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TYPES OF NON-LINEAR BEHAVIOUR OF THE SYSTEM OF ION TRANSFER ACROSS THE MEMBRANE ON EXPOSURE TO A WEAK ELECTRIC FIELD*

T. Yu. PLYUSNINA and G. Yu. RIZNICHENKO

Biology Faculty of the Lomonosov State University, Moscow

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A mathematical model of ion transport across the membrane via a carrier is explored. The fundamental non-linearity of the model governs the possibility of pH changes in the near-membrane layer in the auto-oscillatory regime. It is shown that the impact of a weak varying electric field may sharply change the character of the auto-oscillations and lead to the appearance of a quasichaotic regime. © 1997 Elsevier Science Ltd. All rights reserved.

It is well known that the rhythms of endogenous origin peculiar to biological systems or imposed by the external conditions are of prime importance for the normal course of many vitally important processes. Cessation of the rhythms or their phase shift may lead to disturbance of biological functions. Some authors point to the special regulatory role of biological rhythms [1, 2]. A host of publications exists, describing the periodic oscillations in processes associated with enzymatic catalysis [3], with respiratory activity [4] and with nerve impulse transmission [5]. Since the role of the cell membranes is not confined to barrier functions but makes a considerable contribution to the regulatory processes of the cell, maintenance of homeostasis and the processes of synthesis of proteins and genetic material, the search for periodic solutions in models of membrane transport processes is an important task.

Earlier in [6, 7], to explain the effects of the impact of weak low-frequency fields on biological systems, we proposed models of ion transport across the membrane, each of which is characterized by a definite type of non-linearity. It was shown that a non-linearly organized system of ion transport may respond to weak periodic exposure by resonance enhancement of the variations in the concentrations of ions [6], or by switching from one regime of functioning to another [7]. This paper is concerned with the response of the system of ion transfer, possessing auto-oscillatory dynamics of behaviour.

Let us consider the case when both protons and potassium ions are transferred in accord with the scheme (1), representing a minor modification of the schemes proposed by us in [6, 7].

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$$v_H(\varphi) \underset{k_H}{\rightleftharpoons} H_1^+ + T^- \underset{k_{-1}}{\overset{k_{+1}}{\rightleftharpoons}} TH,$$

$$H_1^+ + TH \underset{k_{-7}}{\overset{k_{+7}}{\rightleftharpoons}} TH^2, \qquad \text{(Scheme 1)}$$

$$H_1^+ + TK \overset{k_{+5}}{\rightleftharpoons} THK^+ \xrightarrow{k_{+6}} TK + H_2^+ \longrightarrow v'_H(\varphi),$$

$$v'_K(\varphi) \longleftarrow K_1^+ + TH \xleftarrow{k_{+4}} THK^+ \underset{k_{-3}}{\overset{k_{+3}}{\rightleftharpoons}} TH + K_2^+ \longleftarrow v_K(\varphi).$$

The subscripts 1 and 2 at concentrations of protons H^+ and potassium K^+ ions correspond to a solution on the two sides of the membrane; $v_H(\varphi)$ and $v_K(\varphi)$ are the rates of inflow of protons H^+ and potassium K^+ ions into the sphere of reactions, depending on the potential gradient in the near-membrane region; $v'_H(\varphi)$ and $v'_K(\varphi)$ are the rates of efflux at the other side of the membrane; $k_{\mp n}$ $(n = 1,3,5,7)$ are the attachment constants of the ions to the carrier and the breakdown of the complex on one side of the membrane; k_{+n} $(n = 4,6)$ are the effective transfer constants of the complex across the membrane and its breakdown on the other side.

As may be seen from the scheme, the system is open thanks to the diffusional processes in the near-membrane region. In the system a feedback mechanism is realized, leading in certain conditions to periodic fluctuations in the concentrations, which, depending on the parameters of the process, may be damping or self-sustaining. Another feature of the non-linear organization of the process is inhibition of transfer by secondary attachment of protons, promoting the onset of bistability in the system.

