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Ion pores in biological membranes as self-organized bistable systems

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It is shown that an ionic channel in biological membranes is a self-organized nonequilibrium dynamic system functioning in a multistable regime. The different components of such a regime can be compared with discrete conductivity levels of the ionic channel. For the case of a channel with two binding sites we have shown that such an effect is a consequence of organization of the conformational channel structure at the expense of the energy of an ion flux itself. The possibility of the control of the channel functioning due to the external electric field is also considered. Calculations show that one may effectively modulate channel lifetimes in their open and closed states using the applied field. It is also shown that the ensemble of channels which mutually interact in a cooperative manner via the bulk solution under the sufficiently strong dependence of the rate constants upon the conformational variable may possess various types of dynamic behavior such as monostability, bistability, and relaxation oscillations.

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I. INTRODUCTION

There are many physical systems in which the phenomenon of bistability occurs [1]. For widely known optical bistable systems, e.g., there are two mechanisms that provide the bistability. In one of them, bistable lasers are used [2]. In another one, the coherently driven cavity filled with two-level atoms is taken and the feedback is realized due to nonlinear properties of the passive medium [3].

In the present paper we wish to show that bistability similar to the latter case may also occur due to interaction of the ion flux through the pores (channels) in biological membranes with conformational degrees of freedom for some polar groups forming such pores. It is a sharp difference between the relaxation time of the pore-former protein and the passage time of the ion through the channel that provides, as will be seen below, the existence of indirect interion interaction and therefore a nonlinear character of ionic transport.

Several papers have appeared in recent years dealing with the problem of understanding the physical mechanisms of the self-organization of biological structures (see Ref. [4] for a review). The ionic channels of biological membranes are structures that have received much theoretical and experimental attention [5–7]. It is well established now that Na^+, K^+, and Ca^{2+} ions in the cell membranes are transported through pores formed by the specialized proteins embedded in the phospholipid bilayer. New experimental methods give the opportunity to study at the molecular level the features of the functioning of a single ionic channel, and evidently a corresponding physical description is needed [5,6]. Passive ionic transport initiated by electrochemical potentials that are different inside and outside the cell is described usually within the framework of continuous or discrete diffusion approaches based on the Eyring transition state theory and on the assumption of the fixed energy channel profile for a separate ion [5].

The idea of a small number of the so-called ion binding sites that correspond to the minima of the channel potential profile is widely held now. Such an idea is in agreement with experimental data concerning the channel conductivity dependence on the concentration of ions in the solution [5], as well as with the molecular-dynamics simulation of ion motion through the channel [7].

For the channel with the single binding site and for the bulk concentration $C_1=C$ (outside) and $C_2=0$ (inside) the mean concentration N near the binding site satisfies the following equation:

$$\frac{dN}{dt}=\Theta C(1-N)-\Gamma N \ , \tag{1}$$

where the first term describes the average number of incoming ions proportional to the concentration of ions in the solution and to a factor that corresponds to the absence of ions in the binding site; the second term describes the leakage of ions from this site to outer solutions; Θ and Γ are the corresponding rate parameters. We can see from Eq. (1) that near a binding site the steady-state ionic concentration can be plotted as a Langmuir function

$$N_{st}=C/(C+C_{1/2}), \quad C_{1/2}=\Gamma/\Theta \ . \tag{2}$$

This saturation curve is derived with the assumption that simultaneous arrival to the binding site of more than one ion is impossible, i.e., one takes into account the interaction between ions inside the channel. Such dependence becomes apparent only for the relatively large values of $C \geq C_{1/2}$.

We start from the idea that the indirect ion interaction has significant effect for high concentration. Such interaction may play a substantial role for the channel functioning even for the relatively low concentration of ions. This interaction we connect with the alteration of the equilibrium positions of some charged and polar groups inside the channel. Then the corresponding influence on the movement of subsequent ions arises.

One must take into account two circumstances for understanding the physical reasons for such a phenomenon. First, the local electric field that is created by the moving ion over the distances 0.5–1 Å is 10^6–10^7 V/cm. This value is 10^2–10^3 times as large as the external fields applied to the membrane and thus a local field will have a significant effect upon a selected polar group. Second, it is well known that the protein macromolecule in the phospholipid membrane possesses a certain mobility and the relaxation times for its separate fragments are in the wide range from 10^{-10}–10^{-9} s to 10^{-3}–10^{-2} s and more [8]. Characteristic transfer time for two adjacent ions in the channel equals approximately 10^{-6}–10^{-7} s, therefore molecular groups having the faster relaxation time will accompany every moving ion, forgetting about its passage until the arrival of the next. As a result, channel groups moving slower will average the effect of the large number of ions apprehending it as some constant mean field. In that way the portion of the energy of an ion flux will be spent on the organization of conformational structure of the channel-former protein. For the simple case of the one-site channel it was shown earlier that due to its interaction with an ion flux, there may appear two possible channel conformational structures having rather different permeability properties [9].

The important measurable quantities for a single ionic channel are the ionic current, the mean channel's lifetimes in each of its possible states, and their dependences on voltage and concentration differences at both sides of the membrane. These parameters play the role of control parameters for the channel. The physical mechanism describing such dependences, in particular, the nontrivial function of the kinetic constants of a potential-dependent ionic channel in the Hodgkin-Huxley model [10] on an applied voltage, was not earlier discussed.

In this study, for the case of a channel with two binding sites we will show that these dependences may arise as a consequence of organization of the conformational channel structure at the expense of the energy of an ion flux itself. This general conclusion confirms quite well the experiments for the investigation of the permeability of calcium and gramicidin channels in respect to one type of ion when another type is present [11]. Such experiments clearly demonstrate the adjustability of a channel structure to a given type of ion, thus inducing the change of channel permeability in respect to another type of ions. The dependence of the channel kinetic parameters on the concentration of ions was also established [5]. This fact may also be connected with "deformation" of a channel by moving ions.

