Undulation Instability of Lipid Membranes under an Electric Field

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The influence of an external electric field on a poorly conductive membrane such as a lipid bilayer is studied theoretically. The unbalanced electric stress created by an ionic current across a nonperfectly flat membrane gives rise to a destabilizing surface energy enhancing undulations. The deformation of a membrane attached to a frame is derived and the electrohydrodynamic instability of a free floating membrane is studied. We find a most unstable mode of undulation, of wavelength in the μm range, connected to the crossover between membrane and solvent dominated dissipations.

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Because of their low permeability to electrolytes, biological or other lipid membranes are strongly influenced by applied electric fields. Researchers are actively investigating phenomena such as *electroporation* (creation of long-lived pores in a lipid membrane under the action of a strong electric field) [1,2] and electroinjection of macromolecules in vesicles and cells [3] in part because of very promising applications for gene therapy. Other topics, such as the *electroformation* of liposomes [4] or the electrofusion of vesicles and cells [5], require a better understanding of the action of electric fields on lipid bilayers.

This paper discusses the out-of-equilibrium properties of a lipid membrane under electric field. We observe qualitatively different and potentially much stronger effects than in the case of bending deformation of charged fluid membranes at thermal equilibrium, which has been investigated both from the statics [6,7] and dynamics [8] points of view. The effect is quite strong because the conduction charges brought by the field at the membrane interfaces are themselves under the action of the field, and render the membrane unstable to deformations in the direction of field. This generic phenomenon occurs at any interface between media of different electrical conductivities [9,10], and the interplay between electric and a variety of mechanical stresses (surface tension, gravity, etc.) may be responsible for the appearance of interfacial patterns [11,12]. As we show below, an electric field has a very specific impact on lipid membranes due to the peculiar statics (bending and stretching energies), and dynamics (viscous dissipation, internal friction between monolayers) of fluid membranes.

We study the effect of a field on (i) the energetics of a fluid membrane attached on a rigid frame, and (ii) the dynamic instability of a free floating membrane. Our main results are as follows. An electric field applied to a tensionless lipid membrane gives rise to a (potentially large) lateral tension in the membrane, which depends only upon the strength of the applied field and a few constitutive parameters of the membrane. Beyond a threshold this tension can be responsible for the electrical breakdown of the membrane (see [1]). The external field leads to an electrohydrodynamic instability of the membrane. A most unstable mode in the micrometer range is selected by the peculiar dynamics of lipid membranes.

The force experienced by an interface in an electric field E can be calculated by evaluating the discontinuity of the Maxwell stress tensor $\sigma_{ij} = \epsilon(E_i E_j - \frac{1}{2}E^2\delta_{ij})$ across the interface [13]. We consider an infinite membrane of dielectric constant $\epsilon_m(\simeq 2\epsilon_0)$ and conductivity $\chi_m^{-1}(\simeq 10^{-6}\ \mathrm{S/m})$ in a solvent of dielectric constant $\epsilon_1(\simeq 80\epsilon_0)$ and conductivity $\chi_1^{-1}(\simeq 10^{-1}\ \mathrm{S/m})$ (numbers are typical for a lipid membrane in water, ϵ_0 is the permittivity of vacuum). A fixed electric field E (in practice, a fixed electric current $j = \chi_1^{-1}E$) is applied across the membrane, and we note E_m the electric field *inside* the membrane. The electric stress at the membrane interfaces can be understood as the force exerted by the conduction charges brought by the field at the interfaces (the surface charge density induced by the field is of opposite sign at each interface, and of order $\Sigma_\pm \simeq \pm\epsilon_m E_m$).

If the membrane is *perfectly* flat, the electric stress is symmetrically balanced on both sides of the membrane (i.e., $\sigma_{el} \simeq \epsilon_m E_m^2 - \epsilon_m E_m^2 = 0$), which experiences a mere compression [14]. As already pointed out in [2], this perfect cancellation of the net electric stress is, however, accidental since any membrane curvature leads to an unbalanced net stress whose order of magnitude can be expressed as $\sigma_{el} \simeq \epsilon_m E_m^2 d/R$, where d is the thickness of the membrane and R its local radius of curvature (a curvature of the membrane leads to a nonuniform surface charge density—see Fig. 1). In the case of a closed vesicle [2], E_m is given by the potential drop at the vesicle scale (i.e., $E_m \sim ER/d$) as most of the electric field goes around the finite sized object, whereas the current continuity across the (infinite) membrane dictates the expression of E_m here, namely $E_m \sim E\chi_m/\chi_1$. This resulting stress σ_{el} tends to *enhance* the (small) local undulations of the membrane $u(r) = \sum_q u_q e^{iqr}$ (Monge representation in real and Fourier space). This can be understood from Fig. 1 from the redistribution of conduction charges at the interfaces, noting that the electric stress σ_{el} can be rewritten in terms of surface charge densities, i.e.,