In real conditions the concentration of the carrier is usually much lower than that of the transferred ions, which accounts for the hierarchy of times in the system, i.e. the rate of change in the concentration of the carrier T^- and its complexes amounts in relation to the rate of turnover of these molecules to a value much closer to zero than the rate of change in the concentration of ions in relation to the rates of their circulation. For the carrier and its complexes, quasisteadiness exists. The use of the Tikhonov theorem on the limiting transition allows one to transform the system, originally consisting of six differential equations to a non-linear system of two differential equations. Finally, having regard to the external action, the system assumes the form:

$$dx/d\tau = v_x(\varphi)(1 + A\sin\omega\tau) - k_x x - bxy/(1 + x + xy + cy + ax^2), \qquad (1)$$
$$dy/d\tau = v_y(\varphi)(1 + A\sin\omega\tau) - xy/(1 + x + xy + cy + ax^2),$$

where x and y are, respectively, the dimensionless concentrations of protons and potassium ions, $v_x(\varphi)$ and $v_y(\varphi)$ are the dimensionless rates of inflow of protons and potassium ions into the reaction sphere, k_x, a, b, c are combinations of the rate constants of the interaction of ions with the carrier and transfer of the complexes formed across the membrane, A is a dimensionless amplitude, and ω is the dimensionless cyclic frequency of the external action. The value of the amplitude indicates the proportion of the voltage of the intrinsic electric field in the near-membrane region in relation to the voltage of the external electric field.

Investigation of the system (1) in absence of exposure (A, $\omega = 0$), using the Hopf bifurcation theorem showed that for certain values of the parameters, the system has a solution in the form of a limiting cycle. Analytical investigation and numerical integration gave four critical values of the controlling parameter v_x, for which in the system bifurcational changes appear (Figs 1 and 2). The region of onset of bifurcations is very narrow: changes in the parameter by ten thousandths leads

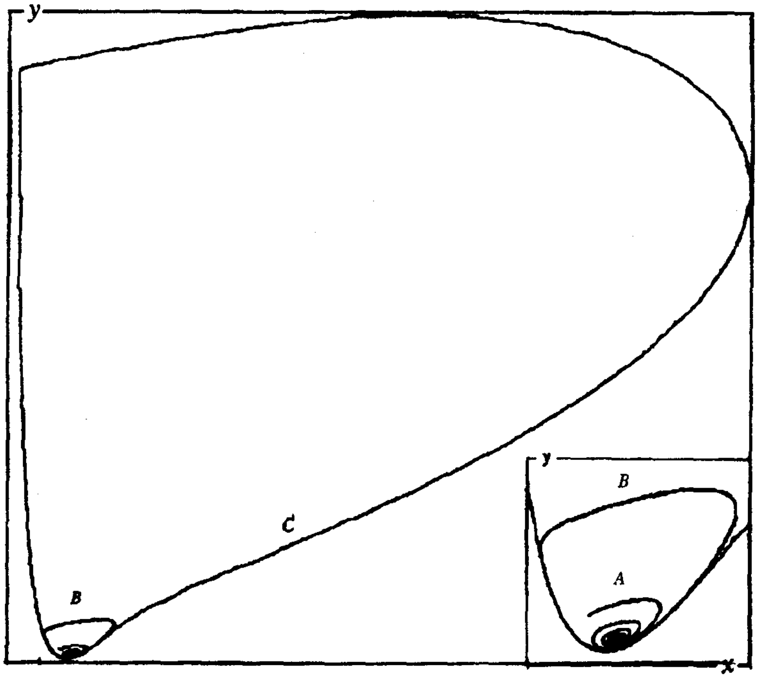

Fig. 1. Change in the structure of the phasic portrait of system (1) in the absence of external action (A, $\omega = 0$) with change in the parameter of inflow of protons v_x. In the right corner, an isolated portion reproduced on a larger scale. x and y are the concentrations of protons and potassium ions in the near-membrane layer. At $v_x = 0.5241$, dying oscillations exist in the system, the stable state is a focus (curve A); at $v_x = 0.5242$ Hopf bifurcation takes place. The stable equilibrium regime gives way to stable auto-oscillations of low amplitude (curve B), which, with increase in v_x, slowly rises. At $v_x = 0.5245$, the amplitude and the period of the natural oscillations sharply grow (curve C), $v_x = 0.5$, $k_x = 0.01$, $a = 10$, $b = 1$, $c = 1$.

to transitions from the regime of dying oscillations to limiting cycles of different amplitude and to the appearance of two attractors.

