Chapter 2
Model of the Interaction of Neurons

The complexity of the pattern of electrical activity of neural ensembles is due to the interaction of their elements. The interaction is associated with the presence of functional contacts between neurons. Since the time of Charles Sherrington, zones of contacts have been called "synapses." Depending on the manner of conducting signals, synapses are divided into two types: electrical and chemical. The synapse of the former type is the zone of direct electrical interaction of the neurons. In this area of the membrane, neurons are in contact with each other, and currents are associated with the gradient of the potentials.

The functional structure of chemical synapses is another one. The branches of the axon are the only centrifugal appendages of the body of the neuron, and they end in the immediate vicinity of the surface of the bodies or dendrites of other neurons. In a synapse, under the action of an incoming nerve impulse, chemical intermediaries called "mediators" are generated. They provide stimulating or inhibitory effects on ion channels of neuron-receiver membranes. Thus, mediators either zoom in or out at the start of the spike of the neuron-receiver. Processes taking place in the electrical synapses are similar to those observed in experiments on the artificial stimulation of neurons by means of electrodes.

2.1 Response to Electrical Action

The artificial stimulation of neurons is carried out with microelectrodes, which are usually placed near the outer surface of the cell. There are variants of experiments with intracellular introduction. In any case, into the balanced equation of currents (1.5.1) flowing through the membrane, we should add the term $I_V(t)$, to characterize the external influence:

$$c\dot{u} = I_{\mathrm{Na}}(t) + I_{\mathrm{K}}(t) + I_V(t).$$

Here, as presented previously, u indicates the current value of the membrane potential. The specific form of $I_V(t)$ depends both on the experimental scheme as well as its mathematical model. We assume that $I_V(t) = g^*(v(t) - u(t))$. The value

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$v(t)$ can be interpreted as the effective value of the potential, which attempts to impose external action on the membrane. The constant $g^* > 0$ is the corresponding coefficient of conductivity. Because we have agreed to count the membrane potential from the minimum possible value (large and negative in absolute value), then the imposed value is $v(t) \geq 0$. Suppose that for sodium $I_{\mathrm{Na}}(t)$ and potassium $I_K(t)$, all of the assumptions of Sect. 1.5 are fulfilled. Taking as time scale the value of the delay of the potassium conductivity (denoted previously as h), and having performed the transformation as described in Sect. 1.5, we change the balanced equation to the form:

$$\dot{u} = \lambda[-1 - f_{\mathrm{Na}}(u) + f_{\mathrm{K}}(u(t-1))]u + g(v(t) - u). \tag{2.1.1}$$

Here, $g = g^* h/c$ is the normalized coefficient of conductivity. The meaning of all other parameters and functions is the same as for Eq. (1.5.7). Below are given all the notations of indicators of exponents and constants approximating the solutions of the equation.

We will begin the study of Eq. (2.1.1) with the case when $v(t) = v_0$ for $t \in [0, T]$ and $v(t) = 0$ at $t \notin [0, T]$, where v_0 is independent of λ constant, and T is a sufficiently large time of action. Let us assume that in Eq. (2.1.1) $f_{\mathrm{Na}}(u) > 0$, $f_{\mathrm{K}}(u) > 0$, and also monotonically and quite rapidly,

$$f_{\mathrm{Na}}(u) \to 0, \quad f_{\mathrm{K}}(u) \to 0 \text{ at } u \to \infty. \tag{2.1.2}$$

As the initial condition for the solution of Eq. (2.1.1), we choose the function $\varphi(s) \in S \subset C[-1, 0]$. Recall that class S includes continuous functions, for which $\varphi(0) = \gamma$ and $\varphi(s) \leq \gamma \exp(\lambda \alpha s/2)$ for $s \in [-1, 0]$. Here the number α is given by formula (1.5.8), i.e., $\alpha = f_{\mathrm{K}}(0) - f_{\mathrm{Na}}(0) - 1$. In this case, algebraic Equation (1.6.1) has no positive roots. We can write $\gamma = 1$. Conventionally, we associate the start and the end of the spike with moments of time when the solution of Eq. (2.1.1) or (1.5.7) crosses the unit value with positive and negative speed, respectively. Denote by $u_v(t, \varphi)$ the solution of Eq. (2.1.1) with the initial condition $u_v(s, \varphi) = \varphi(s) \in S$. As before, δ is an arbitrarily small number.

