linearized equations of motion by Fourier transformation. Define:

$$u(\mathbf{q}_\perp, t) = \int {\rm d}^2 r_\perp \, {\rm e}^{i \mathbf{q}_\perp \cdot \mathbf{r}_\perp} u(\mathbf{r}_\perp, t). \tag{2.11}$$

After Fourier transformation of equation (2.2) and elimination of the hydrodynamic flow field, we find the following Langevin equation for $u(\mathbf{q}_\perp, t)$:

$$\frac{\partial u(\mathbf{q}_\perp,t)}{\partial t} + \tau_{\rm m}^{-1}(\mathbf{q}_\perp)u(\mathbf{q}_\perp,t) = \lambda_{\rm p}\left\{f_{\rm p}(\mathbf{q}_\perp,t) + \frac{1}{2\pi\eta\lambda_{\rm p}}\int\frac{{\rm d}q_z}{q^2}\mathbf{f}_{\rm h}(\mathbf{q},t)\hat{\mathbf{z}} + f_{\rm a}(\mathbf{q}_\perp,t)\right\}\cdot \qquad (2.12)$$

The relaxation time $\tau_{\rm m}(\mathbf{q}_\perp)$ on the left-hand side of the Langevin equation is given by:

$$\tau_{\rm m}(\mathbf{q}_\perp)^{-1} = \left(\lambda_{\rm p} + \frac{1}{4\eta q_\perp}\right)(\gamma q_\perp^2 + \kappa q_\perp^4). \qquad (2.13)$$

If $\gamma = 0$ (no tension), in the long-wavelength limit, equation (2.13) reduces to the well-known result $\tau_{\rm m}(\mathbf{q}_\perp)^{-1} \propto \kappa q_\perp^3/\eta$ for relaxation by hydrodynamic flow of tensionless membranes. A cross-over to relaxation by permeation takes place when $q_\perp$ exceeds a value of order $1/(\lambda_{\rm p}\eta)$. The quantities $f_{\rm p}(\mathbf{q}_\perp,t)$, $\mathbf{f}_{\rm h}(\mathbf{q},t)$, and $f_{\rm a}(\mathbf{q}_\perp,t)$ on the right-hand side of equation (2.12) are the Fourier transforms of the three noise sources of equations (2.2) $f_{\rm p}(\mathbf{r}_\perp,t)$, $\mathbf{f}_{\rm h}(\mathbf{r},t)$, and $f_{\rm a}(\mathbf{r}_\perp,t)$ (we used the same notations for simplicity). Note the $1/q^2$ factor in the hydrodynamic noise term: the bulk noise contribution is weighted heavily towards long wavelengths. The Langevin equation (2.12) can be solved straightforwardly by Fourier transformation with respect to time and the height correlation function $\langle u^2(L)\rangle$ of the membrane can be computed using the noise-noise correlation functions specified above (as was done in [8]).

2.3 Membrane Langevin equation: with wall

We now place a wall parallel to the $x-y$ plane at a distance $z = -d$ of the mean position of the membrane $z = 0$ (Fig. 1b). As before, the drift velocity is zero and the net force per unit area $\rho F_{\rm a}$ applied on the membrane must be balanced, in steady state, by a suitable external force to which adds the repulsive wall force. A membrane near a wall can relax either by hydrodynamic flow or by permeation. Relaxation by flow is a conserved process, while relaxation by permeation is non-conserved. Consequently, for long wavelengths (*i.e.* $q_\perp \ll q^*$, where q^* will be specified later), permeation must be the dominant relaxation mechanism — especially for small d — while for shorter wavelengths (*i.e.* $q_\perp \gg q^*$), relaxation by flow must be dominant. We give in reference [10] a full derivation of the membrane hydrodynamics for any wavelength shorter than $L_{\rm c}$ and discuss here only the limiting cases. We first discuss the case of hydrodynamic relaxation.

2.3.1 Hydrodynamic relaxation ($\mathsf{q}_\perp \gg \mathsf{q}^*$)

In this regime, we assume that the contribution to relaxation by permeation is small. This does not mean that we can simply set the permeability coefficient to zero: because the active force centers only act through a permeative term in the equation of motion (see Eq. (2.12)), we must keep that term. We distinguish between two cases:

(i) $\mathsf{q}_\perp \gg 1/\mathsf{d}$

For $q_\perp$ large compared to $1/d$, membrane fluctuations are not expected to be significantly perturbed by the wall and we can still use the Langevin equation equation (2.12). The reason is that hydrodynamic relaxation involves flows near the membrane which decay within a distance of order $1/q_\perp$ of the membrane so that the presence of a wall at a distance d should not affect the relaxation provided $q_\perp \gg 1/d$.

(ii) $1/\mathsf{L}_{\rm c} \ll \mathsf{q}_\perp \ll 1/\mathsf{d}$

Long-wavelength fluctuations with $q_\perp \ll 1/d$ are clearly affected by the wall. To construct a Langevin equation in this regime, we use the lubrication approximation for the flow in the gap between the membrane and the wall. The lubrication approximation is used to describe flow in thin films or flow in the gap between two plates. In the lubrication approximation, we assume: a) that the spatial variation of the flow and the hydrodynamic pressure in the gap between the membrane and the wall is much more rapid along the z-direction than in the $x-y$ plane and b) that the flow is predominantly in the $x-y$ plane. We also assume no-slip boundary conditions on both the membrane and the wall.

Under these conditions and neglecting permeation, it is easy to demonstrate that the solvent current density $\mathbf{Q}$ is given by:

$$\mathbf{Q}(\mathbf{r}_\perp,t) = -\frac{1}{12}\frac{(d+u(\mathbf{r}_\perp,t))^3}{\eta}\nabla_\perp P(\mathbf{r}_\perp,t). \qquad (2.14)$$

The hydrodynamic pressure in the gap region is the sum of the elastic pressure $\frac{\delta F_{\rm H}}{\delta u(\mathbf{r}_\perp,t)}$ exerted by the membrane and of a contribution $\tilde{P}(\mathbf{r}_\perp,t)$ from equilibrium hydrodynamic fluctuations:

$$P(\mathbf{r}_\perp,t) = -\frac{\delta F_{\rm H}}{\delta u(\mathbf{r}_\perp,t)} + \tilde{P}(\mathbf{r}_\perp,t) \qquad (2.15)$$

(the non-equilibrium force centers cannot contribute to the pressure in the absence of permeation). The equation of motion for the membrane height variable is found by imposing conservation of solvent flow:

$$\frac{\partial u(\mathbf{r}_\perp,t)}{\partial t} + \boldsymbol{\nabla}\cdot\mathbf{Q}(\mathbf{r}_\perp,t) \approx \lambda_{\rm p} f_{\rm a}(\mathbf{r}_\perp,t). \qquad (2.16)$$

To be able to use Fourier transformation again, we must linearize equation (2.14) assuming that $|u(\mathbf{r}_\perp,t)| \ll d$. Linearization then leads to the following Langevin equation:

$$\frac{\partial u(\mathbf{q}_\perp,t)}{\partial t} + \tau_{\rm la}^{-1}(\mathbf{q}_\perp)u(\mathbf{q}_\perp,t) \cong \frac{d^3q_\perp^2}{\eta}\tilde{P}(\mathbf{q}_\perp,t) + \lambda_{\rm p} f_{\rm a}(\mathbf{q}_\perp,t) \qquad (2.17)$$

with

$$\tau_{\rm la}^{-1}(\mathbf{q}_\perp) = \frac{d^3}{12\eta} q_\perp^2(\gamma q_\perp^2 + \kappa q_\perp^4) \tag{2.18}$$

where $\tau_{\rm la}^{-1}$ is the membrane relaxation rate in the lubrication approximation. The q^6 dependence of the relaxation rate of a tensionless membrane in this limit has been first derived in [11].

So far we did not specify the correlation function of the pressure fluctuations. We determine this correlation function in the time-honored way by requiring that the equal time correlation function must reduce to the well-known equilibrium result for $f_{\rm a} = 0$:

$$\langle |u(\mathbf{q}_\perp)|^2 \rangle = \frac{k_{\rm B}T}{(\gamma q_\perp^2 + \kappa q_\perp^4)} \cdot \tag{2.19}$$

This is the case only if we impose the following noise correlation function:

$$\langle \tilde{P}(\mathbf{q}_\perp, t) \rangle = 0 \tag{2.20a}$$

$$\langle \tilde{P}(\mathbf{q}_\perp, t)\tilde{P}(\mathbf{q}'_\perp, t') \rangle \cong \frac{k_{\rm B}T\eta}{d^3 q_\perp^2} \delta(\mathbf{q}_\perp + \mathbf{q}'_\perp)\delta(t - t') \tag{2.20b}$$

(we left out a numerical prefactor on the right-hand side of Eq. (2.20b)).

