J. theor. Biol. (1994) **168**, 383–393

Ferroelectric Active Models of Ion Channels in Biomembranes

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(*Received on* 11 *March* 1993, *Accepted in revised form on* 10 *December* 1993)

Ferroactive models of ion channels in the theory of biological membranes are presented. The main equations are derived and their possible solutions are shown. The estimates of some experimentally measured parameters are given. Possible physical consequences of the suggested models are listed and the possibility of their experimental finding is discussed. The functioning of the biomembrane's ion channel is qualitatively described on the basis of the suggested ferroactive models. The main directions and prospects for development of the ferroactive approach to the theory of biological membranes and their structures are indicated.

1. Introduction

One of the problems of contemporary mathematical biophysics is the study of structures of biological membranes and their functions, among which the problem of transport is the most important. In this context formation of functional structures responsible for charge transfer is of special interest.

At present molecular structures have been elucidated for only a few molecular channels (Hille, 1984; Noda *et al.*, 1984; Rubin, 1987; Boldyrev, 1990) among which is the electroexcited Na^+ channel (Noda *et al.*, 1984). However, knowledge of the channel's primary structure contributes only a little to the understanding of the mechanism of its function.

Nevertheless, calculations and estimates, including those obtained by powerful methods of molecular dynamics (Veresov, 1991) have already appeared, which try to describe the process of the channel's functioning. The authors of such investigations have had to make many assumptions, because the secondary, the tertiary and the quaternary structures are unknown.

Thus the development of an appropriate biophysical model of the functioning of the ion channel is a problem which is acute now as never before. It is expected that the model would be capable of predictions on the physical and biological peculiarities of the channel's behavior under functioning and would point the way for future experimental investigations.

The models which already exist (Hille, 1984; Boldyrev, 1990) are very interesting, especially the protochannel models (Geletyuk & Kazachenko, 1990) for example. But in our opinion the most interesting are *ferroelectric-active models* (Leuchtag, 1987*a*,*b*, 1988; Bystrov, 1992).

2. The Existing Models of Ion Channels of Biomembranes

There exist various types of ion transport and various types of ion channels (Hille, 1984; Boldyrev, 1990), which may be classified into two main groups: potential-dependent ion channels and indifferent ones (Boldyrev, 1990; Rubin, 1987).

The potential-dependent ion channels, which we are mainly interested in, are thought to have the following *functional* organization (Boldyrev, 1990). The channel-structure integral protein, incorporated into the lipid biomembrane forms a *pore* in it. Besides there is a selectivity *filter*, imparting specificity of the channel with respect to various ions, and a *sensor* of the membrane potential, responsible for the so-called "*gate mechanism*", i.e. the device to open and to close the ion channel in function of the potential's sign and its value (Hille, 1984; Rubin, 1987; Boldyrev, 1990; Geletyuk & Kazachenko, 1991).

Structurally the "ion channel" is considered in contemporary biomembranology (Boldyrev, 1990) as an integral protein (or glycoprotein), located in the lipid bilayer of the membrane and mediating the ion motion across the membrane by its electrochemcial potential. However, the study of a real molecular structure of ion channels allows no definite conclusions about their functional organization and ion transfer processes. Therefore, in addition to the experimental data on the ion channel structure, the existing models use some assumptions as well as the material on the artificial ion channels. Thus the models on the basis of *gramicidin* (Urry, 1971; Rubin, 1987), *alamecithin* (Rubin, 1987; Veresov, 1991) and other sufficiently simple macromolecules (Rubin, 1987; Lear *et al.*, 1988) forming experimentally observable spiral structures are of knowledge. Note that separate molecules may aggregate into complexes.

It is characteristic that functioning of ion channels in such structures is analyzed either on the basis of conformational transitions with a jump of a dipole moment or by changing the molecular orientation, which is also connected with changing of a dipole moment (Urry, 1971; Mintz & Kononenko, 1982; Rubin, 1987; Lear *et al.*, 1988; Boldyrev, 1990). Though the nature of dipoles of separate molecular groups is unknown the general mechanisms and principles of local ordering are valid here. They ensure a mean integral value of polarization in the vicinity of lipid protein complexes (Owicki *et al.*, 1978; Rubin, 1987; Fishbain, 1989; Veresov, 1991), which actually present integral channel proteins, incorporated into a lipid membrane, as impurities in the liquid-crystal bilayer under various phase transitions, affected by changing of both the membrane's electric field and the lateral pressure or composition.

It is known that the estimated value of a bound charge near the ion channel is of the order of 0·02 C m^{-2} (Chandler *et al.*, 1965; Rubin, 1987; Smith-Maxwell & Begenisich, 1987; Leuchtag, 1988; McConnell *et al.*, 1990; Bystrov, 1992). This coincides with the value of a polarization jump in clusters and domains of the lipid bilayer in the vicinity of a phase transition (Ivkov & Berestovsky, 1982; Keller *et al.*, 1987; Pasynkov, 1987; Losch & Mohwald, 1989; Petrov *et al.*, 1991; McConnell, 1991) and with the value of polarization in ferroelectric liquid crystals (Pikin, 1981; Blinov & Beresnev, 1984) and this is an order of magnitude smaller than the polarization in some solid ferroelectrics (in barium titanate ~0·2 C m^{-2}) (Lines & Glass, 1977). Leuchtag (1991a,b) pointed out that the spontaneous polarizations of the order–disorder ferroelectrics Rochelle salt (0·0025 C m^{-2}) and triglycine sulfate (0·028 C m^{-2}) (Lines & Glass, 1977) bracket the estimated Na-channel surface charge.

In this context it seems interesting to consider in greater detail the properties of the Na$^+$ channel, which were obtained experimentally in Noda *et al.* (1984). In this work the method of restoring the amino acid protein sequence from the nucleotide sequence of complementary DNA was used to obtain the Na$^+$-channel primary structure from the electric organ of the *eel electrophorus electricus*.