Exposure of the bifurcational parameter v_x, depending on the potential gradient, to an external periodic electric field, was studied both close to the point of bifurcation and in the intervals of parameters far from bifurcation. With the electric field acting on the parameters of the rates of inflow far from the points of bifurcation, the system retains stability over a wide range of amplitudes and frequencies of exposure, i.e. the character of the intrinsic oscillations practically does not change.

Close to the critical values of v_x, an external minor perturbation by the field characterized by definite amplitude and frequency, alters the regime of functioning. Thus, for a lower critical value of the parameter $v_x = 0.5241$ corresponding to the stable state of the focus, a weak external action will take the system from the regime of dying oscillations into the regime of auto-oscillations. If the action occurs at the moment when the system is in the regime of auto-oscillations (for v_x close to bifurcation), then in the system transitions are possible from oscillations of low amplitude to those of high amplitude (Fig. 3), i.e. passage from the cycle B to the cycle C in Fig. 1.

Close to the upper critical value $v_x = 0.7065$ in response to external weak periodic perturbation in the system as a function of frequency several types of behaviour may also be realized. At relatively high frequencies of the action the system, depending on the initial conditions, performs oscillations either close to the stable focus (D in Fig. 2), or the solution tends to the limiting cycle (F in Fig. 2). At certain critical (resonance) frequencies of action, the system, close to the stable

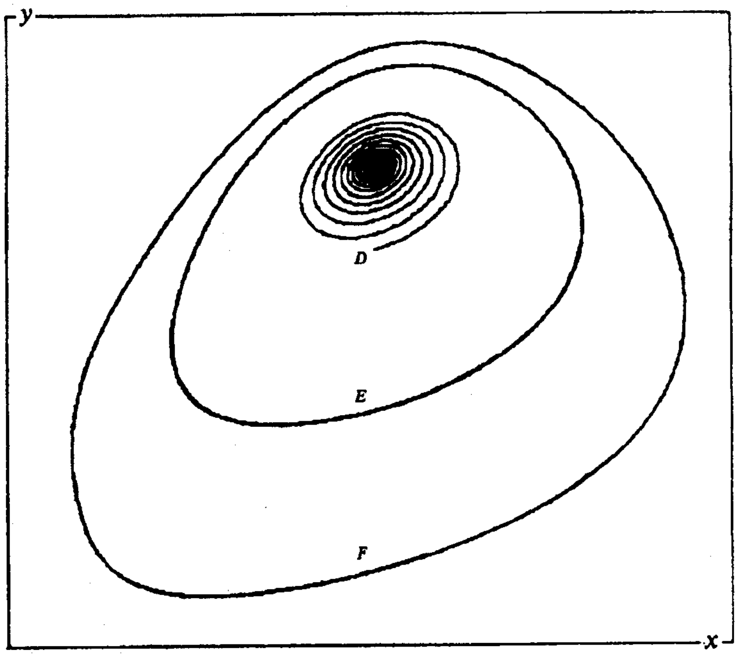

Fig. 2. Existence of a multiplicity of solutions in the system (1) in the absence of an external action (A, $\omega=0$) with change in the initial conditions. x and y are the concentrations of protons and potassium ions in the near-membrane layer. At $v_x=0.7014$–0.7067, in the system a stable focus (D), an unstable (E) and stable (F) limiting cycles exist. Depending on the initial conditions, the solution will tend either to the stable limiting cycle (F) or to the stable focus (D). At $v_x>0.7067$, only the stable focus remains in the system. $v_x=0.5$, $k_x=0.01$, $a=10$, $b=1$, $c=1$.