Equation (2.1.1) is integrated by steps with an asymptotic as $\lambda \to \infty$ simplification of formulas. For the time interval $t \in [\delta, 1 - \delta]$, Eq. (2.1.1) takes the form:

$$\dot{u} = \lambda(\alpha_1 + o(1))u + g v_o, \tag{2.1.3}$$

where $\alpha_1 = f_K(0) - 1$. In the asymptotic integration of Eq. (2.1.3), the term $g v_0$ can be neglected. We obtain for the ascending part of spike the approximate formula from Theorem 1.6.1:

$$u_v(t, \varphi) = \exp \lambda \alpha_1 (t + o(1)), \quad t \in [\delta, 1 - \delta]. \tag{2.1.4}$$

By virtue of (2.1.2), in the time interval $t \in [1+\delta, T_1 - \delta](T_1 = \alpha_1 + 1)$, Eq. (2.1.1) goes over into

$$\dot{u} = \lambda(-1 + o(1))u + gv_0,$$

from which, in accordance with Theorem 1.6.1,

$$u_v(t, \varphi) = \exp \lambda(\alpha_1 - (t-1) + o(1)), \quad t \in [1+\delta, T_1 - \delta]. \tag{2.1.5}$$

In the next time interval $t \in [T_1 - \delta, T_1 + 1 + \delta]$ for $u_v(t, \varphi)$, we obtain equation:

$$\dot{u} = \lambda[-1 - f_{\mathrm{Na}}(u) + o(1)]u + g(v_0 - u).$$

The assumptions made about the properties of functions $f_{\mathrm{Na}}(u), f_{\mathrm{K}}(u)$, guarantee the existence of a unique exponentially stable equilibrium state $u^* > 0$ for the latter equation. Its asymptotic approximation is at $\lambda \to \infty : gv_0/\lambda\alpha_2$ where $\alpha_2 = f_{\mathrm{Na}}(0) + 1$. As a result, we obtain:

$$u_v(t, \varphi) = gv_0/\lambda\alpha_2 + O(1/\lambda), \quad t \in [T_1 + \delta, T_1 + 1 - \delta]. \tag{2.1.6}$$

This asymptotic representation significantly differs from the appropriate formula (1.6.8) of Theorem 1.6.1. In the time interval $t \in [T_1 + 1 + \delta, T_1 + 2 - \delta]$, Eq. (2.1.1) again passes into (2.1.3). We obtain asymptotic formula (2.1.4) with a time shift on $T_1 + 1$. The sequence of operations can be continued as long as $t < T$.

The solution $u_v(t, \varphi)$ of Eq. (2.1.1) has properties other than the solution $u(t, \varphi)$ of Eq. (1.5.7). Asymptotic formulas (2.1.4)–(2.1.6) for $u_v(t, \varphi)$ are cyclically repeated through a period of time $T_v = \alpha_1 + 2$ [in contrast to $T_2 = \alpha_1 + \alpha_2/\alpha + 2$ for (1.5.7)]. The duration of spike, as before for (1.5.7), is close to T_1, but the time interval between the end of one pulse and the beginning of the next one is nearly equal to the lag length (for (1.5.7) it is close to $\alpha_2/\alpha + 1$).

The described type of neural activity wherein the pulses follow frequently is called "bursting." It has been observed in biological experiments. The neuron responds with salvo bursts (Khodorov 1975, p. 229) on the constant electric depolarizing action, thus decreasing the absolute value of the membrane potential.

