

Effect of voltage on pores in membranes

M. Winterhalter and W. Helfrich

Institut für Theoretische Physik, Freie Universität Berlin, Arnimallee 14, D-1000 Berlin 33, West Germany

(Received 30 June 1987)

In our model, a voltage is applied across an insulating lipid membrane embedded in a conducting aqueous medium and containing a pore. It is shown to produce along the pore boundary negative contributions to both the edge energy and the lateral tension of the membrane. One effect promotes opening and the other closure of the pore. Surprisingly, we find that voltage may inhibit pore opening and stabilize pores of a certain size.

Pores in lipid bilayers may be generated thermally or by electric fields. Thermal pores have been invoked to explain the opening of small vesicles by osmotically induced lateral tensions.¹ They have also been employed to account for the rupture of black lipid membranes under the combined action of a lateral tension and a transverse electric field.² Electrically generated pores appear to be instrumental in the rapid electrical breakdown preceding the slow mechanical rupture of bilayers.³

A pore may tend to open or close, depending on the forces acting on its boundary. The present note examines the role of a transverse voltage in this context. We show that the electric field promotes opening or, in other situations, closure of the pore. Moreover, it may stabilize pores of a certain size. The calculations are based on a continuum model of fluid membranes and neglect the thickness of the space-charge layers produced by the voltage. We assume the membrane to be unstretchable and the pore to be circular.

Pore opening due to lateral tension was treated for the first time by Deryagin and Gutop⁴ and later by others.^{1,5} The mechanical energy of a pore consists of two parts. One is the energy of the membrane edge surrounding the pore,

$$E_\gamma = 2\pi a \gamma, \tag{1}$$

where a is the radius of the pore and γ the energy per unit length of edge. The second part,

$$E_\sigma = -\pi a^2 \sigma, \tag{2}$$

arises from increasing the effective membrane area in the presence of a lateral tension σ . The total energy has its

maximum $\pi\gamma^2/\sigma$ at the radius

$$a^* = \gamma/\sigma. \tag{3}$$

The pore will grow to infinity if this radius of unstable equilibrium is reached, e.g., by a thermal fluctuation, thus causing membrane rupture.

In the past the effect of a transverse electric field has been dealt with in terms of a condenser energy.⁶⁻⁸ Inside the pore the lipid was thought to be replaced with nonconducting water. The associated change of pore energy is

$$E_c = \pi a^2 (\epsilon_L - \epsilon_W) \epsilon_0 \frac{\varphi_0^2}{2d}. \tag{4}$$

Here d is the thickness of the membrane and φ_0 is the applied voltage, while $\epsilon_L = 2$ and $\epsilon_W = 80$ are the dielectric constants of lipid and water, respectively. The condenser energy acts as an additional lateral tension which promotes the opening of the hole. However, since the pore is conductive, the applied voltage will collapse in the region of the pore unless the radius of the hole is very small.

In a system with free electric charges one cannot use dielectric energies to treat the interaction with the electric field. Instead, the forces exerted by the field have to be calculated from the Maxwell stresses

$$T_{l,m} = \epsilon \epsilon_0 [E_l E_m - \frac{1}{2} \delta_{l,m} E^2], \tag{5}$$

where \mathbf{E} is the field strength. The electric potential φ in the conducting water around a pore in an insulating membrane may be expressed by that of a conducting disk in an insulating medium, provided we neglect the finite thickness of the membrane. Taking the latter potential from textbooks⁹ and adjusting it to the present case [by putting $\varphi(0,0) = 0$ and reversing the sign of φ on one side], we find

$$\varphi(r,z) = \pm \frac{\varphi_0}{\pi} \operatorname{arccot} \left(\frac{2a^2}{r^2 + z^2 - a^2 + [(r^2 + z^2 - a^2)^2 + 4a^2 z^2]^{1/2}} \right)^{1/2}, \tag{6}$$

where $r^2 = x^2 + y^2$ and φ_0 is the potential difference across the membrane far away from the pore. The positive and the negative sign holds, respectively, for the upper ($z > 0$) and the lower ($z < 0$) side of the membrane which coincides with the xy plane. The potential (6) and its derivatives are readily seen to be continuous at $z = 0$ for $r < a$.

