The effect of intercellular medium salinity on the dielectric constant of cell membranes and the excitation thresholds of the action potential

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Abstract
A mechanism for axon swelling in the area of action potential passage, which is associated with a localized increase in charge on the membrane surfaces when Na^+ ions flow from the extracellular electrolyte into the intracellular space, is considered in this study. A comparative analysis of the effect of electrostatic forces and the changes in osmotic pressure is performed. The change in dielectric constant of the axon membrane is also discussed, and a possible explanation for the decrease in the excitation threshold of the action potential with an increase in salinity of the external electrolyte is proposed.

I. Introduction
In [1-6] it was shown that during the passage of an action potential in nerve fibers, for example, in the axons of a squid, the radius of the axons follows the action potential, that is, it initially increases and then decreases. The authors attribute this effect to the injection of sodium ions into the axon during the passage of the action potential. The conclusions drawn in [5, 6] indicate that the swelling of the squid axon in the region of action potential cannot be explained by the redistribution of fluid inside the axon, which occurs during mechanical excitation of surface waves.

Numerous works have been devoted to the experimental study of the effect of the ionic composition of electrolyte on nerve fibers. In this paper, we will highlight only a few of these works, those which—in our opinion—are the most important. It was shown in [7] that an increase in the amount of divalent ions in the external electrolyte reduces the potential difference between the internal and external electrolytes in the squid axon, significantly lowering the threshold of sodium channel opening. Based on the analysis of X-ray diffraction data, [8] reported that high concentrations of KBr and KCl salts lead to an increase in the distance between phospholipid heads and, accordingly, to an almost twofold decrease in the van der Waals forces of attraction between them.

The theory of surface charge on phospholipid membranes was proposed in [9], from which it follows that the inner and outer surfaces of the membrane create a system of potential wells for negative ions near the dipole phospholipid heads of the membrane, which are turned by positive charges into the external electrolyte. The theory makes it possible to estimate the depth of these wells depending on the type of ion in the electrolyte and estimate the surface charge of the membrane based on the modified model [7]. It follows from [9] that an increase in the density of negative ions in the electrolyte increases the surface charge on the outer surfaces of the membrane.

During the injection of sodium ions into the area of the action potential passage, the local salinity of both the internal electrolyte and external electrolyte increases. As a result of osmosis, previous experiments [1–6] indicate an outflow of water from the axon, leading to its compression rather than swelling. The reasons for axon swelling at the growth stage of the action potential are discussed in Part II of our work. It is shown that the outer and inner surfaces of the phospholipid membrane are always subject to tension

regardless of the magnitude and sign of the charges on its surfaces. This is due to the fact that the Debye length of the extracellular and intracellular electrolytes is always much smaller than the thickness of the membrane; accordingly, the electric field on the outer surface of the membrane is always much larger than the field inside the membrane. Phospholipid bilayer membrane is subject to compression only in a very weak electrolyte when the ion density $n_i \approx 1[\text{mM/L}]$ [9], that is, almost three orders of magnitude less than the ion density in the extracellular and intracellular liquids of living organisms. Note that in the case of weak electrolytes, the membrane charge density is proportional to the ion density in the electrolytes, whereas for strong electrolytes, the membrane charge density cannot exceed the surface density of phospholipids in the membrane [10]. Thus, charge density of the membrane in distilled water should be 0. Since the charges on the inner and outer surfaces of the membrane are not equal, which always takes place in nerve cells [11], the membrane as a whole experiences pressure leading either to axon compression or axon swelling, as observed in experiments [1–6]. Part II shows that the additional osmotic pressure drop due to the redistribution of ions between the outer and inner sides of the membrane is less than the additional pressure drop associated with a change in the surface charge on the membrane. Note that a model of the surface charge of a phospholipid membrane was proposed in [7], which took into account the existence of Debye layers adjacent to the inner and outer surfaces of the membrane. However, the model [7] did not consider the cellular structure of the membrane and the electrostatic forces acting on it.

