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The Mechanism of the Excitability of Biological Membranes

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The phenomenology of the excitation of a cell membrane is described. It is shown that, in the adsorption inhibition of a mobile transferring agent, the descending branch of the voltage-current characteristic can be obtained. The Hodgkin-Huxley model is interpreted in terms of ionic channels and the statistical properties of such a system are examined. In particular, the spectrum of the electrical fluctuations of potassium channels is analysed. Experiments in which "gating currents" were measured are briefly described and interpreted in terms of the cooperative dipole model.
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I. INTRODUCTION

The phenomenology of the electrical phenomena occurring on excitable cell membranes can be described in detail by the Hodgkin–Huxley empirical equations[1]. Until recently the attempts to create physically consistent models outside the framework of a formal description have been speculative, since a suitable experimental basis was lacking. Nevertheless the endeavour to achieve some kind of physical model is quite justified. Strictly speaking, Hodgkin and Huxley themselves indicated, although not without reservations, one of the simplest possible interpretations of the formal scheme. Studies in recent years on the selectivity and permeability of ionic channels[2,3], experimental and theoretical investigations of the electrical noise spectra of membranes[4-7], and finally brilliant experiments in which measurements were made of the so called "gating currents"[8-11] altered the situation radically. On the one hand, a need arose for certain modifications to the formal Hodgkin–Huxley scheme and on the other a basis appeared for the development of a physical model of excitability. This paper is devoted to a brief analysis of the present state of the problem of excitability.

II. PHENOMENOLOGY OF THE EXCITATION PROCESS

Here we shall describe only briefly the well known model of the squid axon and shall note certain details which we believe to be important. According to the Hodgkin–Huxley model, the membrane potential satisfies the following equation in the process of three-dimensional homogeneous excitation:

$$C\frac{d\varphi}{dt} = -I. \tag{1}$$

The significance of this equation is that the membrane is regarded as a condenser with a capacitance $C \simeq 1\ \mu F\ cm^{-2}$. The ionic current I is formulated as the sum of three currents—the sodium, potassium, and leakage currents:

$$I = I_{Na^+} + I_{K^+} + I_L. \tag{2}$$

In its turn each current is regarded as the current generated by a battery with a constant e.m.f. and a variable resistance (apart from the leakage resistance):

$$I_{Na^+} = g_{Na^+}(\varphi - \varphi_{Na^+}); \tag{3}$$

$$I_{K^+} = g_{K^+}(\varphi - \varphi_{K^+}); \tag{4}$$

$$I_L = g_L(\varphi - \varphi_L);\ g_L \approx 3 \cdot 10^{-4}\ \Omega^{-1}\ cm^{-2}. \tag{5}$$

Each of the three e.m.f.'s (φ_{Na^+}, φ_{K^+}, and φ_L) is assumed to be known and determined by the differences between the concentrations of the corresponding ions in accordance with the Nernst formula. Under physiological conditions, these quantities are $\varphi_{Na^+} = +115$ mV, $\varphi_{K^+} = -12$ mV, and $\varphi_L = +10$ mV. On the other hand, the conductivities of the membrane with respect to potassium and sodium, g_{Na^+} and g_{K^+}, can vary with time; their dynamics is defined as follows: for conductivity with respect to sodium, two dynamic variables, denoted by m and h, are introduced and the following relation is postulated:

$$g_{Na^+} = \bar{g}_{Na^+} \cdot m^3 h;\ \bar{g}_{Na^+} = 0.12\ \Omega^{-1}\ cm^2, \tag{6}$$

where $\bar{g}_{Na^+}$ is the maximum possible conductivity. On the other hand, m and h satisfy the relaxation equation in which the coefficients (which are different for m and h) depend on the potential:

$$\frac{dm}{dt} = \alpha_m(1-m) - \beta_m m, \tag{7}$$

$$\frac{dh}{dt} = \alpha_h(1-h) - \beta_h h. \tag{8}$$

The dynamics of the conductivity of the membrane with respect to potassium is formulated in an exactly similar way:

$$g_{K^+} = \bar{g}_{K^+} n^4,\ \bar{g}_{K^+} = 3.6 \cdot 10^{-2}\ \Omega^{-1}\ cm^{-2}, \tag{9}$$