Four homologous domains were identified in the protein structure. Each of them contains five hydrophobic and amphiphilic segments and one segment with a characteristic strong positive charge. Its nature is not yet clearly understood. However Noda *et al.* (1984) suggest that the protein may be incorporated into the membrane as shown in Fig. 1.

In this case it is supposed that the ion pore is formed by twisting of homologous domains into a cylinder structure, so that the hydrophilic parts of amphiphilic segments remain inside the cylinder (they form the pore's sides) and the hydrophobic parts inter-acting with the membrane's lipids appear outside.

It has been found experimentally in Noda *et al.* (1984) that the availability of rather a large positive charge at the domain's segment on the inside of the biomembrane leads to an important physical consequence. Such a charge may be screened, but in the dielectric non-conductive media (such as biomembrane) or, at least, in weakly conductive media it induces a bound surface charge (polarization) in the vicinity of a lipid–protein complex of the channel.

Thus, the experimental data suggest the possibility of formation of the bound state on the inside of the membrane, that is, to the possibility of a corresponding polarized state with the electric polarization vector

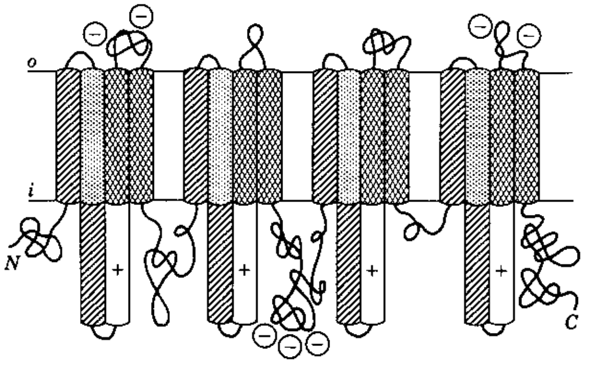

FIG. 1. Domain structure of Na$^+$ channel (by Noda *et al.*, 1984).

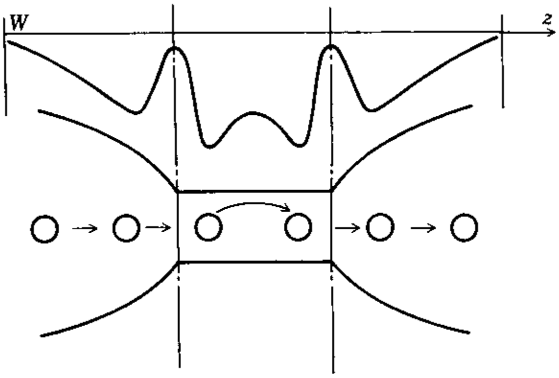

FIG. 2. Ion channel by Veresov (1991).

directed along the channel from outside to inside of the membrane.

In Veresov (1991) some additional segments are introduced for the convenience of constructing of the molecular-dynamic model, which leads to highly interesting quantitative results and yields a channel's profile, shown in Fig. 2. However Veresov (1991) does not use the fact of the charge's availability to derive the possible potential gradient along the channel. As a result the internal electric field along the channel is left out of account.

The charge may also be partially screened when trapping, for example, electrons, which are presented here, though in small concentrations. This in turn, stabilizes the whole complex and results in appearance of electron-bound states.

The availability of polarization, comparable in value with ferroelectric liquid cyrstals and the significant non-linearity of the biomembrane's media near the phase transitions naturally lead us to consider ferroactive models of the biomembrane's ion channel. The ferroactive models of biomembrane ion channels seem most promising, since they describe successfully a *large quantity* of the existing *experimental data*, such as:

(i) The very fact of the ion transfer (Rubin, 1987; Leuchtag, 1987*a*,*b*);

(ii) The gate currents (Armstrong & Bezanilla, 1973; Rubin, 1987; Leuchtag, 1988);

(iii) Hysteresis phenomena and volt–ampere characteristics (Leuchtag, 1987*a*,*b*, 1988; Duch *et al.*, 1988; Bystrov, 1992);

(iv) Heat effects (Chapman, 1967; Leuchtag 1988, 1991*a*; Bystrov 1992), etc.

Some of these effects are considered in the Leuchtag works (Leuchtag 1987*a*,*b*, 1988, 1990, 1991*b*). All these effects are the consequences of the ferroelectric phenomena (Lines & Glass, 1977; Smolensky, 1985).

Below we formulate the simplest ferroactive, models and variants of their mathematical interpretation (Section 3, Sections 3.1 and 3.2), general physical consequences (Section 4) and describe qualitatively the functioning of the ion channel on the basis of the introduced ferroactive model (Section 5). At the end of the paper we consider some of new consequences, which may be derived from these interpretations of the functioning of the biomembrane's ion channels and touch upon the research prospects in the field (Sections 6 and 7).

3. Ferroactive Models of Biomembrane Ion Channels and Their Mathematical Description

The papers (Leuchtag, 1987*a*,*b*, 1988) carry out probably the most complete and detailed analysis of the available extensive experimental data, pointing directly to various properties and physical effects, occurring in the functioning of ion channels, which are relative to ferroelectrics and processes attendant on the phase transition in it.

This has made it possible to put forward a hypothesis on the ferroactive nature of ion channel and formulate the model of a ferroelectric channel unit (Leuchtag, 1988).