II. DYNAMIC MODEL OF IONIC CHANNEL WITH MOBILE STRUCTURE

The case of mobile barriers for a potential profile in a single ionic channel was discussed by Ciani [12] (see also Ref. [13] and references therein). For such a notion, which reflects the possibility of changing the equilibrium positions of channel molecular groups, these authors used a concept of polarized and nonpolarized channel states, the transition between them being described by the detailed balance equation. Such an approach directly postulates the channel states with different levels of conductivity.

Using the idea of the continuous channel deformation, we develop here an approach that takes into account interaction between ionic and conformational degrees of freedom in a self-consistent manner. Thus the channel states with different levels of conductivity result as a consequence of the theory.

Let us consider a single channel with a symmetric potential profile and with two binding sites (Fig. 1). The height ε_{12} of the main central barrier (all values of the potentials will be used hereafter in units of $k_B T$, where k_B is the Boltzmann constant and T is the absolute temperature) we assume to be a function of some conformational variable r:

$$\varepsilon_{12}=\varepsilon_{12}(0)+r/r_0, \quad \left[r_0=\left.\frac{\partial \varepsilon_1}{\partial r}\right|_{r=0} \right] . \tag{3}$$

The quantity r is a generalized coordinate connected with a position of a charged group in a channel. The characteristic relaxation time of the conformational coordinate we assume to be much greater than the mean transfer time for an ion in a channel (10^{-6}–10^{-7} s). When there are no charges in the binding sites, the conformational coordinate r undergoes an action of recovering (to the equilibrium position) force $F=-\kappa r$, where κ defines the elastic properties of a polar group.

If there are charges q_1 and q_2 in the binding sites 1 and 2, respectively (q is a charge of an ion), the expression for such a force transforms to $F=-\kappa r-\chi(q_1-q_2)$, where χ defines the interaction force of an ion with a polar group.

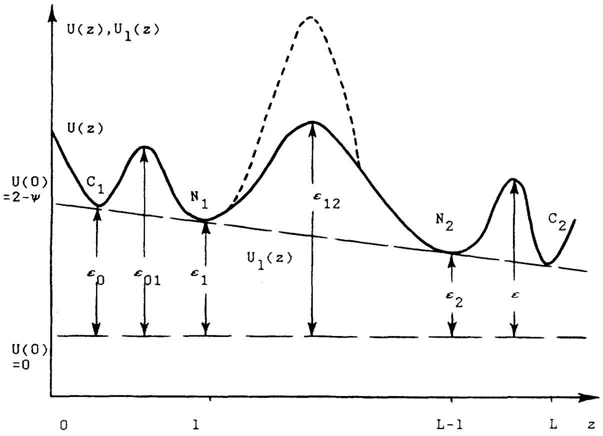

FIG. 1. One-ion potential profile $U(z)$ (solid line) and voltage distribution of the external electric field $U_e(z)$ (dashed line) along the channel in the Goldman approximation. The dotted line marks the varying potential profile of the central barrier. C_1 and C_2 are bulk concentrations (left and right, respectively). The quantities ε_i are the energies of barriers and wells of the profile; N_i are the mean occupancies of ions in the binding sites. L is the length of a channel, 1 defines the first and $L-1$ defines the second binding site, respectively.

For example, for the polar group with the dipole moment D we have $\chi = D/R^2$, where R is a distance of the polar group from the binding site.

In this case the expression for the potential function takes the form

$$\varphi = k[r^2/2 - r_\infty r(N_1 \pm N_2)] ,$$

where $r_\infty = \kappa q/k$, and the equation of motion for the conformational variable r obtains the following form:

$$M\frac{d^2r}{dt^2} + \eta_{\text{vs}}\frac{dr}{dt} + kr = kr_\infty(N_1 \pm N_2) , \tag{4}$$

where M is a mass of the conformational coordinate, and η_{vs} is a viscosity coefficient. Equation (4) corresponds to the motion of the harmonic oscillator in the viscous environment. In the real situation we will have, apparently, the inequality

$$\eta_{\text{vs}} > 2(Mk)^{1/2} , \tag{4$'$}$$

and therefore we can neglect the first term in Eq. (4). [In Eq. (4) we did not include the term that describes direct action of the electric field on the polar group, which we must take into account in a more general case.] Owing to the symmetry of the problem, a plus sign (+) on the right-hand side of Eq. (4) corresponds to the scalar coordinate r (e.g., the pulling into the channel of the molecular group perpendicularly to the z axis), while a minus sign (−) corresponds to the pseudoscalar r (e.g., to the angle of rotation of some group overlapping the part of a channel).

It can be easily shown that the first case lead to trivial results. We shall consider below only the second case.

Using the above-mentioned assumptions as well as the mean-field assumption (the Goldman approximation [5]), we can disregard the voltage drop on the fixed "entrance" and "exit" barriers due to the inequality $L \gg 1$ (Fig. 1).

Then the kinetic equations describing the evolution of the occupancies N_1 and N_2 in the binding sites will have the following form:

$$\begin{aligned}\frac{dN_1}{dt} &= I_1 - [\Lambda + \Omega\exp(-r/r_\infty + \Psi)]N_1 \\ &\quad + \Omega\exp(-r/r_\infty - \Psi)N_2 , \\ \frac{dN_2}{dt} &= I_2 - [\Lambda - \Omega\exp(-r/r_\infty - \Psi]N_2 \\ &\quad + \Omega\exp(-r/r_\infty + \Psi)N_1 ,\end{aligned} \tag{5}$$

where the expressions

$$I_1 = \Omega_{01}\exp(-\varepsilon_{01} + \varepsilon_0)C_1 ,$$

$$I_2 = \Omega_{32}\exp(-\varepsilon_{32} + \varepsilon_3)C_2$$

define inward currents entering the channel (from the left and from the right, respectively). They are regulated by the corresponding concentrations C_1 and C_2; the expressions

$$\Lambda = \Omega_{10}\exp(\varepsilon_{10} + \varepsilon_1) = \Omega_{23}\exp(-\varepsilon_{23} + \varepsilon_2)$$

are the exit ion rates from the channel, and

$$\Omega = \Omega_{12}\exp[-\varepsilon_{21}(0) + \varepsilon] \quad (\varepsilon_1 = \varepsilon_2 = \varepsilon) .$$

