COOPERATIVE OPERATION MODE OF A SYNAPTIC CHANNEL

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The work considers the problem of the signal (nervous pulse) transmission through a synaptic cleft (synaptic channel). For this purpose, we propose a nonlinear dynamic model that describes the kinetics of biochemical reactions taking place in a synapse during the pulse propagation. In the framework of this model, the arrival of a signal at a synaptic cleft is considered as a perturbation that disturbs the system from the stationary state, whereas the mechanism of signal transmission is realized through the evolution of the system to the initial stationary state. We have found the conditions, under which it is possible to transfer periodic pulses through a synaptic channel, and present the results of corresponding numerical calculations.

1. Introduction

A characteristic feature of modern science consists in solving the problems lying on a junction of different fields. Moreover, one usually uses universal models and approaches for this purpose. A similar situation is characteristic of the investigation of physical mechanisms of nervous activity at various levels, starting from general neural networks (see, e.g., [1–6]) and finishing with their separate areas such as synaptic junctions between nerve cells (see, e.g., [7–20]).

It is interesting that the problem of the transmission of a nervous signal through a synapse (the term introduced in 1897 by the English physiologist Ch. Sherrington to designate a contact between neurons) was widely investigated by physiologists. Moreover, its investigators have received several Nobel prizes in their days. For example, the Nobel prize in Physiology or Medicine in 1970 (B. Katz, J. Axelrod, and U. von Euler) was awarded for the results obtained in the course of studying the processes of release and inactivation of mediators of nerve fibers. In 2000, the Nobel prize in Physiology or Medicine (A. Carlsson, P. Greengard, and E. Kandel) was awarded for investigations of the processes of signal transmission in the nervous system, in particular for the so-called *slow synaptic transmission* (signal transmission by mediators of the catecholamine type that is slower by several orders of magnitude as compared to that by mediators of the acetylcholine type). Nevertheless, in spite of such a considerable contribution of colleagues-physiologists, the problem of the development of an effective biophysical model remains open. Moreover, the study of peculiarities of the signal transmission through synaptic channels is not only of a specific applied importance but also meets certain theoretical and methodological difficulties. In this case, the principal problem is related to the development of an adequate theoretical model that can explain the processes of pulse transmission through a synaptic cleft. For today, there exist several basic approaches that allowed one to successfully solve a number of important problems. In particular, the hypothesis about the isomorphism of processes taking place in a synaptic cleft to those of critical separation in a binary liquid [21, 22] appeared to be rather effective. This allowed one to obtain a number of interesting results. It is worth to separate the studies devoted to the calculations of the dimensions of the activation area of acetylcholine complexes in different approximations, as well as those

aimed at the determination of dynamic characteristics of the process of signal passage through a synapse (see, e.g., [23–26]). The cited works mainly use the dynamic model first proposed in [21].

Along with considerable progress, there exist a number of problems that are to be solved, among them the problem of analysis of the synchronous action of synaptic channels united into a general network. Certain attempts to investigate this problem with the help of a mathematical modeling were made in [27]. However, the problem still requires the further investigation.

Based on the dynamic model that describes the process of signal transmission through a synaptic cleft, the present work analyzes the operation of a synaptic channel in the self-organized network mode, or in the cooperative mode, with the transmission of periodic single-type signals.

2. Initial Dynamic Model

The dynamic model we used describes a system of mediator-receptor complexes in a synaptic cleft [21, 23]. The pulse transmission through the cleft is accompanied by a biochemical reaction that can be presented in the simplified form as

$$ACh + R \rightarrow AChR \rightarrow R,$$

where ACh denotes acetylcholine, R stands for free (non-activated) receptors of the postsynaptic membrane, $AChR$ are acetylcholine-receptor complexes. The sequence of processes running in the synaptic cleft can be described in the following way. Due to the arrival of a signal at the synaptic cleft, there takes place an injection of the biologically active substance – acetylcholine. The latter interacts with free receptors on the postsynaptic membrane forming acetylcholine-receptor complexes. In turn, the formation of these complexes results in the generation of a signal by the postsynaptic membrane. The acetylcholine-receptor complexes decay (under the action of esterase); after that, the synapse is ready for the transmission of the following pulse [21, 23, 26].