The Langevin equation (2.17) is however not valid for arbitrarily small wavevectors. We saw in Section 1 that the collision length $L_{\rm c}$ is the lengthscale such that an $L_{\rm c}$ by $L_{\rm c}$ patch of membrane has an RMS displacement of order d around the mean value of the displacement ($\langle u \rangle = 0$ in our case). This means that if, at some position $\mathbf{r}_\perp = 0$, the membrane is at a distance of order d from the wall, then we should expect to encounter a "collision" of the membrane with the wall within an area of size $L_{\rm c}^2$ surrounding the point $\mathbf{r}_\perp = 0$. Note again that this is not a genuine collision, but rather a process where non-linearities become important. On lengthscales exceeding $L_{\rm c}$, the linearization condition $|u(\mathbf{r}_\perp, t)| \ll d$ is no longer valid, so the Langevin equation (2.17) holds provided we restrict to $q_\perp \gg 1/L_{\rm c}$.

2.3.2 Permeative relaxation ($\mathsf{q}_\perp \ll \mathsf{q}^*$)

We now assume that relaxation is by permeation. It is easy to show that in this regime the bulk relaxation rate for permeation (see Eq. (2.13)) is still valid:

$$\tau_{\rm per}(\mathbf{q}_\perp)^{-1} \approx \lambda_{\rm p}(\gamma q_\perp^2 + \kappa q_\perp^4). \tag{2.21}$$

Permeative relaxation does not require any hydrodynamic flow so it is not influenced by the presence of the wall. The Langevin equation of motion in this regime is:

$$\frac{\partial u(\mathbf{q}_\perp, t)}{\partial t} + \lambda_{\rm p}(\gamma q_\perp^2 + \kappa q_\perp^4) u(\mathbf{q}_\perp, t) \cong \lambda_{\rm p}(f_{\rm a}(\mathbf{q}_\perp, t) + f_{\rm p}(\mathbf{q}_\perp, t)). \tag{2.22}$$

By comparing the hydrodynamic relaxation rate (Eq. (2.18)) with the hydrodynamic relaxation rate (Eq. (2.21)), it is easy to show that permeative relaxation dominates over hydrodynamic relaxation for wavevectors $q_\perp \ll q^*$ with $q^* = \frac{\sqrt{\lambda_{\rm p}\eta}}{d^{3/2}}$.

2.4 Force rectification

To gain further insight into the nature of a collision between the membrane and a wall, and the effects of the neglected non-linear terms, let us consider the following model problem. Take an initially flat membrane at $z = 0$, and divide it into a checker-board of "black" and "white" patches, each of size L by L, with L large compared to d. The black patches are subjected to a force $F_{\rm b}$ along the $-z$-direction, driving the black patches towards a wall at $z = -d$, while the white patches are subjected to a constant force $F_{\rm w}$ along the $+z$-direction, driving the white patches away from the wall ($F_{\rm w}$ and $F_{\rm b}$ play here the role of force fluctuations on a lengthscale L). The square patches are allowed to move individually up or down but we demand that the average membrane position remains the same. Let $u_{\rm w}(t)$ be the displacement of the white patches and $u_{\rm b}(t)$ the displacement of the black patches.

The applied forces must overcome viscous losses due to the fluid flow from below the black patches. According to a well-known formula by Reynolds [12], the velocities of the squares are related to the applied forces by:

$$\frac{{\rm d}u_{\rm w}}{{\rm d}t} \cong \frac{(u_{\rm w} + d)^3}{\eta L^4} F_{\rm w}$$
$$\frac{{\rm d}u_{\rm b}}{{\rm d}t} \cong \frac{(u_{\rm b} + d)^3}{\eta L^4} F_{\rm b} \cdot \tag{2.23}$$

Solvent conservation requires that solvent volume flow from under the black patches equals the solvent volume flow to the columns below the white patches:

$$\frac{{\rm d}u_{\rm b}}{{\rm d}t} = -\frac{{\rm d}u_{\rm w}}{{\rm d}t} \tag{2.24}$$

at all times t, so $u_{\rm w} = -u_{\rm b} = u$. The shape fluctuations are symmetric and the average position of the membrane remains the same. Combining equations (2.23, 2.24) gives:

$$\frac{F_{\rm b}}{F_{\rm w}} = \frac{(d + u)^3}{(d - u)^3} \cdot \tag{2.25}$$

The mean force exerted by the membrane along the $-z$-direction is equal to $(F_{\rm b} - F_{\rm w})/2L^2$. By Newton's Third law, this is also the mean pressure P exerted by the wall on the membrane. If we now make the same linearization approximation as in the previous section and assume that $|u| \ll d$, we find that $F_{\rm b} = F_{\rm w}$: the up/down force fluctuations are symmetric so $P = 0$. The actual answer is:

$$P = F_{\rm w}\left(\frac{(d + u)^3}{(d - u)^3} - 1\right)/2L^2. \tag{2.26}$$

The effect of a wall on symmetric membrane shape fluctuations is thus to produce asymmetric force fluctuation, *i.e.* to rectify force fluctuations. On lengthscales L larger than d, this leads to a net pressure on the membrane by the wall, when u is of order d. It is these rectified force fluctuations which are the hydrodynamic basis of the Helfrich force (and its non-equilibrium variants).

A very similar force rectification is at work in the permeative regime. In that case, the pressure is osmotic rather than hydrodynamic. Impermeable chemical species trapped between the membrane and the wall produce a pressure on a membrane approaching a wall because the osmotic pressure is inversely proportional to the spacing between the membrane and the wall by van't Hoff's law. It is easy to show that a symmetric shape fluctuation again leads to a rectified force fluctuation provided we include non-linear terms.

It is clear from this example that we cannot hope to compute the wall pressure from equation (2.17) alone and that we must take the non-linear rectification effect into account. Instead of solving a set of non-linear hydrodynamics, we develop a scaling procedure, outlined in the next section, to account for non-equilibrium membrane fluctuations and the resulting wall pressure.

3 Scaling method

3.1 Height correlation functions (no wall)

We start by noting that there are two relaxation mechanisms playing a different role. A deformed membrane relaxes either by permeation or by hydrodynamic flow (with relaxation rates given by Eq. (2.13) or Eq. (2.18)). According to equation (2.9), the force due to the centers relaxes either through intrinsic individual relaxation of a center characterized by the autocorrelation time τ (as described by Eq. (2.7)) or by their number density fluctuation characterized by the diffusion time L^2/D (see Eq. (2.10)). Our approach consists in identifying the dominant relaxation mechanism and the dominant source of force fluctuation for a given range of lengthscales $L \gg b$ (with b a short-distance cut-off), while absorbing force fluctuations at shorter length scales into the force amplitude $F(b)$.

To implement this strategy, divide a patch of membrane of size L by L into $N_\mathrm{s}(L) = (L/b)^2$ small squares of size b by b (with $b \ll L$). We number the small squares by $j = 1, 2, ..., N_\mathrm{s}$. Next, let $F_j(t)$ describe the time-dependent force fluctuations on the j'th small square ($F_j(t)$ may describe equilibrium thermal fluctuations or active forces). Let $\tau_\mathrm{f}(b)$ be the autocorrelation time and $F(b)$ the magnitude of these force fluctuations. The origin of shape fluctuations of the membrane lies in the *statistical imbalance* of the sum of the force fluctuations $F_j(t)$ over the $N_\mathrm{s}(L)$ small squares integrated over the relaxation time $\tau_\mathrm{m}(L)$ of the membrane at the scale L of the patch. There are of order $N_\tau(L) = \tau_\mathrm{m}(L)/\tau_\mathrm{f}(b)$ "firing events" suffered by an individual small square over the life-time of the shape fluctuation. The statistical imbalance of the force fluctuations on one small square is thus of order $\pm F(b) N_\tau(L)^{1/2}$ (according to the central-limit theorem), with a random sign for each small square. If there are no correlations between the force fluctuations on different squares, then the statistical imbalance $F(L)$ of the force on the L by L patch is

$$F(L) \propto \pm F(b)\sqrt{N_\mathrm{s}(L) N_\tau(L)} \tag{3.1}$$

by the same argument.

A similar sequence of arguments applies to the average displacement of the membrane. Let $u_j(t)$ describe the displacement of the j'th small square and let $\pm u(b)$ be the displacement suffered in response to an individual firing event. The final displacement u_j of the j'th small square over the life-time $\tau_\mathrm{m}(L)$ of the shape fluctuation is then of order $\pm N_\tau(L)^{1/2} u(b)$. The mean displacement $u(L)$ of the L by L patch of membrane is the average of the $N_\mathrm{s}(L)$ displacements of individual small squares. If there is no spatial correlation between the displacements of the small squares, then

$$u(L) \propto \pm u(b)\sqrt{N_\tau(L)/N_\mathrm{s}(L)}. \tag{3.2}$$

We have in equations (3.1, 3.2) a set of scaling "laws" for the displacement and force provided we can identify the appropriate force amplitude $F(b)$ and displacement amplitude $u(b)$.