If in Eq. (2.1.1) we consider the value of the external action v_0 to be small and to agree with the parameter $\lambda(v_0 = \exp(-\lambda\sigma),$ where $0 < \sigma < \alpha_2)$, then the time interval between the end of one spike and the start of the next spike will be asymptotically close to $\sigma/\alpha + 1$. We assume that the action time T is sufficiently long.

A similar construction can be applied to neurons with a resting state of the membrane potential (i.e., neurons as detectors). Here the external action should be considered as large and consistent with the parameter $\lambda : v_0 = \lambda\omega$. We describe the results on a qualitative level. One can distinguish the class of functions $f_{\mathrm{Na}}(u)$ and $f_{\mathrm{K}}(u)$ such that Eq. (2.1.1) will possess the following property: For $g = 0$, it has a stable positive equilibrium state u_0. In this case, however, if in the initial condition $u(0)$ is greater than some constant independent of λ, then the corresponding solution

will have a peak of exponentially large amplitude at λ. Furthermore, suppose that for $t<0$ $u_v(t,\varphi)\equiv u_0$. There exists such a threshold value ω_p that at $\omega<\omega_p$ and $t\in[0,T]$, Eq. (2.1.8) also has a stable positive equilibrium state. If $\omega>\omega_p$, then we observe a spike at $t>0$ for the solution $u_v(t,\varphi)$. At a greater value of the parameter ω, the spike is cyclically repeated. However, its amplitude, being exponentially large at λ, is different than that of the spike starting at time zero. The time interval between the end of one spike and the start of the next one is close to 1.

The described behavior of the solutions of Eq. (2.1.1) is consistent with the results of biological experiments. The weak action on the neuron whose membrane potential is at rest does not lead to the generation of a spike. Such an action is described as "sub-threshold." If the force of depolarizing current flowing through the membrane exceeds the threshold, the neuron responds with a pulse. Increased action leads to a burst response (see Khodorov 1975; Eckert et al. 1991).

A similar pattern of the behavior of the solution $u_v(t,\varphi)$ of (2.1.1) can be observed in the case when the functions $f_{\mathrm{Na}}(u)$ and $f_{\mathrm{K}}(u)$ satisfy the conditions of Theorem 1.6.3, which describes a no-spike evolution of the membrane potential. The difference lies in the fact that at the sub-threshold values of the external action, the solution $u_v(t,\varphi)$ does not tend to the equilibrium state but abruptly wanders in the system of ledges.

Consider the general case of action on the neuron of arbitrary signal v_t. We assume that in Eq. (2.1.1), the functions $f_{\mathrm{Na}}(u)$ and $f_{\mathrm{K}}(u)$ are such that the conditions of Theorem 1.6.1 or 1.6.2 are fulfilled, i.e., the modes of the pulse structure are realized without external action. The results of comparison of the solution $u_v(t,\varphi)$ of Eq. (1.5.7) with $u_v(t,\varphi)$ gives:

Lemma 2.1.1 *At every fixed function $v(t)$ uniformly with respect to $\varphi(s)\in S$ for all $t\in[0,m+T_1]$ holds asymptotic equality as $\lambda\to\infty$: $u(t,\varphi)/u_v(t,\varphi)=1+o(1)$, and at $t\in[m+T_1+\delta,m+T_1+1-\delta]$ respectively, $u(t,\varphi)/u_v(t,\varphi)=o(1)$ and besides, $u_v(t,\varphi)=o(1/\lambda)$.*