The indicated processes running in a synaptic cleft are described by the system of differential equations [21, 23]

$$\frac{dx}{dt} = k_2(x_0 - x) - k_1 xy, \tag{1}$$

$$\frac{dy}{dt} = f(t) - k_1 xy, \tag{2}$$

where x and y denote the concentrations of non-activated receptors and acetylcholine, respectively, x_0 is the concentration of receptors on the postsynaptic membrane, $k_{1,2}$ are the kinetic coefficients of the reaction, whereas $f(t)$ is a function that determines the rate of acetylcholine injection into the synaptic cleft. Actually, the specific dynamics of parameters of the system is determined by this function. Moreover, some particular cases were already considered (see, e.g., [27]). Here, we study the situation where the synaptic channel operates as an element of the general network, where signals propagate. In this case, an important role is evidently played by the structure of the network and the character of transmitted signals. We consider a periodic process where a signal arrives at the presynaptic membrane periodically, in fixed time intervals. As for the function $f(t)$ of the intensity of acetylcholine injection, we have all grounds to assume that this process is almost instantaneous – at least by one order of magnitude faster as compared with the other processes running in the synaptic cleft [21, 22]. Under such conditions, it is reasonable to suppose that $f(t) = 0$ and to involve the process of acetylcholine injection through the initial conditions.

Taking the relation $f(t) = 0$ into account and passing to dimensionless parameters (the substitution $x(t) \rightarrow x_0 x(t)$, $y(t) \rightarrow x_0 y(t)$, and $t \rightarrow t/x_0/k_1$), the initial system of equations (1) and (2) can be presented in the form

$$\frac{dx}{dt} = k(1 - x) - xy, \tag{3}$$

$$\frac{dy}{dt} = -xy, \tag{4}$$

where $k = k_2/k_1/x_0$. It is also worth to consider the initial conditions

$$x(0) = a, \tag{5}$$

$$y(0) = A, \tag{6}$$

where the parameter a determines the share of free receptors at the time moment of the arrival of a signal, whereas A represents the relative concentration of acetylcholine injected as the signal arrives at the presynaptic membrane. The system of equations (3), (4) with the corresponding initial conditions can be solved numerically, which will be used in what follows. First, we perform some qualitative analysis.

First of all, it is worth noting that system (3), (4) has a single stable stationary point $x_s = 1$ and $y_s = 0$ corresponding to the case where acetylcholine is absent in

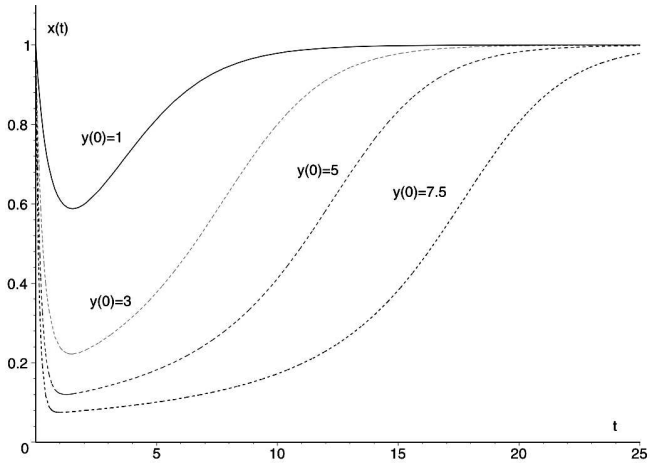

Fig. 1. Time dependence of the free-receptor concentration $x(t)$ under the condition $x(0) = 1$ for different acetylcholine concentrations $y(t)$ at the initial time moment: $y(0) = 1$, $y(0) = 3$, $y(0) = 5$, and $y(0) = 7.5$, respectively (see notations in the figure). The model parameter $k = 0.5$

