ELECTRIC REST MEMBRANE POTENTIALS WITH REGARD FOR BARODIFFUSION PHENOMENA

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The influence of pressure gradients on the stationary membrane potential, which is the most realistic electric rest potential, has been studied. The dependence of the electric membrane potential on the pressure gradient has been analyzed taking the variation of the ultrasonic radiation frequency under non-isobaric conditions into account. Quantitative estimations of the influence of barodiffusion effects on the value of electric rest membrane potential were obtained.

1. Introduction

In a normally functioning cell, there is a lot of various molecules and ions, the concentrations of which are considerably lower or much higher than those in the cell environment. There exists a definite disparity between the distributions of those particles in the cell and in the intercellular medium. It is a cell membrane that provides such a difference [1, 2].

The generation and propagation of electric potentials belong to the major phenomena in alive cells and tissues; they form the basis of cell excitation, regulation of endocellular processes, muscular contraction, functioning of the nervous system, and so on. Transfer processes give rise to a potential difference across the membrane (it is the so-called membrane potential).

The membrane potential in equilibrium (the Nernst potential), which will be related here, for the sake of definiteness, to the distribution of K^+-ion concentration, looks like

$$\varphi_m = \varphi_e - \varphi_i = \frac{RT}{F} \ln \frac{[\mathrm{K}]_i}{[\mathrm{K}]_e}, \tag{1}$$

where $\varphi_m = \varphi_e - \varphi_i$ is the difference between the electric potentials of external and internal cell media; $[\mathrm{K}]_i = 392$ mmol/l and $[\mathrm{K}]_e = 22.4$ mmol/l are the K^+-ion concentrations inside and outside the axon of a squid, respectively; R is the gas constant; F the Faraday number; and T the absolute temperature. Since $RT/F = 25.2$ mV at the temperature $T = 293$ K, we obtain $\varphi_m \approx -72$ mV.

The Goldman–Hodgkin–Katz stationary potential makes also allowance for the fluxes of other ions and looks like

$$\phi_{\mathrm{stat}} = \frac{RT}{F} \ln \frac{P_{\mathrm{K}}[\mathrm{K}]_i + P_{\mathrm{Na}}[\mathrm{Na}]_i + P_{\mathrm{Cl}}[\mathrm{Cl}]_e}{P_{\mathrm{K}}[\mathrm{K}]_e + P_{\mathrm{Na}}[\mathrm{Na}]_e + P_{\mathrm{Cl}}[\mathrm{Cl}]_i}, \tag{2}$$

where $\phi_{\mathrm{stat}} = (\phi_e - \phi_i)_{\mathrm{stat}}$ is the difference between the electric potentials of the external and internal media of the cell; $[\mathrm{K}]_i$, $[\mathrm{Na}]_i$, and $[\mathrm{Cl}]_i$ are the concentrations of the corresponding ions inside the cell; $[\mathrm{K}]_e$, $[\mathrm{Na}]_e$, and $[\mathrm{Cl}]_e$ the corresponding concentrations in the extracellular solution; and P_{K}, P_{Na}, and P_{Cl} are the cell membrane permeabilities for the corresponding ions. This potential describes the actual rest potential more adequately, than the Nernst concentration potential does. It should be noted that, in the giant axon of a squid, $P_{\mathrm{K}} : P_{\mathrm{Na}} : P_{\mathrm{Cl}} = 1 : 0.04 : 0.045$ at rest. Therefore, the main role in the establishment of rest membrane potential is played by potassium ions. In what follows, we take into consideration that, generally speaking, the pressure values are different for two membrane's sides, with that in the cell being higher. The so-called osmotic pressure provides the exchange, absorption, distribution, and removal of substances through the membrane. It depends on the concentrations of substances dissolved outside and inside the cell.

An extra pressure can be also created owing to the local action of external fields, in particular, ultrasound ones, which became widely applied in modern medicine. The effective use of available diagnostic methods, as well as the development of essentially new ones, is impossible without studying the mechanisms of ultrasound action on molecules, cells, and tissues. The intensity of acoustic waves affects the variation of the pressure difference across the membrane

$$\Delta p = \sqrt{2I\rho v}, \tag{3}$$

where I is the ultrasound intensity, ρv the acoustic resistance of the medium, ρ the medium density, and v the sound velocity in the medium. Since $I \sim \omega^2$, where ω is the frequency of the ultrasound wave, the pressure difference is proportional to the frequency:

$$\Delta p = A\omega, \tag{4}$$

where A is a quantity which does not depend on the ultrasound frequency if there is no effect of frequency dispersion for the sound velocity. Of special interest is a critical range, where fluctuation effects, which may substantially influence the behavior of various equilibrium and nonequilibrium properties of the substance (in particular, those which govern the electric membrane potential), should be taken into account.

