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Membrane properties revealed by spatiotemporal response to a local inhomogeneity

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ABSTRACT

We study theoretically the spatiotemporal response of a lipid membrane submitted to a local chemical change of its environment, taking into account the time-dependent profile of the reagent concentration due to diffusion in the solution above the membrane. We show that the effect of the evolution of the reagent concentration profile becomes negligible after some time. It then becomes possible to extract interesting properties of the membrane response to the chemical modification. We find that a local density asymmetry between the two monolayers relaxes by spreading diffusively in the whole membrane. This behavior is driven by intermonolayer friction. Moreover, we show how the ratio of the spontaneous curvature change to the equilibrium density change induced by the chemical modification can be extracted from the dynamics of the local membrane deformation. Such information cannot be obtained by analyzing the equilibrium vesicle shapes that exist in different membrane environments in light of the area-difference elasticity model.

1. Introduction

During cell life, membranes are submitted to an inhomogeneous and variable environment. Local inhomogeneities can be strongly related to biological processes, which has led to experiments investigating the effect of local modifications on biomimetic membranes [1]. For instance, in the inner membrane of mitochondria, the enzymes that use the local pH difference across the membrane to synthesize adenosine triphosphate, the cell's fuel, are located in membrane invaginations called cristae [2]. Experiments on model lipid membranes have shown that a local pH change can induce a local dynamical membrane deformation [3–7], and in particular the formation of cristae-like invaginations [3]: membrane shape is tightly coupled to local pH inhomogeneities. Other concentration inhomogeneities in the environment of a cell have a crucial biological role, for instance in chemotaxis or in paracrine signaling. It is therefore of great interest to study the response of a biological membrane to a local modification of its environment.

Motivated by experiments conducted on biomimetic membranes, we have developed a theoretical description of the dynamics of a lipid bilayer membrane submitted to a local concentration increase of a substance that reacts reversibly and instantaneously with the membrane lipid headgroups. We focus on the regime of small deformations, and we treat linear membrane dynamics in the spirit of Ref. [8]. While our first works focused on the simple case of a constant modification of the membrane involving only one wavelength [4,5], we have recently extended our theoretical description in order to take into account the spatiotemporal profile of the fraction of chemically modified lipids resulting from the local reagent concentration increase [7]. This profile is determined by the diffusion of the reagent in the solution that surrounds the membrane. In Ref. [7], we compared the predictions of this theoretical description to experimental measurements of the deformation of the membrane of giant unilamellar vesicles caused by local microinjection of a basic solution, and we obtained good agreement between theory and experiment.

In the present article, we pursue the theoretical investigation of the effect of a local chemical modification on a lipid membrane. In general, the dynamics that results from a local reagent concentration increase is quite complex, as it involves the evolution of the reagent concentration profile simultaneously as the response of the membrane. This is the case in the experimental data analyzed in Ref. [7], which corresponds to microinjection steps lasting a few seconds. Here, we show that the effect of the evolution of the reagent concentration profile on the membrane dynamics becomes negligible some time after the beginning of the reagent concentration increase, after what the dynamics corresponds to the response of the membrane to a chemical modification imposed instantaneously. We find that studying this regime enables to extract interesting properties of the membrane response.

The article is organized as follows. First, in Section 2, we review the linear dynamics of a membrane submitted to a local chemical modification. Then, in Section 3, we study separately the dynamics associated with each of the two effects that can arise from a chemical modification, namely a spontaneous curvature change and an equilibrium density change of the external monolayer. We find that a local asymmetric density perturbation between the two monolayers of the membrane relaxes by spreading diffusively in the whole membrane. Intermonolayer friction plays a crucial part in this behavior.

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Subsequently, in Section 4, we treat the general case where both effects are present, and we show how the ratio of the spontaneous curvature change to the equilibrium density change induced by the local chemical modification can be extracted from the dynamics. This ratio cannot be deduced from the study of global modifications of vesicle equilibrium shapes in light of the area-difference elasticity model [9]. Finally, Section 5 is the conclusion.

2. Dynamics of a chemically modified membrane

For the article to be self-contained, the present section reviews the linear dynamics of a membrane submitted to a local chemical modification, starting from first principles. The main points of this description were presented in Ref. [7]. In that article, we compared theoretical predictions to experimental measurements of the deformation of a membrane submitted to a local and brief pH increase. Here, our aim will be to go further in the analysis of our theoretical description in order to understand the fundamental properties of the response of a membrane to a local chemical modification.

2.1. Monolayer free energy

Our description of the bilayer membrane is based on a local version of the area-difference elasticity membrane model [8,10,11]. We focus on small deformations of an infinite flat membrane, and we denote the upper monolayer by + and the lower one by −.

In the absence of a chemical modification, the local state of each monolayer is described by two variables: the local total curvature c defined on the membrane midlayer, which is common to both monolayers, and the local scaled density $r^{\pm}=(\rho^{\pm}-\rho_0)/\rho_0$, defined on the midlayer of the membrane, ρ_0 being a reference density. The sign convention for the curvature is chosen in such a way that a spherical vesicle has $c<0$. The free energy $f^{\pm}$ per unit area in monolayer $\pm$ reads [11]:

$$f^{\pm}=\frac{\sigma_0}{2}+\frac{\kappa}{4}c^2\pm\frac{\kappa c_0}{2}c+\frac{k}{2}\left(r^{\pm}\pm ec\right)^2, \tag{1}$$

where σ_0 represents the tension of the bilayer and κ its bending modulus, while k is the stretching modulus of a monolayer, and e denotes the distance between the neutral surface [12] of a monolayer and the midsurface of the bilayer. As we assume that the two monolayers of the membrane are identical before the chemical modification, these constants are the same for both monolayers. The spontaneous curvatures of the two monolayers have the same absolute value c_0 and opposite signs, since their lipids are oriented in opposite directions. The expression for $f^{\pm}$ in Eq. (1) corresponds to a general second-order expansion in the small dimensionless local variables $r^{\pm}$ and ec, around the reference state which corresponds to a flat membrane with uniform density $\rho^{\pm}=\rho_0$. It is valid for small deformations around this reference state: $r^{\pm}=\mathcal{O}(\epsilon)$ and $ec=\mathcal{O}(\epsilon)$, where ϵ is a small dimensionless parameter used for bookkeeping purposes, which characterizes the amplitude of the small deformations of the membrane around the reference state. Mathematically, ϵ is considered infinitesimal. Note that in general, both c and $r^{\pm}$, which describe local small deformations around the reference state, are functions of time and of position on the membrane.