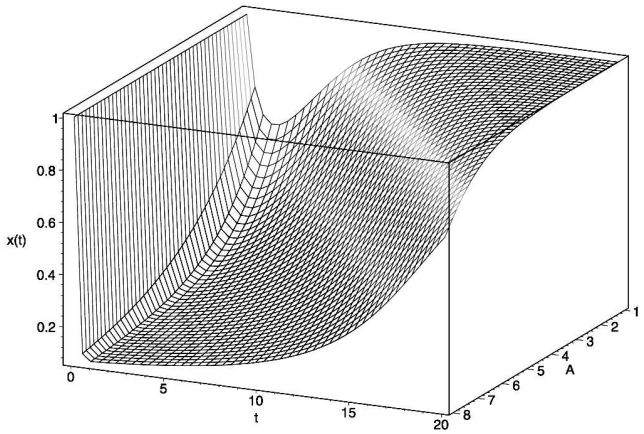

Fig. 2. Dependence of the solution of the problem (free-receptor concentration $x(t)$) for different concentrations of acetylcholine injected into the cleft at the parameters $a = 1$ and $k = 0.5$

the synaptic cleft, and all receptors on the postsynaptic membrane are free (non-activated). From the physical point of view, such a result is evident – after the injection of acetylcholine, it activates receptors but afterwards completely disappears from the cleft (in this case, receptors pass in the inactive state) – in correspondence with the above-described reactions running in the cleft. In the case of an individual signal, the situation would be trivial. But we consider the process of passage of a pulse group; moreover, different synaptic channels must operate in the synchronous mode. This means that, at the time moment of the arrival of every following pulse, the number of free receptors must be the same as in the case of the arrival of the previous one. If the pulses arrive with period T, this means that $x(0) = x(T) = a$. In other words, the process of activation of receptors runs as follows: acetylcholine is injected into the cleft at the initial concentration of free receptors $x(0) = a$, which results in a decrease of the latter. At a certain time moment, the free-receptor concentration reaches a minimum, after which it increases again up to the value a and, at that time moment, there arrives the following pulse. In this case, we assume that acetylcholine is injected in such an amount that its concentration in the cleft will be equal to A. The typical dynamics of the time dependence of the free-receptor concentration in the case of the transmission of one pulse for different concentrations of acetylcholine is presented in Fig. 1.

From the viewpoint of the free-receptor concentration dynamics, the most important parameters are the following two: the concentration of acetylcholine $y(0) = A$ injected into the cleft and the concentration of free receptors at the time moment of the arrival of a signal $x(0) = a$, i.e. the initial conditions. We are interested only in the operation of the synaptic channel in the regular mode, where the postsynaptic membrane has time to recover before the arrival of the next signal. This means that the free-receptor concentration at the initial time moment must be close to 1, i.e. $1 - a \ll 1$. As for the acetylcholine concentration at the initial time moment A, the dynamics of the system qualitatively differs at $A \sim 1$ and $A \gg 1$. In the first case, the concentration of free receptors decreases rather rapidly down to a minimal value and after that slowly increases. In the second case, this concentration falls almost to zero, remains on such low level for a certain time (temporary saturation state) and then starts to increase (see Fig. 1). A more complete information on the dependence of the solution of the problem on the parameter A is given in Fig. 2.

As was already noted, an increase of the parameter A results in an essential rise of the time, in which the system reaches a stationary state (after the arrival of a pulse). As for the parameter of the model k, it is related to the recovery rate of activated receptors and influences only the profile of the time dependence of the concentration and, what is most important, the minimal value of the free-receptor concentration. Figure 3 demonstrates the dependence of the solution on the value of the parameter k.