In the spirit of this approximation, the radial component of the electric field strength is taken to be

$$E_r^L = \lim_{\epsilon \rightarrow 0} \left(-\frac{\partial \varphi}{\partial r}(r,z = \epsilon) \right) = -\frac{\varphi_0}{\pi} \frac{a}{r(r^2 - a^2)^{1/2}} \tag{7}$$

on the upper interface and equal but opposite on the lower one. Recalling now the finite thickness of the membrane, we write for the transverse field strength inside the membrane

$$E_z^L = \lim_{\epsilon \rightarrow 0} \left[-\frac{\varphi(r, z = +\epsilon) - \varphi(r, z = -\epsilon)}{d} \right] \\ = -\frac{2\varphi_0}{d\pi} \arctan \left[\frac{r^2}{a^2} - 1 \right]^{1/2}. \quad (8)$$

There are several ways of calculating the interaction of the electric field with the pore. It seems advantageous to divide the electrical forces into those acting at the lipid/water interfaces where the latter are parallel to the xy plane and those felt by the membrane edge. The normal forces exerted on the upper and the lower interface cancel each other. We neglect the thinning of the membrane which they may produce. The radial force density is

$$f_{rz} = -\epsilon_L \epsilon_0 E_r^L E_z^L < 0 \quad (9)$$

on either interface. Replacing the sum of the two by a Maxwell lateral tension σ_M through

$$2f_{rz} = \frac{\partial \sigma_M}{\partial r}, \quad (10)$$

one finds

$$\sigma_M = -2\epsilon_L \epsilon_0 \int_a^r dr E_r^L E_z^L \\ = -\frac{1}{2} \epsilon_L \epsilon_0 \frac{[2\varphi(r, z = +\epsilon)]^2}{d}. \quad (11)$$

The result is identical to the usual condenser force which tries to expand the area of the membrane by pushing its boundaries outwards. In fact, the same σ_M can be obtained directly from the Maxwell stress

$$T_{rr} = -\frac{1}{2} \epsilon_L \epsilon_0 \frac{[2\varphi(r, z = +\epsilon)]^2}{d^2} \quad (12)$$

inside the membrane. The force density $2f_{rz}$ has to be balanced, in an immobile membrane, by a mechanical force. Accordingly, there is an electrically induced mechanical lateral tension σ_{el} obeying $\sigma_M + \sigma_{el} = \text{const}$. We may expect $\sigma_{el} = 0$ far away from the pore and

$$\sigma_{el}(a) = -\frac{1}{2} \epsilon_L \epsilon_0 \frac{\varphi_0^2}{d} \quad (13)$$

at the pore boundary where φ has practically come down to zero. Being negative, $\varphi_{el}(a)$ will resist an opening of the pore.

The edge of an infinitely thin disk or, alternatively, membrane, represents a singularity which, for the moment, may be regarded as a straight line. The force acting on it can be obtained by integrating the Maxwell stresses over a surrounding cylinder of infinitesimal radius. The electric potential in the water near the membrane edge obeys the approximation

$$\varphi = \frac{\varphi_0}{\pi} \left[\frac{2\rho}{a} \right]^{1/2} \sin \frac{\theta}{2}, \quad (14)$$

which again is adapted from the well-known formula valid for the disk.⁹ The old variables are related to the new ones by $z = \rho \sin \theta$ and $r - a = \rho \cos \theta$. Carrying out the integration, one finds for the force per unit length

$$F_r = \frac{\epsilon_W \epsilon_0 \varphi_0^2}{2\pi a}. \quad (15)$$

This can be converted via $F_r = -\gamma_{el}/a$ into an electric contribution to the edge energy

$$\gamma_{el} = -\frac{\epsilon_W \epsilon_0 \varphi_0^2}{2\pi}. \quad (16)$$

The result is, of course, independent of the radius of the surrounding cylinder (and of the shape of the enclosure) as long as we consider a straight edge and use the potential (14). However, if a finite ρ is chosen at which E_z^L is substantial the integration must not include the interior of the membrane. Incidentally, the same edge energy may be obtained directly via the capacitance $C_{\text{disk}} = 8\epsilon_W \epsilon_0 a$ of the conducting disk.