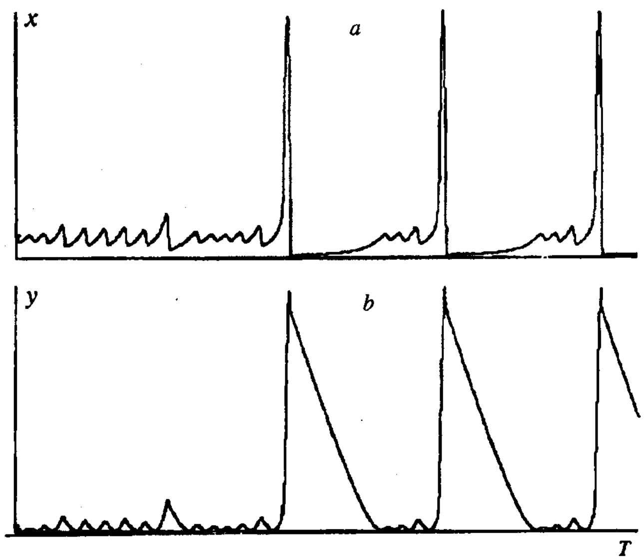

Fig. 3. Changes in the concentration of protons x (a) and potassium ions y (b) in the near-membrane layer appearing in response to external periodic perturbation by a weak electric field. At $v_x=0.5243$ periodic transitions from low amplitude to high amplitude oscillations appear in the system. Amplitude of external action $A=0.0003$, frequency $\omega=0.004$, $v_x=0.5$, $k_x=0.01$, $a=10$, $b=1$, $c=1$.

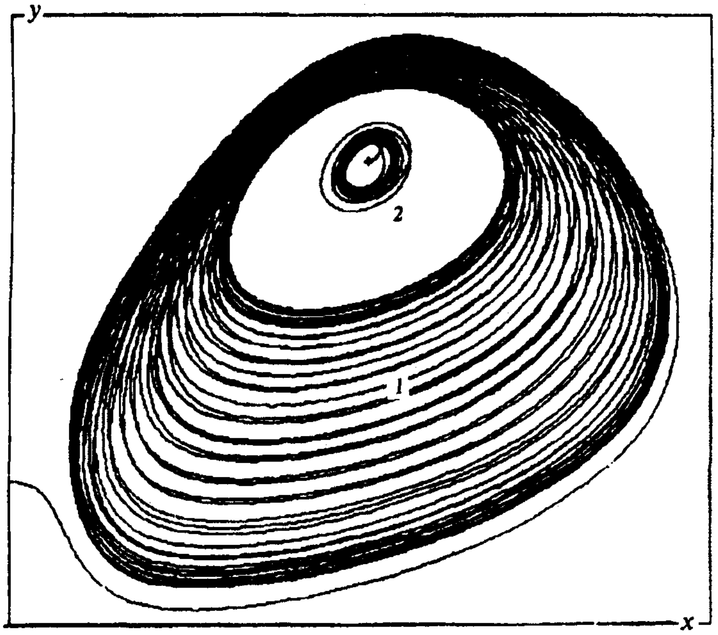

Fig. 4. Changes in the concentration of protons x and potassium ions y in the near-membrane layer in response to external periodic perturbation by a weak electric field. For an amplitude of the external action $A = 0.003$ and critical frequency $\omega = 0.0025$ a quasichaotic regime appears. At other frequencies, periodic oscillations take place, $v_x = 0.7065$, $v_y = 0.01$, $k_x = 10$, $a = 10$, $b = 1$, $c = 1$.

focus, may be "thrown over" into the state of the limiting cycle. With fall in the frequency of the external action to $\omega = 0.0025$ close to the limiting cycle (F in Fig. 2), a limiting set (Fig. 4, region *1*) appears, reminding one in terminology [8] of the odd attractor since the phasic trajectories with passage of time draw to this limiting set and entering the region occupied by it remain there forever. In the attractor itself, movement is unstable. As well as the odd attractor at the frequency of action considered, in the system there exists a limiting periodic trajectory (Fig. 4, curve *2*). Therefore, depending on the initial conditions, either periodic or quasichaotic oscillations may be realized in the system.

The numerical investigations run show that for certain values of the parameters far from the points of bifurcations, the system possesses a high degree of stability to weak electrical influences. Then, as with the values of the parameters close to the bifurcation points, the actions of a field of low amplitude and frequency produce considerable effects.

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