A rise of the parameter k results in an increase of the lower limit of the free-receptor concentration. The given effect is explained by the fact that, at higher recovery

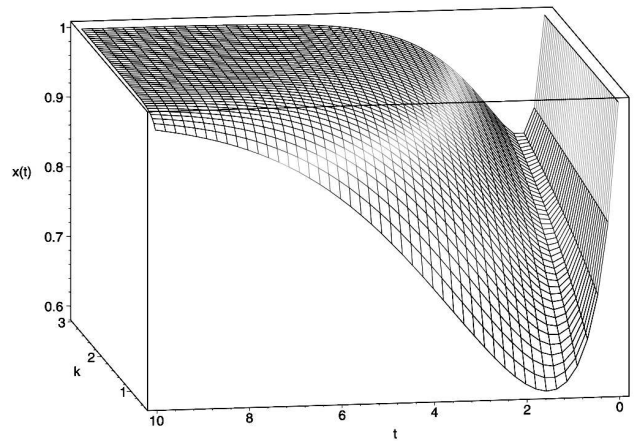

Fig. 3. Dependence of the solution (free-receptor concentration $x(t)$) for different values of the parameter k (relative recovery rate of activated receptors) at the parameters $a = 1$ and $A = 1$

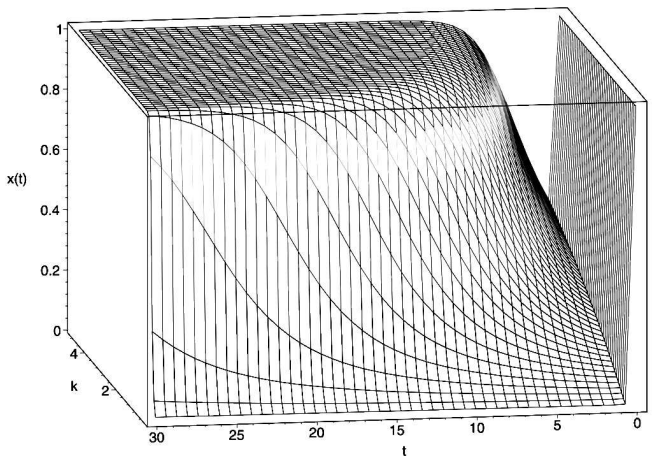

Fig. 4. Dependence of the solution (free-receptor concentration $x(t)$) for different values of the parameter k (relative recovery rate of activated receptors) at the parameters $a = 1$ and $A = 10$

rates of activated receptors, the postsynaptic membrane recovers faster. Therefore, acetylcholine has no time to compensate the deactivation reaction.

Figure 4 shows the solution depending on the parameter k of the model in the case where the acetylcholine concentration at the initial stage exceeds the free-receptor concentration by an order of magnitude.

As was noted above, higher concentrations of acetylcholine correspond to a flatter minimum in the time dependence of the concentration. Such a flat minimum can be compensated due to the increase of the rate of the receptor deactivation reaction, i.e. by means of the increase of the parameter k. It is worth noting here that the action of many poisons, for example curare, is

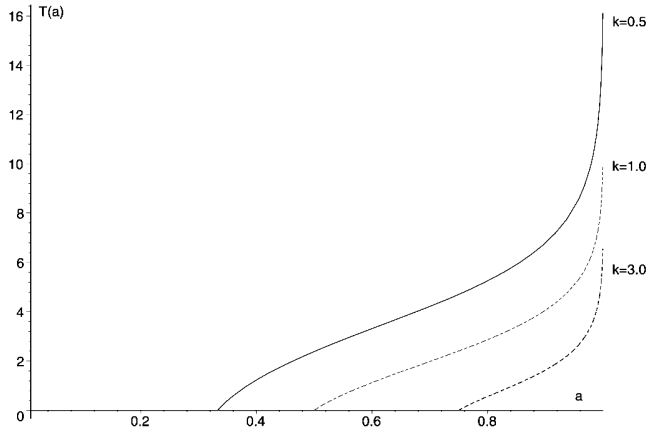

Fig. 5. Dependence of the period of signal transmission on the initial free-receptor concentration for different values of the parameter k (0.5, 1.0, and 3.0). The calculations are performed at $A = 1$

based on the blocking of receptor complexes, which can be considered from the viewpoint of the given model as an essential decrease of the parameter k.