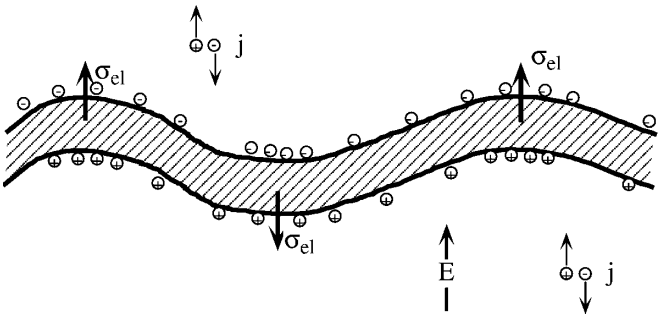

FIG. 1. Net accumulation of conduction charges near a curved lipid membrane under electric field.

$\sigma_{el} = (\Sigma_+^2 - \Sigma_-^2)/\epsilon_m$. After a short transient time $\tau_e \simeq (\epsilon_m/d)\chi_1 H \simeq 10^{-6}$–$10^{-5}$ s (H is the distance between the electrodes), the solution of the Poisson equation (in the limit $\epsilon_m\chi_m^2 \gg \epsilon_1\chi_1^2$) yields the following expression for a given Fourier mode: $\sigma_{el} = 2\epsilon_m(E\chi_m/\chi_1)^2(e^{qd} - 1)/(e^{qd} + 1)u(r)$. Hence, integrating the work of the electric stress (in the large wavelength limit $qd \ll 1$) yields a net decrease in energy

$$F_{el} = -\frac{\Gamma_{el}}{2}\int dS(\nabla u)^2, \qquad \Gamma_{el} = \epsilon_m\left(\frac{\chi_m}{\chi_1}\right)^2 E^2 d\,. \tag{1}$$

At the linear order, this amounts to an effective *negative* surface tension Γ_{el} acting on the membrane (an example of nonlinear effect is discussed in [15]). In the presence of a lipid reservoir (or at the interface between two immiscible fluids of different conductivity), the electric field induces a decrease of the interfacial tension, known as the *electrocapillary effect* [9]. On the contrary, for a fixed number of surfactants, enhancing membrane undulations under electric field builds a concomitant mechanical tension because of deviation from the nominal area per molecule. Hence we expect a tense yet floppy-looking membrane in this case. For typical values of the electric field used in the electroporation and electroformation experiments $E \sim 10^3$ V/m, the electrostatic surface tension reaches $\Gamma_{el} \sim 10^{-3}$ J/m^2, which is comparable to the mechanical tension needed to rupture a lipid membrane [1].

Two consequences of this destabilizing effect are studied below: (i) a membrane on a fixed frame is deformed until the electric stress is balanced by an opposing mechanical stress, and (ii) a free membrane undergoes strong undulations under electric field.

Deformation of a bilayer attached to a fixed frame.—The elastic behavior of a lipid membrane is generally characterized by a bending modulus κ ($\sim 5 \times 10^{-20}$ J), and a stretching modulus K_s ($\sim$0.2 J/m^2) [16]. Typically, bending a lipid membrane involves energies of order $1 - 10k_BT$, while stretching it requires much larger energies. To simplify the description below, we will not include the bending rigidity in the treatment of the static deformation of the membrane, nor will we include the thermal fluctuations of the membrane, restricting ourselves to large electric fields.

