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2014 J. Phys.: Conf. Ser. 558 012018

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Electromechanical properties of biomembranes and nerves

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Abstract. Lipid membranes are insulators and capacitors, which can be charged by an external electric field. This phenomenon plays an important role in the field of electrophysiology, for instance when describing nerve pulse conduction. Membranes are also made of polar molecules meaning that they contain molecules with permanent electrical dipole moments. Therefore, the properties of membranes are subject to changes in trans-membrane voltage. Vice versa, mechanical forces on membranes lead to changes in the membrane potential. Associated effects are flexoelectricity, piezoelectricity, and electrostriction.

Lipid membranes can melt from an ordered to a disordered state. Due to the change of membrane dimensions associated with lipid membrane melting, electrical properties are linked to the melting transition. Melting of the membrane can induce changes in trans-membrane potential, and application of voltage can lead to a shift of the melting transition. Further, close to transitions membranes are very susceptible to piezoelectric phenomena.

We discuss these phenomena in relation with the occurrence of lipid ion channels. Close to melting transitions, lipid membranes display step-wise ion conduction events, which are indistinguishable from protein ion channels. These channels display a voltage-dependent open probability. One finds asymmetric current-voltage relations of the pure membrane very similar to those found for various protein channels. This asymmetry falsely has been considered a criterion to distinguish lipid channels from protein channels. However, we show that the asymmetry can arise from the electromechanical properties of the lipid membrane itself.

Finally, we discuss electromechanical behavior in connection with the electromechanical theory of nerve pulse transduction. It has been found experimentally that nerve pulses are related to changes in nerve thickness. Thus, during the nerve pulse a solitary mechanical pulse travels along the nerve. Due to electromechanical coupling it is unavoidable that this pulse generates a trans-membrane voltage. In the past, we have proposed that this electromechanical pulse is the origin of the action potential in nerves.

1. Introduction

Biological membranes are thin quasi-twodimensional layers mainly consisting of proteins and lipids. While research mostly focusses on the properties of individual macromolecules, e.g., on ion channel proteins or ion pumps, the total membrane possesses macroscopic cooperative features such as melting transitions and curvature fluctuations that cannot be understood on the molecular level. These properties are expressed in susceptibilities such as heat capacity, lateral compressibility, bending elasticity or capacitive susceptibility. Lipid membranes can melt from a solid to a liquid phase. In these transitions, the order of the lipids changes. Thus, the melting is associated to both, enthalpy and entropy changes. Such transitions can also be found in biological membranes under physiological conditions. As an example, a heat



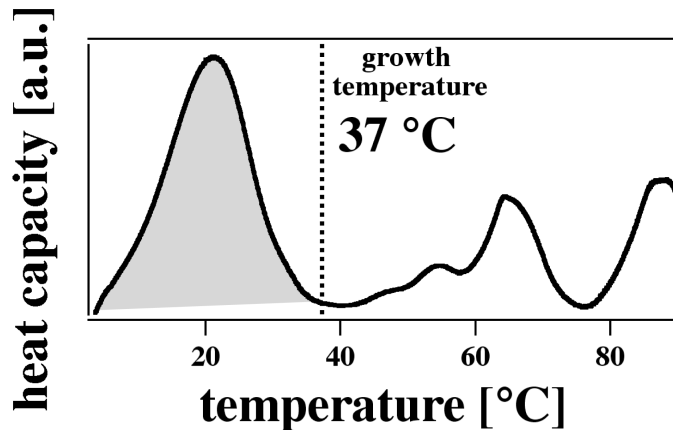


Figure 1. Heat capacity profile of *E. coli* membranes. The grey-shaded region below growth temperature represents the membrane melting transition. The peaks above growth temperature show protein unfolding. From [5].

capacity profile of *E. coli* membranes is shown in figure 1. In the melting transition, the spatial dimensions of the membrane change. For instance, upon melting the synthetic lipid dipalmitoyl phosphatidylcholine (DPPC) increases its area by about 24% and reduces its thickness by 16%. The heat absorbed in the transition is about 35 kJ/mol.