Equations (4) and (5) define the evolution of a system: channel plus ionic flux in a self-consistent manner due to the ion-conformational interaction. Analysis of Eqs. (4) and (5) shows that the conformational coordinate and ionic flux evolve to some stable values, and one can consider this as a self-organization of conformational structure of the channel by mutual concordance with the ionic flux initiated by the difference of electrochemical potentials on both sides of the membrane.

We will use further the dimensionless quantities

$$\begin{aligned}&X = r/r_0, \quad A = (r_\infty/r_0)(I_1 - I_2)/\Lambda , \\ &B = (r_\infty/r_0)(I_1 + I_2)/\Lambda .\end{aligned} \tag{6}$$

For the inward ionic flux J_i and for the outward flux J_o we have the expressions

$$J_i = I_1 - \Lambda N_1, \quad J_o = I_2 - \Lambda N_2 . \tag{7a}$$

The following expression will be also useful:

$$J = (J_i + J_o)/2 = I_0(A - X)/2, \quad I_0 = (r_0/r_\infty)\Lambda . \tag{7b}$$

Assuming $dN_1/dt = dN_2/dt = dr/dt = 0$ for the steady values of the dimensionless variables given by Eq. (6), we can find the following relationships:

$$\begin{aligned}&N_- = (r_0/r_\infty)X , \\ &X = [A - 2\eta B\exp(-|x|)\sinh\Psi]/[1 + 2\eta\exp(-|x|)\cosh\Psi] , \\ &\eta = (\Omega_2/\Omega_1)\exp\{-[\varepsilon_{12}(0) - \varepsilon_{10}]/k_B T\} .\end{aligned} \tag{8}$$

The analysis of conditions needed for the appearance of the bistability in a given system (Fig. 2) shows that the necessary condition is just the inequality

$$\eta^* > \eta^*_{\text{cr}} , \tag{9}$$

where

$$\eta^*_{\text{cr}} = e^2, \quad \eta^* = 2\eta\cosh\Psi\exp(B\tanh\Psi) .$$

In this case, when one has the inequalities

$$I \geq AB\tanh\Psi, \quad B\tanh\Psi < A \ ,$$

the system possesses bistability in the region $I_{\mathrm{cr}1} < I < I_{\mathrm{cr}2}$, where the values I_{cr} are defined by the equations

$$\eta^* \exp(-Y_i)Y_i = I_{\mathrm{cr}} - Y_i \ ,$$

$$Y_i = I_{\mathrm{cr}}/2 + (-1)^i (I_{\mathrm{cr}}^2/4 - I_{\mathrm{cr}})^{1/2} \quad (i=1,2) \ .$$

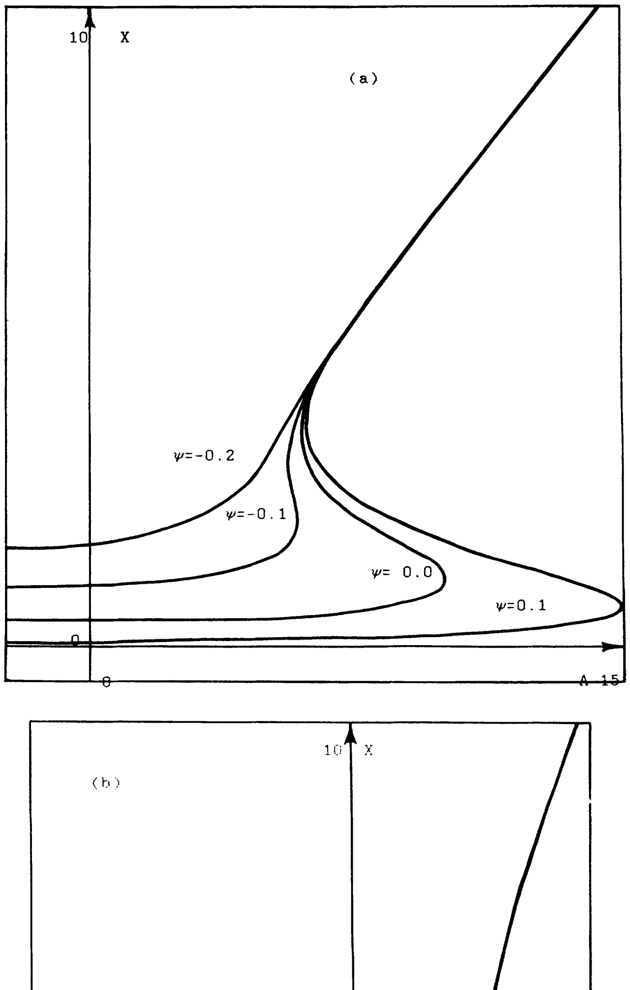

FIG. 2. Depenedence of the steady values of conformational coordinate X on A for various values of Ψ (a) and B (b) (at $\eta=20$).