For an alive organism considered as a physical system, there exists a hierarchy of spatial scales, namely, the dimensions of atoms (L_1), macromolecules (L_2), cells (L_3), organs (L_4), and so on. The action of external physical fields is characterized by introducing an additional spatial scale. In the case where such an external factor is sound, the role of this extra scale is played by the sound wavelength λ. Usually, the latter satisfies the condition $L_3 \ll \lambda \ll L_4$ [3].

2. Stationary Membrane Potential Under Non-isobaric Conditions

A condition for the system to be stationary means that the total current density caused by fluxes of all ions through the membrane is equal to zero, i.e.

$$\vec{J}_{\rm sum} = \sum \vec{J}_n = 0. \tag{5}$$

Note that every quantity J_n, in general, is distinct from zero. It is this circumstance that makes the stationary potential different from the Nernst equilibrium one; the condition for the latter to be established is a zero current for only one, predetermined kind of ions. We will take into consideration only monovalent ions of potassium, sodium, and chlorine. In this case, the stationary condition, which describes the currents of sodium, Na^+, and chlorine, Cl^-, ions into the cell and the current of potassium K^+ ions from it, looks as follows:

$$\vec{J}_{\rm sum} = \vec{J}_{\rm K} + \vec{J}_{\rm Na} + \vec{J}_{\rm Cl} = 0, \tag{6}$$

where $\vec{J}_{\rm K} = e\vec{I}_{\rm K}$, $\vec{J}_{\rm Na} = e\vec{I}_{\rm Na}$, $\vec{J}_{\rm Cl} = -e\vec{I}_{\rm Cl}$, e is the elementary charge, and $\vec{I}_{\rm K}$, $\vec{I}_{\rm Na}$, and $\vec{I}_{\rm Cl}$ are the fluxes of the corresponding ions through the membrane.

The passive flux of ions through the biomembrane, provided that there are simultaneously two thermodynamic forces associated with the gradients of concentration and electric field potential, is determined by the following expression (see, e.g., work [2]):

$$I = \psi P \frac{C_e \exp\psi - C_i}{1 - \exp\psi}. \tag{7}$$

Here, P is the coefficient of membrane permeability for a definite kind of ions; C_e and C_i are the concentration of those ions outside and inside the cell, respectively; and ψ is a generalized dimensionless membrane potential. The latter can be presented in the form

$$\psi = \varphi - \sigma\Delta p, \tag{8}$$

where $\varphi = \frac{F}{RT}(\varphi_e - \varphi_i)$ is the dimensionless membrane potential, Δp the pressure difference between the internal and external media, z the valency of this kind of ions, and σ the kinetic factor which is responsible for barodiffusion effects.

Under non-isobaric conditions, the fluxes of potassium ions $I_{\rm K}$ are described by the following expression:

$$I = (\varphi - \sigma_{\rm K}\Delta p) P_{\rm K} \frac{[{\rm K}]_e \exp(\varphi)\exp(-\sigma_{\rm K}\Delta p) - [{\rm K}]_i}{1 - \exp(\varphi)\exp(-\sigma_{\rm K}\Delta p)}. \tag{9}$$

Here, $\sigma_{\rm K}$ is the coefficient in the barodiffusion term for K^+-ions, which characterizes the diffusion-induced distribution for those ions taking the pressure gradient into account. This expression can be simplified:

$$I = (\varphi - \sigma\Delta p) P \frac{C_e \exp(\varphi\exp(-\sigma\Delta p) - C_i}{1 - \exp(\varphi)\exp(-\sigma\Delta p)}, \tag{10}$$

$$I \approx P(\varphi - \sigma\Delta p)\frac{C_e e^{\varphi} - C_i}{1 - e^{\varphi}} - \varphi P \frac{C_e e^{\varphi}}{1 - e^{\varphi}} -$$

$$-\varphi P e^{\varphi} \frac{C_e e^{\varphi} - C_i}{(1 - e^{\varphi})^2}\sigma\Delta p. \tag{11}$$