We write a linear theory for small deformations of the membrane $qu_q \ll 1$. The membrane is characterized by its total area S, its projected area S_p, and its optimum area for which it is not stretched S_0 (corresponding to a membrane thickness d_0) . We use the two small parameters $\delta \equiv (S_p - S_0)/S_0$ and $\mathcal{I} \equiv (S - S_p)/S_0 \simeq (1 + \delta)\frac{1}{2}\sum q^2|u_q|^2 \simeq \frac{1}{2}\sum q^2|u_q|^2$. The total membrane energy (including electric effects and stretching) reads

$$F = S_0[\tfrac{1}{2}K_s(\delta + \mathcal{I})^2 - \Gamma_{el}\mathcal{I}]. \tag{2}$$

The electric field-induced undulation term (Γ_{el}) is quadratic in qu_q, while the stretching term (K_s) goes up to the fourth order, consistent with the large value of the ratio of the stretching over the electrostatic parameters $\beta \equiv K_s/\Gamma_{el} > 100$.

The minimization of this energy with respect to the area difference $\mathcal{I}$ leads to an equilibrium class of membrane shapes corresponding to a total area difference Δ_S

$$\Delta_S = \delta + \mathcal{I}_{eq} = \frac{\Gamma_{el}}{K_s} \sim 10^{-2}. \tag{3}$$

The energy of the membrane only is $F_m = \frac{1}{2}S_0\Gamma_{el}^2/K_s$, and the energy of the system, including the electrostatic energy, is $F = F_m + F_{el} = -\frac{1}{2}S_0\Gamma_{el}^2/K_s + S_0\Gamma_{el}\delta$. The surface tension of the lipid membrane is given by $\gamma = \partial F_m/\partial S$ with $S = S_0(1 + \delta + \mathcal{I})$. At equilibrium, the mechanical tension is equal, but opposite in sign, to the electrostatic energy per unit area: $\gamma = \Gamma_{el}$. The building of a mechanical tension in a membrane under electric field is due to an increase of its area.

Note that the membrane thinning under stretching does not need to be taken into account, as it contributes to higher order terms ($\sim\Gamma_{el}\mathcal{I}\delta$) only. Note also that the linear theory presented here assumes that membrane parameters such as χ_m and ϵ_m remain constant upon small membrane stretching. Beyond this linear regime, we expect, in particular, the creation of holes in the membrane, which abruptly increase the membrane electrical conductivity.

It is clear from Eq. (3) that the balance between electric field-induced undulation and membrane stretching does not select a particular equilibrium membrane shape, as both effects depend on the global increase of membrane area only. Including the bending energy of the membrane selects the shape of lowest curvature, namely the first harmonic $q_1 = \pi/\sqrt{S_p}$. The energy gap between the different harmonics is, however, small (of order k_BT) for $q\lambda_\kappa < 1$, where $\lambda_\kappa = 2\pi\sqrt{\kappa/\Gamma_{el}}$. For large electric fields ($E \sim 10^3$ V/m), λ_κ is very small ($\sim$50 nm). For small electric fields, the thermal fluctuations dominate both the membrane shape and tension. We postpone the study of the interesting crossover between these two limits to a future publication.

Instability of free floating membranes under electric field.—We now study the case of a free floating membrane under electric field. The dynamics of a free membrane under the action of a field can be decomposed into two mechanisms. (i) The normal deformation of the membrane (described in the previous section), which creates a tension γ in the membrane and saturates when $\gamma = \Gamma_{el}$. (ii) The lateral sliding (contraction) of the membrane, in an attempt to release this tension. The characteristic time for the normal deformation for a given undulation mode of wavelength λ is $\tau_\perp \sim \eta\lambda/\Gamma_{el}$ ($\sim 10^{-6}$ s for $\lambda = 1$ μm), while the sliding motion involves the whole membrane $\tau_\parallel \sim \eta L/\Gamma_{el}$ ($\sim 10^{-3}$ s for $L \sim 1$ mm, see details below). The two mechanisms occur at very different time scales, and can be treated separately.

A thorough treatment of the undulation modes of a film immersed in a solvent can be found in the literature [17]. The electrohydrodynamic instability of a layer of nonconducting fluid between two semi-infinite conducting fluids has been studied in [10], where special attention is given to the peristaltic deformation modes (the two interfaces undulating in antiphase), as these modes lead to the destruction of the film when the two interfaces make contact. In the case of a lipid membrane, these peristaltic modes are suppressed because of the very low compressibility of the film. We study below the bending instability (interfaces undulating in phase) of the membrane.