Thus, the time interval $t\in[0,m+T_1+1]$ is an area of low susceptibility to external influence. One can use formulas from Theorems 1.6.1 and 1.6.2 as the asymptotic representation for the solution $u(t,\varphi)$ at $t\in[0,m+T_1]$, Pay attention to important details. In the time interval $t\in[m+T_1+\delta,m+T_1+1-\delta]$, the solution $u(t,\varphi)$ of (1.5.7) is exponentially small, and the solution $u_v(t,\varphi)$ of Eq. (2.1.1) has the order of smallness $o(1/\lambda)$. This is consistent with biological data. After a spike, the external depolarizing action counteracts hyperpolarization of the membrane [54, 151]. The fact is that $u_v(t,\varphi)=o(1/\lambda)$ at $t\in[m+T_1+\delta,m+T_1+1-\delta]$ has one more corollary. Let $t_{2v}(\varphi)$ be the second positive root of equation $u_v(t,\varphi)=\gamma$. We have valid asymptotic as $\lambda\to\infty$ equality $t_{2v}(\varphi)=m+T_1+1+o(1)$, which differs substantially from the asymptotic representation of the corresponding moment of time $t_2(\varphi)$ for the solution $u(t,\varphi)$ [by virtue of Theorems 1.6.1 and 1.6.2 $t_2(\varphi)=m+T_1+1+\alpha_2/\alpha+o(1)$]. Note that $u_v(t_{2v}(\varphi)+s,\varphi)\notin S$, but nevertheless we can continue construction of the asymptotics $u_v(t,\varphi)$ for $t>t_{2v}(\varphi)$.

Thus, the response of the neuron to external action for the time interval $t \in [m + T_1 + 1, t_2(\varphi)]$ has a completely different character. To illustrate this more clearly, assume that the continuously differentiable nonnegative function v_t is as follows: $v_t = 0$ at $0 \le t \le t_0$, where $m + T_1 + 1 < t_0 < t_2(\varphi)$ and $\ddot{v}t_0 > 0$.

Lemma 2.1.2 *Holds for* $\lambda \to \infty$ *equality*

$$t_{2v}(\varphi) = t_0 + 3(\alpha\lambda)^{-1}(\ln \lambda)(1 + o(1)). \tag{2.1.7}$$

For proof, it suffices to note that for $t > t_0$ Eq. (2.1.1) has the form:

$$\dot{u} = \lambda(\alpha + o(1))u + v(t).$$

Its solution is approximately

$$u_v(t, \varphi) = \exp[\lambda\alpha(t - t_0)]u_v(t_0, \varphi) + \exp[\lambda\alpha(t - t_0)] \int_0^{t-t_0} \exp[-\lambda\alpha\tau]v(\tau + t_0)\mathrm{d}\tau,$$

where $u_v(t_0, \varphi)$ is exponentially small. Neglecting the first term and using the Laplace approximation for the integral, we obtain:

$$u_v(t, \varphi) \approx \exp[\lambda\alpha(t - t_0)]\ddot{v}(t_0)/(\lambda\alpha)^3.$$

Hence and from equation $u_v(t, \varphi) = \gamma$ follows formula (2.1.7).

Thus, according to (2.1.7), even short-term and relatively low external action on the area $(m + T_1 + 1, t_2(\varphi))$ can dramatically change the behaviour of the solutions (compared with $u(t, \varphi)$): The mechanism relocating for $u_v(t, \varphi)$ to the interval $[t_0, t_0 + m + T_1]$ almost instantly "starts" the values of $u(t, \varphi)$ from the interval $[0, m + T_1]$.

The above-mentioned mechanism leads to an important conclusion: Periodic with period $T_0 \in (m + T_1 + 1, t_2(\varphi))$, external action imposes its period on the solutions of (2.1.1). In this case, the leading terms of all but one of the main characteristics of the asymptotic expansions of $u(t, \varphi)$ and $u_v(t, \varphi)$ are the same. The only difference lies in the time of the slow exponential growth of these functions after passing through a minimum. For $u(t, \varphi)$, this time is as close as $\lambda \to \infty$ is to $t_2\ (\varphi) - (m + T_1 + 1)$. In turn, for $u_v(t, \varphi)$ this is determined by external action $v(t)$. Let, for example, $v(t)$ periodic pulse be a function with the period $T_0 \in (m + T_1 + 1, t_2(\varphi))$ given for $t \in [0, T_0]$ by the relations:

$$v(t) = \begin{cases} \psi_0(t) > 0, & t \in (0, t^0) \\ 0, & t \in (t^0, T_0) \end{cases}, \tag{2.1.8}$$

where $0 < t^0 < m + T_1$. Then the mentioned period of time is close to $T_0 - (m + T_1)$.