To establish the validity range of equations (3.1, 3.2), we first note that if the membrane displacement obeys over a range of length scales $L \gg b$ a linearized Langevin equation is of the form:

$$\frac{\partial u(\mathbf{q}_\perp, t)}{\partial t} + \tau_\mathrm{m}^{-1}(\mathbf{q}_\perp) u(\mathbf{q}_\perp, t) \propto \mathrm{f}(\mathbf{q}_\perp, t) \tag{3.3}$$

with $f(\mathbf{r}_\perp, t)$ a random force having a spatial coherence length b, an autocorrelation time $\tau_\mathrm{f}(b)$, and an amplitude $F(b)$, then equations (3.1, 3.2) follow *provided* $\tau_\mathrm{f}(b) \ll \tau_\mathrm{m}(L)$. If the force autocorrelation time $\tau_\mathrm{f}(b)$ exceeds the membrane relaxation time $\tau_\mathrm{m}(L)$, then we must set $N_\tau(L) = 1$ in equations (3.1, 3.2). Next, since equations (3.1, 3.2) implicitly assume a *linearized* Langevin equation we cannot extend L beyond the collision length L_c since we know from last section that the linearized equation of motion is not valid if the membrane is close to a wall. Also recall from the previous section that a wall has a "rectifying" effect on force fluctuations: they no longer have a random sign. Finally, if the forces exerted on the membrane are mediated by hydrodynamic coupling, then long-range spatial correlation are introduced between the force fluctuations. We will address these various cases individually below. If all of the above validity conditions are satisfied, then it follows from equation (3.2) that the mean square $\langle u^2(L) \rangle$ of membrane height fluctuations obeys:

$$\langle u^2(L) \rangle \propto \left(\frac{b}{L}\right)^2 N_\tau(L) u(b)^2 \quad \text{(uncorrelated)}. \tag{3.4}$$

It follows from equation (2.13) that for lengthscales $L < \lambda_\mathrm{p}\eta$, relaxation is by permeation while for $L > \lambda_\mathrm{p}\eta$,

relaxation is by hydrodynamic relaxation. For lengthscales L larger than $\lambda_p\eta$, the equilibrium force fluctuations experienced by the membrane are due to fluctuations in the bulk of the solvent rather than the surface force fluctuations of permeative transport. These bulk fluctuations are transferred to the membrane *via* hydrodynamic interactions. The scaling relation equation (3.4) has to be corrected for $L > \lambda_p\eta$ since the hydrodynamics introduces long-range correlations between force fluctuations exerted on different parts of the patch. To find this new scaling relation, we now use $b = \lambda_p\eta$ as the small distance cutoff. Divide a three-dimensional block of solvent of volume L^3 surrounding the L by L membrane patch into $(L/b)^3$ small cubes of volume b^3. The solvent in each cube experiences force fluctuations, which are assumed to be uncorrelated (for the case of equilibrium hydrodynamic fluctuations this is indeed the case, see Eq. (2.4)). In Appendix A, we show that the height correlation function for the case of hydrodynamic fluctuations is:

$$\langle u^2(L)\rangle \propto \left(\frac{b}{L}\right) N_\tau(L) u(b)^2 \quad \text{(correlated)}. \tag{3.5}$$

In Appendix B, we show that if we apply equations (3.4, 3.5) to calculate $\langle u^2(L)\rangle$ for a membrane with no active force centers in an infinite embedding medium (*i.e.* without wall) then we reproduce the equilibrium result equation (1.4) both in the permeative and in the hydrodynamic regime.

We next apply the method to the case of active force centers. For convenience, we simply "switch-off" the thermal fluctuations and only include the active firing events.

3.1.1 Shot-noise

For a homogeneous collection of force centers with no diffusion, the force fluctuations are spatially and temporally uncorrelated. The autocorrelation time of shot-noise is $\tau_f(b) = \tau$. In this case, we can directly apply equation (3.4) with $N_\tau(L) = \tau_m(L)/\tau$. Note that $N_\tau(L)$ is large compared to one for large L. The amplitude $F(b)$ of force fluctuations can be equated to $I_0^{1/2}$ in equation (2.7) setting b equal to $\rho^{-1/2}$, the mean spacing between force centers. The step length $u(b)$ is found from the Langevin equation:

$$\frac{\partial u(\mathbf{q}_\perp, t)}{\partial t} + \tau_m^{-1}(\mathbf{q}_\perp) u(\mathbf{q}_\perp, t) = \lambda_p f_a(\mathbf{q}_\perp, t). \tag{3.6}$$

For short force autocorrelation times $\tau \ll \tau_m$, we can neglect the relaxational term on the left-hand side of equation (3.6). The step length is then:

$$u(b) \approx \lambda_p \tau \rho I_0^{1/2} \tag{3.7}$$

and the height correlation function:

$$\langle u^2(L)\rangle \propto \frac{\rho\tau\lambda_p I_0}{\left(1 + \frac{L}{\lambda_p\eta}\right)(\gamma + \kappa L^{-2})} \quad \text{(shot-noise)}. \tag{3.8}$$

Note that for L large compared to $\lambda_p\eta$ the effect of shot-noise decreases with patch size L as $1/L$ ($\lambda_p\eta$ is the crossover length between hydrodynamic and permeative relaxation). Comparing this result with the equilibrium correlation function at finite tension (Eq. (1.4)), we see that the effect of shot-noise on the height correlation function of bulk membranes is weak in the large L limit.

3.1.2 Concentration fluctuations

A force fluctuation on a scale L can also be due to a concentration fluctuation of the force centers rather than to fluctuations in the output of individual centers. An excess or deficit of force centers on a membrane patch leads to a force fluctuation on the patch, provided the force centers apply a finite mean force F_a (see Eq. (2.9)). This is analogous to the case of hydrodynamic fluctuations, since the force is uniformly applied over the L by L patch. In other words, $b \equiv L$. Since the force fluctuations are now coherent, we apply equation (3.5) with $N_\tau(L) = \tau_m(L)/\tau_f(L)$ where $\tau_f(L) \approx L^2/D$ is the autocorrelation time of concentration fluctuations. Large scale concentration fluctuations apply a net force which varies only slowly with time. Following the same steps as for the shot-noise case, we find

$$\langle u^2(L)\rangle \propto \frac{\eta\lambda_p^2 F_a^2 \rho}{D\kappa} L^3 \quad \text{(tensionless)} \tag{3.9}$$

for tensionless membranes. Comparing with equation (1.4), we see that the height correlation function of an active membrane diverges more strongly with patch size L than an equilibrium tensionless membrane. For a tense membrane on the other hand, we must pay attention to the inequality $\tau_f(L) \gg \tau_m(L)$; we obtain:

$$\langle u^2(L)\rangle \propto \frac{\eta^2\lambda_p^2 F_a^2 \rho}{\gamma^2} \quad \text{(tense)} \tag{3.10}$$

which, like for tense membranes in equilibrium, is independent of L. Comparing this with the equilibrium correlation function (Eq. (1.4)), we see that the introduction of mobile force centers in tense membranes can be qualitatively described through the introduction of an effective *noise temperature* given by:

$$k_B T_{\text{noise}} \approx \frac{\eta^2\lambda_p^2 F_a^2 \rho}{\gamma} \tag{3.11}$$

(recall though that our method cannot be expected to account for any logarithmic dependency in correlation functions). The results for the correlation function of active membranes derived in this section all can be confirmed by direct solution of the Langevin equation of motion of Section 2 as shown in [8].

3.2 Wall pressure

As discussed in Section 2.4, in the presence of a wall, the *downwards* force on the membrane in the sections of

the membrane closer to the wall must be larger than the *upwards* force in the sections of the membrane further from the wall (the rectification effect). The same holds for the pressure variation in the layer of fluid between the membrane and the wall so there is an overall net pressure exerted by the wall on the membrane. On the one hand, rectification does not play any role for modulations with wavelengths smaller than d, since the hydrodynamic flow pattern in the vicinity of the membrane with a modulation wave-vector q decays as $\exp(-qz)$. On the other hand, modulations with wavelengths large compared to the collision length L_c mentioned in Section 1 are suppressed by the presence of the wall. In a dynamical description of the wall pressure, we must thus focus on rectified force fluctuations with wavelengths in a range of length scales between d and L_c: $L_c \gg L \gg d$.

As is evident from equation (2.26), the largest pressure is exerted by those modulations which have an amplitude u comparable to d, *i.e.* by modulations with wavelengths of order the collision length L_c. In our scaling procedure, we thus should take patches of size L_c by L_c and use the mean membrane wall spacing d as a short distance cut-off.