and the dynamic variable n satisfies an equation analogous to Eqns. (7) and (8):

$$\frac{dn}{dt} = \alpha_n(1-n) - \beta_n n. \tag{10}$$

By fixing the potential on the membrane and by separating the sodium and potassium currents, Hodgkin and Huxley

found the required form of the relation between the coefficients α_i and β_i ($i = m$, n, or h) on the one hand and the potential on the other:

$$\alpha_m = 0.1\,(\varphi - 25)\,[1 - \exp(2.5 - 0.1\,\varphi)]^{-1}, \quad (11)$$

$$\beta_m = 4\exp(-\varphi/18); \quad (12)$$

$$\alpha_h = 0.07\exp(-0.05\,\varphi); \quad (13)$$

$$\beta_h = [1 + \exp(3 - 0.1\,\varphi)]^{-1}; \quad (14)$$

$$\alpha_n = 0.01\,(\varphi - 10)\,[1 - \exp(1 - 0.1\,\varphi)]^{-1}; \quad (15)$$

$$\beta_n = 0.125\exp(-\varphi/80). \quad (16)$$

In Eqns. (11)–(16) the coefficients α and β have the dimensions of the reciprocals of milliseconds and the potential is expressed in millivolts and is reckoned from the so called rest potential, defined as the difference between the internal and external potentials of the fibre at rest and equal to −60 mV.

The main attempts, of which we are aware, at a physical interpretation of the system described by the Hodgkin–Huxley equations are set out below.

III. INTERPRETATION OF THE HODGKIN–HUXLEY MODEL

In fact the problem is to discover the physical significance of the dynamic variables m, n, and h. In the first studies by Hodgkin and Huxley an attempt was already made to treat these variables as the concentrations of transferring species. Subsequent experiments showed that ion transport across biological membranes is not achieved with the aid of transferring species but takes place via ionic channels. However, an action potential was recently obtained on two-layer lipids membranes under conditions where the mechanism involving mobile transferring agents is extremely probable[12]. It is therefore useful to consider briefly the nature of excitability in a simple example[13].

Adsorption Inhibition of a Transferring Agent

Suppose that the ions A and B can cross the membrane with the aid of different transferring agents T and M. We shall assume that the solution contains a substance X which can bind the transferring agent T on the surface of the membrane. Then the partial voltage–current characteristic of the ion A is

$$I_A = (1 - \Gamma)\,I_A^*(\varphi), \quad (17)$$

where I_A^* is the voltage-current characteristic in the absence of the inhibitor and Γ the fraction of bound transferring agents.

The equation for the membrane potential is

$$C\frac{d\varphi}{dt} = -(I_A + I_B) + I, \quad (18)$$

where I is the external current. The fraction of bound transferring agents is described by the equation of adsorption kinetics:

$$\frac{d\Gamma}{dt} = \alpha(1 - \Gamma) - \beta\Gamma; \qquad \alpha = k_1 e^{z\varphi/s}, \quad \beta = k_2 e^{-z\varphi/s}. \quad (19)$$

We shall examine the special case where the partial voltage–current characteristics are arranged as shown in Fig. 1. The isoclinic lines for this system of equations are presented in Fig. 2*a*. In this case the point of intersection represents the unique stable stationary state. However, the system possesses threshold properties and is capable of generating single pulses. If the system is deflected sufficiently from the state of equilibrium, its subsequent motion will be described by the dashed line in Fig. 2*a*.

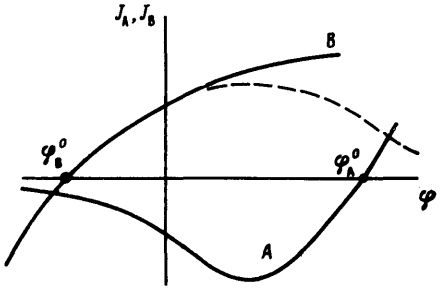


Figure 1. Partial characteristics of the ions A and B. The intercepts made by the curves on the abscissa axis define the equilibrium potentials φ_A^0 and φ_B^0. The dashed line represents the possible variation of I_B.