(i) The normal displacement of the membrane involves viscous dissipation in and around the membrane [18,19]. There are three main sources of dissipation, namely the dissipation in the solvent (viscosity $\eta = 10^{-3}$ Pa · s), which dominates the dynamics of large wavelengths deformation, the friction between the two monolayers (friction coefficient $b_{fr} = 10^8$ Pa · s/m), dominant at intermediate wavelengths, and the membrane surface dissipation (surface viscosity $\mu = 10^{-10}$ Pa · s · m). For fluid lipid membranes, the latter mechanism is relevant at very small wavelength of the order of the bilayer thickness $d = 5$ nm only, and will be neglected altogether. We present below a simplified description of the interplay between external and internal dynamics. For a thorough treatment of membrane dynamics, see Seifert [18].

Neglecting inertia, a normal deformation of the membrane (of typical lateral size $2\pi/q$ and typical velocity $\dot{u}_q$) creates a motion in the surrounding fluid which propagates to a distance $\sim 1/q$. The curvature of the membrane leads to a velocity difference of order $\delta v = qd\dot{u}_q$ between the two monolayers. The power dissipated by viscous effect around and in the membrane can be written, respectively,

$$P_\eta = \eta \int dV(\nabla v)^2 = S\eta \sum_q q\dot{u}_q^2,$$
$$P_{fr} = b_{fr} \int dS(\delta v)^2 = Sb_{fr} \sum_q d^2q^2\dot{u}_q^2. \tag{4}$$

This dissipated power must compensate the power stored in the membrane $P_m = \partial_t F$ [the energy F is given by Eq. (2)]. This condition leads to an evolution equation for each deformation mode:

$$(\eta q + b_{fr}d^2q^2)\dot{u}_q(t) = [\Gamma_{el}q^2\{1 - \beta[\delta(t) + \mathcal{I}(t)]\} - \kappa q^4]u_q(t) \tag{5}$$

with $\beta \equiv K_S/\Gamma_{el} > 100$. The left hand side of this equation describes the viscous dissipation in and around the membrane and the right hand side consists of the electric field-induced undulation term (Γ_{el}) with a stretching saturation (β term). Note that the bending rigidity of the membrane has been added to the membrane energy (κ term), for it is mandatory if one wishes to describe the small wavelength deformations $q > \sqrt{\Gamma_{el}/\kappa}$. This equation is nonlinear, since the saturation involves the total increase of area $\mathcal{I} = \frac{1}{2}\sum_q q^2|u_q|^2$. Thanks to the different time scales for normal and lateral motions, the projected area of the membrane $S_p(t) = S_0[1 + \delta(t)]$ can be considered as constant for the short time evolution.

The nonlinear equation can be solved, but for our purpose, it is sufficient to consider its linearized form, and to treat the saturation dynamics separately. The short time evolution is described by the linear equation

$$(\eta q + b_{fr}d^2q^2)\dot{u}_q = (\Gamma_{el}q^2 - \kappa q^4)u_q. \tag{6}$$

The amplitude of a given Fourier mode has a time evolution $u_q(t) \sim e^{\alpha_q t}$ with

$$\alpha_q = \frac{\Gamma_{el}}{\eta} q\left(\frac{1 - (q/q_{\text{stat}})^2}{1 + q/q_{\text{dyn}}}\right) \tag{7}$$

with the two characteristic wave vectors

$$q_{\text{stat}} = \sqrt{\frac{\Gamma_{el}}{\kappa}} \sim 10^8 \text{ m}^{-1},$$
$$q_{\text{dyn}} = \frac{\eta}{bd^2} \sim 5 \times 10^5 \text{ m}^{-1}. \tag{8}$$

The evolution rate presents a sharp maximum at

$$q^* = (q_{\text{dyn}}q_{\text{stat}}^2)^{1/3} = 2 \times 10^7 \text{ m}^{-1} \tag{9}$$

for $q_{\text{stat}} \gg q_{\text{dyn}}$. This defines a particular length scale which grows exponentially faster than the others: $\lambda^* = 2\pi/q^* \sim 0.5$ μm. The corresponding growth rate is $\alpha_q^* \sim \frac{\Gamma}{bd^2} \sim 5 \times 10^5 \text{ s}^{-1}$. The evolution saturates similarly for all length scales when $\beta[\delta(t) + \mathcal{I}(t)] = 1$, at which point a mechanical tension Γ_{el} is established, leading to a contraction of the membrane.