3. Signal Transmission

It is evident that the initial concentration of free receptors $x(0) = a$ is related to the pulse arrival periodicity T by the relation $x(T) = a$. The characteristic dependences of the period of signal transmission through a synapse in the cooperative operation mode of the channel for some values of the parameter k of the model are given in Fig. 5.

It is significant that, at the fixed parameter A that determines the initial concentration of acetylcholine, there exists such a critical value $a_{\rm crit}$ of the parameter a of the free-receptor concentration at the initial time moment that the system cannot transfer periodic signals at $a < a_{\rm crit}$.

The situation is illustrated in Fig. 6 that presents the dependence of the free-receptor concentration at its initial values lying above and below the critical value. The other case is characterized by the absence of a minimum in the time dependence of the receptor concentration – here the free-receptor concentration monotonously increases from the very beginning up to the equilibrium level. Such a mechanism is inconsistent with the operation mode of the synaptic channel, in which periodic pulses are transmitted.

The critical value $a_{\rm crit}$ is determined from the condition $\dot{x}(0) = 0$ and depends on the parameters k and A

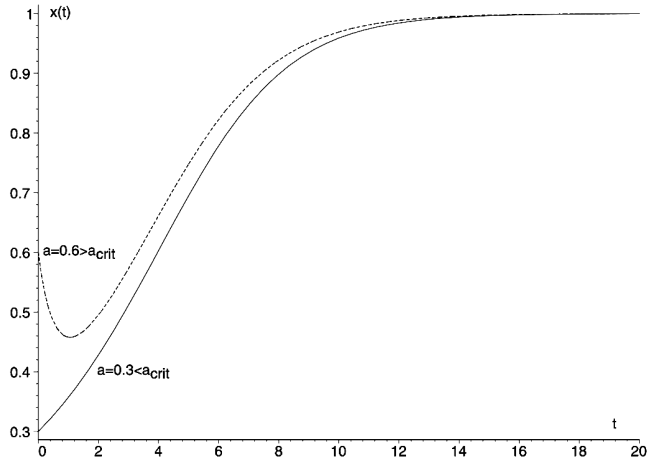

Fig. 6. Qualitative change of the time dependence of the free-receptor concentration at their initial concentrations $a > a_{\rm crit}$ and $a < a_{\rm crit}$. The calculations are performed at $k = 0.5$, $A = 1$, $a_{\rm crit} = 1/3 \approx 0.33$. The graphs are given for $a = 0.3 < a_{\rm crit}$ and $a = 0.6 > a_{\rm crit}$

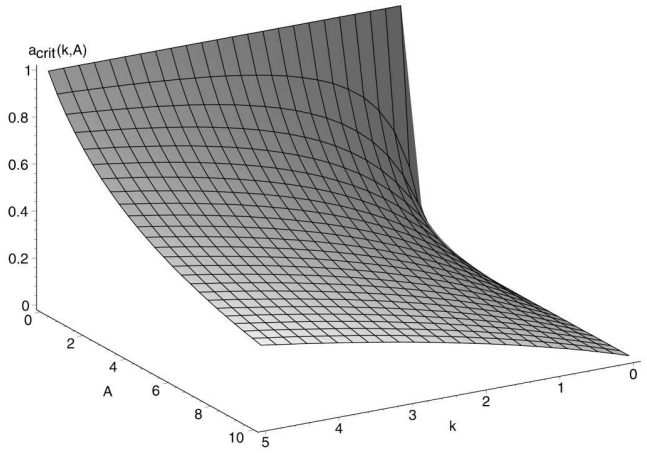

Fig. 7. Dependence of the critical value $a_{\rm crit}$ on the parameters k and A. The given dependence determines the possibility of the transmission of pulses through a synaptic channel in the cooperative mode of its operation

of the model in the following way:

$$a_{\rm crit} = \frac{k}{k+A}. \tag{7}$$

Figure 7 graphically illustrates the dependence of $a_{\rm crit}$ on the parameters k and A.