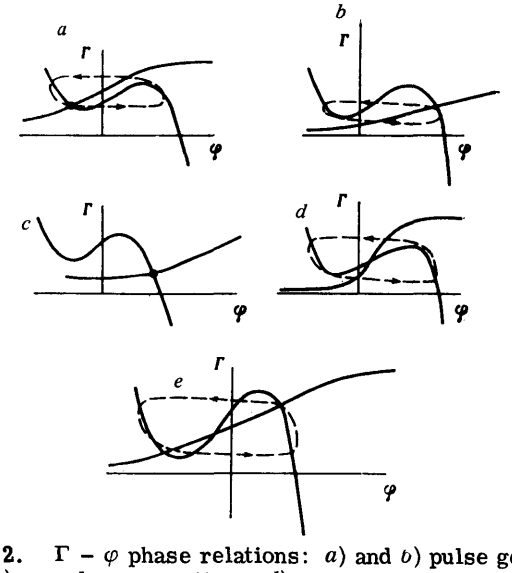


Figure 2. $\Gamma - \varphi$ phase relations: *a*) and *b*) pulse generation; *c*) no pulse generation; *d*) auto-oscillations; *e*) transitions from one stable state to another. The dashed line illustrates the phase trajectories.

In case *b* (Fig. 2) the situation is analogous except that the "action potential" has a different sign. In case *c* the stationary state is stable but the generation of a pulse is impossible, since whatever the deviation from the state of rest the system returns to the latter. In case *d* the only stationary state is unstable, since an auto-oscillatory process takes place in the system. In case *e* there are three stationary states, of which the extreme ones are stable and the intermediate one is not. By a stimulus

exceeding the threshold value, the system can be transferred from one stable state to another, where it can remain indefinitely.

We have analysed the behaviour of the membrane potential in the presence of an inhibitor, the surface concentration of which played the role of a dynamic variable. Another model of an excitable membrane, in which there are no inhibitors but significant diffusion-dependent restrictions are imposed on one of the ions in the layer of solution near the membrane, has been investigated in an analogous manner[13].

Ionic Channels

We shall consider, for example, the potassium channel which "opens" on simultaneous "activation" of four species which do not interact. The rate constants for "activation" α_n and "inactivation" β_n depend on the potential. When these rate constants are interpreted by Eyring's procedure, we have for the constant α_n in the range of negative potentials

$$\alpha_n = e^{2.5\, e\frac{\varphi}{kT}}.$$

Hence it follows that the potassium channel is "activated" when a certain hypothetical species overcomes an activation barrier with a height of $2.5e\varphi$. If the activation is achieved with migration of the charged species in the direction of the force driving the current, then such activation may be attained by transferring a species with a charge of $2.5e$ through the entire thickness of the membrane. On the other hand, when the activation occurs with partial charge transfer, say over a distance $\epsilon\delta$, where δ is the thickness of the membrane, then the field could execute the required work by transferring the $2.5e/\epsilon$ charge between points corresponding to the potential difference $\epsilon\varphi$ (in terms of the constant field approximation). If the elementary displacement amounts to, for example, 5 Å, then $\epsilon = 1/20$ and the charge transferred will be equal to 50 electronic charges or 25 electronic charges when $\epsilon = 1/10$. Both versions are relatively unsuitable from the physical standpoint. The large charge might be accounted for by attributing its displacement to many species and not to a single species. However, in this case the problem would then arise of the explanation of the rigid linkage between these species, because the required potential relation $\alpha_n(\varphi)$ would arise only if the possibility of an asynchronous migration of the species were ruled out.

Below we shall consider in detail one of the cooperative models, but now we shall formulate a convenient method for describing excitable ionic channels in terms of transitions between different conformational states[6]. For brevity, we shall confine ourselves to the potassium channel, since there is no difficulty in extending the treatment to the sodium channel. We postulate that the potassium channel contains x identical independent subunits, each of which can exist in one or two states—0 ("passive" state) and 1 ("active" state). The channel conducts only when all x subunits are in state 1.