The described phenomenon of imposing frequency of impulsation with the help of an external stimulus is well known in physiology (Livanov 1972). For the visual cortex, it is actively being studied, for example, by Singer et al. (1975, 1976) who —by the method of probing electrodes—in particular found that periodic flashes of light impose their frequency on biopotentials of the cortex.

Because according to current views the columns of the visual cortex are formed by the neuron-detectors (Hubel and Wiesel 1977), it is necessary to make the following remark. As already mentioned, for neurons as detectors, the spike is a response to an external and sufficiently strong action. Within the framework of our model, this is possible if for Eq. (1.5.7) the conditions of Theorem 1.6.3 are met or if Eq. (1.5.7) has a stable equilibrium state. In such a situation, strong $(v(t) = \lambda\omega(t))$ external periodic action, generally speaking, will impose its frequency on the solution of Eq. (2.1.1). The response to action can be complex, e.g., generating structures with ledges. Such multimode responses have been observed in biological experiments.

2.2 Model of Electrical Synapse

In physiological studies on the giant axons of annelids and crabs, it is has been shown that there are synapses with electrical transfer of excitation (see Pappas and Waxman 1973; Eckert et al. 1991; Green et al. 1993). The most important criterion for the identification of neural connection, such as the electrical synapse, is the presence of close contact between membranes of the neurons. The presence of contact, generally speaking, does not mean that the neurons must interact. However, in a number of experiments, previously associated cells were disjoined. As a result, the correlation between the dynamics of their membrane potentials disappeared.

Two alternative hypotheses about the nature of the electric interaction are conceivable: Either the interaction is related to electrical cross-talk, or it is conditioned by conduction currents. Preference is given to the latter assumption (Nicholls et al. 2003). In experiments with dyes, it was found that in the contact zone, the intracellular substance of one neuron is able to diffuse into another neuron. Thus, the channels have been found to be relating to the contents of the cells with which it is in contact. At the same time, it was found that intercellular fluid is present in the contact gap. According to Plonsi and Barr (1992), two coupled neurons can be thought of simply as two tanks connected by a system of parallel tubes. Tanks and tubes themselves are washed by intercellular fluid. The transport of ions is possible through the walls of the tanks. To effectively take into account the electric interaction, we can add terms depending on the difference of the membrane potentials in balanced equations for the membrane currents.

We consider two identical neurons in contact with each other. Denote the membrane potentials by u_1, u_2. Balanced equations for membrane currents have the form:

$$c\dot{u}_1 = I_{\mathrm{Na}}(u_1) + I_{\mathrm{K}}(u_1) + I_1,$$
$$c\dot{u}_2 = I_{\mathrm{Na}}(u_2) + I_{\mathrm{K}}(u_2) + I_2.$$

Here, $c\dot{u}$ is the current through the capacitance; $I_{\mathrm{Na}}(u)$ and $I_{\mathrm{K}}(u)$ are sodium and potassium currents, respectively; and I_1 and I_2 are currents caused by the difference of the membrane potentials. It would seem that $I_1 = -I_2$; however, as biological data show, in many cases there is no symmetry in the interaction [124, 172, 33].