The terms of the second order of smallness, i.e. proportional to $(\sigma\Delta p)^2$, are neglected. The first term in Eq. (11) describes the flux of ions of a definite kind if the gradient of pressure is not taken into account. We use a notation I_0 for it. Then, expression (11) reads

$$I = I_0 - \frac{\varphi P}{1 - e^{\varphi}}\sigma\Delta p \left\{ C_e \left(\frac{1}{\varphi} + 1 + \frac{e^{\varphi}}{1 - e^{\varphi}} \right) e^{\varphi} -\right.$$

$$-C_i\left(\frac{1}{\varphi}+\frac{e^{\varphi}}{1-e^{\varphi}}\right)\Bigg\}. \tag{12}$$

We introduce a notation

$$f(\varphi)=\frac{1}{\varphi}+\frac{e^{\varphi}}{1-e^{\varphi}}. \tag{13}$$

Now, formula (12) looks like

$$I=\frac{\varphi P}{1-e^{\varphi}}\{C_e(1-(f+1)\sigma\Delta p)e^{\varphi}-C_i(1-f\Delta p)\}. \tag{14}$$

Let

$$F_1^{\mathrm{K}}=1-(f+1)\sigma_{\mathrm{K}}\Delta p, \qquad F_2^{\mathrm{K}}=1-f\sigma_{\mathrm{K}}\Delta p, \tag{15}$$

In this case, taking formula (9) into account, we obtain

$$I_{\mathrm{K}}=\varphi P_{\mathrm{K}}\frac{[\mathrm{K}]_e\exp\varphi F_1^{\mathrm{K}}-[\mathrm{K}]_iF_2^{\mathrm{K}}}{1-\exp\varphi}. \tag{16}$$

for the potassium ion flux. Analogously, for the sodium and chlorine ion fluxes, we have

$$I_{\mathrm{Na}}=\varphi P_{\mathrm{Na}}\frac{[\mathrm{Na}]_e\exp\varphi F_1^{\mathrm{Na}}-[\mathrm{Na}]_iF_2^{\mathrm{Na}}}{1-\exp\varphi}, \tag{17}$$

$$I_{\mathrm{Cl}}=-\varphi P_{\mathrm{Cl}}\frac{[\mathrm{Cl}]_e\exp\varphi F_1^{\mathrm{Cl}}-[\mathrm{Cl}]_iF_2^{\mathrm{Cl}}}{1-\exp\varphi}, \tag{18}$$

where

$$F_1^{\mathrm{Na}}=1-(f+1)\sigma_{\mathrm{Na}}\Delta p, \qquad F_2^{\mathrm{Na}}=1-f\sigma_{\mathrm{Na}}\Delta p, \tag{19}$$

$$F_1^{\mathrm{Cl}}=1+(f+1)\sigma_{\mathrm{Cl}}\Delta p, \qquad F_2^{\mathrm{Cl}}=1+f\sigma_{\mathrm{Cl}}\Delta p. \tag{20}$$

Substituting expressions (16)–(18) into the stationary condition (9), we obtain

$$(P_{\mathrm{K}}[\mathrm{K}]_eF_1^{\mathrm{K}}+P_{\mathrm{Na}}[\mathrm{Na}]_eF_1^{\mathrm{Na}}+P_{\mathrm{Cl}}[\mathrm{Cl}]_iF_1^{\mathrm{Cl}})e^{\varphi}=$$

$$=P_{\mathrm{K}}[\mathrm{K}]_iF_2^{\mathrm{K}}+P_{\mathrm{Na}}[\mathrm{Na}]_iF_2^{\mathrm{Na}}+P_{\mathrm{Cl}}[\mathrm{Cl}]_eF_2^{\mathrm{Cl}}. \tag{21}$$

Whence, for the dimensionless membrane potential φ, we have the expression

$$\varphi=\ln\frac{P_{\mathrm{K}}[\mathrm{K}]_iF_2^{\mathrm{K}}+P_{\mathrm{Na}}[\mathrm{Na}]_iF_2^{\mathrm{Na}}+P_{\mathrm{Cl}}[\mathrm{Cl}]_eF_2^{\mathrm{Cl}}}{P_{\mathrm{K}}[\mathrm{K}]_eF_1^{\mathrm{K}}+P_{\mathrm{Na}}[\mathrm{Na}]_eF_1^{\mathrm{Na}}+P_{\mathrm{Cl}}[\mathrm{Cl}]_iF_1^{\mathrm{Cl}}}. \tag{22}$$