Consider an assembly of N identical channels. It is possible to introduce a concentration of channels in which the number of subunits in state 0 is i. It will be designated by c_i. Evidently we have c_0, c_1, ..., c_x, in all $x + 1$ concentrations, corresponding to $x + 1$ different states of the channel. Denoting the rate constant for the transition from 0 to 1 by α and that for the transition from 1 to 0 by β, we obtain a system of equations describing the kinetics of the changes in the concentrations:

$$\left.\begin{aligned}
&\frac{dc_0}{dt} = \alpha c_1 - \beta x c_0;\\
&\frac{dc_1}{dt} = 2\alpha c_2 + \beta x c_0 - \alpha c_1 - \beta(x-1)c_1;\\
&\cdots\cdots\cdots\cdots\cdots\\
&\frac{dc_j}{dt} = -j\alpha c_j + (x-j+1)\beta c_{j-1} - (x-j)\beta c_j + \alpha(j+1)c_{j+1},\\
&\cdots\cdots\cdots\\
&\frac{dc_x}{dt} = -x\alpha c_x + \beta c_{x-1}.
\end{aligned}\right\} \quad (20)$$

By considering the coefficients α and β as functions of the potential, it is possible to describe by Eqns. (20) experiments in which the potential is fixed, because, within the framework of our scheme, the conductivity varies in proportion to the concentration c_0: $g_K = Ng_0c_0$.

We shall now define the steady-state distribution of channels between the states. Putting $d/dt = 0$ in Eqns. (20), we have

$$\left.\begin{aligned}
&\bar{c}_1 = x\frac{\beta}{\alpha}\bar{c}_0 \equiv x\zeta\bar{c}_0;\\
&\bar{c}_2 = \frac{x-1}{2}\zeta\bar{c}_1 = \frac{x(x-1)}{2}\zeta^2\bar{c}_0;\\
&\cdots\cdots\cdots\cdots\cdots\\
&\bar{c}_j = \frac{x!}{(x-j)!\,j!}\zeta^j\bar{c}_0 = c_x^j\zeta^j\bar{c}_0\ ,
\end{aligned}\right\} \quad (21)$$

where a bar over symbol denotes a steady-state value of the given quantity. From the condition

$$\sum_{i=0}^{x} c_i = 1\ , \quad (22)$$

we find

$$\sum c_x^j\zeta^j\bar{c}_0 = 1; \quad (23)$$

hence we have

$$\bar{c}_0 = \frac{1}{(1+\zeta)^x}\ . \quad (24)$$

Thus, after introducing the definition

$$n = \frac{\alpha}{\alpha+\beta} = \frac{1}{1+\zeta}\ , \quad (25)$$

it is immediately seen from Eqn. (24) that, when $x = 4$, the expression for $\bar{c}_0$ is the same as the Hodgkin–Huxley equation for conductivity. Therefore one can write

$$c_0 = n^x.$$

When an experiment with a fixed potential is considered, we have the following solution of Eqn. (10):

$$n = n_\infty - (n_\infty - n_0)e^{-\lambda t}, \quad (26)$$

where $\lambda = \alpha + \beta$. Therefore the conductivity under the conditions of a fixed potential is given by

$$g_K = Ng_0[n_\infty - (n_\infty - n_0)e^{-\lambda t}]^x. \quad (27)$$

When $x = 4$, this expression is exactly the same as the Hodgkin–Huxley equation, provided that we put $\alpha = \alpha_n$ and $\beta = \beta_n$.

Eqns. (24) and (27) confirm that the kinetic scheme described can be regarded as a physical interpretation of the Hodgkin–Huxley model. However, until recently it was impossible to test this scheme directly. The spectra of current fluctuations, which should in principle throw light on the validity of the kinetic scheme, were measured

a comparatively long time ago[14,15]. However, the spectrum usually measured varied with the reciprocal of the frequency $1/f$. This type of variation could not be obtained not only in the Hodgkin–Huxley scheme but also in any other. Therefore it was not certain that the measured quantities are associated with the fluctuations in the conductivity of ionic channels. In 1973 Fishman[7] measured the spectrum of the conductivity fluctuations of the potassium channel, having defined it as the difference between the fluctuation spectra of a normal membrane and a membrane with blocked potassium channels. His spectrum had a density defined by

$$G(\omega) = \frac{f_1(\varphi)}{\lambda^2 + \omega^2}; \quad \omega = 2\pi f,$$