In [7], it was shown that the addition of divalent chloride salts such as $\mathrm{CaCl_2}$, $\mathrm{MgCl_2}$, and $\mathrm{MnCl_2}$ to a solution of $\mathrm{NaCl_2}$ reduces the potential difference (resting potential) across the membrane of nerve fibers, although it would seem that the effect should have been the opposite. Indeed, an increase in the salinity of the solution leads to an increase in the surface charge on the membrane and, accordingly, to an increase in the potential difference on $U_m = \frac{\Sigma_m}{C_m}$, where Σ_m is the surface charge density, $C_m = \varepsilon_m \varepsilon_0 / d_m$ is the membrane capacitance per unit area, ε_m is the membrane dielectric constant, ε_0 is the vacuum permittivity, and d_m is the membrane thickness.

The experiments carried out in [8] showed that an increase in electrolyte salinity leads to an increase in membrane porosity, that is, an increase in the distance between phospholipid heads. Therefore, it can be expected that an increase in the density of ions in the electrolyte will also increase the amount of water in the membrane. In Part III of this work, saturation of the membrane with water is found to increase the dielectric constant of the phospholipid membrane, which leads to a decrease in the potential difference on the membrane of nerve fibers and, accordingly, lowers the opening threshold of sodium channels. Since water within the phospholipid membrane significantly influences the effective dielectric constant, an increase in the amount of water in the membrane is expected to result in a corresponding increase in the dielectric constant. In our opinion, saturation of the membrane with water explains the decrease in resting potential in the nervous tissue observed in [7] and, accordingly, the decrease in the threshold for opening transmembrane sodium channels.

II. Forces acting on a bilayer phospholipid membrane in an electrolyte

Typical intracellular and extracellular ion densities are shown in Table 1 [11]. As an example let us consider muscle fibers with an ion composition close to that of neurons [11]. In this case, Debye length is

$$r_D = (\varepsilon_w \varepsilon_0 k_B T / 2e^2 n_\infty), \tag{1}$$

where ε_0 is the dielectric permittivity of vacuum; $\varepsilon_w = 81$ and $T = 300$ K are the dielectric permittivity and temperature of electrolyte, respectively; n_∞ is the ion density inside the cell or outside far from membrane; e is the elementary charge; and k_B is the Boltzmann constant. For the parameters given in Table 1, $r_D \approx$ 1 nm [7].

Table 1: Intracellular and extracellular ion densities (following [11]).

Ions	Squid Axon		Muscle Fibers (neurons)	
	Intercellular mM/L	Extracellular mM/L	Intercellular mM/L	Extracellular mM/L
Na^+	50	460	10	125
Ka^+	400	10	124	2
Ca^{2++}	–	10	5	2
Mn^{2++}	10	54	14	1
total	460	534	153	130
Cl^-	135	560	2	77
HCO_3^-	–	–	12	27
$(A)^-$	345	–	74	13
Others	–	–	65	13
Total	460	560	153	130

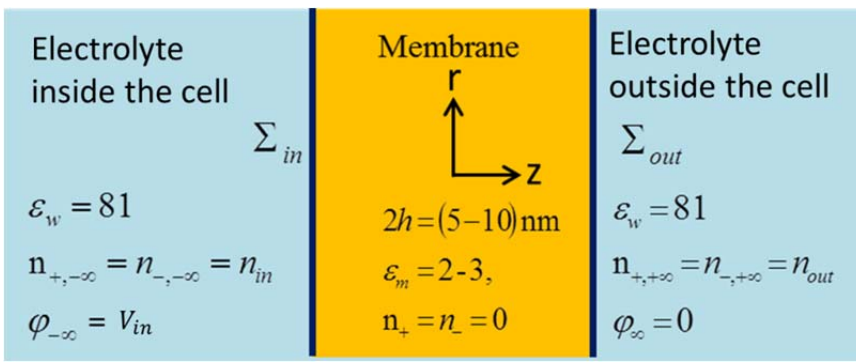

Figure 1. Model of phospholipid bilayer membrane in electrolyte. Σ_{in} and Σ_{out} are surface charges on the inner and outer surface of the membrane, respectively; n_{in} and n_{out} are ion densities inside the cell and outside far from the membrane. Charge density inside the membrane is 0.