When the inequality $I < AB\tanh\Psi$ is fulfilled, the system possesses bistability in the region

$$I_{\mathrm{cr}} < I < B\tanh\Psi(1+2\eta\cosh\Psi) \ .$$

Bistability is absent totally when the following inequality is fulfilled:

$$I \geq AB\tanh\Psi, \quad B\tanh\Psi > A \ ,$$

where

$$I = A + B\tanh\Psi = (I_1 e^{\Psi} - I_2 e^{-\Psi})/\cosh\Psi.$$

The inequality (9), as was shown above, is a necessary condition for the appearance of the bistability needed for the functioning of the ionic channel. For $\Psi=0$ it means, in particular, that the height of the central barrier must exceed the height of the entrance (exit) barrier no less than on the value of $2k_BT$:

$$\varepsilon_{12}(0) - \varepsilon_{10} > 2k_BT \cong 0.05 \text{ eV} \quad (\text{when } \Omega_1 \cong \Omega_2) \ .$$

The bistable character of the channel functioning manifests itself also in the dependence of ionic current on the voltage difference applied to the membrane (current-voltage relationship). This dependence is shown in Fig. 3. One can see that for $A \geq 10$ is has a pronounced S-like shape.

We must also estimate the values of quantity A in a real situation. If the energy gain is $(2-5)k_BT$ for an ion entering a channel, and the probability of occupancy of the channel's vestibule is C (we have let C_2 be equal to zero), then

$$A \cong (10^0 - 10^1) r_\infty r_0^{-1} \ .$$

Evidently, one can expect the appearance of attractive nonlinear effects for the channels with $r_\infty r_0^{-1} \geq 10$. In other words this signifies that there is either sharp dependence of the rate of hopping on the turning of polar groups (small r_0), or large polarizing force for ions and

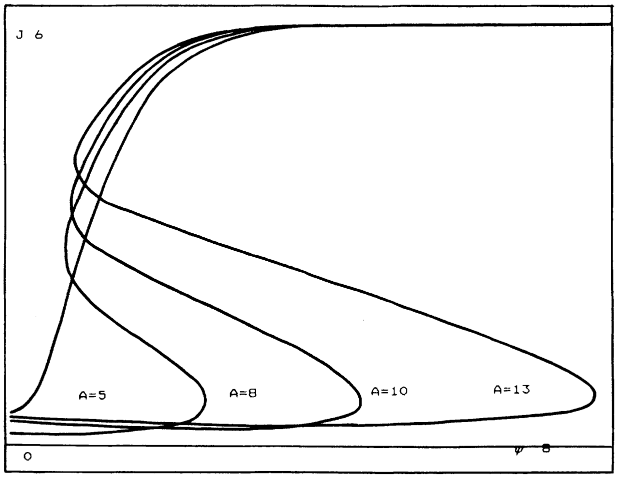

FIG. 3. Stationary current-voltage relationship for the channel with different values of A ($\eta=20$).

the channel pliancy on the structural changes (large r_∞).

In that way for given concentrations C_1 and C_2 and a field Ψ it was established in a considered system the possibility of existence of two stable dynamical regimes for the current flow.

III. KINETIC PROPERTIES OF CHANNEL WITH MOBILE STRUCTURE

Within the framework of a model discussed in the last section the dynamical behavior of the channel (its structure together with an ionic flux) is described by Eqs. (4) and (5). Equation (4) describes the relaxation of the conformational variable and Eq. (5) describes the relaxation of an ionic flux.

If relaxation times for ionic and conformational variables differ substantially, we may put a "slaving condition" [14] on the fast variable and then the dynamical behavior of the ionic channel will be described by a single nonlinear equation for assumed assumptions. We consider this in detail below.

Let the channel permeability be small and the conformational variable relaxes faster than an ionic flux ($\tau=\eta/k$ remains much greater than the characteristic times for successive passing of the channel by two ions). In that case the slaving condition derived from Eq. (4), when the derivative on t is put to zero, has the following form:

$$X(t)=X_\infty N_-(t)\ , \tag{10}$$

where $X_\infty=r_\infty/r_0=\chi\kappa/kr_0$. Using the expression for the quasistationary value of the dimensionless conformational coordinate (10), we may rewrite the system of Eqs. (5) as the following:

$$\begin{aligned}\tau_{\rm ion}\frac{dX_-}{dt}&=A-[1+2\eta\cosh\Psi\exp(-|X|)]X\\&\quad-2\eta\sinh\Psi\exp(-|X|)X_+\ ,\\\tau_{\rm ion}\frac{dX_+}{dt}&=B-X_+\ ,\end{aligned}\tag{11}$$

where

$$X_\pm(t)=(r_\infty/r_0)/N_\pm(t),\quad \tau_{\rm ion}=\Lambda^{-1}\ . \tag{12}$$

Instead of the variables N_- and N_+ are have used here the quantities X_- and X_+, respectively. We note also that the system of Eq. (11) is not gradient when $\Psi\neq0$.

Otherwise, the variables N_+ and N_- relax to their stationary values when X is fixed. Assuming that $dN_+/dt=dN_-/dt=0$, we will get the equations

$$\begin{aligned}N_+&=(r_0/r_\infty)B\ ,\\N_-(t)&=(r_0/r_\infty)\{A-2B\eta\exp[-X(t)]\sinh\Psi\}\\&\quad\times\{1+2\eta\exp[-X(t)]\cosh\Psi]\}^{-1}\ .\end{aligned}\tag{13}$$

Substituting N_- from Eq. (13) to (4) and taking into account Eq. (4′), we will obtain the following equation:

$$\tau_X\frac{dX}{dt}=\frac{\partial U^{\rm eff}}{\partial X},\quad \tau_X=\eta/k\ , \tag{14}$$

where for the case $A=B$ ($I_2=0$) we will have an expression

$$U^{\rm eff}(X)=X^2/2+A(X\tanh\Psi+{\rm sgn}(X)\exp(X)\ln\{(2\eta\cosh\Psi+1)/[2\eta\cosh\Psi+\exp(|X|)]\}/\cosh\Psi)\ . \tag{14′}$$

The shape of the modified dimensionless conformational potential (14′) is shown in Figs. 4 and 5 for different values of A and Ψ, respectively.