where $\lambda = \alpha_n + \beta_n$ and $f_1(\varphi)$ is a function. These experiments enabled Chen and Hill[6] to compare Hodgkin's kinetic scheme with Fishman's experiments, which led to the observation of a discrepancy between the theory and experiment: the theoretical variation of the critical frequency λ with potential was described by a line lying appreciably above the experimental points (the critical frequency was determined from the point of intersection of the zero and infinite asymptotes in the plot of G against $\ln\omega$). This discrepancy was appreciably reduced by Chen and Hill[6], who assumed the possibility that the current may be conducted by the potassium channel not only in state 0 but also in others. The comparison of Hodgkin's scheme with the results of fluctuation analysis has so far been merely in the nature of a preliminary step. However, it is already clear that fluctuation analysis will be one of the most important instruments for the investigation of the nature of excitability.

IV. GATING CURRENTS

There have been considerable advances in recent years in the elucidation of the physical nature of the excitation process. The brilliant experiments of Armstrong, Bezanilla, Keynes, Rojas, Meves, and others[8-11], led to the observation of asymmetric currents, all the characteristics of which show them to be migration currents of the charged species within the membrane. There is reason to believe that these currents are directly related to the migration of charged groups controlling the conductivity of the sodium channel.

In view of the importance of the problem, it is necessary to define briefly the so called gating current. In the method with fixation of the potential, a membrane incapable of transmitting ions is maintained at a certain potential. Next a potential pulse with a specified amplitude (about 150 mV) and of sufficient duration is applied, the resulting current is recorded, and, after the cessation of the potential pulse, the system is again maintained at the initial potential. Next, a potential pulse of the opposite sign is applied; this leads to a new record of the current as a function of the time elapsed from the beginning of the pulse. The so called gating current is obtained by subtracting the currents corresponding to the same time from one another. The sign of equality then naturally depends on the initial potential and for a certain value of the latter the amplitude of the gating current is zero[9]. It is remarkable that an approximate agreement between the characteristic time of the change in the gating current and the time of the change in the variable m has been observed experimentally over the entire range of potentials. On the other hand, no indication has been obtained of any correlation between the gating current and the variables h and n. Apparently this cannot be accounted for by the inadequate accuracy of the measurements—it is better to change the hypothesis concerning the kinetics of the activation of the sodium current and to seek an appropriate kinetic scheme.

V. THE COOPERATIVE DIPOLE MODEL

The interpretation of gating currents in the Hodgkin–Huxley scheme is based on the hypothesis that several charged groups, which are a constituent part of the channel, migrate through the entire thickness of the membrane. From the physical standpoint, this assumption is unlikely. It is more reasonable to postulate that there is a reorientation of dipoles surrounding the channel, which is equivalent to the transport of a charge across the entire membrane. Then the gating current reflects the rearrangement of the system of dipoles. It differs from the usual displacement current by the asymmetry of the sign of the field. The system of dipoles must be cooperative, since otherwise it would be impossible to explain the marked dependence of the electrical characteristics on the potential.

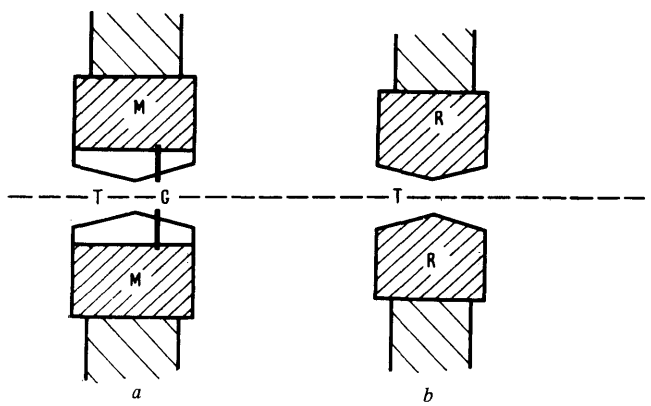


Figure 3. Model of the excited ion channel: *a*) regulation by the alteration of the molecular geometry of the transport system T (M—measuring device; G—gate); *b*) electrostatic scheme for the regulation of conductivity; rigid geometry of transport system; R—regulation system.