Let us use the obtained formula (22) for estimating the value of the rest potential, taking only the flux of potassium ions into consideration. In the numerator and the denominator of the fraction under the logarithm, we preserve only terms which contain P_{K}. In this case,

$$\varphi=\ln\frac{[\mathrm{K}]_iF_2^{\mathrm{K}}}{[\mathrm{K}]_eF_1^{\mathrm{K}}}. \tag{23}$$

Now, consider the relations

$$\frac{F_2^{\mathrm{K}}}{F_1^{\mathrm{K}}}=\frac{1-f\sigma_{\mathrm{K}}\Delta p}{1-(f+1)\sigma_{\mathrm{K}}\Delta p}\approx$$

$$\approx(1-f\sigma_{\mathrm{K}}\Delta p)(1+(f+1)\sigma_{\mathrm{K}}\Delta p), \tag{24}$$

$$\frac{F_2^{\mathrm{K}}}{F_1^{\mathrm{K}}}=1-(f+1)\sigma_{\mathrm{K}}\Delta p-f\sigma_{\mathrm{K}}\Delta p+0(\sigma_{\mathrm{K}}\Delta p)^2. \tag{25}$$

Therefore, we obtain the formula

$$\varphi=\ln\left\{\frac{[\mathrm{K}]_i}{[\mathrm{K}]_e}(1+\sigma_{\mathrm{K}}\Delta p)\right\}=\ln\frac{[\mathrm{K}]_i}{[\mathrm{K}]_e}+\ln(1+\sigma_{\mathrm{K}}\Delta p)\approx$$

$$\approx\ln\frac{[\mathrm{K}]_i}{[\mathrm{K}]_e}+\sigma_{\mathrm{K}}\Delta p. \tag{26}$$

While deriving this expression, we used the approximate equality $\ln(1+x)\approx x$ for $x=\sigma_K\Delta p\ll 1$. As a result, the rest potential is estimated as

$$\phi=\frac{RT}{F}\left\{\ln\frac{[\mathrm{K}]_i}{[\mathrm{K}]_e}+\sigma_{\mathrm{K}}\Delta p\right\}. \tag{27}$$

Thus, taking only potassium ions into account, we passed from formula (22) to the formula for Nernst concentration potential which makes allowance for barodiffusion effects. A similar formula was obtained in work [4], where the thermodiffusion effect was considered.

It should be noted that the concentrations of ions in formulas (22) and (27) are determined taking into account their redistributions owing to barodiffusion processes.

Now we intend to derive an expression for the stationary potential under non-isobaric conditions with regard for all kinds of ions. To make mathematical calculations convenient, we introduce the following notations:

$$\alpha=P_{\mathrm{K}}[\mathrm{K}]_i+P_{\mathrm{Na}}[\mathrm{Na}]_i+P_{\mathrm{Cl}}[\mathrm{Cl}]_e, \tag{28}$$

$$\beta = P_{\rm K}[{\rm K}]_e + P_{\rm Na}[{\rm Na}]_e + P_{\rm Cl}[{\rm Cl}]_i, \tag{29}$$

$$\chi = P_{\rm K}[{\rm K}]_i\sigma_{\rm K} + P_{\rm Na}[{\rm Na}]_i\sigma_{\rm Na} - P_{\rm Cl}[{\rm Cl}]_e\sigma_{\rm Cl}, \tag{30}$$

$$\delta = P_{\rm K}[{\rm K}]_e\sigma_{\rm K} + P_{\rm Na}[{\rm Na}]_e\sigma_{\rm Na} - P_{\rm Cl}[{\rm Cl}]_i\sigma_{\rm Cl}. \tag{31}$$

With these notations in view, formula (22) reads

$$\varphi = \ln\frac{\alpha - \chi f\Delta p}{\beta - \delta(f+1)\Delta p}. \tag{32}$$

Then

$$\varphi = \ln\frac{\alpha - \chi f\Delta p}{\beta(1 - \frac{\delta}{\beta}(f+1)\Delta p)} \approx$$

$$\approx \ln\left\{(\frac{\alpha}{\beta} - \frac{\chi}{\beta}f\Delta p)(1 + \frac{\delta}{\beta}(f+1)\Delta p)\right\}, \tag{33}$$

$$\varphi \approx \ln\left\{\frac{\alpha}{\beta} + \frac{\alpha}{\beta}\frac{\delta}{\beta}\Delta p + [\frac{\alpha}{\beta}\frac{\delta}{\beta} - \frac{\chi}{\beta}]f\Delta p\right\}. \tag{34}$$