In many practical situations, fixed boundaries or walls at a distance h from the membrane may strongly modify the solvent hydrodynamics. From wavelengths larger than the distance to the wall, the membrane displacement creates a solvent flow which is mostly parallel to the wall and varies mostly in the direction normal to the wall. Because of the incompressibility of the solvent, the lateral velocity is of order $v_x = \dot{u}/(qh)$ and the dissipated power [Eq. (4)] becomes $P_{\eta,h} = S\eta\sum_q \dot{u}_q^2/q^2h^3$ for $qh < 1$. The left hand side of Eq. (6) is modified accordingly, and shows an optimal wave vector $q_h^* \sim \sqrt{q^*/h}$ where q^* is given by

Eq. (9). For $h = 10$ nm, the fastest growing wavelength is of order $2\pi/q_h^* \sim 0.1$ μm.

(ii) The lateral motion of the membrane occurs at an almost constant surface tension, because the time needed to build up the tension $\tau_\perp$ is much smaller than the time over which it could be released. The contraction of the membrane involves solvent flow over large length scales (the membrane size ~mm). In consequence, (i) solvent inertial effects must be included to calculate the viscous dissipation, and (ii) the shape of membrane corrugations have little effect on the solvent flow, which depends only on the total area reduction. Hence the evolution of the membrane projected area S_p [or the variable $\delta \equiv S_p/S_0 - 1$ in Eq. (5)] *does not influence* the value of the fastest growing mode q^* [Eq. (9)]. We give below some qualitative arguments to derive $\delta(t)$ both for a free membrane and for a membrane in the vicinity of a solid wall [20]. More than the actual form of $\delta(t)$, we stress again that the important point here is that the contraction dynamics does not modify q^*.

The solvent flow near an impulsively started plate of size L_0 extends over a size $L_z = L_0/\sqrt{1 + L_0^2/\nu t}$ where $\nu = \eta/\rho$ is the kinematic viscosity ($\sim 10^{-6}$ m^2/s for water—ρ is the density of water) [21]. For a membrane near a wall, this size quickly saturates to $L_z = h$, for a free membrane, it saturates to $L_z = L_0$ after a time $\tau_\nu = L_0^2/\nu$ (~ 1 s for $L_0 = 1$ mm). Balancing the viscous dissipation with the energy gain (per unit time) accompanying the contraction of the membrane under (constant) surface tension, one obtains qualitatively the short time kinetics of contraction: $\delta \simeq -(t/\tau_{\rm slide})^{3/2}$ for a free membrane, and $\delta \simeq -t/\tau_{{\rm slide},h}$ for a membrane near a wall. Both kinetics involve the characteristic times $\tau_\Gamma \equiv \eta L_0/\Gamma_{el} \simeq 10^{-3}$ s and $\tau_\nu = L_0^2/\nu \simeq 1$ s. The contraction time for a free membrane is fairly fast: $\tau_{\rm slide} = (\tau_\Gamma^2 \tau_\nu)^{1/3} \sim 10^{-2}$ s, while it is much slower for a membrane near a wall: $\tau_{{\rm slide},h} = \tau_\Gamma L_0/h \sim 10^2$ s (note that a quantitative theory should include solvent permeation through the membrane in this confined situation).

To conclude this paper, we propose that the electrodynamic instability described above may play an important role in the first stage of the electroformation of liposomes, which consists in a controlled swelling of an electrode deposit of (charged *or* neutral) lipids to form vesicles of fairly well controlled sizes under electric field [4]. A remarkable feature of this technique is that it produces vesicles of fairly well defined size. We find a fastest growing undulation mode of wavelength in the μm range [Eqs. (8) and (9)]. This mode might be the precursor of large scale deformations of the membrane which, after a complex process partly sketched in Ref. [4] and involving coalescence of neighboring blisters, lead to the formation of closed vesicles. Future developments will include the treatment of small pores which are expected to be present in a membrane under tension, and their influence on both the membrane electrical conductivity (hence Γ_{el}) and dynamics (solvent permeation through the membrane).

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