The change in the permeability to ions in the course of the reorientation of dipoles may be due to various causes. If the reorientation is coupled with appreciable conformational changes in the system, then the "opening" or "closing" of the channel can have the significance of a change in its molecular geometry. Another case is also possible, where the dipole reorientation influences the electrostatic component of the energy of the ions in the channel, without altering its geometry, and hence influences the concentration of the ions in the membrane and their effective mobility[16].

Models of the channel constructed taking into account the above possibilities are illustrated in Fig. 3. The ion channel probably consists of the transport system proper

(T) and the system regulating the permeability (R). The R unit can include a device measuring the field on the membrane (M), which is linked via certain degrees of freedom with the "gate" (G), i.e. with mobile molecular groups which alter the geometry of the transport system (Fig. 3*a*). There are so far no data which would provide an answer to the question whether the gate is localised or whether the rearrangement involves a considerable proportion of the transport system. Fig. 3*b* represents the electrostatic version of the regulation. There is no point in separating the measuring system from the gate proper, since the geometry of the transport system is assumed to be rigid and the R unit measures the field and regulates the permeability simultaneously. In any of these models the so called gating current is associated with the dipole reorientation in the R or M system. The problem of the calculation of the gating current is entirely independent and requires no hypotheses concerning the mechanism of the regulation of permeability.

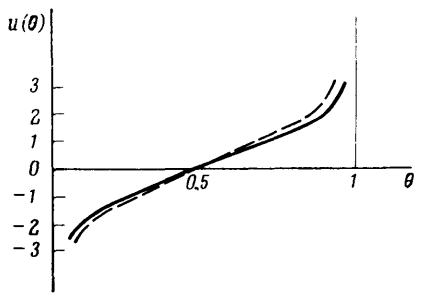


Figure 4. Variation of the cooperative energy of the subunit with θ. The continuous curve corresponds to $\epsilon = 0.2$ and the cooperativity parameter $w = 3.5$. Dashed line—$\epsilon = 0.05$ and $\omega = 3.88$; the phase transition takes place when $w = 4$.

We shall assume that the R (or M) system of the ion channel consists of a large number of subunits, each of which has a dipole moment. Suppose that each subunit can be in one of three states (0, 1, or 2), which differ in the magnitude of the projection of the dipole moment on the axis of the channel and correspond to the transition of the latter from the state of rest to activation and inactivation. In the quasichemical approximation the energy of the subunit in the ith state $V_i(\theta_1, \theta_2, \varphi)$ can be formulated as follows:

$$V_i = w_i(\theta_1, \theta_2) + \varepsilon_i(\theta_1, \theta_2)\,\psi, \tag{28}$$

where $\psi = e\varphi/kT$ is the membrane potential, ϵ_i the effective displacement of the charges in units of the thickness of the membrane, θ_i the degree of filling of the ith state, and w_i the cooperative component of the energy. The rate constants for the transitions are expressed as usual in terms of the differences between the energies of the states, for example:

$$k_{01} = Ae^{\alpha(u_1+\varepsilon_1\psi)};\ u_1 + \varepsilon_1\psi = V_0 - V_1. \tag{29}$$

It is easy to formulate kinetic equations within the framework of the linear scheme:

$$\dot{\theta}_i = -(k_{i1} + k_{i0})\,\theta_i - k_{ij}\theta_j + k_{ji};\ i, j = 0, 2;\quad i + j = 2. \tag{30}$$

We shall confine ourselves to the case of two states, which corresponds to the activation of the ion channel. Assuming that $\theta_2 = 0$, we obtain from Eqn. (30) the equation

$$\dot{\theta}_0 = -(k_{01} + k_{10})\,\theta_0 + k_{10}, \tag{31}$$

the steady-state solution of which has the form analogous to the familiar Frumkin isotherm:

$$\frac{\theta_1}{1-\theta_1}\,e^{-u(\theta_1)} = \frac{A}{B}\,e^{\varepsilon\psi};\ \theta_0 = 1 - \theta_1. \tag{32}$$

According to the experimental data[9], the charge displacement on activation of the sodium channel is described satisfactorily by the formula

$$\theta(\psi) = \frac{1}{1 + e^{-z\psi}};\quad z = 1, 3. \tag{33}$$

Fig. 4 illustrates the $u(\theta)$ relations for different values of ϵ found from the condition that Eqns. (32) and (33) become identical. It follows from Fig. 4 that, in the region of moderate degrees of saturation, $u(\theta)$ is represented satisfactorily by a linear function with cooperativity constants of 3.88 ($\epsilon = 0.05$) and 3.5 ($\epsilon = 0.2$). For low and high degrees of saturation, the cooperativity is still greater.