Membranes are very thin. They possess a thickness of about 5nm in their solid state. The core of the membrane is composed of hydrocarbon chains. Therefore, the membrane interior can be considered an insulator. Consequently, the biomembrane has the properties of a capacitor. Typically, the capacitance of a membrane is of the order of 1 $\mu\text{F}/\text{cm}^2$. In biological cells, the membrane is exposed to voltage differences of the order of 100 mV. Thus, the biological membrane is charged under physiological conditions.

The dimensional changes in the melting transitions have a number of consequences. Among those are [1]:

- both hydrostatic and lateral pressure changes influence the phase state of the membrane and are intrinsically coupled to heat absorption or release.
- hydrostatic and lateral pressure changes voltage across the membrane, and the charge on the membrane capacitor can change. Thus, the membrane is piezoelectric.
- voltage changes can induce membrane melting.

These features are important for various properties of biological membranes. For instance, it was shown that biomembranes slightly above a melting transition can support electromechanical solitons that resemble nerve pulses [2]. Further, in the transition one finds density fluctuations that result in the spontaneous formation of pores in the membrane [3]. These pores display open-close characteristics very similar to those reported for protein ion channels [4].

The thermodynamics of biological membranes putatively explains many properties of excitatory cells on the level of macroscopic physics rather than on the level of molecular biology. This review will introduce into some of these phenomena.

2. Membrane capacitors

The capacitance, C_m , of a planar membrane is given by

$$C_m = \varepsilon \varepsilon_0 \frac{A}{D}, \quad (1)$$

where ε_0 is the vacuum permittivity, ε is the dielectric constant, A is the membrane area and D is the membrane thickness. The charge, q , on a capacitor is given by

$$q = C_m \cdot V_m, \quad (2)$$

where V_m is the transmembrane voltage. Since in the transition the area changes by about 24%

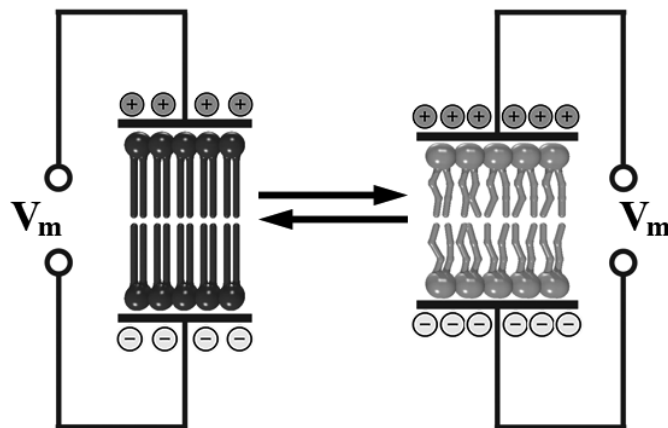


Figure 2. During the melting transition of a membrane both its area and thickness changes. This implies that the capacitance of the membrane varies as a function of phase state. It is higher in the liquid state.

and the thickness by -16%, one finds an increase in capacitance upon melting from a solid to a liquid membrane phase of approximately 50%.

2.1. Capacitive susceptibility

The capacitance solely depends on the dimensions of the membrane, if $\varepsilon = \text{constant}$. However, the opposite charges on the two plates of a capacitor attract each other and generate a force on the membrane. This effect is called 'electrostriction'. If the voltage across a membrane increases, the forces on the membrane also increase. Therefore the capacitance changes as well. For a symmetric membrane, the capacitance always increases upon increasing the voltage. This effect can be taken into account by considering the capacitive susceptibility, \hat{C}_m :

$$\hat{C}_m = \frac{dq}{dV_m} = C_m + V_m \frac{\partial C_m}{\partial V_m}, \quad (3)$$

where the charge, q , is given by equation (2). The second term in this equation could be considered an excess capacitance. It assumes a maximum in the melting transition (see figure 3).