Let us consider a system of governing equations for potential distribution for the configuration shown in Fig. 2. In this case, the problem of the potential distribution in the membrane is described by the Laplace equation, and outside – by the Poisson equation:

$$\frac{d^2\varphi}{dz^2} = \begin{cases} -\frac{2en_{out}}{\varepsilon_w\varepsilon_0}\sinh\left(\frac{e\varphi}{k_BT}\right), & z > h \\ 0, & -h \le z \le h \\ -\frac{2en_{in}}{\varepsilon_w\varepsilon_0}\sinh\left(\frac{e\varphi}{k_BT}\right), & z < -h \end{cases} \tag{2}$$

The boundary value problem (2) is nonlinear and requires a numerical solution. To simplify the analysis, suppose that there is a range of φ for which $e|\varphi| < k_BT \approx 0.026$ eV. In this region, nonlinear equation (2) can be linearized. However, in the general case, this condition on the potential of the outer and inner surfaces of the membrane may not be satisfied, so the results obtained in this approximation could only be regarded as qualitative. Thus, by linearizing Equations (2), we obtain a system of equations:

$$\frac{d^2\varphi}{dz^2} \approx \begin{cases} -\frac{\varphi}{r_{D,out}^2}, & z > h \\ 0, & -h \le z \le h \\ -\frac{\varphi}{r_{D,in}^2}, & z < -h \end{cases}. \quad (3)$$

With the boundary conditions on $\pm\infty$

$$\varphi|_{\infty} = 0, \varphi|_{-\infty} = V_{in} \quad (4)$$

and at the boundaries of the membrane:

$$\varepsilon_0\varepsilon_m \frac{d\varphi}{dz}\Big|_{h-0} - \varepsilon_0\varepsilon_w \frac{d\varphi}{dz}\Big|_{h+0} = \Sigma_{out}, \varepsilon_0\varepsilon_w \frac{d\varphi}{dz}\Big|_{-h-0} - \varepsilon_0\varepsilon_m \frac{d\varphi}{dz}\Big|_{-h+0} = \Sigma_{in}. \quad (5)$$

In (3), $r_{D,in}$ and $r_{D,out}$are the Debye radii in the electrolyte outside and inside the cell, respectively. Since the density of ions outside the cell differs from that inside by no more than 20% (see Table 1), we further assume that $n_{in} = n_{out} = n_{\infty}$ and, accordingly, $r_{D,in} = r_{D,in} = r_D$.

Figure 2 shows the structure of the potential corresponding to the solution of the Poisson equation (3). (details of calculations can be found in [9]).

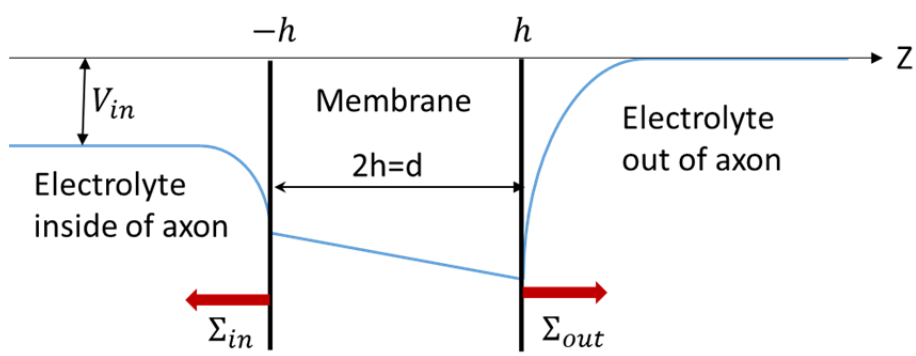

Figure 2. Schematics of potential distribution across the membrane. Debye length is much smaller than the membrane thickness. The arrows show the directions of the forces acting on surface charges Σ_{in} and Σ_{out} ($\Sigma_{in}, \Sigma_{out} < 0$). These forces are determined by a potential drop in electrolytes outside and inside the cell. V_{in} is the potential inside the cell. The arrows show the direction of the forces acting on the surface charge attached to the membrane.