In essence this model suggests that the "closed" state of the ion channel corresponds to the polar (polarized) ferroelectric phase, and the "open" one arises during the phase transition to the nonpolar paraelectric phase. The actual process of phase transition in the electro-excited membrane's ion channel goes on gradually from the outside to inside of the membrane in response to the change in the electric field. The displacing interphase boundary, containing the negative bound charge, also carries with it the positive ion, which has been screening the bound charge outside the membrane in the "closed" channel's state (see Fig. 3). It is important to stress that this mechanism offers a simple and natural

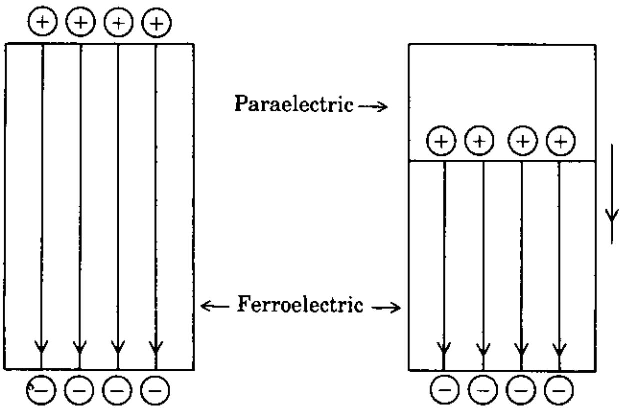

FIG. 3. Ferroelectric channel unit model by Leuchtag (1987*a*,*b*, 1988).

interpretation of the so-called "gate currents" (Armstrong & Benazilla, 1973; Rubin, 1987), which are hardly explicable in other models. The matter is that in the absence of the ion's screening charge, the movement of the interphase boundary with a bound charge gives rise to the displacement current, which has another direction.

This model has appeared as a result of attempts to generalize the known electrodiffusion models (Rubin, 1987) to the case of a non-linear medium (Leuchtag, 1987*a,b*) and, in principle, has no need in the concept of "pore", as a zone providing the actual ion passage along the channel. Moreover, further development of this model in Leuchtag (1990, 1991*b*) has suggested the idea of the superionic conductivity, i.e. the possibility of the phase transition from the non-conductive ferroelectric phase to the conductive superionic one. As was noted, this model is possible owing to the existence of quasi-crystal organic compounds, which possess properties of both ferroelectrics and superionic conductivity.

On the other hand, any ferroelectric model is possible owing to the long-known fact that some proteins, like amino acids, exhibit ferroelectric properties (Gutman & Lions, 1967; Tarasevich *et al.*, 1989).

The phason ferroactive model is developed in Bystrov (1992). This model takes account of the bound electron or other charge states (related to polaron ones), which screen partially the bound charge on the inside of the membrane (channel). This leads to the formation of a ferroactive channel as a complex of the phason (fluctuon) type (Krivoglaz, 1969; Bystrov 1983; Bystrov *et al.*, 1993).

It is noteworthy for our further analysis that the interphase boundary motion considered in these ferroactive models may be mathematically described, as it was done when studying the domain wells and interphase boundaries, for example, in the form of kinks in various ferroelectrics (Zhirnov, 1958; Ivanchick, 1961; Bulaevsky, 1963; Darinsky & Fedosov, 1974; Gordon, 1986; Dec & Yurkevich, 1990).

In the ferroactive models given below, the mathematical description of ferroelectrics is based on the thermodynamic theory by Landau, Ginzburg and Devonshire (Lines & Glass, 1977; Smolensky, 1985).

3.1. THE MODEL WITH FERROACTIVE LAGRANGIAN

Let us consider a one-dimensional model in the simplest classical case without free charges and external fields. The polarization distribution P in this case is given by the lagrangian:

$$\mathscr{L} = \lambda\left(\frac{\partial P}{\partial t}\right)^2 - \delta\left(\frac{\partial P}{\partial x}\right)^2 - \alpha P^2 - \tfrac{1}{2}\beta P^4 - \tfrac{1}{3}\gamma P^6. \quad (1)$$

Here the values of λ, δ, γ are always positive. For a second-order phase transition (PT2) the value of $\beta > 0$ and $\alpha = \alpha_0(T - T_c)$, where T_c is the Curie–Weiss temperature. Value of $\alpha > 0$ for $T > T_c$ (paraphase, $P = 0$) and $\alpha < 0$ for $T < T_c$ (ferrophase, $P = \pm(-\alpha/\beta)^{1/2}$ for $\gamma = 0$). In the case of a first-order transition (PT1) the value of $\beta < 0$, and the expression for α takes the form:

$$\alpha = \alpha_0' + \alpha_0(T - T_0),$$

where $\alpha_0' = \alpha_0(T_0 - T_c)$ and T_0 is the phase transition temperature.

The corresponding equation of motion may be written as:

$$\lambda\frac{\partial^2 P}{\partial t^2} - \delta\frac{\partial^2 P}{\partial x^2} + \alpha P + \beta P^3 + \gamma P^5 = 0. \quad (2)$$

3.1.1. *Free waves*

All the degrees of P are absent and the motion is free ($\alpha = 0$)

$$\frac{\partial^2 P}{\partial t^2} = c^2\frac{\partial^2 P}{\partial x^2}, \quad \text{or} \quad \frac{\partial^2 P}{\partial x^2} = c^{-2}\frac{\partial^2 P}{\partial t^2}, \quad (3)$$

where the rate is:

$$c = (\delta/\lambda)^{1/2} = \omega/k \quad (4)$$

for the plane-wave propagation $P = P_0\exp(i(kx - \omega t))$.

3.1.2. *Linear waves*

Taking account of the term αP^2 from the Lagrangian (1), eqn (2) turns into:

$$\frac{\partial^2 P}{\partial x^2} - c^{-2}\frac{\partial^2 P}{\partial t^2} \mp \omega_0^2 c^{-2} P = 0, \quad (5)$$

where the characteristics frequency ω_0 is $\omega_0 = (\pm\alpha/\lambda)^{1/2} = \tau_0^{-1}$. Here the sign "+" is for $\alpha > 0$ (i.e. $T > T_c, \omega_0 > 0$), and sign "−" is for $\alpha < 0 (T < T_c, \omega_0 > 0)$. The corresponding dispersion law is:

$$\omega^2 = k^2c^2 \mp \omega_0^2. \quad (6)$$

Then, the phase velocity of the front of the free phase plane wave is:

$$v_{\mathrm{ph}} = \omega/k = c/(1 \pm \omega_0^2/\omega^2)^{1/2}, \quad (7)$$

where "$-\omega_0^2$" is for $\alpha > 0$ and "$+\omega^2$" is for $\alpha < 0$.