3. Fluctuations

Due to the fluctuation-dissipation theorem, all response functions (susceptibilities) are related to the mean square fluctuations of extensive variables. For instance, the heat capacity, $c_p = (\partial H / \partial T)_p$, is given by

$$c_p = \frac{\langle H^2 \rangle - \langle H \rangle^2}{kT^2}, \quad (4)$$

while the isothermal volume compressibility, $\kappa_T^V = -(\partial V / \partial p)_T$, is related to volume fluctuations

$$\kappa_T^V = \frac{\langle V^2 \rangle - \langle V \rangle^2}{kT}, \quad (5)$$

and the capacitive susceptibility is given by

$$\hat{C}_m = \frac{\langle q^2 \rangle - \langle q \rangle^2}{kT}. \quad (6)$$

Similarly, fluctuations in area are related to the isothermal area compressibility and fluctuations in curvature to the bending elasticity. The heat capacity assumes a maximum in the melting

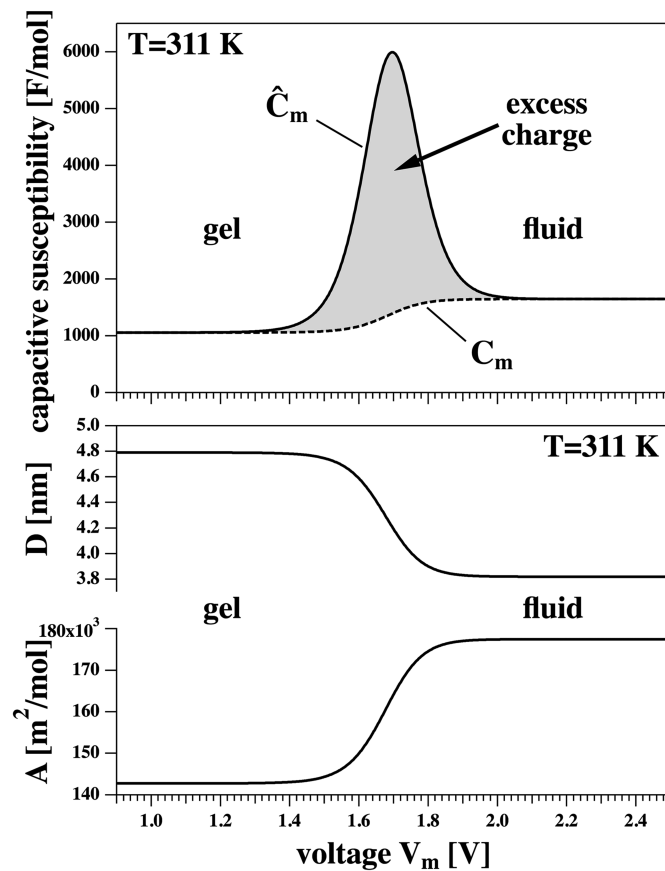


Figure 3. Increase in voltage reduces thickness and increases area. As a consequence, membranes can be moved through their melting transition by voltage changes. The capacitive susceptibility, \hat{C}_m , reaches a maximum at the melting temperature. The voltage-induced transition is associated to an excess charge. From [1].

transition and thus the fluctuations are at maximum. Similarly, compressibility, bending elasticity and capacitive susceptibility all assume maxima in the transition regime.

It has been shown that in melting transitions, excess volume changes are proportional to excess enthalpy changes, i.e., $\Delta V(T) = \gamma_V \Delta H(T)$. Here, γ_V is a material constant. This implies that excess volume and enthalpy fluctuations are also proportional functions. A consequence is that excess heat capacity and isothermal volume compressibility are proportional functions of temperature, pressure, etc. I.e.,

$$\Delta c_p \propto \Delta \kappa_T^V \quad (7)$$

Similarly one can directly or indirectly conclude from experiment that the excess heat capacity is proportional to other response functions of lipid membranes close to transitions [6, 7, 1], f.e.,

$$\begin{aligned} \Delta c_p &\propto \Delta \kappa_T^A \quad (\text{area compressibility}) \\ \Delta c_p &\propto \Delta \kappa_B \quad (\text{bending elasticity}) \\ \Delta c_p &\propto \Delta \hat{C}_m \quad (\text{capacitive susceptibility}) \end{aligned} \quad (8)$$

These relations are not based on first principles and should be taken as empirical correlations found to be true for membranes. The proportionality constants depend on the dimensions of the solid and liquid membrane. The heat capacity is easy to measure in a calorimeter. The other response functions can readily be calculated from the calorimetric experiment.