Expression (34) is a transcendental equation for the parameter φ. It can be solved by the iteration method. In the zero-order approximation, i.e. at $\Delta p = 0$, we have $\varphi^{(0)} = \ln(\alpha/\beta)$. Substituting this expression into the right-hand side of Eq. (34), we find the first approximation

$$\varphi^{(1)} = \ln\left\{\frac{\alpha}{\beta} + \left(\frac{\alpha}{\beta}\frac{\delta}{\beta} + \left[\frac{\alpha}{\beta}\frac{\delta}{\beta} - \frac{\chi}{\beta}\right]f_0\right)\Delta p\right\}, \tag{35}$$

where

$$f_0 = f(\varphi^{(0)}) = \frac{1}{\ln\frac{\alpha}{\beta}} + \frac{\alpha}{\beta - \alpha}. \tag{36}$$

Let us rewrite formula (35) in another form, namely,

$$\varphi^{(1)} = \ln\left\{\frac{\alpha}{\beta}(1 + \left[\frac{\delta}{\beta} + \frac{\delta}{\beta}f_0 - \frac{\chi}{\alpha}f_0\right]\Delta p)\right\}, \tag{37}$$

From this expression, we obtain, for small pressure gradients, that

$$\varphi^{(1)} = \ln\frac{\alpha}{\beta} + \left(\frac{\delta}{\beta} + \frac{\delta}{\beta}f_0 - \frac{\chi}{\alpha}f_0\right)\Delta p. \tag{38}$$

At last, the general formula for the stationary membrane potential in the presence of pressure gradient is as follows:

$$\tilde{\varphi}_{\rm stat} = \frac{RT}{F}\left(\ln\frac{\alpha}{\beta} + \left(\frac{\delta}{\beta} + \frac{\delta}{\beta}f_0 - \frac{\chi}{\alpha}f_0\right)\Delta p\right). \tag{39}$$

Thus, we obtained generalized analytical expressions for ionic fluxes through membrane structures, which allow the application limits of the theory of ionic transport developed by now to be extended onto the case with pressure gradients.

3. Results and Conclusions

Thus, the obtained expression (39) contains the analytical dependence of the stationary membrane potential under non-isobaric conditions on such major factors as 1) the stationary ion concentrations on both membrane sides, 2) the coefficients of membrane permeability for various kinds of ions, 3) the parameters of barodiffusion distribution ($\sigma_{\rm K}$, $\sigma_{\rm Na}$, and $\sigma_{\rm Cl}$), and 4) the pressure difference across the membrane. It should be noted that, if $\Delta p = 0$, formula (39) transforms into formula (2) for the stationary membrane potential under isobaric conditions.

It should be noted that the coefficient $\sigma_{\rm K}$ for the barodiffusion term in formula (27) was estimated on the basis of the following considerations. In work [4], electrodiffusion processes were studied taking the influence of the temperature gradient into account. The multiplier before the temperature difference in the linear law for the diffusion flux was the Soret coefficient σ_T for a definite kind of ions; its dimension is an inverted temperature unit. According to the available experimental data, the numerical value to this coefficient is $\sigma_T \approx 10^{-3}$ K^{-1}. Therefore, it was natural to consider the coefficient σ_T to be equal to the inverse critical temperature of water, which – by its consistence – corresponds to liquids that the biological membranes are made up of [4]. Such a suggestion is also supported by the fact that the cell membrane, besides structured sections of the bilayer, also contains boundary sections with a high water content, as well as a plenty of pores filled with water [5]. Therefore, in this work, by analogy with work [4], an assumption was made that the coefficient σ in formula (27) is approximately equal to the inverse critical pressure of water:

$$\sigma \approx \frac{1}{p_c} = \frac{1}{22\cdot 10^6 \quad {\rm Pa}} = 4,6\cdot 10^{-8}{\rm Pa}^{-1}. \tag{40}$$