In the case when $\omega > \omega_0$, all values of the v_{ph} are real and the waves propagate along OX axis (i.e. along the ion channel axis) with the rate $v_{\mathrm{ph}} > c$ (as with the soliton case).

In the case, when $\omega < \omega_0$, the values of v_{ph} are imaginary. Then putting $k = ia$ for $\omega < \omega_0$ $(i = \sqrt{-1})$, $a > 0$ and real, we obtain:

$$P = P_0 \exp(-ax)\exp(-i\omega t),$$

which is the attenuating wave. The characteristic damping length is:

$$d_0 = 1/a = c/(\omega_0(1-\omega^2/\omega_0^2)^{1/2}) \sim c/\omega_0 = (\delta/\alpha)^{1/2}.$$

3.1.3. *Non-linear waves*

The simplest case for PT2 is given by putting $\beta = -\alpha$ in the term βP^3:

$$\frac{\partial^2 P}{\partial x^2} = c^{-2}\frac{\partial^2 P}{\partial t^2} \pm \omega_0^2 c^{-2}(P - P^3), \tag{8}$$

which yields solutions of the type of *kink* or a *domain wall* (in the case of "$+\omega_0^2$"):

$$P(x,t) = \tanh\{\pm(x - vt)\gamma_0/d_0\sqrt{2}\}, \tag{9}$$

and the solutions of the type of *solitary wave* (in the case of "$-\omega_0^2$") (Yakushevich, 1990):

$$P(x,t) = \operatorname{sech}\{\pm(x - vt)\gamma_0/d_0\sqrt{2}\}. \tag{10}$$

Here v is the rate of motion of the order-parameter amplitude (the rate of the domain wall), $v < c$, a characteristic thickness $d_0 = c/\omega_0 = c\tau_0 = (-\delta/\alpha)^{1/2}$ is of the order of the domain wall thickness $\sim\sqrt{2}d_0/\gamma_0$, where $\gamma_0 = (1 - v^2/c^2)$.

In the case $v > c$ the solution of the soliton type is obtained (Yurkevich & Rolov, 1985; Yakushevich, 1990).

A general solution may be presented in the form of the first-order elliptic integral (Krumhansl & Schrieffer, 1975).

3.1.4. *Non-linear waves*

Non-linear waves, when the term γP^6 is taken into account and β is arbitrary, constitute the case of the first-order phase transition (PT1) and the PT2. They are described by more complex equations, which are given below. The analysis is carried out in dimensionless form.

The rate dependence from external field E is also considered below. It should be noted that for the free waves and for the non-linear soliton waves, the accelerated movement is exhibited in the constant external field (Yurkevich & Rolov, 1985). However, when the dissipative force is applied

$$-\eta(\partial P/\partial t),$$

the movement has the stationary character with the constant rate (Pasynkov & Alekseev, 1986):

$$v_t = -(3\sqrt{6}/16)(\omega_0^2/d_0\eta)(E/E_c),$$

where E_c is the critical field, in which the domain wall is discharged.

On the other hand, proceeding from the Landau–Khalatnikov equation for the simplest case of PT2 (and for $PE = 0$) (Lifshitz & Pitaevsky, 1979):

$$\frac{\partial P}{\partial t} = -(\lambda_0^{-1/2})\frac{\partial F}{\partial P},$$

where F is the free energy, and in the linearizing equation the relaxation time is written as:

$$\tau_0^2 = \lambda_0/4\alpha^2,$$

that is for the phase boundary's rate $v < c$ we have

$$v^2 = d_0^2/\tau_0^2 = -(\delta/\alpha)/(\lambda_0/4\alpha^2) = -4\delta\alpha/\lambda_0,$$

that coincides with expression (19) (see below in 3.2.).

3.2. A MODEL OF KINK ON THE BASIS OF THE TIME DEPENDENT EQUATION BY LANDAU–GINZBURG–KHALATNIKOV

The Landau–Ginzburg equation, describing the time evolution of the order parameter (polarization of P along the axis OX in this case), yields (Smolensky, 1985; Lifshitz & Pitaevsky, 1979):

$$\frac{\partial P}{\partial t} = -\Gamma\frac{\partial F}{\partial P}, \tag{11}$$

where $\Gamma = \lambda^{-1/2}$ is the Landau–Khalatnikov coefficient, which has no critical dependency on temperature. For the free energy F in the case of the PT1 we write as usual (Rolov & Yurkevich, 1978; Smolensky, 1985):

$$F = F_0 + \alpha P^2 + \tfrac{1}{2}\beta P^4 + \tfrac{1}{3}\gamma P^6 + \delta\left(\frac{\partial P}{\partial x}\right)^2, \tag{12}$$

where α, β, γ are coefficients of the Landau–Ginzburg–Devonshire thermodynamical expansion, (for PT1 $\beta < 0$), δ is the coefficient at a gradient term, $\alpha = \alpha_0' + \alpha_0(T - T_0) = \alpha_0(T - T_c)$, T_c is the Curie–Weiss temperature, T_0 is the temperature of PT to the paraelectric phase, $\alpha_0' = \alpha_0(T_0 - T_c) = \alpha(T_0)$.

Substituting (12) into (11) yields:

$$\frac{\partial P}{\partial t} + 2\Gamma(\alpha P + \beta P^3 + \gamma P^5) + 2\Gamma\delta\left(\frac{\partial^2 P}{\partial x^2}\right) = 0. \tag{13}$$

Setting $s = x - vt$, (13) becomes:

$$-\frac{\partial^2 P}{\partial s^2} + \left(\frac{v}{2\Gamma\delta}\right)\frac{\partial P}{\partial s} - \frac{1}{\delta}(\alpha P + \beta P^3 + \gamma P^5) = 0. \tag{14}$$

Solutions of this equation look stationary in the system of co-ordinates, moving with the rate v and are analogous to the wave front.