First consider the case of incoherent force fluctuations. Let $F(d)$ be the amplitude of a rectified force fluctuation on a small square of size d by d, with $N_s(L_c) = (L_c/d)^2$ squares per L_c by L_c patch. Next, let $N_\tau(L_c)$ be the number of force fluctuations applied over the repeat time $\tau_c(L_c)$ of the membrane-wall collisions of the patch. Note that an upper bound on $\tau_c(L_c)$ is given by $\tau_m(L_c)$, the linear-response lifetime of a modulation of wavelength L_c. If $\tau_f(d)$ is the force autocorrelation time of the force fluctuation $F(d)$, then $N_\tau(L_c) = \tau_c(L_c)/\tau_f(d)$ if $\tau_f(d)$ is less than $\tau_c(L_c)$, while $N_\tau(L_c) = 1$ if $\tau_f(d)$ exceeds $\tau_c(L_c)$.

The contribution to the pressure on an L_c by L_c patch of membrane during a force fluctuation of a d by d small square is $F(d)/L_c^2$. The RMS of the pressure fluctuations summed over the small squares and averaged over the "observation period" $\tau_c(L_c)$ would be $\pm(N_s(L_c)/N_\tau(L_c))^{1/2}$ times this quantity. For perfectly symmetric force fluctuations, the average pressure $\langle P(d)\rangle$ would vanish. Rectification is now included by simply removing the fluctuations which have the "minus" sign. The average pressure can then be estimated as:

$$\langle P(d)\rangle \propto \sqrt{\frac{N_s(L_c)}{N_\tau(L_s)}}\frac{F(d)}{L_c^2} \quad \text{(uncorrelated)}. \tag{3.12}$$

Just as for the height correlation function in Section 3.1, we must derive a separate expression for the wall pressure in the case of coherent force fluctuations. Assume that the force $F(t)$ is applied uniformly over the patch size L_c with an autocorrelation time $\tau_f(L_c)$ and fluctuations amplitude $F(L_c)$. The time-averaged pressure over one "observation period" $\tau_c(L_c)$ is then:

$$P \propto \frac{1}{L_c^2\tau_c(L_c)}\int_{\tau_c(L_c)} F(t)\mathrm{d}t. \tag{3.13}$$

Using $\langle P(d)\rangle \approx \langle P^2\rangle^{1/2}$, we find:

$$\langle P(d)\rangle \propto \sqrt{\frac{\tau_f(L_c)}{\tau_c(L_c)}}\left(\frac{F(L_c)}{L_c^2}\right) \tag{3.14}$$

or, with $N_\tau(L_c) = \tau_c(L_c)/\tau_f(L_c)$:

$$\langle P(d)\rangle \propto \sqrt{\frac{1}{N_\tau(L_c)}}\left(\frac{F(L_c)}{L_c^2}\right) \quad \text{(correlated)}. \tag{3.15}$$

Note that taking $d = L_c$ in equation (3.12) directly leads to equation (3.13). As discussed previously, if $\tau_f(L_c)$ exceeds $\tau_c(L_c)$ we set $N_\tau(L_c)=1$, and then $\langle P(d)\rangle \propto \left(\frac{F(L_c)}{L_c^2}\right)$.

For equilibrium thermal fluctuations, equations (3.12, 3.13) can be shown to reproduce the equilibrium result equations (1.1, 1.2) (see Appendix C). In the next section, we use equations (3.12, 3.13) to compute the non-equilibrium wall pressure.

4 Wall-induced fluctuation magnification and wall-induced pressure

4.1 Height correlation function (with wall)

We now return to the geometry discussed in Section 2.3 of a membrane in the vicinity of a wall. The mean position of the membrane is at $z = 0$ while the wall is at $z = -d$. We first compute the collision length, *i.e.* the mean spacing between membrane-wall contacts. The collision length is found from the condition $\langle u^2(L_c)\rangle \approx d^2$. For membranes in thermal equilibrium, it is sufficient to use for $\langle u^2(L)\rangle$ the equilibrium height correlation function computed *in the absence of wall*. It would seem natural to adopt the same procedure for active membranes and use the height correlation functions computed in the previous section. This immediately would imply that tense membranes carrying active centers with either shot-noise or concentration fluctuations have a collision length which could be *infinite* for large enough d, since in neither case the height correlation function diverges with L (see Eqs. (3.8, 3.10)). The collision length also could be exponentially large instead of infinite, as in equation (1.5), due to neglect of a logarithmic dependence on L in equation (3.15). In both cases, tense membranes would only suffer a short-ranged repulsion from a wall. It is a key point of this paper that this naive estimate greatly underestimates the true wall force: *the collision length of active membranes is much shorter than that of equilibrium membranes. The presence of a wall greatly magnifies the height fluctuations of a non-equilibrium membrane.*

Demonstrating this claim simply involves replacing the bulk membrane relaxation time (Eq. (2.13)) in the calculation which led to equations (3.8-3.10) by the relaxation time (Eq. (2.18)) of a membrane near a wall. We first return to the Langevin equation of a membrane near a wall in the lubrication approximation (see Eq. (2.17)):

$$\frac{\partial u(\mathbf{q}_\perp,t)}{\partial t} + \tau_m^{-1}(\mathbf{q}_\perp)u(\mathbf{q}_\perp,t) \cong \lambda_p f_a(\mathbf{q}_\perp,t) \tag{4.1}$$

where thermal fluctuations have been neglected. The membrane relaxation time $\tau_{\rm m}$ is given by equation (2.18) for hydrodynamic relaxation and by equation (2.21) for permeative relaxation:

$$\tau_{\rm m}^{-1}(\mathbf{q}_\perp) \cong \begin{cases} \tau_{\rm la}^{-1}(\mathbf{q}_\perp) = \dfrac{d^3}{12\eta} q_\perp^4(\gamma + \kappa q_\perp^2) \\ \\ \tau_{\rm per}^{-1}(\mathbf{q}_\perp) = \lambda_{\rm p}(\gamma q_\perp^2 + \kappa q_\perp^4). \end{cases} \tag{4.2}$$

For the lubrication approximation to be valid, wavevectors $q_\perp$ must be small compared to $1/d$.

It follows from equation (4.2) that relaxation is permeative over large length scales ($q_\perp \ll q^*$) and hydrodynamic over shorter length scales ($q_\perp \gg q^*$). The cross-over wavevector is $q^*(d) = \frac{\sqrt{\lambda_{\rm p}\eta}}{d^{3/2}} \propto \frac{1}{L^*(d)}$. Since for a membrane fluctuating in bulk without wall, hydrodynamic relaxation dominates for small q, *i.e.* length scales large compared to $\lambda_{\rm p}\eta$, this statement may look surprising. It is a simple consequence of the fact that the motion of an impermeable membrane close to a wall requires transport of fluid over large length scales in the thin layer between the membrane and the wall, which is a very slow process.

For length scales where permeative relaxation dominates ($L \gg L^*(d)$), we can still use the height correlation functions computed in Section 3 in the absence of wall (Eqs. (3.8-3.10)), since no dependence on d remains in equation (4.1) in the permeative regime. Using the bulk correlation function in $\langle u^2(L_{\rm c})\rangle \approx d^2$ gives the correct collision length. For length scales where hydrodynamic relaxation dominates ($L \ll L^*(d)$), we have to recalculate the collision length.

4.1.1 Hydrodynamic relaxation: shot-noise

Assume that we are in the hydrodynamic regime with $q > q^*(d)$. Consistency thus requires the collision length to be less than $1/q^*(d)$ in this regime. For shot-noise, the autocorrelation time $\tau_{\rm f} = \tau$ of the force fluctuations does not depend on L. For large L, the membrane relaxation time — which grows as a powerlaw with L (see Eq. (4.2)) — is large compared to τ so we can neglect the relaxational term in equation (4.1) with respect to $\partial u/\partial t$. Repeating the arguments which lead to equation (3.8) and using the method of Appendix B, it easily follows from equation (4.1) that for an L by L patch of membrane, the mean square displacement over a time t is:

$$\langle u^2(L,t)\rangle \propto \left(\frac{\tau\lambda_{\rm p}^2 I_0\rho}{L^2}\right) t. \tag{4.3}$$

The steady-state height-correlation function is found from equation (4.3) by replacing t with the life-time $\tau_{\rm m}(L)$ of the height fluctuation at the scale L. Using equation (4.2) gives:

$$\langle u^2(L)\rangle \propto \left(\frac{\eta\tau\lambda_{\rm p}^2 I_0\rho}{d^3(\gamma L^2 + \kappa)}\right) L^4 \tag{4.4}$$

for L large compared to d, but small compared to $L^*(d) = \frac{d^{3/2}}{\sqrt{\lambda_{\rm p}\eta}}$ ($L^*(d) \gg L \gg d$). If we compare this result with equation (3.8) for shot-noise driven bulk fluctuations, we see that the effect of the nearby wall is indeed to magnify the height fluctuations. The height correlation function of tense membranes diverges with patch size as L^2, whereas according to equation (3.8) it actually was expected to decrease with L as $1/L$. The magnification factor is of order $(L/d)^3$ for both tense and tensionless membranes. This fluctuation magnification is due to the reduced relaxation rate of a membrane near a wall as compared to a membrane in bulk, while the non-equilibrium force fluctuations themselves are not directly affected by the wall. The effect is entirely due to the non-equilibrium nature of the force centers. It does not occur for equilibrium membranes since for equilibrium membranes, reduced relaxation rates necessarily would go hand in hand with reduced noise levels through the fluctuation-dissipation theorem. Note finally that according to equation (4.4), $\langle u^2(d)\rangle \propto \left(\frac{\eta\tau\lambda_{\rm p}^2 I_0\rho}{d(\gamma+\kappa d^{-2})}\right)$, which is consistent with equation (3.8) for $L = d$.