The highest values of the critical parameter $a_{\rm crit}$ are realized at small parameters A and large parameters k of the model. In particular, at low k, an increase of the parameter A results in the abrupt decrease of $a_{\rm crit}$, which testifies to the prevalence of the effect of saturation of the synaptic cleft by acetylcholine. With increasing k, the given effect is not very pronounced. Similarly, at low acetylcholine concentrations in the cleft, the system significantly responds to the variation of the parameter k. In this case, the dominant processes are those of deactivation of the postsynaptic membrane. Finally, Fig. 8 presents the characteristic time dependences of the free-receptor concentration in the case of the transmission of periodic signals through a synaptic channel.

At the model parameters used in our calculations, the process of activation of the postsynaptic membrane is almost instantaneous (at least much faster than the process of its deactivation). From the physical viewpoint, the mechanism of operation of the channel in this mode is reduced to periodic perturbations of the system that trends to return to the stationary stable point. Every following pulse arrives just at the time moment when the system appears in the state with the parameters corresponding to the beginning of perturbation.

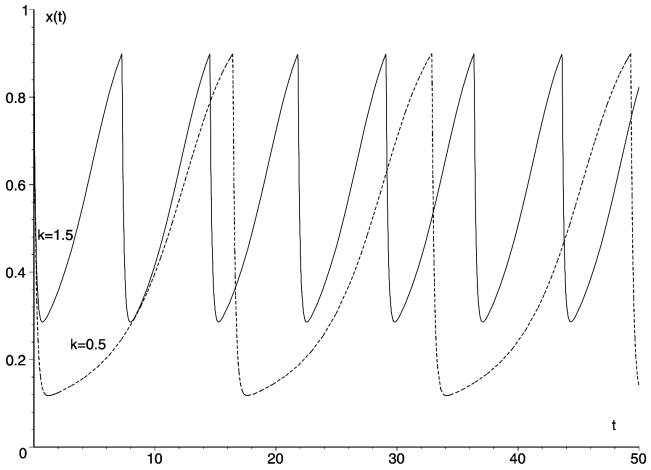

Fig. 8. Characteristic time dependence of the free-receptor concentration in the course of the transmission of periodic signals through a synaptic channel in the cooperative operation mode. The calculations are performed at $a = 0.9$, $A = 5$ for $k = 0.5$ and $k = 1.5$

4. Conclusions

Summing up the above-obtained results, let us mark out the basic statement that is important from the viewpoint of the physical understanding of mechanisms of synaptic information transfer. The rather simple model considered above explains an important, if not principal, effect in the synapse operation: it has a transmission capacity both with respect to the period of pulse transmission and with respect to the magnitude of the signal arriving to the presynaptic membrane. It is clear that, from

the biological, chemical, and physical viewpoints, the real situation is much more complicated. However, the above-obtained qualitative result agrees very well with the available data on the synaptic mechanism of information transmission. As for the further investigations, the obtained results concerning the parameters and characteristics of the process of transmission of periodic pulses through a synaptic channel can be useful and determinative for the prognosis of parameters and the construction of neural networks aimed at the explanation of complicated processes taking place in the nervous activity.

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КООПЕРАТИВНИЙ РЕЖИМ РОБОТИ СИНАПТИЧНОГО КАНАЛУ

О.М. Васильєв, О.В. Чалий

Р е з ю м е

У статті розглянуто проблему передачі сигналу (нервового імпульсу) через синаптичну щілину (синаптичний канал). Для цього запропоновано нелінійну динамічну модель, яка описує кінетику біохімічних реакцій, що відбуваються в синапсі при проходженні імпульсу. В межах цієї моделі надходження сигналу до синаптичної щілини розглядається як збурення, що виводить систему зі стаціонарного стану, а механізм передачі сигналу реалізується через еволюцію системи до вихідного стаціонарного стану.