The physical ferroactive model of the ion channel (Leuchtag, 1988; Bystrov, 1992), imposes the following boundary conditions on the solutions to (14):

$$\frac{\mathrm{d}P}{\mathrm{d}s} \to 0, \quad \text{when} \quad s \to \pm\infty$$

and

$$P \to P_1, \quad \text{when} \quad s \to +\infty,$$

$$P \to P_2, \quad \text{when} \quad s \to -\infty,$$

where P_1, and P_2 correspond to the extreme (minimum and maximum) of the free energy of the studied system, (which is a ferroelectric ion channel in a biomembrane), as a function of the polarization P. The solutions of (14) with the above boundary conditions are of the kink-form:

$$P(s) = P_1[1 + \exp(-s/\Delta)]^{-1/2}. \tag{15}$$

In the stationary case this corresponds to the appearance of a boundary between phases, when the temperature goes upward from the stable state with the minimum at $P = P_1$ (ferrophase) to the stable state with the maximum at $P = P_2 = 0$ (paraphase), that is when the ferrophase contains a region of paraphase.

The boundary between paraphase and ferrophase ($s = 0$) moves from the paraphase, appeared on heating, deep into the ferrophase at a rate of v and has a thickness of Δ (Gordon, 1986; Dec & Yurkevich, 1990):

$$\Delta = \tfrac{3}{4}\delta^{1/2}\{\alpha'(T_0 - T_c)[1 - \tfrac{3}{8}\tau + (1 - \tfrac{3}{4}\tau)^{1/2}]\}^{-1/2}, \tag{16}$$

$$\tau = (T - T_c)/(T_0 - T_c), \tag{17}$$

$$P_1^2 = \left(\frac{\beta}{2\gamma}\right)\left[1 + \left(1 - \frac{4\alpha\gamma}{\beta^2}\right)^{1/2}\right], \tag{18}$$

$$v = 2\Gamma\delta^{1/2}[\alpha'(T_0 - T_c)]^{1/2} \times \frac{\{\tau - \frac{2}{3}[1 + (1 - \frac{3}{4}\tau)^{1/2}]\}}{[1 - \frac{3}{8}\tau + (1 - \frac{3}{4}\tau)^{1/2}]^{1/2}}. \tag{19}$$

Here

$$T_0 = T_c + \frac{3}{16}\frac{\beta^2}{\alpha_0\gamma},$$

$$\alpha = \alpha_0' + \alpha_0(T - T_0), \quad \alpha_0' = \alpha_0(T_0 - T_c). \tag{20}$$

The analysis of the stability for the free energy of F, given by (12), taking account of relations (20) (in the simplest case $\delta = 0$) shows that the kink motion of the interphase boundary is possible only in a short temperature interval near the point T_0 (see Fig. 4):

$$\frac{3}{16}\frac{\beta^2}{\alpha_0'\gamma} < T^* - T_c < \frac{\beta^2}{\alpha_0'\gamma}$$

$$\left[\frac{3}{16}\frac{\beta^2}{\gamma} - \alpha_0'\right]\alpha_0^{-1} < T^* - T_0 < \left[\frac{\beta^2}{4\gamma} - \alpha_0'\right]\alpha_0^{-1} \tag{21}$$

Thus the kink motion of the interphase boundary (15) is possible within this narrow hysteresis region of temperatures: $\Delta T^* = T^* - T_0$ (see Fig. 4.).

The external electric field, applied to ferroelectric, as is known (Lines & Glass, 1977; Smolensky, 1985) leads to the shift of the PT point of a ferroelectric to the paraelectric phase and to diffusion of this phase

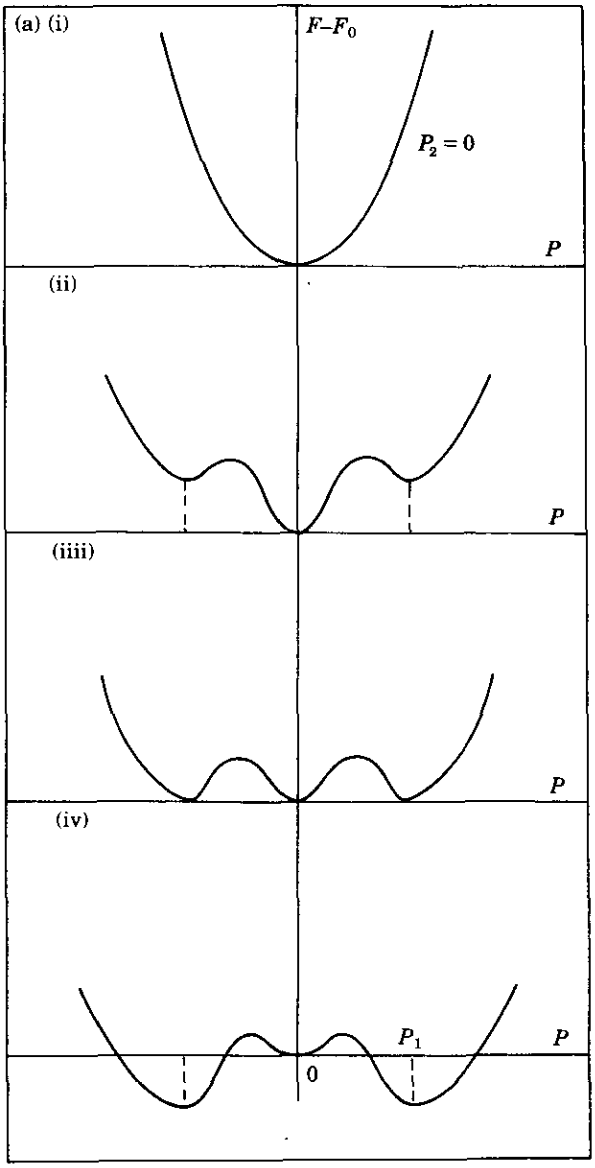

Fig. 4a. (Caption on opposite page).