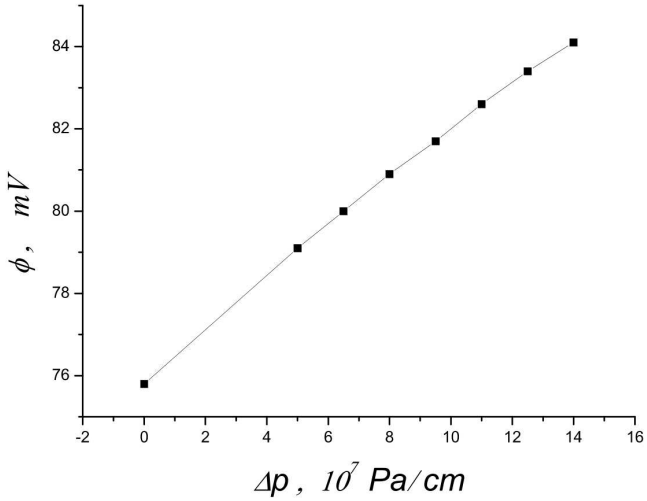

Fig. 1. Dependence of the rest membrane potential on the pressure difference across the membrane

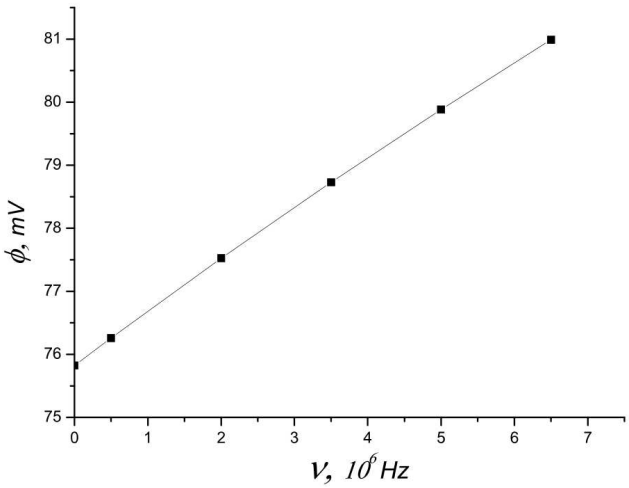

Fig. 2. Dependence of the electric membrane potential on the ultrasonic wave frequency

Using the theoretical results obtained in this work, the dependences of membrane potential on the pressure gradient for the giant axon of a squid at the temperature of the endocellular medium $T = 293$ K were plotted. In Fig. 1, the dependence of the rest membrane potential on the pressure difference $\Delta p = p_e - p_i$ across the membrane for K^+-ions, calculated using Eq. (27), is depicted. We also plotted the dependence of the potential on the ultrasonic wave frequency (Fig. 2), making use of formula (3).

Now, let us analyze the characteristic features of the dependence of membrane potential on the pressure gradient in more details. As one can see from formula (39), the term $\ln(\alpha/\beta)$, besides a usual difference between ion concentrations across the membrane, also takes barodiffusion into account in the form of the exponential dependence on the $\sigma_j \Delta p$ products. The expression before the quantity Δp in the second term also contains the exponential dependence on the $\sigma_j \Delta p$ product. For $\sigma_j \Delta p \ll 1$, the exponents can be expanded in series up to the linear terms, so that the obtained dependence of the membrane potential on Δp can be described (Fig. 1). Thus, the analysis of the theory demonstrates that the results obtained give the important estimations (both quantitative and qualitative) to the barodiffusion processes in membrane structures and their influence on biological potentials. In particular, with increase in the pressure outside the membrane, the rest potential grows, i.e. the endocellular medium becomes more electronegative with respect to the external solution.

The numerical calculations have shown that the dependences of the membrane potential on the pressure difference and the ultrasonic wave frequency are almost linear in the intervals $\Delta p = (0 \div 15) \times 10^7$ Pa/cm and $\nu = (0.5 \div 7) \times 10^6$ Hz, with the variation of membrane potential in the indicated intervals reaching almost 15% of its value under isobaric conditions.

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ЕЛЕКТРИЧНІ МЕМБРАННІ ПОТЕНЦІАЛИ СПОКОЮ З УРАХУВАННЯМ БАРОДИФУЗІЙНИХ ЯВИЩ

Г.В. Шліхта, О.В. Чалий

Р е з ю м е

Вивчено вплив градієнтів тиску на стаціонарний мембранний потенціал, який є найбільш реальним електричним потенціалом спокою. Досліджено і проаналізовано залежність електричного мембранного потенціалу від перепаду тиску з врахуванням зміни частоти ультразвукового випромінювання для неізобаричних умов. Отримано чисельні оцінки впливу бародифузійних ефектів на значення електричних мембранних потенціалів спокою.