Expressions for algebraic values of the forces, normal to the membrane surfaces (shown in Fig. 2) and acting on the inner and outer sides of the membrane, have the forms

$$F_{in} = E_{in}\Sigma_{in} < 0, E_{in} = -\frac{\partial\varphi}{\partial z}\Big|_{-h+0} - \frac{\partial\varphi}{\partial z}\Big|_{-h-0} \approx -\frac{\partial\varphi}{\partial z}\Big|_{-h+0} > 0 \quad (6)$$

and

$$F_{out} = E_{out}\Sigma_{out} > 0, E_{out} = -\frac{\partial\varphi}{\partial z}\Big|_{h+0} - \frac{\partial\varphi}{\partial z}\Big|_{h-0} \approx -\frac{\partial\varphi}{\partial z}\Big|_{h+0} < 0. \quad (7)$$

Note that F_{in} is always negative and F_{out} is positive regardless of the signs of Σ_{in} and Σ_{0ut}.

Since the potential difference, V_{in} (Fig. 2), between the electrolyte inside and outside is ~0.09 V [12], the surface charge on the membrane lies within $\Sigma = 0.002 - 0.3\ \mathrm{C/m^2}$ [12,13], the half-thickness of the membrane h varies from 2.5 nm to 5 nm, one can argue that the contribution of V_{in} to the calculation of the fields and energy can be neglected if $V_{in}\frac{\varepsilon_0(\varepsilon_m\varepsilon_w)^{1/2}}{(2hR_D)^{1/2}} \approx 0.004\ C/m^2 < |\Sigma_{in}|, |\Sigma_{out}|$ [9]. In this case,

$$E_{h+0} \approx \frac{\Sigma_{out}}{\varepsilon_0 \varepsilon_w}. \quad (8)$$

$$E_{-h-0} \approx -\frac{\Sigma_{in}}{\varepsilon_0 \varepsilon_w}. \quad (9)$$

The forces acting on the unit area of the outer and inner surfaces of the membrane are equal, respectively, and are denoted as follows:

$$F_{out} = E_{h+0}\Sigma_{out} \approx \frac{\Sigma_{out}^2}{\varepsilon_0 \varepsilon_w}, \quad (10)$$

and

$$F_{in} = E_{-h-0}\Sigma_{out} \approx -\frac{\Sigma_{in}^2}{\varepsilon_0 \varepsilon_w}. \quad (11)$$

It can be seen that F_{in} always directed into the cell, and F_{out} – out the cell, as it shown on Fig.2. Subtracting (11) from (10) we obtain the value of the wedging force acting on the cell membrane (see Fig.2):

$$F_{\Sigma,streach} = F_{out} - F_{in} = \frac{\Sigma_{out}^2}{\varepsilon_0 \varepsilon_w} + \frac{\Sigma_{in}^2}{\varepsilon_0 \varepsilon_w}. \quad (12)$$

Note that tension force $F_{\Sigma,streach}$ does not depend on the sign of the charge on the inner and outer surfaces of the membrane and grows quadratic. For example, when $\Sigma_{out} = \Sigma_{in} = \Sigma = 0.016, 0.032$ and $0.064\ \mathrm{C/m^2}$, it follows that $F_{\Sigma,streach} = 720, 2880,$ and 11520 kPa, correspondingly.

In [9], it was shown that the distance between the lipid heads of the bilayer phospholipid membrane depends on the density of ions in the solution, corresponding to an increase in the wedge forces when the ion density on the surface of the membrane changes. This effect can be explained by the changes in the surface charge on the membrane and, correspondingly, by the increase in the wedge forces predicted by the current model.