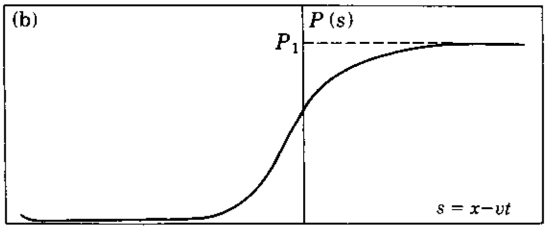

Fig. 4b.

FIG. 4. (a) Thermodynamic potential of the systems under various values of α. (i) $\alpha > \beta^2/4\gamma$; (ii) $3\beta^2/16\gamma < \alpha < \beta^2/4\gamma$; (iii) $\alpha = 3\beta^2/16\gamma$; (iv) $\alpha < 0$. (b) Moving interphase boundary in the *kink* model.

transition. Mentioned circumstances are clearly demonstrated by the numerical solution of the problem if the external field E is taken into accunt [the program TRAX (Levitin, 1990), see Fig. 5. (for $E \neq 0$ the solutions with $v = 0$ are constant)].

In this case functional (11) contains one more term $-EP$ and (14) takes the form:

$$\frac{\mathrm{d}P}{\mathrm{d}s} = Y,$$

$$-\frac{\mathrm{d}Y}{\mathrm{d}s} + \frac{v}{2\Gamma\delta}Y - \frac{1}{\delta}(\alpha P + \beta P^3 + \gamma P^5 - E) = 0. \quad (22)$$

The example of a numerical solution in dimensionless form for various values of a dimensionless field is given in Fig. 5. The field is seen to strongly influence the position of the PT point and its diffusion. The model is simple. In a real biomembrane the ion channel is influenced by a complicated electric field (depolarizing field of the biomembrane in itself, electric fields of ions, etc), but the qualitative behavior remains essentially the same.

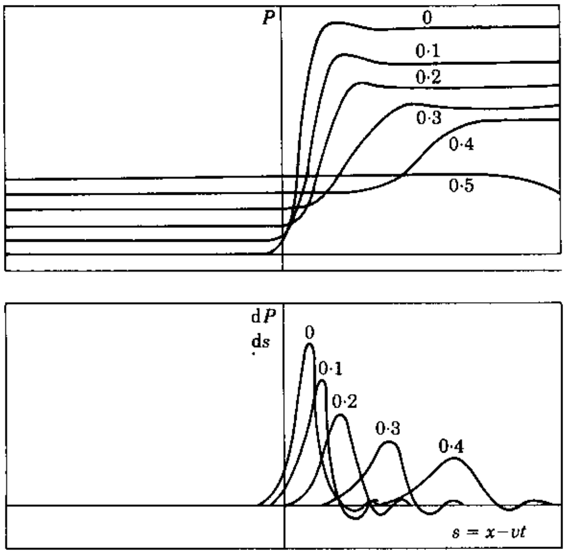

FIG. 5. Influence of electric field on the interphase boundary.

The change in the affected PT temperature may be written as (Lines & Glass, 1977; Rolov & Yurkevich, 1978; Smolensky, 1985):

$$\frac{\mathrm{d}T}{\mathrm{d}E} = \frac{\Delta P}{F'_{T_1} - F'_{T_2}} \sim \frac{\Delta P}{\alpha(P_{II}^2 - P_I^2)} \sim \frac{1}{\alpha P}. \quad (23)$$

For barium titanate the estimated value of the temperature change is $\sim 1{\cdot}3 \times 10^{-3}\,\mathrm{K \cdot cm\,V^{-1}}$ and for the Na$^+$ channel $\sim 3 \times 10^{-4}\,\mathrm{K \cdot cm\,V^{-1}}$.

3.3. THE GENERALIZED FERROACTIVE MODEL

In the general case, taking into account dissipation and external field, for the moving phase boundary from the generalized lagrangian we obtain the equation in the dimensionless form for P and E

$$\frac{\partial^2 P}{\partial x^2} - c^{-2}\frac{\partial^2 P}{\partial t^2} = \pm(\omega_0^2/c^2)P + \delta_r^{-1}\left(\mp P^3 + P^5 - E - \eta_r\frac{\partial P}{\partial t}\right),$$

which in the moving co-ordinates $s = x - vt$ has the form:

$$\gamma_0\frac{\mathrm{d}^2 P}{\mathrm{d}s^2} = \pm(\omega_0^2/c^2)P + \delta_r^{-1}\left(\mp P^3 + P^5 - E - \eta_r\frac{\mathrm{d}P}{\mathrm{d}s}\right).$$

Here δ_r, η_r are the same parameters δ, η in the dimensionless form, $\gamma_0 = 1 - v^2/c^2$ and for $\gamma_0 = 1$ this equation coincides with the above considered Landau–Khalatnikov equation in the external field and is nearly to the electrodiffusion model (Rubin, 1987; Leuchtag, 1988).

Then, rewriting this equation as a system (22), but with the dimensionless parameters, we obtain the system of equations, which a computing investigation may carry out by the program TRAX (Levitin, 1990).

In the more general case it may be to account the dimensional dispersion of the dielectric permeability and write the term $-PE(r)$ in the integral unlocal type.

4. The General Consequences of the Suggested Models

Here we take a brief look at some of the general consequences of the suggested ferroelectric, or in more general case, ferroactive nature of the biomembrane ion channel.

4.1. CHANGE OF THE DIELECTRIC PERMITTIVITY

One of the most general properties of ferroelectrics is the sharp change of the dielectric permittivity ϵ in the region of PT, which obeys, as a rule, the Curie–Weiss law (Kholodenko, 1971; Lines & Glass, 1977; Smolensky, 1985):

$$\epsilon \sim \alpha^{-1} \sim \frac{C_W}{2\pi}(T - T_c)^{-1},$$

where C_w is the Curie–Weiss constant.