Fig. 5 illustrates the steady-state $\theta - \psi$ curve obtained for the linear approximation $u(\theta) = 3.5\ (\theta - 0.5)$. Thus, even a slight reorientation of small dipoles yields the required slope of the $\theta - \psi$ curve as a result of the marked cooperativity.

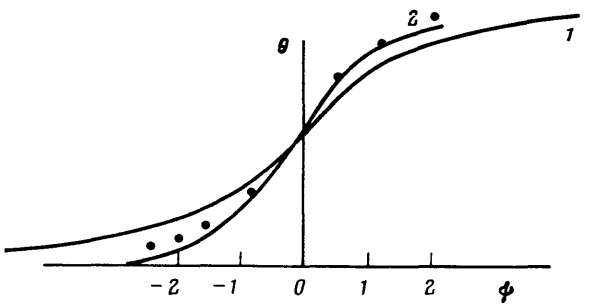


Figure 5. The fraction of transferred charge as a function of potential. Curve *1* was plotted on the basis of Eqn. (32) with a linear fit to the function $u(\theta)$. Curve *2* was calculated by Eqn. (33); circles—experimental data[9].

In order to calculate the gating current, it is necessary to determine the time variation of θ. This relation is illustrated in Fig. 6 for $\alpha = 1$. In this case the $\theta - t$ relation is quasiexponential at a fixed potential. The gating current is found by differentiating the expression for the $\theta(t)$ function.

The method for the determination of conductivity depends on the version of the model of the channel considered—that in Fig. 3*a* or 3*b*. In the former case it is possible to find the conductivity by fitting the function $\varphi(\theta)$ on the basis of experimental data. This procedure is analogous to the selection of the power function ($g_{K^+} \propto n^4$ and $g_{Na^+} \propto m^3h$) in the Hodgkin-Huxley model. In the

second case it is possible to find the form of the $g(\theta)$ function from physical considerations by calculating the concentration of carriers in the channel and the conductivity from the formulae:

$$c \simeq \bar{c} \cdot e^{F};\ g \simeq c, \tag{34}$$

where F is the change in the energy of the ion in the channel on reorientation of the dipoles, which can be readily estimated:

$$F \simeq \frac{eQ\delta\xi}{4\pi kTSN}(1-\theta). \tag{35}$$

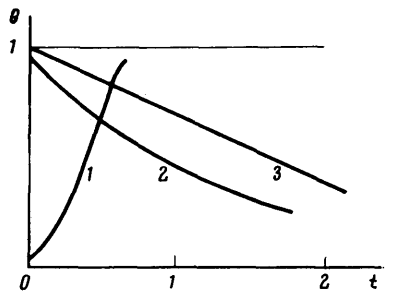


Figure 6. Variation of θ with t: 1) "direct clamp" from $\theta = 0.05$ to $\theta = 0.95$; 2) "reverse clamp" from $\theta = 0.95$ to $\theta = 0.05$; 3) variation of $\lg\theta$ with t corresponding to curve 2.

Here $Q\delta$ is the total change in the dipole moment ($Q \propto 2 \times 10^3 e/\mu^2$), S is the area of the lateral surface of the channel, N the density of the channels, and ξ the structure factor. When $\xi \simeq 10^3$, the energy $F \simeq 10\theta$. Calculations show that there is a great similarity between the variation of θ^4 and $e^{6(\theta-1)}$ in the region of moderate values of θ. The exponential relation between conductivity and θ has the advantage that it makes it possible to explain readily, by the additivity of the energy, the formula $g_{Na^+} \simeq m^3h$ and also the shift of the conductivity current maximum relative to the gating current maximum.

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