The dynamically stable state of the ionic channel corresponds to the minimum of the conformational potential. From Figs. 4 and 5 we can see that bistability corresponding to the two minima of the conformational potential, appears when control parameters A and Ψ take some critical values. This is an accordance with a general notion about a self-organization of an nonequilibrium system [14].

For the description of a real behavior of the single channel we must introduce the random force to the right-hand side of Eqs. (11) and (14). In the simplest case it does not depend on r and it is a function of time $\xi(t)$. For the delta-correlated noise

$$\overline{\xi(t)\xi(t+\tau)}=2D\delta(\tau) \tag{15}$$

(the bar here denotes an ensemble average and D is a constant characterizing the intensity of the noise), one may use the methods of the theory of the stochastic

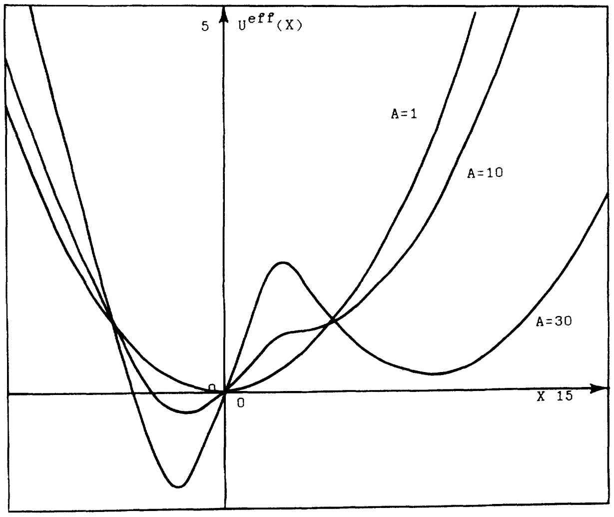

FIG. 4. Modified conformational potential for various values of A ($\eta=20$, $\Psi=5$).

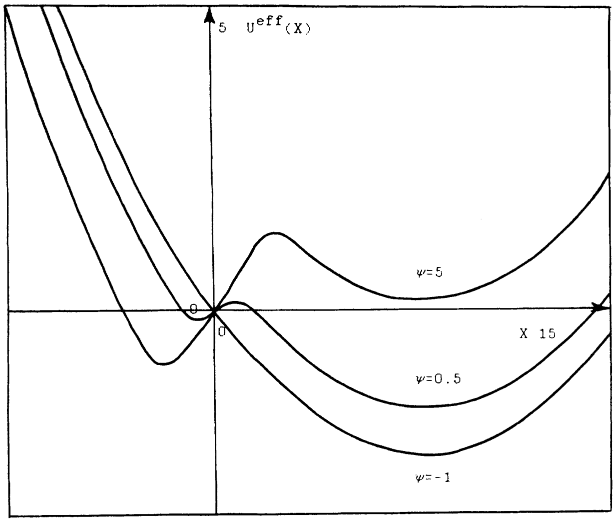

FIG. 5. Modified conformational potential for various values of Ψ ($\eta=20$, $A=30$).

differential equations [15] and define the probability density function for the realization of a value X at a time t

$$\rho(X,t)=\delta(X-X(t)) , \tag{16}$$

which satisfies the Fokker-Planck equation

$$\frac{\partial\rho(X,t)}{\partial t}=\frac{\partial\left[\dfrac{\partial U^{\mathrm{eff}}}{\partial X}\rho\right]}{\partial X}+D\frac{\partial^2\rho}{\partial X^2} . \tag{17}$$

From Eq. (17) it follows that in the limit of $t\to-\infty$ the distribution function $\rho(X,t)$ approaches an equilibrium one,

$$\rho_s(X)=\Theta\exp[-U^{\mathrm{eff}}(X)/2D] , \tag{18}$$

where Θ is the normalization factor.

It should be noted that in the case of a double-well potential the stationary distribution function will have two maxima corresponding to minima $X_i^{\min}$ of the conformational potential defined by Eq. (14). If these minima are strongly pronounced and the time the system spent far from their vicinities is very small, it is expedient to use probabilities describing the sojourn of a system near the first (I) and the second (II) minima ρ_1 and ρ_2, respectively. Then Eq. (17) takes an even more simple form [15], namely,

$$\frac{d\rho_1}{dt}=-\kappa_{12}\rho_1+\kappa_{21}\rho_2, \quad (\rho_1+\rho_2\approx 1) , \tag{19}$$

where

$$\kappa_{ij}=\exp(-\Delta_i/D), \quad \Delta_i=U^{\mathrm{eff}}(X_i^{\max})-U^{\mathrm{eff}}(X_i^{\min}) . \tag{19'}$$

The stationary values ρ_1 and ρ_2 are defined from Eqs. (19) and (19′) as

$$\begin{aligned}\rho_1&=1/[1+\exp(-\Delta_{12}/D)] ,\\ \rho_2&=\exp(-\Delta_{12}/D)/[1+\exp(-\Delta_{12}/D)] ,\end{aligned} \tag{20}$$

$$\Delta_{12}=U^{\mathrm{eff}}(X_1^{\min})-U^{\mathrm{eff}}(X_2^{\min}) . \tag{20'}$$

Thus, from Eqs. (18), (8), (20), and (20′) it follows that the probability of finding an ionic channel in the state with the currents $J(X_1)$ or $J(X_2)$ is defined by the value of $\Delta_{12}(I,\Psi)$. The dependence of the values ρ_1 and ρ_2 on the control parameter A is shown in Fig. 6.

The mean lifetime for the channel in the state $i-\tau_i$ is defined by the constant $\kappa_{ij}=\tau_i^{-1}$, i.e., by the value of $\Delta_i(I,\Psi)$.

We must note here that dependences Δ_i on Ψ were postulated earlier without the elucidation of their physical nature (see Ref. [7]). The result of numerical calculation of the stationary fluctuations described by the modified random force $\xi(t)$ in Eq. (14) for the considered double-well potential is shown in Fig. 7.