It has been recently found (Leuchtag, 1991*a*) that the Curie–Weiss law fits data (Palti & Adelman, 1969) for squid axon membrane, presumably reflecting the dielectric behavior of the Na channel.

4.2. EXISTENCE OF BOUNDARIES BETWEEN VARIOUS PHASES

If the channel's conductivity is connected with the PT between the ferroelectric and the paraelectric phases, then in some temperature intervals and ion conductivity of the channel may be realized, and in other intervals, not. This fact has long been known experimentally (Chapman, 1967), but it was theoretically accounted for only due to works by Leuchtag (1987*a*,*b*).

4.3. CHANGE (JUMP) IN THE WIDTH OF THE GAP AND OF THE CONDUCTIVITY BAND

For an extensive class of ferroelectrics the change (jump) of polarization during PT causes the energy change of the band structure (Fridkin, 1979):

$$\Delta E \sim a\Delta P^2, \quad \Delta E_g \sim a\Delta P^2,$$

where ΔE, ΔE_g are changes of the width of the conductivity band and the gap, respectively. In the case of the ion channel this effect should be realized at the inlet/outlet of the ion channel of the biomembrane.

These effects usually are connected with the influence of the electron subsystem (Fridkin, 1979) and would be due to phason and fluctuon states (Bystrov, 1983; Bystrov *et al.*, 1993) in the proposed phase on model (Bystrov, 1992).

4.4. OPTICAL PHENOMENA

This effect will also give rise to some optical phenomena, such as the shift of the absorption edge, photorefractive effect, luminescence, etc (Lines & Glass, 1977; Fridkin, 1979; Smolensky, 1985).

These phenomena have not been widely studied for biological specimens, though some of them were pointed to by Leuchtag (1987*a*,*b*, 1988, 1990*b*, 1991).

4.5. PIEZOEFFECT

Since all the ferroelectrics are piezoelectrics, they exhibit change of piezomodule during PT (Lines & Glass, 1977; Smolensky, 1985; Leuchtag, 1988).

Interesting experimental material has been accumulated on the piezoeffect in biosystems (Leuchtag, 1988, 1990*b*, 1991; Petrov *et al.*, 1991), but interpretation of the observed phenomena in terms of PT in ferrelectrics is still in its developmental stage.

4.6. PYROEFFECT

All the ferroelectrics demonstrate pyroelectric properties as well (Lines & Glass, 1977; Smolensky, 1985). The change of the pyro-coefficient, and piezomodulus during PT occurs rather sharply and may be detected both experimentally and theoretically.

There is already some experimental evidence on manifestation of this effect in biological specimens, but correct and purposeful investigations lie ahead (Leuchtag, 1988, 1990*b*, 1991; Bystrov, 1992).

4.7. KINETIC CHARACTERISTICS

Rather simple relationships, describing such kinetic characteristics as the ultrasound speed in a medium, rate of relaxation processes during PT in ferroelectrics were derived in Lines & Glass (1977) and Smolensky (1985). These effects may be also studied experimentally.

4.8. THE INFLUENCE OF PRESSURE AND CONCENTRATION

All the above effects are usually realized in the vicinity of PT depending on the temperature. But there are two more important thermodynamic parameters—the pressure P and the impurity concentration x. But there exist some regularities which have been described analytically to some approximation (Rolov & Yurkevich, 1978), allowing one to carry out the corresponding experiments on biomembranes.

4.9. INFLUENCE OF EXTERNAL FIELDS

Finally an important ferroelectric property is the strong dependency of conditions and the process of PT on the applied electric fields (not only the electric field E, but also the magnetic field H, and the mechanical strains σ) (Lines & Glass, 1977; Rolov & Yurkevich, 1978; Smolensky, 1985), which have been already mentioned above.

5. Qualitative Description of Processes of the Channel Functioning

The model of the biomembrane ion channel in the form simulated by an extended ferroelectric thread (in the closed state) corresponds to the appearance and motion of the interphase boundary from the paraphase deep into the ferrophase. This gives rise to the motion of the paraelectric state along the channel into the membrane and gradual disappearance of the polarized ferroelectric state of the channel. As a result the channel turns into the open paraelectric state.

The motion of the interphase boundary along the channel into the membrane gives rise to the displacement current I_s, since the interphase boundary carries a bound charge, inducing a polarized state on the side of the ferrophase.

This fact allows natural interpretation to the appearance of the so-called "gate currents" (Armstrong & Bezanilla, 1973). At the same time the availability or occurrence of a charged ion near the emerged interphase boundary may lead to its binding with the boundary (owing to the coulomb interaction the bound charge of a kink is screened by the ion charge) followed by its carrying inside the membrane, which moves along the ion channel.

The analogous picture, but with reverse movement of the interphase boundary, appears on a certain cooling of the system. Ferrophase arises on the inside of the membrane and starts gradual propagation along the ion channel to the outside of the membrane.

Finally, at temperature coinciding with the temperature T_0 of PT, the rate of the motion v is zero, as is follows from (19), which corresponds to the equilibrium state of the system with free energy of coexisting phases (Lines & Glass, 1977). In the vicinity of PT the rate v and the thickness Δ change with the temperature according to (17), (19).

It should be stressed that the considered conditions of the existence and motion of the interphase boundary in the kink-form giving rise to new currents along the channel are extremely sensitive to the change in the external thermodynamic conditions of the system's equilibrium. Thus, it is known (Lines & Glass, 1977; Smolensky, 1985), that the presence of the external electric field and mechanical strains lead to the shift of the PT point. Therefore the change of the electric field and the pressure in the lipidous bilayer may be considered as factors influencing the PT point in the ion channel. These effects will be considered separately.