In contrast to the force that stretches the membrane (12), the value of the force that tends to displace the membrane as a whole is equal to (see Fig. 2) the following:

$$F_{\Sigma,total} = F_{out} + F_{in} = \frac{\Sigma_{out}^2}{\varepsilon_0 \varepsilon_w} - \frac{\Sigma_{in}^2}{\varepsilon_0 \varepsilon_w}. \quad (13)$$

Let us turn our attention to Eq. (13). The main negative ion in extracellular electrolyte is $\mathrm{Cl^-}$, while intracellular ions are mainly aspartic acid anion $Asp\mathrm{A^-}$, glutamic acid anion $Glu\mathrm{A^-}$, and bicarbonate ion $\mathrm{HCO_3^-}$ (Table 1). Since density $\mathrm{Cl^-}$ is much smaller than intracellular negative ions, according to [9,10], one can assume that $|\Sigma_{out}| > |\Sigma_{in}|$ and $F_{\Sigma,total} > 0$.

It was found experimentally [1, 2] that at the leading edge of the action potential, the time dependence of the change in the radius of the squid axon exactly follows the dynamics of the action potential and reaches ~1 nm at the moment when the action potential reaches its maximum. In the recovery phase, when the action potential decreases, the radius of the axon also decreases and, at the action potential minimum point, becoming 1–4 nm less than the equilibrium value. Then it slowly recovers.

Given that the scale of variation of the axon radius in [1, 2] is close to half the thickness of the membrane, it is recommended to choose the displacement of membrane as a whole, denoted by (13), rather than the displacement associated with the stretching of the membrane, denoted by (12), in the squid axon.

Let us evaluate the role of changes in the osmotic pressure on the membrane due to a local increase in the density of sodium ions in the region of action potential. Let the density of sodium ions near the inner surface of the membrane increase by Δn_{Na^+}. In this case, the excess osmotic pressure on the membrane surface increases as follows [14]:

$$\Delta P_{osm} \sim k_B T \Delta n_{Na^+} = k_B T n_0 \frac{\Delta n_{Na^+}}{n_0}. \quad (14)$$

For simplicity, let us consider the case when the change in surface charge on the outer membrane $\Delta\Sigma_{Na^+}$ due to the flow of sodium ions is less than the charge Σ_0 on it before the passage of the action potential. In this case,

$$\Delta F_{\Sigma,\text{total}} \sim \frac{2\Sigma_o^2}{\varepsilon_w \varepsilon_0} \cdot \frac{\Delta\Sigma_{Na^+}}{\Sigma_0} = \frac{2\Sigma_o^2}{\varepsilon_w \varepsilon_0} \frac{\Delta n_{Na^+}}{n_0}. \quad (15)$$

Assuming that $\frac{\Delta\Sigma_{Na^+}}{\Sigma_0} \sim \frac{\Delta n_{Na^+}}{n_0}$,

$$\xi = \frac{\Delta P_{osm}}{\Delta F_{\Sigma,\text{total}}} \approx \frac{\varepsilon_w \varepsilon_0 k_B T n_0}{2\Sigma_o^2}. \quad (16)$$

Substituting in (14) the value $n_0 = 10^{26}$ m^{-3}, corresponding to saline [11], we obtain

$$\xi \approx 1.2 \cdot 10^{-4} \frac{1}{\Sigma_o^2}. \quad (15)$$

Thus, if $\Sigma_0 > 10^{-2}\text{C/m}^2$, then $\Delta P_{osm} < \Delta F_{\Sigma,\text{total}}$. In this case, the surface charge on the membrane plays a more important role in axon swelling than excess osmotic pressure.

III. Change in the dielectric constant of the membrane with increasing salinity of the solution

Let us briefly describe the setting of experiments and the results of [7], which showed that the addition of divalent chloride salts such as $CaCl_2$, $MgCl_2$, and $MnCl_2$ to a solution of NaCl reduces the voltage across the membranes nerve fibers. In [7], divalent chloride salts were added to a 120 mM/L NaCl solution in a vessel with frog myelinated nerve fibers, and the potential difference between the inner and outer surfaces of the membrane was measured. The experiments show that adding 0.1 mM/L $CaCl_2$ results in the measured potential difference $U_m = -115$ mV, adding 2 mM/L leads to $U_m = -90$ mV, and adding 6.0 mM/L leads to $U_m = -80$ mV. Similar results were obtained with the addition of other divalent chloride salts (e.g., $ZnCl_2$). Thus, adding 0.07 mM/L results in $U_m = -100$ mV, adding 0.2 mM/L results in $U_m = -95$ mV, and adding 2 mM/L results in $U_m = -75$ mV.