We now use the steady-state correlation function equation (4.4) to compute the collision length $L_{\rm c}(d)$ using $\langle u^2(L_{\rm c})\rangle \approx d^2$ in the same way as for equilibrium fluctuations. The result is:

$$L_{\rm c}(d) \approx \begin{cases} \sqrt{\dfrac{\gamma}{\eta\tau\lambda_{\rm p}^2 I_0\rho}}\, d^{5/2} & \text{(tense)} \\ \\ \left(\dfrac{\kappa}{\eta\tau\lambda_{\rm p}^2 I_0\rho}\right)^{1/4} d^{5/4} & \text{(tensionless).} \end{cases} \tag{4.5}$$

Consistency first requires $L_{\rm c}(d)$ to be less than $L^*(d) = \frac{d^{3/2}}{\sqrt{\lambda_{\rm p}\eta}}$. For tensionless membranes, this is always the case provided d is large enough, explicitly $d \gg \frac{\kappa\eta}{\tau I_0\rho}$. For tense membranes, there is a cross-over length given by $d_{\rm co} \approx \sqrt{\frac{\tau\lambda_{\rm p}\rho I_0}{\gamma}}$: if $d \gg d_{\rm co}$ permeative relaxation dominates. In the permeative regime, there is no wall-induced increase in the lifetime of fluctuations. We thus expect wall-induced forces on tense membranes with shot-noise to have a finite range equal to $d_{\rm co}$.

There is a second self-consistency condition namely $L_{\rm c}(d)$ must be large compared to d. If this condition is not satisfied, then membrane collisions are taking place for lengthscales shorter than the short-distance cut-off d required by the lubrication approximation. As can be seen from equation (4.5), for large d this condition is also satisfied.

4.1.2 Hydrodynamic relaxation: concentration fluctuations

(i) Tense membranes

In the case of force fluctuations produced by concentration fluctuations of mobile force centers, the force autocorrelation time $\tau_{\rm f}(L) \approx L^2/D$ is scale dependent. If we compare

$\tau_{\rm f}(L)$ with the hydrodynamic lifetime $\tau_{\rm m}(L) \propto \frac{\eta}{\gamma d^3} L^4$ of the shape fluctuation of a tense membrane (see Eq. (4.2)), then $\tau_{\rm m}$ exceeds $\tau_{\rm f}$ provided $L \gg \tilde{L} \propto \sqrt{\frac{\gamma d^3}{\eta D}}$. Recall now that consistency requires $L^* = \frac{d^{3/2}}{\sqrt{\lambda_{\rm p}\eta}} \gg L$ in the hydrodynamic regime. As long as the hydrodynamic regime is valid, we must have $L^* \gg \tilde{L}$, *i.e.* $1 \gg \gamma\lambda_{\rm p}/D$. For reasonable values of γ, D and $\lambda_{\rm p}$ (see estimates given in Sect. 5), $\gamma\lambda_{\rm p}/D$ is large compared to one. This means that as long as we stay in the regime of hydrodynamic relaxation, the force autocorrelation time always exceeds the lifetime of shape fluctuations. A force fluctuation is thus "turned-on" continuously over the fluctuation lifetime which allows us: i) to neglect $\partial u/\partial t$ in equation (4.1) with respect to the relaxational term and ii) to set $N_\tau = 1$.

The height correlation function is again computed from equation (4.1) by repeating the steps which led to equation (3.10):

$$\langle u^2(L)\rangle \propto \left(\frac{\eta^2\lambda_{\rm p}^2 F_{\rm a}^2 \rho}{\gamma^2}\right)\left(\frac{L}{d}\right)^6 \quad \text{(tense)} \tag{4.6}$$

where we still assume that L is large compared to d, but small compared to $L^*(d)$ ($L^*(d) \gg L \gg d$). Just as for the shot-noise case, when compared to equation (3.10), there is a fluctuation-magnification effect now proportional to $(L/d)^6$. It is easy to check that around $L = d$, the required cross-over to equation (3.10) is indeed obtained.

The corresponding collision length is:

$$L_{\rm c}(d) \propto \left(\frac{\gamma}{\eta\lambda_{\rm p}F_{\rm a}\sqrt{\rho}}\right)^{1/3} d^{4/3}. \tag{4.7}$$

Consistency requires again that $L_{\rm c}(d)$ must be larger than d but less than the cross-over length $L^*(d) = \frac{d^{3/2}}{\sqrt{\lambda_{\rm p}\eta}}$ ($L^*(d) \gg L_{\rm c}(d) \gg d$) beyond which permeative relaxation takes over. This is the case if $d \gg d_{\rm co}$ with $d_{\rm co} \approx \frac{\lambda_{\rm p}\eta\gamma}{\rho F_{\rm a}^2}$ the cross-over length, while $\langle u^2(d)\rangle \leq d^2$ for large d. If $d \ll d_{\rm co}$, the system crosses over to the permeative regime.

(ii) Tensionless membranes

For tensionless membranes, the fluctuation lifetime $\tau_{\rm m}(L) \propto \frac{\eta}{\kappa d^3} L^6$ exceeds the force autocorrelation time $\tau_{\rm f}(L) \approx L^2/D$ provided L exceeds $\tilde{L} \propto \left(\frac{\kappa d^3}{\eta D}\right)^{1/4}$. If $L > \tilde{L}$, we can neglect the relaxational term in equation (4.1) with respect to $\partial u/\partial t$. Solving equation (4.1) and using the method which led to equation (4.3) gives the mean square displacement for an L by L patch of membrane over a time t:

$$\langle u^2(L,t)\rangle \propto \left(\frac{\tau_{\rm f}(L)\lambda_{\rm p}^2\rho F_{\rm a}^2}{L^2}\right) t. \tag{4.8}$$

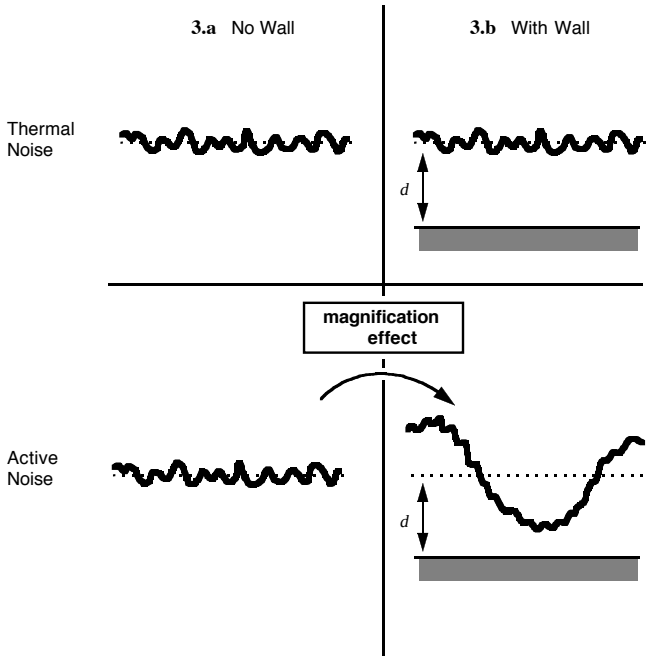

Fig. 3. Illustration of the wall influence on the fluctuations of a membrane under tension: a) thermal noise: the influence is negligible, b) active noise: the presence of the wall leads to an amplitude comparable to d, the average distance to the wall.