SOME ESTIMATES

For barium titanate the values of coefficients in rationalized mks units are (Kholodenko, 1971; Smolensky, 1985): $\beta = (3{\cdot}4\text{–}5{\cdot}4) \times 10^{-13}$, $\gamma = 11{\cdot}4 \times 10^{-23}$, $\alpha_0 = 0{\cdot}4 \times 10^{-5}$, $\alpha_0' = (0{\cdot}4\text{–}0{\cdot}6) \times 10^{-4}$. According to (21) we have the estimate $\Delta T^* = T - T_0 \sim 10$ K, which for calculated values of the rate (19) $v = 4{\cdot}5 \times 10^{-3}$ cm/s, and the thickness of the interphase boundary (16) $\Delta = 1{\cdot}4 \times 10^{-6}$ cm coincides with experimental values (Gordon, 1986; Rubin, 1987; Dec & Yurkevich, 1990): $v \sim 10^{-3}\text{–}10^{-2}$ cm sec^{-1}, $\Delta \sim 10^{-7}\text{–}10^{-6}$ cm.

Other ferroelectrics exhibit similar values. It is characteristic that the hypothesized availability of ferroactive structures in biological objects is supported by independent experiments, for example, on the temperature measuring of capacitance (Leuchtag, 1991*a*) which leads to the Curie–Weiss law analogous to ferroelectrics with the value of $\alpha_0 \sim 0{\cdot}4 \times 10^{-3}$ K^{-1}.

If we assume that all the other expansion coefficients are similar, taking into account that the polarization jump in bio- and lipidous membranes is an order of magnitude less (Leuchtag, 1988; Mintz & Kononenko, 1982; Bystrov, 1992), then the rate is estimated as: $v \sim 10^{-3}\text{–}10^{-1}$ cm sec^{-1} $\sim 10^{-5}\text{–}10^{-3}$ m sec^{-1}.

Thus for the length of the ion channel $R \sim 10$ 100 nm we get the time estimate of the ion transfer process: $t \sim R/v \sim 10^{-5}$ sec, which coincides with known experimental data on channel currents and times of these processes (Leuchtag, 1987*a*, 1988; Rubin, 1987; Boldyrev, 1990; Bystrov, 1992).

NEW CONSEQUENCES, RESULTING FROM THE SUGGESTED CONCEPTS OF THE ION CHANNEL FUNCTIONING

Besides the listed effects, which, as is mentioned above, have not been studied experimentally for biological specimens, other consequences of the suggested models are also possible. One of the most important among them is the strong dependency of the rate of the motion (and accordingly the value of the mean ion current) on the change of the external conditions around the channel and the reorganization of the biomolecule of the channel itself. This leads to considerable *fluctuations* occurring in passing of the ion current, which has been observed experimentally (Sakmann & Neher, 1983; Rubin, 1987).

6. Directions and Prospects of Development of the Suggested Theory

One of the most important steps to be made in developing the theory is taking account of the medium around the channel—both in the membrane itself and at the inlet/outlet of the channel. This means addition to the suggested model of electrodiffusion equations, allowing for screening and mechanical strains in the lipidous layers of the membrane.

The next step could be to create the two-component model, which would possibly allow one to describe the whole cycle, including the restoration of the initial closed state of the channel, i.e. to close the feedback.

The further development of the model supplemented by detailed calculations may form the basis of making new experimental studies of ion channels in biological membranes.

As an example, we show the equations for the *two-component* ferroelectric–ferroelastic model of an ion channel, where the interaction of these two subsystems induces such shifts of PT points between para-, ferro- and ferroelastic phases, which bring the system back to its original state.

If we consider the simplest case of the thermodynamic potential (or the free energy) in the vicinity of the second-order PT and do not allow for the external fields, the system's free energy may be written as:

$$F(P, u, x, p) = F_0 + [\alpha + \alpha_2 u^2 + \alpha(x, p)]P^2 + \tfrac{1}{2}\beta P^4 + [\alpha_1 + \alpha_1(x, p)]u^2 + \tfrac{1}{2}\beta_1 u^4,$$

where the expansion coefficients:

$$\alpha(x, p) = \alpha_3 x + \alpha_4 x^2 + \alpha_{33} p + \alpha_{44} p^2,$$

$$\alpha_1(x, p) = \alpha_5 x + \alpha_6 x^2 + \alpha_{55} p + \alpha_{66} p^2,$$

take account of the system's dependency on the external medium (concentration of impurities or protein molecules x and pressure p in the channel surrounding, i.e. lateral pressure in lipid bilayer).

Here u is the ordering parameter of the ferroelastic subsystem, corresponding to the component of the deformation tensor (Lines & Glass, 1977; Smolensky, 1985).

This is analogous to the case of two-component systems such as ferroelectric–superconductor (Bystrov & Rolov, 1989) or ferroelectric–magnetic (Yurkevich *et al.*, 1989).

The important implication of the analysis of such systems is that even in the simplest case of neglecting the x and p influence, the system exhibits mutually conditioned shifts of PT point between para-, ferro- and ferroelastic phases. Leaving the detailed analysis for further investigation we outline the *possible sequence of events*:

(i) The jump of the electric field E in the biomembrane induces in the ion channel a PT from ferrophase to paraphase.

(ii) As a result of the subsystems interaction the PT point is displaced to the ferroelastic subsystem. Suppose the PT point moves upward, then the PT from paraphase to ferroelastic phase takes place.

(iii) The created ferroelastic phase displaces the PT point back to the ferroelastic phase (and if taking into account the pressure, the mechanism of affecting the PT point starts working through the changes in the lateral pressure under deformation u).

(iv) The PT into ferrophase takes place, that is the system is returned to the original state. The ferroelastic phase may disappear, otherwise it persists till the moment of transition into paraphase.

This sequence is only one of the possible mechanisms of realization of our model.

Further development of the model and performing of detailed calculations may be the basis for conducting new experimental studies of the ion channels of biological membranes.

The authors wish to thank Prof. A. B. Rubin, K. V. Shaitan, R. V. Polozov, S. S. Kolesnikov, V. G. Ivkov and N. K. Balabaev for useful discussions and Prof. V. M. Fridkin for referring us to H. R. Leuchtag's works.

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