It can be seen from Fig. 7 that when the system possesses monostability [Fig. 7(a)], it has small deviations from the equilibrium position and in the case of the bistability [Fig. 7(b)], the new effect of the switching of the system between two stable states arises. It can be easily shown that the time course of an ionic current determined by simulation coincides qualitatively with the dependences that may be obtained in the single-channel current recordings [5].

The mean value of the single-channel current $\langle J\rangle$ for the small interval $t\gg\tau_i$ (or its average value on the membrane) is defined by the equation

$$\langle J\rangle=[P_1J(X_1)+P_2J(X_2)]q , \tag{21}$$

where the expression for the stationary ionic flux $J(X_i)$ is defined by Eq. (7b). Within the framework of an approach developed here it is possible to show that one can get a reasonable physical interpretation for a notion concerning so called "gating particles," which was introduced more than 30 years ago by Hodgkin and Huxley [10], and describes the kinetics of the current evaluation in an ionic channel.

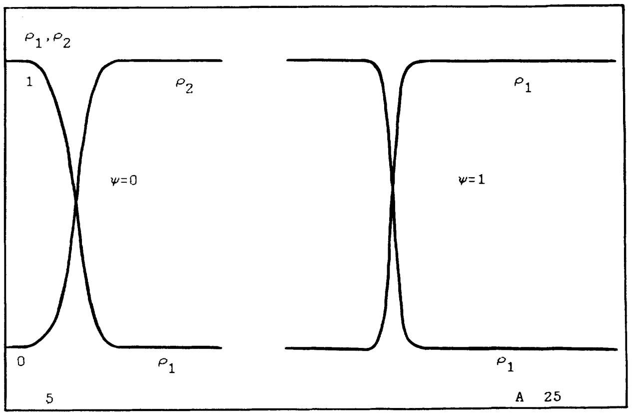

FIG. 6. Dependence of the values ρ_1 and ρ_2 on the control parameter A ($\eta=20$).

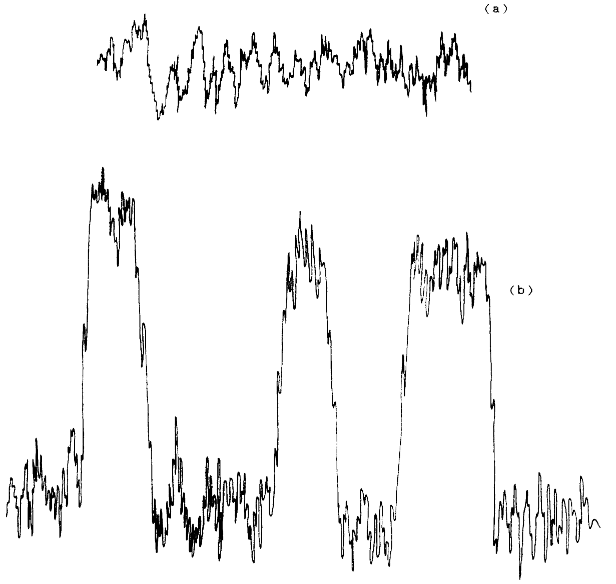

FIG. 7. Time course of the ionic current. (a) The system is in the monostability regime. (b) The system is in the bistability regime.

IV. HOMOGENEOUS STABLE REGIMES FOR BEHAVIOR OF THE ENSEMBLE OF IONIC CHANNELS IN BIOLOGICAL MEMBRANE

Let us consider the principal scheme of an experiment for the investigation of an ionic flux through the membrane proposed in Ref. [16] [Fig. 8(a)]. The corresponding equivalent electrical circuit is shown in Fig. 8(b).

The control parameters for this problem are the potential difference on the electrode E and the concentration of ions C_1 and C_2. (For the single ionic channel we have used in Sec. III the values of Ψ and A.) It is convenient for later discussions to take the transmembrance potential 2Ψ and the ionic flux through the membrane J_s as new dynamical variables.

Using the equivalent electrical circuit shown in Fig. 8(b), we will find for the evolution of the transmembrane potential the following equation:

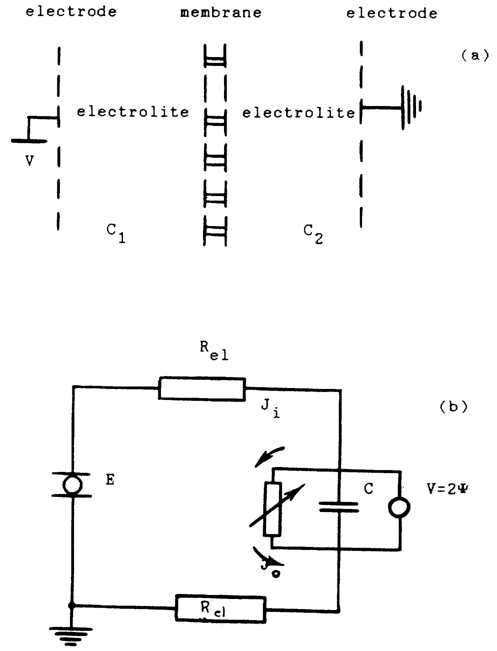

FIG. 8. Schematic representation of an experiment for studying the behavior of the ensemble of channels (a). (b) Equivalent electrical circuit.