4. The nervous impulse

The nerve pulse consists of a propagating voltage pulse with typical velocities of 1-100 m/s that last about 1 ms. It follows that the typical dimension of a nerve pulse is about 1 mm to 10 cm.

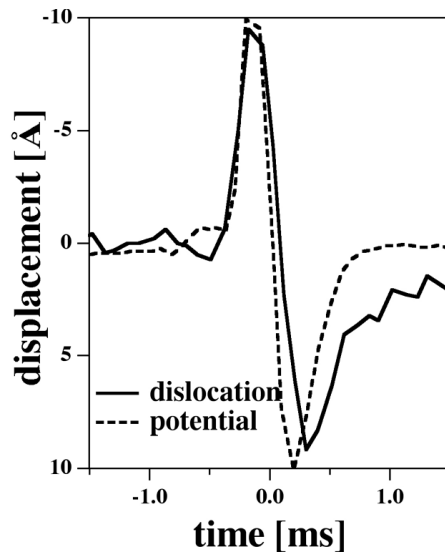


Figure 4. Thickness change of a squid axon during the action potential as a function of time (solid line). The dashed line represents the voltage change. The two functions are within error proportional. Adapted from [8].

Thus, it is of macroscopic dimension. In the biological literature, the nerve pulse is considered a purely electrical phenomenon involving capacitors (the membrane), resistors (ion channel proteins) and electrical currents (ion flows). However, during the nerve pulse one also finds changes in nerve dimensions (thickness and length [8, 9], see figure 4) and in temperature [10]. Thus, the nerve pulse should be considered a thermodynamic or hydrodynamic phenomenon. Below, we show that the nerve pulse can be seen as a localized density pulse related to the propagation of sound.

4.1. Sound velocity

The above relations (equation (8)) help to determine other membrane properties that are related to the response functions. The lateral sound velocity, c , in membranes is defined as

$$c^2 = \left(\frac{\partial \rho^A}{\partial p} \right)_S = \frac{1}{\kappa_S^A \rho^A} \quad (9)$$

Thus, it depends both on the lateral density and on the adiabatic compressibility, κ_S^A . The adiabatic compressibility is a function of frequency because it depends on the translocation of heat from the membrane to the membrane environment. The smaller the frequency, the larger is the aqueous volume that contributes as a heat reservoir and the larger is the adiabatic compressibility [11]. In the limit of zero frequency one obtains the isothermal limit and the adiabatic compressibility, κ_S^A is equal to the isothermal compressibility, κ_T^A . The frequency dependence of the sound velocity is called 'dispersion'. The sound velocity in membranes is generally higher at higher frequencies

Using the above thermodynamic relations between heat capacity and compressibility, one can calculate the low frequency sound velocity as a function of temperature (or as a function of density). Since the compressibility displays a maximum in the melting transition, the lateral sound velocity displays a minimum (shown in figure 5, left. From [2]). In this figure, small density corresponds to the liquid membrane phase while high density corresponds to the solid membrane phase. The membrane in the liquid phase is thus a spring with interesting spring properties: upon compression of the liquid phase the spring first becomes softer (in the transition) and then becomes stiffer (in the solid phase).

The lateral density of the membrane shall be given by $\rho^A = \rho_0^A + \Delta\rho^A$, where ρ_0^A is the density of the liquid membrane. The sound velocity is a non-linear function of the lateral density change,