The steady-state height correlation function is found by setting t equal to the fluctuation life-time:

$$\langle u^2(L)\rangle \propto \left(\frac{\eta\lambda_p^2\rho F_{\rm a}^2}{D\kappa d^3}\right) L^6 \quad \text{(tensionless)}. \tag{4.9}$$

Compared with the bulk height correlation function (see Eq. (3.9)), the fluctuation magnification factor is of the order $(L/d)^3$. The cross-over to $L = d$ is again correct. The corresponding collision length is:

$$L_{\rm c} \propto \left(\frac{\kappa d^5 D}{\eta\lambda_{\rm p}^2\rho F_{\rm a}^2}\right)^{1/6}. \tag{4.10}$$

Consistency requires $L_{\rm c}(d) > \tilde{L}$ and again $L^*(d) \gg L_{\rm c}(d) \gg d$. For large d, the collision length is large compared to $\tilde{L} \propto \left(\frac{\kappa d^3}{\eta D}\right)^{1/4}$ so the fluctuation life-time indeed exceeds the force autocorrelation time, while it is small compared to the cross-over length $L^*(d) = \frac{d^{3/2}}{\sqrt{\lambda_{\rm p}\eta}}$. Unfortunately, since $L_{\rm c}(d)$ increases with d as $d^{5/6}$, $L_{\rm c}(d)$ is less than d in the large d limit indicating failure of the lubrication approximation. We will not address this question in this paper, and simply assume that d is large enough for the first two conditions to be satisfied, while $L_{\rm c}(d)$ still exceeds d, *i.e.* $d \ll d_{\rm co}$ with $d_{\rm co} = \frac{\kappa D}{\eta\lambda_{\rm p}^2\rho F_{\rm a}^2}$.

4.2 Wall force

Having demonstrated the fluctuation magnification effect (Fig. 3), it is now straightforward to compute the wall

force using equation (3.12) in the case of shot-noise (uncorrelated force fluctuations) and equation (3.13) in the case of concentration fluctuations (correlated force fluctuations). We identify the repeat time $\tau_c(L_c)$ of the membrane-wall collisions of the patch with the life-time $\tau_m(L_c)$ of the membrane height fluctuation as given by equation (2.18) with $L = L_c$.

4.2.1 Shot-noise

The amplitude $F(d)$ of force fluctuations on a scale d is of order $I_0^{1/2}\sqrt{\rho d^2}$ while $N_s(L_c) = (L_c/d)^2$. For membranes exposed to shot-noise, equation (3.12) then leads to:

$$\langle P(d)\rangle \propto \sqrt{\frac{\rho}{\tau_m(L_c)/\tau}}\frac{I_0^{1/2}}{L_c}\,. \tag{4.11}$$

i) Tense membrane

For tense membranes, the fluctuation life-time is $\tau_m(L_c) = \eta L_c^4/\gamma d^3$ while the collision length is given by equation (4.5):

$$\langle P(d)\rangle \propto \begin{cases} \dfrac{\tau^2\eta\lambda_p^3\rho^2 I_0^2}{\gamma d^6} & d \ll d_{co} = \sqrt{\dfrac{\tau\lambda_p\rho I_0}{\gamma}} \\ 0 & d \gg d_{co} \end{cases} \quad \text{(tense)}. \tag{4.12}$$

If we compare equation (4.12) with equation (1.2) for the wall force due to thermal fluctuations, we see that shot-noise dominates over thermal noise provided $\tau\lambda_p\rho I_0 \gg k_B T$.

ii) Tensionless membrane

For tensionless membranes $\tau_m(L) \propto \eta L^6/\kappa d^3$. The resulting wall force is:

$$\langle P(d)\rangle \propto \frac{\eta^{1/2}(\tau\rho)^{3/2}\lambda_p^2 I_0^{3/2}}{\kappa^{1/2} d^{7/2}} \quad \text{if } d \gg \frac{\kappa\eta}{\tau I_0\rho} \quad \text{(tensionless)}. \tag{4.13}$$

If we compare equation (4.13) with equation (1.1), then we see that in the large d limit the wall force due to shot-noise decays with a power law $d^{-7/2}$ which is close to that of the Helfrich force (d^{-3}), but thermal fluctuations dominate in the large d limit.

4.2.2 Concentration fluctuations

i) Tense membrane

For tense membranes exposed to long-wavelength concentration fluctuations of force centers, the number N_τ of force fluctuations applied over a fluctuation lifetime must be set equal to one (as discussed above for Eq. (4.6)). According to equation (3.13), and using $F(L_c) = \rho^{1/2} F_a L_c$ for the amplitude of the force due to concentration fluctuations, the wall force is then inversely proportional to the collision length:

$$\langle P(d)\rangle \propto \frac{\rho^{1/2} F_a}{L_c}\,. \tag{4.14}$$

From equations (4.7, 4.14) we then find:

$$\langle P(d)\rangle \propto \frac{F_a^{4/3}\rho^{2/3}(\eta\lambda_p)^{1/3}}{\gamma^{1/3} d^{4/3}} \quad d \gg d_{co} = \frac{\lambda_p\eta\gamma^2}{\rho F_a^2} \quad \text{(tense)}. \tag{4.15}$$

The non-equilibrium contribution to the wall force due to concentration fluctuation on a tense membrane thus dominates over the thermal contribution (Eq. (1.2)) in the large d limit.

ii) Tensionless membrane

For a tensionless membrane, the collision time does not exceed the fluctuation lifetime in the large d limit. According to equation (3.13), equation (4.14) must be replaced by:

$$\langle P(d)\rangle \propto \sqrt{\frac{L_c^2}{\tau_m(L_c) D}}\frac{F_a\rho^{1/2}}{L_c} \tag{4.16}$$

with $\tau_m(L) \propto \eta L^6/\kappa d^3$. Using equation (4.10) in equation (4.16) gives an extraordinarily long-ranged wall repulsion:

$$\langle P(d)\rangle \propto \frac{\lambda_p F_a^2\rho}{Dd} \quad d \ll d_{co} = \frac{\kappa D}{\eta\lambda_p^2\rho F_a^2} \quad \text{(tensionless)}. \tag{4.17}$$

This wall force again would overwhelm the thermal repulsion in the large d limit. However, it should be recalled that for this case our method fails for $d \gg \frac{\kappa D}{\eta\lambda_p^2\rho F_a^2}$ due to failure of the lubrication approximation.

4.2.3 Results

We can rewrite these results in the form of equation (1.6), namely:

$$P(d) \propto P_0\left(\frac{\delta}{d}\right)^\alpha$$

with $P_0 = F_a/l^2$ the local pressure in the case of concentration fluctuations, $P_0 = I_0^{1/2}/l^2$ in the case of shot-noise

and:

	Tense	Tensionless
Shot-noise	$\alpha = 6$, $\delta = \left(\frac{b\delta_1(\tau\lambda_{\rm p} I_0^{1/2})^2}{l^2}\right)^{1/6}$	$\alpha = 7/2$, $\delta = \left(\frac{b(\tau\lambda_{\rm p} I_0^{1/2})^3}{l^2\delta_\kappa}\right)^{1/7}$
Concentration Fluctuations	$\alpha = 4/3,\ \delta = (l^2\delta_{\rm a} b)^{1/4}$	$\alpha = 1,\ \delta = \frac{\lambda_{\rm p} F_{\rm a}}{D}$

where l is the spacing between active centers defined by $\rho = 1/l^2$, $b = \lambda_{\rm p}\eta$ is the cross-over length between permeative and hydrodynamic relaxation in the absence of wall (see Eq. (2.13)), $\delta_{\rm a} = F_{\rm a}/\gamma$, $\delta_I = I_0^{1/2}/\gamma$, $\delta_\kappa = \kappa/I_0^{1/2}$ are three length scales mixing quantities associated either with the active centers or with the membrane. Note also that $\lambda_{\rm p} F_{\rm a}$ and $\lambda_{\rm p} I_0^{1/2}$ are the volume of solvent transferred through the membrane per unit time and per force center due to the averaged activity of the centers and to shot-noise respectively.

5 Orders of magnitude and concluding remarks

According to our scaling arguments, membrane fluctuations of non thermal origin are strongly enhanced in the presence of a wall. With the only exception of a tense membrane in the hydrodynamic regime responding to shot-noise, the fluctuations amplitude becomes comparable to the average distance to the wall, even though it would be much smaller under the same conditions in an infinite medium. This enhancement is due to the increase in the membrane response time at large enough scale. This effect cannot show up when only thermal sources are at work: equal time correlation functions cannot depend on hydrodynamic parameters. Thermal noise sources depend on boundary conditions in such a way that any dynamic information must disappear in the equal time correlation functions. "Chemical" or "biological" noise which is purely local can, on the contrary, take full advantage of the considerable increase in the membrane response time: the "information" conveyed by hydrodynamic boundary conditions can be "processed" by the membrane which should respond in a spectacular way according to the present theory. If the membrane is adhesive, bonding is facilitated. If it is not, a long range repulsive pressure is generated even for a tense membrane in conditions under which the Helfrich entropic force would be entirely negligible. This pressure could easily supersede other long-range forces such as van der Waals forces.