On the other hand, it was shown in experiments [8] that an increase in electrolyte salinity leads to an increase in membrane porosity, that is, an increase in the distance between phospholipid heads. Therefore, it can be expected that with an increase in salinity, which is unambiguously associated with an increase in the density of ions in the electrolyte, the amount of water in the membrane also increases. The water contained in the phospholipid membrane contributes to the effective permittivity. Therefore, an increase in the amount of water in the membrane should lead to an increase in its dielectric constant.

Considering the water contained in the lipid membrane as an impurity with a relative volume, to estimate the effective permittivity of the membrane ε_m, it is convenient to use the simplest approximate Rayleigh formula for the permittivity of two substances, one of which is continuous, and the second is uniformly distributed small droplets of the impurity substance [15]:

$$\varepsilon_m = \varepsilon_e \left(1 + f \frac{3(\varepsilon_i - \varepsilon_e)}{\varepsilon_i + 2\varepsilon_e - f(\varepsilon_i - \varepsilon_t)}\right). \quad (16)$$

Here, ε_m, ε_e, and ε_i are the respective permittivities of the mixture, the main medium, and the impurity droplets. From (17), it follows that at $f \to 0$: $\varepsilon_m \to \varepsilon_e$, and at $f \to 1$: $\varepsilon_m \to \varepsilon_i$. Substituting in (16) the values of the permittivity $\varepsilon_e = 2$ for a dehydrated phospholipid membrane [16–18] and $\varepsilon_i = \varepsilon_w = 81$ for water, we obtain the dependence of the membrane permittivity ε_m according to the volume fraction of water f (see Fig. 3).

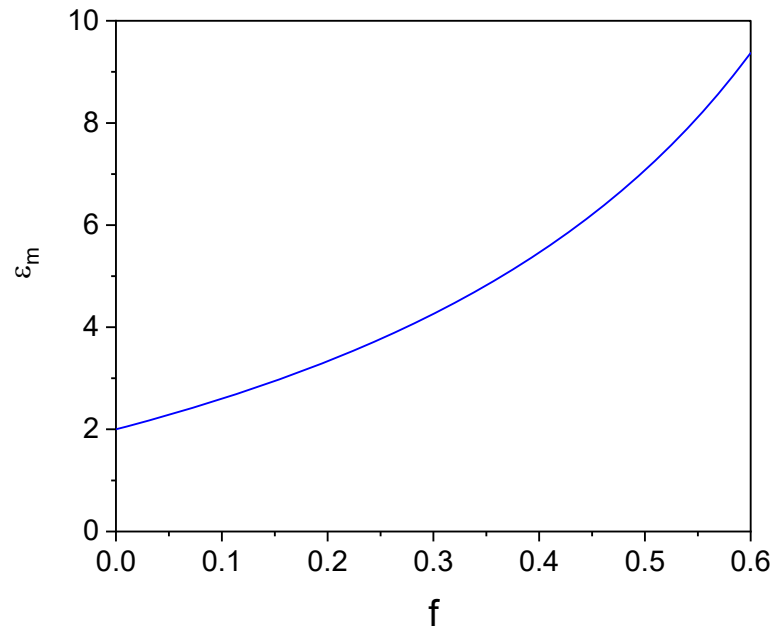

Figure 3. Dependence of the effective dielectric constant of the membrane ε_m on the water content f for $\varepsilon_e = 2$ and $\varepsilon_i = \varepsilon_w = 81$, calculated by Formula (16)

Since the capacitance of a unit area of the membrane is equal to $C_m = \varepsilon_m \varepsilon_0 / d_m$, then the potential difference across the membrane with the surface charge density σ_m is equal to

$$U_m = \sigma_m d_m / \varepsilon_m \varepsilon_0. \quad (17)$$

If we assume that with an increase in water salinity, the surface charge on the membrane and its thickness increase slightly compared to the water content, then $U_m \sim 1/\varepsilon_m$. The water content dependence of the ratio $U_m(f)/U_m(f = 0)$ is shown in Fig. 4.