Let us now focus on the way the membrane free energy is affected by the local chemical modification. We consider that the reagent source, which corresponds to the micropipette tip in an experiment, is localized in the water above the membrane. Besides, membrane permeation and flip-flop are neglected given their long timescales. Hence, the chemical modification only affects the upper monolayer, i.e., monolayer +, and not the lower one. Let us denote by ϕ the local mass fraction of the lipids of the upper monolayer that are chemically modified: ϕ depends on time and position since it arises from the local chemical modification. We assume that the reagent concentration is small enough for ϕ to remain small at every time and position on the membrane, and we characterize this smallness through $\phi=\mathcal{O}(\epsilon)$. In order to describe the chemically modified membrane, we have to include the third small variable ϕ in our second-order expansion of f^{+}. We obtain [11]:

$$f^{+}=\frac{\sigma_0}{2}+\sigma_1\phi+\frac{\sigma_2}{2}\phi^2+\tilde{\sigma}\left(1+r^{+}\right)\phi\,ln\,\phi+\frac{\kappa}{4}c^2+\frac{\kappa}{2}(c_0+\tilde{c}_0\phi)c+\frac{k}{2}\left(r^{+}+ec\right)^2, \tag{2}$$

where the constants σ_1, σ_2, and $\tilde{c}_0$ describe the response of the membrane to the chemical modification. These constants depend on the reagent that is injected. Their physical meaning will be explained in the next paragraph. Besides, the non-analytical mixing entropy term $\tilde{\sigma}\left(1+r^{+}\right)\phi\,ln\,\phi$ has been added to our second-order expansion [11]. Note that we assume that the three small dimensionless local variables ϕ, $r^{\pm}$ and ec are of the same order. In fact, in the present work, the deformation of the membrane and the density variation are caused by the local chemical modification, i.e., they are a response to ϕ, which justifies that ec and $r^{\pm}$ are of the same order as ϕ. We refer the reader to Ref. [11] for more details on the derivation of Eqs. (1) and (2).

The effect of the chemical modification (i.e., of ϕ) on the upper monolayer is twofold. First, the scaled equilibrium density on the neutral surface of the upper monolayer is changed by the amount $\sigma_1\phi/k$ to first order. Second, the spontaneous curvature of the upper monolayer is changed by the amount $-\bar{c}_0\phi$ to first order, with $\bar{c}_0=\tilde{c}_0+2\sigma_1 e/\kappa$. These results are obtained by minimization of the free energy of a homogeneous monolayer with constant mass (see Appendix A). Hence, the constants σ_1 and $\bar{c}_0$ describe the linear response of the monolayer equilibrium density and of its spontaneous curvature, respectively, to the chemical modification. This explains the physical meaning of the constants σ_1 and $\tilde{c}_0$ in Eq. (2). Note that σ_2 corresponds to the quadratic response of the membrane to the chemical modification, but it will not have any relevant effect in the following.

2.2. Dynamical equations

The elastic force densities in a monolayer described by the free-energy densities in Eqs. (1) and (2) have been derived in Ref. [11] to first order in ϵ, using the principle of virtual work. As we focus on small deformations of an infinite flat membrane, it is convenient to describe it in the Monge gauge by the height $z=h(\boldsymbol{r})$, $\boldsymbol{r}\in\mathbb{R}^2$, of its midlayer with respect to the reference plane $z=0$. Then, $ec=e\nabla^2 h$ to second order. Such a description is adapted to practical cases where the distance between the reagent source and the membrane is much smaller than the vesicle radius. The force per unit area of the reference plane, which we call "force density", then reads to first order in ε

$$\boldsymbol{p}_{\mathrm{t}}^{+}=-k\boldsymbol{\nabla}\left(r^{+}+e\nabla^2 h-\frac{\sigma_1}{k}\phi\right), \tag{3}$$

$$\boldsymbol{p}_{\mathrm{t}}^{-}=-k\boldsymbol{\nabla}\left(r^{-}-e\nabla^2 h\right), \tag{4}$$

$$p_z=\sigma_0\nabla^2 h-\tilde{\kappa}\nabla^4 h-ke\nabla^2 r_{\mathrm{a}}-\left(\frac{\kappa\bar{c}_0}{2}-\sigma_1 e\right)\nabla^2\phi, \tag{5}$$

where $\boldsymbol{p}_{\mathrm{t}}^{\pm}$ is the tangential component of the force density in monolayer "±", while $p_z=p_z^{+}+p_z^{-}$ is the total normal force density in the membrane. In these formulas, we have introduced the antisymmetric scaled density $r_{\mathrm{a}}=r^{+}-r^{-}$, and the constant $\tilde{\kappa}=\kappa+2ke^2$. These expressions show that both the equilibrium density change and the spontaneous curvature change (i.e., both σ_1 and $\bar{c}_0$) can yield a normal force density, and thus a deformation of the membrane, while only the equilibrium density change can yield a tangential force density and induce tangential lipid