The quantities σ_{el} and γ_{el} are independent of the pore radius a . Therefore we may introduce

$$\gamma_{\text{eff}} = \gamma + \gamma_{el}; \quad \sigma_{\text{eff}} = \sigma + \sigma_{el}(a) \quad (17)$$

as the effective values of the edge energy and of the lateral tension acting on the pore boundary. They are used to calculate in the same way as before an equilibrium radius

$$a^* = \frac{\gamma - \epsilon_W \epsilon_0 \varphi_0^2 / 2\pi}{\sigma - \epsilon_L \epsilon_0 \varphi_0^2 / 2d} \quad (18)$$

and the associated extremum of the energy $\pi \gamma_{\text{eff}}^2 / \sigma_{\text{eff}}$. In principle, γ_{eff} and σ_{eff} can be negative at high enough voltages φ_0 . If both of them are negative, the pore radius a^* represents stable equilibrium. Its asymptotic value a_{∞}^* at high enough voltages is given by the simple formula $a_{\infty}^* = \epsilon_W d / (\epsilon_L \pi) \approx 13d$ for the quoted values of ϵ_W and ϵ_L and thus about 50 nm for the typical membrane thickness of 4 nm. There is no physical solution $a^* > 0$ of Eq. (18) if γ_{eff} and σ_{eff} differ in sign. The response of the pore when the voltage is increased will, of course, depend very much on whether γ_{eff} or σ_{eff} reaches zero first.

The lateral tension of black lipid membranes is usually on the order of a few 10^{-3} Nm^{-1} and sometimes less than that.¹¹ Edge energies have been measured only for lecithin and similar membranes; they are about 10^{-11} Jm^{-1} .^{1,2,10} In Fig. 1 we have plotted the equilibrium radius versus the applied voltage for the case $\sigma = 2 \times 10^{-3} \text{ Nm}^{-1}$ and $\gamma = 2 \times 10^{-11} \text{ Jm}^{-1}$. The effective edge energy, and thus a , reaches zero at $\varphi_0 = 0.45 \text{ V}$ where the effective lateral tension is still positive. If there is a pore, it must then open, which means rupture of the film. Thermal fluctuations of the radius will allow opening at some lower voltage. The equilibrium radius and the energy barrier of rupture are controlled not only by γ_{eff} but also by σ_{eff} . The decrease of the latter tends to stabilize the pore. This should be an important effect if γ_{eff} and σ_{eff} approach zero at similar voltages.

An example of the opposite case, in which σ_{eff} changes sign at a lower voltage than γ_{eff} , is shown in Fig. 2. We have altered only the lateral tension which is now

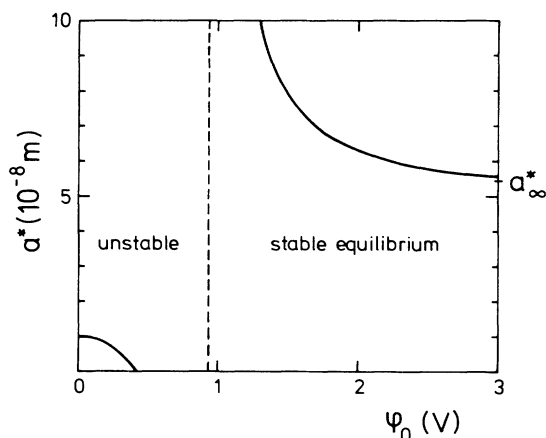


FIG. 1. Equilibrium pore radius a^* vs applied voltage φ_0 for the edge energy $\gamma=2\times 10^{-11}$ J/m and the lateral tension $\sigma=2\times 10^{-3}$ N/m. Other quantities involved are $\epsilon_w=80$, $\epsilon_L=2$, $d=4$ nm.