$$\tau_C \frac{d\Psi(t)}{dt} = E/2 - \Psi - R_{el} J_s \;, \tag{22}$$

where $\tau_C = R_{el} C$ and $J_s(t)$, is the current through the membrane defined by the expression

$$J_s(t) = GSq\,[I_i(t) + I_o(t)]/2 \;. \tag{23}$$

Here G is a surface density of channels, S is a membrane surface, and $I_i(t)$ and $I_o(t)$ are the values of ionic currents through the single channel corresponding to the conformational coordinate $X(t)$. They are defined by Eq. (7a). Thus, Eq. (22) with regard to Eqs. (23) and (7) may be solved in a consistent way with Eq. (12) when $\tau_X > \tau_{\text{ion}}$, or in a consistent way with Eq. (14) when $\tau_{\text{ion}} > \tau_X$. In the latter case $J_i = J_o$, and using Eq. (7a) we can get the final system of equations in the following form:

$$\tau_X \frac{dX}{dt} = -\frac{\partial U^{\text{eff}}(X)}{\partial X} = -X + A\,[1 - 2\eta \exp(-|X|)\sinh\psi]/[1 + 2\eta \exp(-|X|)\cosh\psi] \;, \tag{24}$$

$$\tau_C \frac{d\psi}{dt} = E/2 = \psi - \nu 2\eta \exp(-|X| + \psi)/[1 + 2\eta \exp(-|X|)\cosh\psi] \tag{24'}$$

where

$$\nu = RGSq^2 I_0 / k_B T$$
$$= RGSq^2 r_0 \Lambda / r_\infty k_B T \;.$$

For the isoclines of Eq. (24) we have the following equations:

$$\begin{aligned} \psi &= \ln((A - X)e^{|X|}/(A - X)2\eta \\ &\quad + \{[(A - X)e^{|X|}/(A - X)2\eta]^2 \\ &\quad + (A - X)/(A - X)\}^{1/2}) \;, \\ \psi &= E/2 - \nu 2\eta \exp(|X| + \psi)/[1 + 2\eta \cosh\psi \exp(-|X|)] \;. \end{aligned} \tag{25}$$

The first of them is in a general case some sort of N-shaped curve represented in X and Ψ coordinates. Combining the first and the second equations in (25), we can transform them in such a way that instead of the second equation we will have

$$\nu X = \psi + A\nu - E/2 \; . \tag{25'}$$

It is evident that the line given by Eq. (25a) will cross the first isocline no more than in three points [Figs. 9(a), 9(b), 9(c)]. We shall consider below Eq. (25′) instead of the second equation in the system of equations (25).

If there is only one intersection placed on section I of the isocline where $X'_\Psi < 0$, then the system moves to the only one possible stable state [Fig. 9(a)], i.e., there is the monostability. If the sole intersection takes place on the same section (I) of the isocline and $X'_\psi > 0$, then the system possesses the periodical behavior [Figs. 9(c) and 10(b)], i.e., there are relaxation oscillations [17].

If the intersection occurs at three points X_1, X_2, and X_3, then according to the initial conditions the system may possess two steady stable regimes X_1 and X_3 [Figs. 9(c) and 10(c)], i.e., there is the bistability. The unstable stationary regime is realized for $X = X_2$ and the point X_2 divides the region of initial values $X(0) \in (-\infty, \infty)$ into two regions $(-\infty, X_2)$ and $(X_2, +\infty)$.

From the first region the system moves to the stationary solution X_1 and from the second to the stationary solution X_3. The limiting case of a contact of the two isoclines corresponds to the situation where the points X_1 and X_2 or X_2 and X_3 coincide and therefore only one stable state is realized.

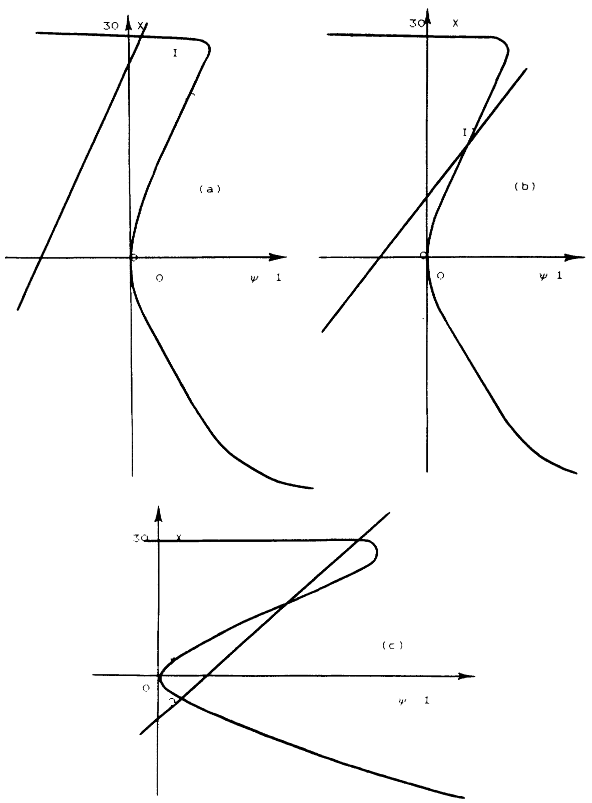

FIG. 9. Isoclines for Eqs. (24) and (25). (a) Monostability regime ($\nu = 2.3$). (b) Oscillatory regime ($\nu = 1.4$). (c) Bistabiltiy regime ($\nu = 0.5$). The parameters are $\eta = 20$, $A = 30$, and $C = 20$.