In order to estimate the order of magnitude of the non-equilibrium pressure, let us consider a collection of ion channels separated from each other on average by a distance $l = \rho^{-1/2} = 10$ nm. We can estimate the average force the following way: in a typical channel, bursts of 10^3 to 10^4 ions can flow in about 10^{-3} s. This means that a single ion velocity is of the order of the membrane thickness (*i.e.* about 5 nm) divided by the transit time of a single ion (*i.e.* 10^{-7} s). The drag of the ion on the membrane is roughly speaking given by Stokes's force, in which the relevant viscosity is the membrane viscosity and the relevant length is the ion radius. The average force $F_{\rm a}$ must be multiplied by the duty ratio which is of the order of 0.1. We find $F_{\rm a} \approx 10^{-6}$–$10^{-7}$ dyne (or 1-10 pN). With these values, we can estimate the distance d_0 beyond which the non-equilibrium repulsive pressure wins over the van der Waals attractive force per unit area $F_{\rm vdW} \propto \frac{A}{d^3\left(1+\frac{d^2}{w^2}\right)}$, where $w \approx 5$ nm is the membrane thickness and A is the Hamaker constant "of the order of $k_{\rm B}T$ ". We find $d_0 \leq w$ for values of the membrane tension all the way up to 1 dyn/cm (we assume $\lambda_{\rm p} \approx 10^{-5}$ cm^2 s/g and $D \approx 10^{-9}$ cm^2/s). A more accurate estimate of d_0 would require the knowledge of various prefactors, but one clearly sees that the pressure due to the channels activity is in general very large and wins over van der Waals very quickly, *i.e.* on microscopic scales. Similar estimates easily show that non-equilibrium wall forces are qualitatively competitive with (and in most regimes exceed) the entropic equilibrium Helfrich force. These effects should be easily observable experimentally.

The predictions we put forward in this article can be generalized in several ways. First, the collective concentration fluctuations of proteins on membranes do not need to be exactly diffusive. In many cases, they seem to be hypodiffusive, and on general grounds, one cannot rule out the possibility of hyperdiffusive behavior. The method we have developed in this article can be used straightforwardly: one finds that hypodiffusive behavior increases the fluctuations as compared to purely diffusive behavior whereas hyperdiffusive behavior decreases them. One could also consider tethered or crystalline membranes. In principle, these problems are more complex, but since most of our results are obtained for membrane under tension, they hold for the above mentioned cases as well. Last, we have assumed that the collective concentration fluctuations do not depend on the membrane configuration (*e.g.* curvature). In general, this is only an approximation: the more complex case will be discussed elsewhere [13].

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Appendix A: Hydrodynamic force fluctuations

In this Appendix, we compute the general form of the membrane height correlation function when hydrodynamic fluctuations dominate. Let $F(b)$ be the amplitude of the random force exerted on the solvent of a given small cube.

The force fluctuation on a small cube creates a flow velocity fluctuation of amplitude $v(b)$. According to the Stokes formula, a fluid drop of size b (and arbitrary shape), which experiences a force $F(b)$, moves with a velocity

$$v(b) \propto F(b)/\eta b. \tag{A.1}$$

The velocity field surrounding the moving drop ("Stokeslet") decays as $1/r$ with r the distance from the drop, while the pressure field decays as $1/r^2$. If the small cube is located at a distance of order L from the membrane, then the pressure δP applied to the membrane due to the force pulse $F(b)$ in the small cube varies smoothly along the membrane and is of the order of

$$\delta P(L) \propto F(b)/L^2. \tag{A.2}$$

If the membrane is again divided into small squares of area b by b, then all small squares move coherently at a distance $u_{\rm c}(L)$ in response to a force pulse. This corresponds to a local displacement $u(b)$ such that:

$$u_{\rm c}(L) \approx \left(\frac{b}{L}\right)^2 u(b) \tag{A.3}$$

with $u(b)$ — proportional to $F(b)$ — to be determined below. The total number N of such force pulses is the number $(L/b)^3$ of small cubes times the number $N_\tau(L) = \tau_{\rm m}(L)/\tau_{\rm f}(b)$ of force pulses per cube. The final mean displacement $u(L)$ of the L by L patch is equal to $\sqrt{N}u_{\rm c}(L)$ or,

$$u(L) \propto \pm u(b)\sqrt{\left(\frac{b}{L}\right) N_\tau(L)}. \tag{A.4}$$

From equation (A.4), we finally obtain equation (3.5) given in the text:

$$\langle u^2(L)\rangle \propto \left(\frac{b}{L}\right) N_\tau(L) u(b)^2. \tag{A.5}$$

Appendix B: Height correlation function of an equilibrium membrane

In this Appendix, we use the scaling relations equations (3.4, 3.5) to compute the height correlation function of an equilibrium membrane (*i.e.* with no active center), in an infinite embedding medium (*i.e.* without wall).

B.1. Permeative regime

We first consider fluctuations on lengthscales $\lambda_{\rm p}\eta \gg L \gg a$ where permeation dominates (the existence of this regime is not guaranteed but the discussion is of pedagogical interest). Here, a is the microscopic cut-off of continuum theory (*i.e.* of the order of the size of the largest membrane-associated molecule). In this regime, the membrane relaxation rate is

$$\tau_{\rm m}(L)^{-1} = \lambda_{\rm p}(\gamma L^{-2} + \kappa L^{-4}) \tag{B.1}$$

according to equation (2.13). The size b of our small squares is now equal to the molecular cut-off a.

We compute the force amplitude $F(a)$ of thermal fluctuations at a lengthscale a by integrating the thermal fluctuation force per unit area $f_{\rm p}(\mathbf{r}_\perp, t)$ in equation (2.2a) over each a by a small square and average it over a time $\tau_{\rm m}(a)$. We are thus identifying the force autocorrelation time $\tau_{\rm f}(a)$ with the membrane relaxation time $\tau_{\rm m}(b)$ with $b = a$. Thermal fluctuations are uncorrelated in space and time (see Eq. (2.3)). However, since a small square cannot respond to the applied random forces over time scales shorter than $\tau_{\rm m}(a)$, we must average the random forces over $\tau_{\rm m}(a)$, so that $\tau_{\rm f}(a)$ must be of the order of $\tau_{\rm m}(a)$. The force F_j on the j'th square is now:

$$F_j \propto \frac{1}{\tau_{\rm m}(a)} \int_{\tau_{\rm m}(a)} {\rm d}t \int_{a^2} {\rm d}^2\mathbf{r}_\perp f_{\rm p}(\mathbf{r}_\perp, t). \tag{B.2}$$

The amplitude $F(a)$ of the force fluctuations is $F(a) \propto \sqrt{\langle F_j^2\rangle}$:

$$F(a)^2 \propto \frac{a^2}{\tau_{\rm m}(a)} \int_{\tau_{\rm m}(a)} {\rm d}t \int_{a^2} {\rm d}^2\mathbf{r}_\perp \langle f_{\rm p}(\mathbf{r}_\perp, t) f_{\rm p}(0,0)\rangle. \tag{B.3}$$

Using equation (2.3b) in equation (B.3) yields the force amplitude for thermal fluctuations in the permeative regime at a lengthscale of order a:

$$F(a) \propto a\sqrt{\frac{k_{\rm B}T}{\lambda_{\rm p}\tau_{\rm m}(a)}}\,. \tag{B.4}$$

We now calculate the displacement amplitude $u(a)$ of the small squares in response to a force fluctuation. The autocorrelation time $\tau_{\rm f}(a)$ of force fluctuations at a lengthscale a is of the order of the membrane relaxation time $\tau_{\rm f}(a)$ so the first and second term of the Langevin equation (3.2) for q of the order of $1/a$ are of comparable magnitude. It follows that

$$\tau_{\rm m}^{-1}(a) u(a) \approx \lambda_{\rm p}\left(\frac{F(a)}{a^2}\right). \tag{B.5}$$

Combining equations (B.4, B.5) gives the desired displacement amplitude:

$$u(a) \propto a^{-1}\sqrt{(\lambda_{\rm p}\tau_{\rm m}(a) k_{\rm B}T)}. \tag{B.6}$$

This displacement amplitude is small. For a tensionless membrane for instance, $u(a) \approx a\sqrt{k_{\rm B}T/\kappa}$ which is of the order of the microscopic cut-off. Inserting equation (B.6) into equation (3.4) with $N_\tau(L) = \tau_{\rm m}(L)/\tau_{\rm m}(a)$ and using equation (B.1) gives the height correlation function of

a free membrane with no active centers in the permeative regime:

$$\langle u^2(L)\rangle \propto \begin{cases} \dfrac{k_{\rm B}T}{\kappa} & \gamma = 0 \\ \dfrac{k_{\rm B}T}{\gamma} & \gamma \neq 0. \end{cases} \quad \text{(B.7)}$$

The dependence on the membrane permeability $\lambda_{\rm p}$ and the microscopic cut-off a drop out. We reproduce the known equilibrium correlation function equation (1.4) up to the logarithmic factor for the $\gamma \neq 0$ case, which was to be expected in view of the nature of our procedure.