$\sigma=1\times 10^{-4}$ Nm $^{-1}$. Both the equilibrium radius and the energy barrier go to infinity as the voltage is raised. This has the startling consequence that pore opening by thermal activation becomes more and more difficult and finally impossible. A pore should remain near some minimum radius of molecular dimension at low voltages. At higher voltages where σ_{eff} is also negative it may be expected to assume the larger, stable radii given by (18). However, the same voltages should destabilize the black film as a whole. This is because $\sigma_{\text{eff}} < 0$ is equivalent to $\sigma + \sigma_M < 0$, which in turn implies that the condenser energy (σ_M) outweighs the mechanical energy (σ) per unit area. Therefore, the black film may bulge and spread into the aqueous medium, provided the so-called torus around the hole supporting it acts as a lipid reservoir¹¹

We believe that there are good chances of finding the stable pores of Eq. (18) in the membranes of vesicles exposed to an electric field. In fact, preliminary evidence for the electric perforation of lecithin vesicle membranes that did not result in microscopically visible holes¹² has prompted us to the present study. Vesicles differ from

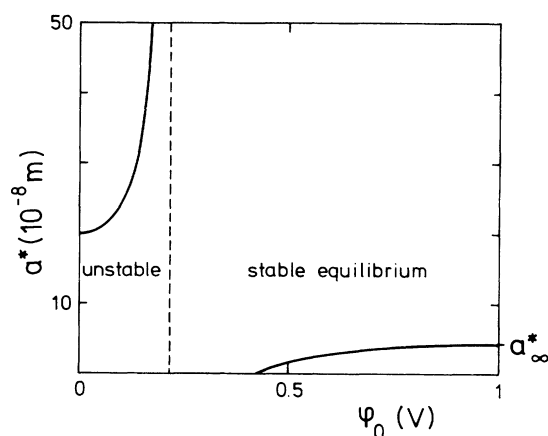


FIG. 2. Equilibrium pore radius a^* vs applied voltage φ_0 for $\gamma=2\times 10^{-11}$ J/m and $\sigma=0.1\times 10^{-3}$ N/m.

black films by their nonplanar geometry, the lack of a lipid reservoir, and vanishing lateral tension at zero-field strength. However, the electric field produces position-dependent lateral tensions and shape changes, both of which are quite difficult to calculate. Only the ellipsoidal deformation of the closed sphere has been treated so far.¹³

Our theory holds for a single pore or pores in a concentration low enough to keep the membrane an insulator. Actually, high enough voltages will always cause electrical breakthroughs. This mechanism could result, for $\gamma_{\text{eff}} > 0$, in a large population of small pores of minimum size that increase the conductivity of the membrane so that the applied voltage limits itself. If the limiting voltage is very low, it may rule out the formation of the stable pores of Eq. (18) and, at high lateral tensions, even prevent a substantial effect of voltage on membrane rupture. However, a dramatic increase of the rupture rate as a function of voltage is well documented up to about 0.5 V.² Summing up, we feel that in dealing with the response of membranes to voltage one has to be aware of both the destabilizing and stabilizing effects of the electric field on pores.

¹C. Taupin, M. Dvolaitzky, and C. Sauterey, *Biochemistry* **14**, 4771 (1975).

²L. V. Chernomordik *et al.*, *Biochim. Biophys. Acta* **812**, 643 (1985).

³R. Benz, F. Beckers, and U. Zimmermann, *J. Membr. Bio.* **48**, 181 (1979).

⁴B. V. Deryagin and Yu. V. Gutop, *Colloid. J. USSR* **24**, 370 (1962).

⁵J. D. Litster, *Phys. Lett.* **53A**, 193 (1975).

⁶I. G. Abidor *et al.*, *Bioelectrochem. Bioenerg.* **6**, 37 (1979).

⁷A. G. Petrov, M. D. Mitov, and A. Derzhanski, in *Advances in Liquid Crystal Research and Applications*, edited by L. Bata (Pergamon, Oxford, 1980), Vol. 2, p. 695.

⁸K. T. Powell and J. C. Weaver, *Bioelectrochem. Bioenerg.* **15**, 211 (1986).

⁹See, e.g., L. D. Landau and E. M. Lifshitz, *Electrodynamics of Continuous Media*, Course of Theoretical Physics, Vol. 8 (Pergamon, New York, 1960).

¹⁰W. Harbich and W. Helfrich, *Z. Naturforsch.* **34a**, 1063 (1979).

¹¹See, e.g., H. T. Tien, *Bilayer Lipid Membranes* (Marcel Dekker, New York, 1974).

¹²G. Weitz, R. M. Servuss, and W. Helfrich (unpublished).

¹³M. Winterhalter and W. Helfrich, *J. Colloid Interface Sci.* (to be published).