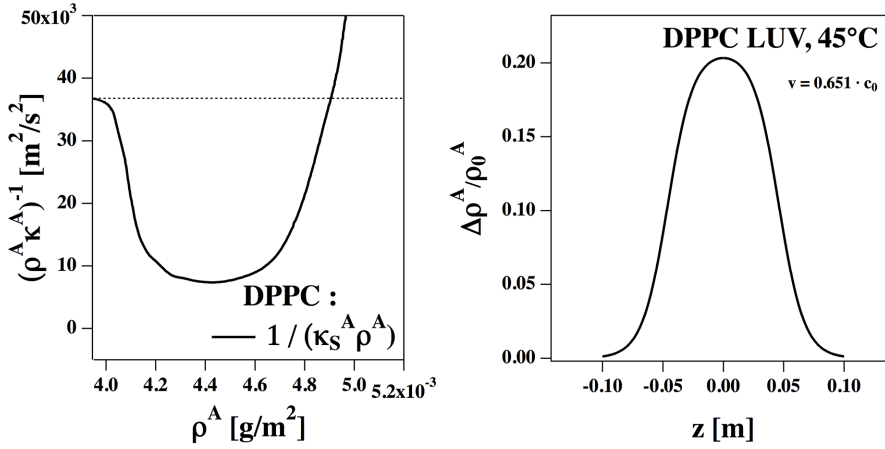


Figure 5. Left: The sound velocity in a lipid membrane close to a transition is a function of density [2]. Small density corresponds to a liquid membrane whereas high density corresponds to a solid membrane. The pronounced minimum is found in the chain melting regime. It is caused by the maximum of area fluctuations in the membrane at the transition. Right: Density soliton in a membrane cylinder using the sound velocity profile shown in the left hand panel [2]

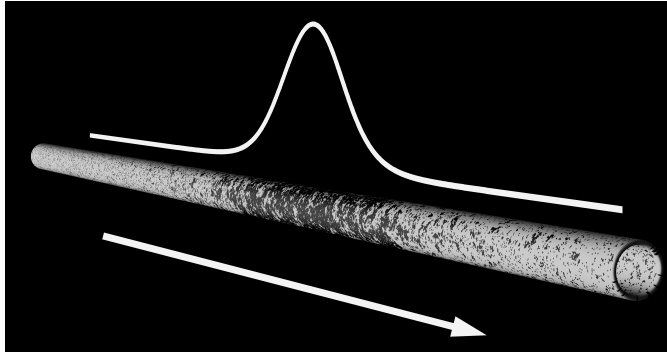


Figure 6. Schematic representation of a density soliton in a cylindrical membrane. The pulse consists of a traveling solid segment (dark shade) traveling in a liquid membrane environment.

$\Delta\rho^A$, which can be Taylor-expanded into

$$c^2 = c_0^2 + p\Delta\rho^A + q(\Delta\rho^A)^2 + \dots \quad (10)$$

4.2. Solitons in nerve axons

The non-linearity of the sound velocity and the presence of dispersion give rise to the possibility of soliton propagation. Below, we show as a quasi-one-dimensional example a long cylindrical membrane comparable to the axon of a nerve. The wave equation for one-dimensional sound propagation is given by [12]

$$\frac{\partial^2}{\partial t^2}\Delta\rho = \frac{\partial}{\partial x} \left(c^2 \frac{\partial}{\partial x} \Delta\rho \right). \quad (11)$$

By inserting equation (10) into this equation, we obtain

$$\frac{\partial^2}{\partial t^2}\Delta\rho = \frac{\partial}{\partial x} \left((c_0^2 + p\Delta\rho + q\rho^2 + \dots) \frac{\partial}{\partial x} \Delta\rho \right) - h \frac{\partial^4}{\partial x^4} \Delta\rho \quad (12)$$

The second term is an ad hoc dispersion term that describes the frequency dependence of the elastic constants. Its introduction into the wave equation is justified in [2]. When inserting the

parameters p and q obtained from fitting equation (10) to the experimental sound velocity profile, one finds that the above equation possesses solitary solution, i.e., localized density pulses that travel along the membrane cylinder without dissipation and without changing shape. A typical solution of equation (12) is shown in figure 5 (right). The pulse possesses a maximum amplitude and a minimum velocity when increasing the overall energy of the pulse. The maximum amplitude corresponds to the density change between liquid and solid membrane phase. Thus, the solitary pulse consists of a solid region traveling in a liquid membrane environment. This is schematically shown in figure 6.