B.2. Hydrodynamic regime

We next consider fluctuations on lengthscales $\lambda_{\rm p}\eta \ll L$ where hydrodynamics dominates. The short distance cut-off is now $b = \lambda_{\rm p}\eta$. The membrane relaxation rate is:

$$\tau_{\rm m}(L)^{-1} = \frac{1}{4\eta}(\gamma L^{-1} + \kappa L^{-3}). \quad \text{(B.8)}$$

To find the force amplitude $F(b)$, we average the hydrodynamic force density $\mathbf{f}_{\rm h}(\mathbf{r},t)$ over the relaxation time of the membrane $\tau_{\rm m}(b)$ of a b by b small square and integrate it over a small cube of size b^3. We equate — as before — the force autocorrelation time $\tau_{\rm f}(b)$ with the membrane relaxation time $\tau_{\rm m}(b)$. The force on the j'th cube is then a random variable:

$$\mathbf{F}_j \propto \frac{1}{\tau_{\rm m}(b)} \int_{\tau_{\rm m}(b)} {\rm d}t \int_{b^3} {\rm d}^3 r\ \mathbf{f}_{\rm h}(\mathbf{r},t) \quad \text{(B.9)}$$

with a mean square

$$\langle \mathbf{F}_j^2\rangle \approx \frac{b^3}{\tau_{\rm m}(b)} \int_{\tau_{\rm m}(b)} {\rm d}t \int_{b^3} {\rm d}^3 r \langle f_{\rm h}(\mathbf{r},t) f_{\rm h'}(0,0)\rangle. \quad \text{(B.10)}$$

Equating the force amplitude $F(b)$ to $\langle \mathbf{F}_j^2\rangle^{1/2}$ and using equation (2.4b) in equation (B.10) gives:

$$F(b) \approx \sqrt{\frac{\eta b k_{\rm B}T}{\tau_{\rm m}(b)}} \quad \text{(B.11)}$$

To find the displacement $u(b)$ in equation (3.5), we note that, since $\tau_{\rm f}(b) = \tau_{\rm m}(b)$, then $u_{\rm c}(L)/\tau_{\rm m}(b)$ must be of the order of the velocity of the membrane which, in turn, must equal the hydrodynamic flow velocity $v(b)(b/L)$ due to the Stokeslet at the membrane. Combining this with equations (A.1, A.3) gives:

$$u(b) \approx \left(\frac{\tau_{\rm m}(b)}{\eta b}\right) F(b). \quad \text{(B.12)}$$

Inserting the expression of the force amplitude at a lengthscale b (Eq. (B.11)) in equation (B.12) yields, together with equation (B.8):

$$u(b) \approx b\sqrt{\frac{k_{\rm B}T}{\kappa}} \quad \text{(B.13)}$$

for tensionless membranes (recall that $b = \lambda_{\rm p}\eta$). If we use equation (B.13) in equation (3.5) with $N_\tau(L) \approx \tau_{\rm m}(L)/\tau_{\rm m}(b) \approx (L/b)^4$, then we recover the appropriate equilibrium scaling relation for a freely fluctuating membrane $\langle u^2(L)\rangle \propto \frac{k_{\rm B}T}{\kappa} L^2$.

Appendix C: Wall-induced pressure for equilibrium membranes

In this appendix, we reproduce the equilibrium result equation (1.1) using the scaling procedure described in Section 3.2. The averaged pressure $\langle P(d)\rangle$ in the case of incoherent force fluctuations is given by equation (3.12):

$$\langle P(d)\rangle \propto \sqrt{\frac{N_{\rm s}(L_{\rm c})}{N_\tau(L_{\rm c})}} \frac{F(d)}{L_{\rm c}^2} \quad \text{(uncorrelated)}$$

with $N_{\rm s}(L_{\rm c}) = (L_{\rm c}/d)^2$ and $N_\tau(L_{\rm c}) = \tau_{\rm c}(L_{\rm c})/\tau_{\rm f}(d)$. In the case of coherent force fluctuations, the pressure is given by equation (3.13):

$$\langle P(d)\rangle \propto \sqrt{\frac{1}{N_\tau(L_{\rm c})}} \left(\frac{F(L_{\rm c})}{L_{\rm c}^2}\right) \quad \text{(correlated)}$$

with $N_\tau(L_{\rm c}) = \tau_{\rm c}(L_{\rm c})/\tau_{\rm f}(L_{\rm c})$.

For equilibrium membranes, the collision length $L_{\rm c}$ is defined by $\langle u^2(L_{\rm c})\rangle \approx d^2$ where $\langle u^2(L_{\rm c})\rangle$ is the height correlation function computed in the absence of wall. It follows from Appendix B that the height correlation function for equilibrium membranes is given by equation (B.7) in both the permeative and the hydrodynamic regimes. We thus find for the collision length:

$$L_{\rm c} \propto \begin{cases} \sqrt{\dfrac{\kappa}{k_{\rm B}T}}\, d & \gamma = 0 \\ \infty & \gamma \neq 0. \end{cases} \quad \text{(C.1)}$$

Note that the collision length is set to infinity for tense membranes since our method is not sensitive enough to account for logarithmic dependencies. If the collision length obeys $L_{\rm c} > L^*(d) = \left(\frac{d^3}{\lambda_{\rm p}\eta}\right)^{1/2}$, then the hydrodynamic relaxation time exceeds the permeation time and permeative relaxation dominates over hydrodynamic relaxation (see Sect. 2.3). It follows from equation (C.1) that the permeative regime is restricted to the range $d \ll \frac{\lambda_{\rm p}\eta\kappa}{k_{\rm B}T}$. For $d \gg \frac{\lambda_{\rm p}\eta\kappa}{k_{\rm B}T}$, relaxation is by hydrodynamic flow rather than by permeation.

For equilibrium membranes, the collision time $\tau_{\rm c}$ and the autocorrelation time of force fluctuations $\tau_{\rm f}$ are both equal to the membrane relaxation time $\tau_{\rm m}$.

C.1. Permeative regime

If $d \ll \frac{\lambda_{\rm p}\eta\kappa}{k_{\rm B}T}$, permeative relaxation dominates and the relaxation rate of the membrane is $\tau_{\rm m}(L)^{-1} = \lambda_{\rm p}(\gamma L^{-2} + \kappa L^{-4})$ (see Eq. (2.21)). Force fluctuations are incoherent

in this case, we thus use equation (3.12) with the amplitude of the force fluctuation $F(d)$ still given by equation (B.4):

$$F(d) \propto d\sqrt{\frac{k_{\rm B}T}{\lambda_{\rm p}\tau_{\rm m}(d)}}$$

since the permeative regime is not influenced by the presence of the wall. We find for tensionless membranes:

$$\langle P(d)\rangle \propto \frac{\sqrt{k_{\rm B}T\kappa}}{L_{\rm c}^3} \tag{C.2}$$

while $\langle P(d)\rangle = 0$ for tense membranes within the precision of our method. Using equation (C.1) in equation (C.2) reproduces the equilibrium Helfrich pressure equation (1.1).

C.2. Hydrodynamic regime

If $d \gg \frac{\lambda_{\rm p}\eta\kappa}{k_{\rm B}T}$, relaxation is by hydrodynamic flow rather than permeation and the relaxation rate of the membrane is now $\tau_{\rm m}(L)^{-1} \propto \frac{d^3}{\eta}(\gamma L^{-4} + \kappa L^{-6})$ (see Eq. (2.18)). In this case, force fluctuations are coherent (as explained in Sect. 3.1 and Appendix A), and we use equation (3.13) to compute the wall pressure. Because of the presence of the wall, in the hydrodynamic regime, we cannot use equation (B.11) for the force amplitude $F(L_{\rm c})$ entering equation (3.13) since it was calculated for a membrane in an infinite embedding medium (*i.e.* without wall). Using equation (2.20b) gives $\langle F(t)F(0)\rangle \propto L_{\rm c}^4 \frac{k_{\rm B}T\eta}{d^3}\delta(t)$ and thus:

$$F(L_{\rm c}) \propto L_{\rm c}^2\sqrt{\frac{k_{\rm B}T\eta}{d^3\tau_{\rm f}(L_{\rm c})}}\,. \tag{C.3}$$

Using equation (C.3) in equation (3.13) leads to $\langle P(d)\rangle \propto \frac{\sqrt{k_{\rm B}T\kappa}}{L_{\rm c}^3}$ for tensionless membranes and to $\langle P(d)\rangle = 0$ for tense membranes. Since the collision length is still given by equation (C.1), we conclude that equation (3.13) reproduces the Helfrich wall pressure in the case of hydrodynamic fluctuations.

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