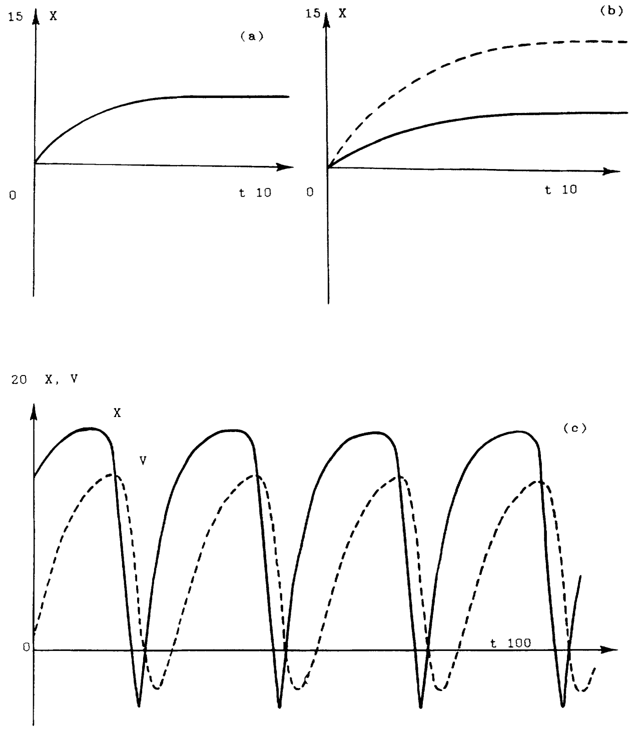

FIG. 10. Time course of the current. Regimes correspond to Fig. 9. (a) Monostability state. (b) Two stable states that correspond to the upper and lower intersection points of the isoclines. (c) Relaxation oscillation of the potential (dashed line) and of the conformational variable (solid line). The parameters are $\nu = 1.4$, $\eta = 20$, and $A = 30$. $C = 20$, $\tau_{\text{ion}} = 0.5$, and $\tau_X = 5.0$.

For the given parameters η and ν any of the three regimes of a dynamical behavior of the system described above is realized for the suitable values of the control parameters A and E (i.e., the differences of the concentrations and potentials, respectively).

If we add to Eq. (25) the condition of contact of the isoclines $\psi'_X = \nu$ given by

$$Q(\varphi + Q)[1 + \nu(A + X)] = [(\varphi + Q)\varphi'_X - X](A + X) \; , \tag{26}$$

where

$$\varphi = (A - X)\exp(|X|)/2\eta \; , \quad Q = (\varphi^2 + A^2 - X^2)^{1/2} \; , \quad \varphi'_X - [\operatorname{sgn} X(A - X) - 1] \; , \tag{26'}$$

we can obtain the system of equations that are satisfied in the space limited by the curve

$$E = f_1(A) \; . \tag{27}$$

The curve (27) $f_1(A)$ divides the space of control pa-

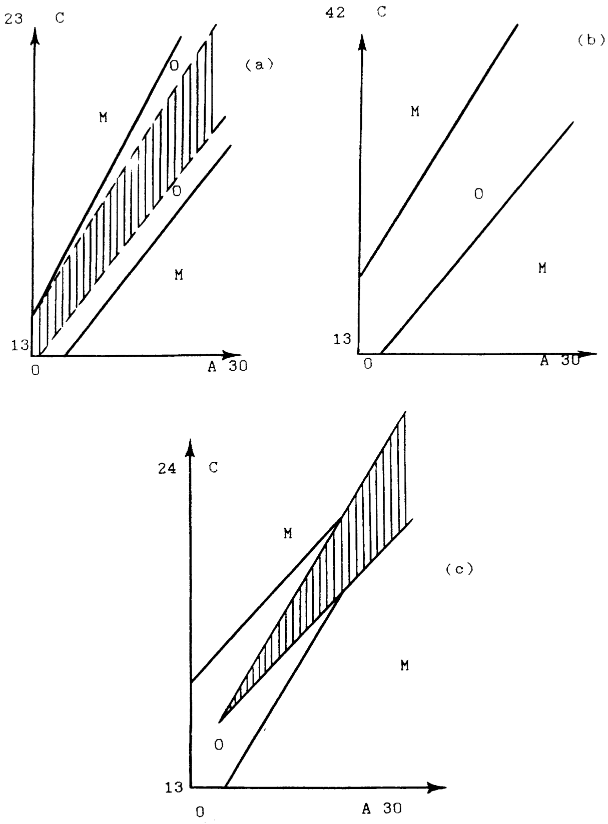

FIG. 11. Phase diagrams of the system. The region of the monostability is defined by M. The region between two solid lines corresponds to the oscillatory regime (0). The bistability domain is shaded.

rameters into two regions. In one of them the monostability or the oscillator regime is realized and in the other there is only the bistability.

If we add to Eq. (25) the condition $\psi'_X=0$, taken in a form

$$Q(\varphi+Q)=[(\varphi+Q)\varphi'_X-X](A+X) , \tag{28}$$

we can get the system of equations that are satisfied in the space limited by the curve

$$E=f_2(A) . \tag{29}$$

Evidently, the curves (27) and (29) together determine the phase space on the A and E plane, i.e., the regions in which only one of the regimes discussed above is realized. The phase diagrams for various values of the parameters η and ν are shown in Fig. 11.

V. SUMMARY AND CONCLUSION

According to the above results we can see that when the protein macromolecules forming the ionic channels have some conformational degrees of freedom with characteristic frequencies that are less than the rates of ionic hoppings (or are of the same order), the essentially new qualitative phenomena appear for the ion transport through the channels. The interaction of the ionic flux with the conformational structure of the channel leads to the appearance of discrete conductivity states. The number of these states and their lifetimes depend on the type and concentrations of ions as well as on the relation between the membrane's parameters and the parameter that describes the length of structural correlations inside the channel.

The possibility of the control of the channel functioning due to the external electric field seems very encouraging. Our calculations show that one may effectively modulate channel lifetimes in their closed and open states using the applied field. Therefore the new physical meaning for the "gating particles" is strongly connected with substantial nonlinear character of the ion transport through the channels of the biological membranes.

Within the framework of an approach considered here the construction of molecular computing devices may be also suggested [17]. As was shown above, the ensemble of channels that mutually interact in a cooperative manner via the bulk solution under the sufficiently strong dependence of the rate constants upon the conformational variable may possess various types of the dynamic behavior such as monostability, bistability, and relaxation oscillations. Therefore, one can use the ensemble of coherently coupled channels as a basic element of a molecular computing device.

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