The soliton described above shares many similarities with the nervous impulse:

- It displays a velocity similar to those of myelinated nerves.
- It is associated to transient changes in membrane thickness.
- It is associated to a reversible release and re-uptake of heat.

However, the physical principles underlying soliton propagation are very different from the mechanisms considered for nerve pulse propagation in the field of electrophysiology.

5. Ion channels

The textbook description for nerve pulse conduction is the Hodgkin-Huxley model [13]. It suggests that the nerve pulse is generated by ion currents through channel proteins. These currents charge the membrane capacitor. According to the model, channel proteins conduct ions in a voltage-dependent manner. Thus, they are considered being "voltage-gated". Combined with cable theory, this generates the possibility of propagating electrical pulses called 'action potentials'. The opening and closing of channels can be experimentally observed in electrical recordings [14]. To the contrary, in the soliton theory described above no ion channel proteins are required.

It is an interesting fact that membranes in the complete absence of proteins can form voltage-gated pores that display properties indistinguishable from protein channels [15, 4]. An example is given in figure 7 where one can see an increase in channel open-likelihood upon increase in voltage. These ion channel events result from area fluctuations in the membrane, as described by equation (8). In the melting transition, the fluctuations are large and the membrane permeability displays a maximum. Every change in a thermodynamic variable that potentially changes the membrane state can alter the permeability of the membrane [16, 3].

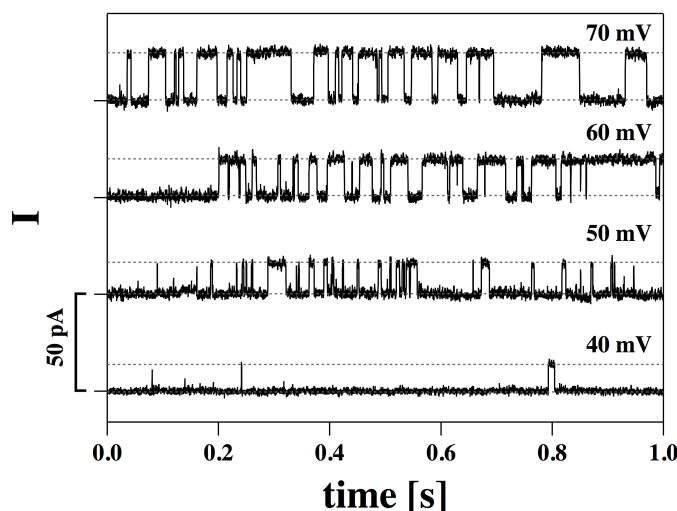


Figure 7. Quantized current events through a synthetic lipid membrane. One finds channel-like events in the complete absence of proteins. The open likelihood of pore displays a pronounced voltage dependence. [4].

Due to the increase in channel open-probability shown in figure 7, the current-voltage relation is not linear. In particular, if the membrane displays a net polarization, V_0 , in the absence of an external field, the current-voltage relation may be asymmetric and different for positive and negative voltages. A spontaneous membrane polarization could originate from an asymmetric distribution of lipids on the two sides of the membrane, or from membrane curvature. The latter effect is called 'flexoelectricity'. Its investigation was pioneered by A. G. Petrov [17]. Flexoelectricity is caused by the different dipole density on the two monolayers in curved membranes. Membrane curvature could possibly originate from slight pressure difference on the two sides of the membrane due to suction on the recording pipette. An example for an asymmetric non-linear current-voltage relation is shown in figure 8.