In our opinion, the saturation of the membrane with water explains the marked decrease in resting potential in the nervous tissue observed in [7] and, accordingly, the decrease in the threshold of sodium channel opening (threshold of action potential excitation).

Note that the considered effect of the dependence of potential difference across the membrane on water content at the same value of the surface charge can be directly related to the selective effect of non-equilibrium low-temperature plasma interacting with various cell cultures in a Petri dish (e.g., healthy and cancerous cells) observed in many experiments (see, for example, [19–22]). As was shown in [23], the interaction of non-equilibrium plasma with a physiological solution changes the ionic composition of the solution and, consequently, the drop of osmotic pressure across the cell membranes. In [23], it was supposed that the displacement of water from membranes and, consequently, the change in their dielectric constant, are different in healthy and cancer cells due to a noticeable difference in the mechanical properties of these cells. If, in addition, electric currents are induced in the solution, charging the membranes of these cells, then with the same additional charge on the membranes, the voltage on the

membrane and the probability of its electroporation will be different for different cells. This, as was stated earlier in [24], may be one of the reasons for the observed selective effect of non-equilibrium plasma on healthy and diseased cells in a physiological solution in a Petri dish.

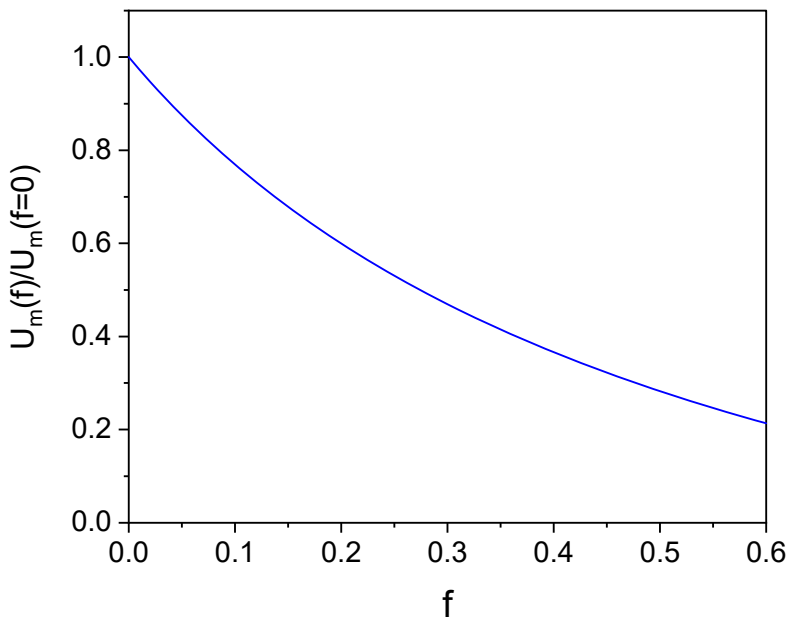

Figure 4. Dependence of the potential difference across the membrane on the water content f at a fixed value of the surface charge σ_m and thickness d_m.

IV. Conclusions

Surface charges on the membrane of the nerve fiber increase the thickness of the membrane and shift it as a whole toward a larger charge. The displacement of the membrane explains the observed swelling of nerve fibers during the injection of sodium ions into the axon in the initial phase of passage of the action potential [1–6].

An increase in water content in the phospholipid membrane increases the dielectric constant of the membrane, which, at the same surface charge density, leads to a decrease in the potential difference across the nerve fiber membrane and, accordingly, lowers the action potential initiation threshold found in [7].

Acknowledgments

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Data Access Statement

All relevant data are within the paper.

Conflict of Interest declaration

There are no conflicts to declare.

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