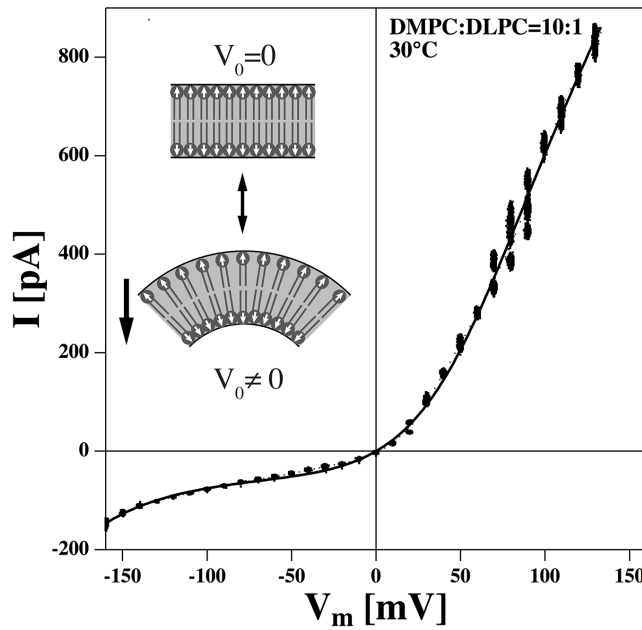


Figure 8. The current-voltage relation of the permeability of a synthetic lipid membrane is not generally symmetric even though the composition of the membrane itself is symmetric [4]. This could be caused by a permanent polarization of the membrane due to flexoelectricity [17, 18] - see insert.

In the absence of spontaneous polarization V_0 of the membrane, the electrostatic force, \mathcal{F} , exerted on a planar membrane by external voltage is given by

$$\mathcal{F} = \frac{1}{2} \frac{C_m V_m^2}{D} \quad (13)$$

where C_m is the membrane capacitance, V_m is the transmembrane voltage and D is the membrane thickness [1]. This force potentially reduces the thickness of the membrane [19]. The electrical work performed on the membrane by a change in thickness from D_1 to D_2 is

$$W_{el} = \int_{D_1}^{D_2} \mathcal{F} dD \equiv \alpha V_m^2 \quad (14)$$

where α is a constant. In the presence of a spontaneous polarization associated to a transmembrane voltage V_0 , the electrical work instead assumes the form $W_{el} = \alpha(V_m - V_0)^2$. Since electrostatic work leads to membrane thinning, it is generally assumed that the work necessary to form a pore is proportional to the work necessary to reduce membrane thickness [20, 21].

Therefore, the free energy for pore formation is given by

$$\Delta G = \Delta G_0 + \alpha(V_m - V_0)^2, \quad (15)$$

where ΔG_0 is a constant.

The probability, $P_{open}(V_m)$, of finding an open pore in the membrane at a fixed voltage is given by

$$P_{open}(V_m) = \frac{K(V_m)}{1 + K(V_m)} \quad ; \quad K(V_m) = \exp\left(-\frac{\Delta G}{kT}\right), \quad (16)$$

where $K(V_m)$ is the voltage-dependent equilibrium constant between open and closed states of a single pore.

The current-voltage relation for the lipid membrane is proportional to the likelihood of finding an open channel for a given voltage:

$$I_m = \gamma_p \cdot P_{open} \cdot V_m \quad (17)$$

where γ_p is the conductance of a single pore (or N identical pores). Eqs. 15-17 contain the theoretical description for the I-V curves of lipid channels. The solid line in figure 8 is a fit using the above description. It fits the experimental data nearly perfectly. Thus, a description based on the concept of forces induced by charging the membrane capacitor is very well able to describe experimental data of membrane permeability.

6. Summary

In this review, we summarized the evidence for electromechanical behavior of the biological membrane. The membrane can be seen as a capacitor with a spontaneous polarization. Due to forces on the capacitor, changes in transmembrane voltage can change the physical state of the membrane. E.g., it can induce membrane melting or freezing. Vice versa, lateral pressure changes in the membrane can alter the voltage on a membrane. Thus, the membrane displays piezoelectric features.

In a melting transition, the membrane displays a non-linear response to lateral pressure changes. This fact leads to the possibility of propagating density solitons in cylindrical membranes that share many similarities with the action potential in nerves. For instance, thickness and temperature changes in the nerve membrane are correctly described by the soliton approach. Further, the presence of melting transitions enhances the probability of area fluctuations in the membrane. These fluctuations lead to ion-channel-like events that are practically indistinguishable from protein ion channels. These protein channels are believed to be responsible for the nerve pulse in traditional theories. However, an electromechanical approach towards the physics of biological membranes intrinsically contains all these phenomena using the language of thermodynamics.

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