One can put forward a number of hypotheses about the nature of the dependence of I_1 and I_2 on the membrane potentials. The simplest of them are the ohmic and the semiconductor hypotheses. According to the former, the currents are proportional to the potential difference, i.e., they obey Ohm's law: $I_1 = g_1^*(u_2 - u_1), I_2 = g_2^*(u_1 - u_2)$, where g_1^* and g_2^* are conductivities. According to the latter, the currents occur only if the potential difference is positive, whereas they have a tendency to saturation with the growth of potential difference. For this reason, we can assume that $I_1 = g_1^*\chi\big((u_2 - u_1)/u_p\big), I_2 = g_2^*\chi\big((u_1 - u_2)/u_p\big)$. Here $\chi(u) = 0$ at $u < 0, \chi(u) = u$ at $0 \le u \le 1$ and $\chi(u) = 1$ at $u > 1$. Value u_p is the potential difference from which saturation begins. Semiconducting properties have, for example, electrical synapses in the giant axons of crayfish [124]. However, in general, it is believed that electrical synapses obey Ohm's law.

Balanced equations for membrane currents can be transformed as was performed in Sect. 1.5. As a result, we obtain for ohmic synapses the following system of equations:

$$\dot{u}_1 = \lambda[-1 - f_{\mathrm{Na}}(u_1) + f_{\mathrm{K}}(u_1(t-1))]u_1 + g_1(u_2 - u_1), \tag{2.2.1}$$

$$\dot{u}_2 = \lambda[-1 - f_{\mathrm{Na}}(u_2) + f_{\mathrm{K}}(u_2(t-1))]u_2 + g_2(u_1 - u_2). \tag{2.2.2}$$

In turn, for the semiconductor synapses, this system has the following form:

$$\dot{u}_1 = \lambda[-1 - f_{\mathrm{Na}}(u_1) + f_{\mathrm{K}}(u_1(t-1))]u_1 + g_1\chi\big((u_2 - u_1)/u_p\big), \tag{2.2.3}$$

$$\dot{u}_2 = \lambda[-1 - f_{\mathrm{Na}}(u_2) + f_{\mathrm{K}}(u_2(t-1))]u_2 + g_2\chi\big((u_1 - u_2)/u_p\big). \tag{2.2.4}$$

In these equations $g_1 = g_1^*h/c$ and $g_2 = g_2^*h/c$, the meaning of h and all other notation was explained earlier in Sect. 1.5.

We consider some peculiarities of the electric interaction between the neurons as described by the system of Eqs. (2.2.1) and (2.2.2). In this section, we assume that positive functions $f_{\mathrm{Na}}(u)$ and $f_{\mathrm{K}}(u)$ monotonically and quite rapidly tend to zero at $\lambda \to \infty$. For isolated neurons, the case corresponds to the conditions of Theorem 1.6.1. In determining class S of the initial functions, we can write the number $\gamma = 1$. We associate the start and end of a spike with an intersection by the membrane potential of a unit value with both positive and negative speed. We introduce the class P_r of continuous functions $\psi(s)$ for $s \in [-1, 0]$, for which $0 < \psi(s) \le \exp(-r\lambda)(r > 0)$. These functions are uniformly exponentially small at

$\lambda \to \infty$. Let Eqs. (2.2.1) and (2.2.2) have the initial conditions $u_1 = \varphi(s) \in S$ and $u_2 = \psi(s) \in P_r$. Thus, the first spike of the neuron starts at zero moment. Assume that g_1 and g_2 are independent of λ constants. Then, at $\lambda \to \infty$, the spike of the first neuron begins at the time moment $\xi = O((\ln \lambda)/\lambda)$, i.e., almost instantly. For each of the functions, $u_1(t)$ and $u_2(t)$ are valid asymptotic formulas (1.6.6) and (1.6.9) of Theorem 1.6.1. A new delay of the start of the spike of the second neuron, relative to the first one, is the value $O((\ln \lambda)/\lambda)$.

A completely analogous picture is observed at the electric interaction between neurons, as described by the system of Eqs. (2.2.3) and (2.2.4), if we assume that the value $u_p > 0$ is independent of λ.

Let us discuss another aspect of the electrical interaction model. A neuron is a distributed system. The membrane potential has some effective characteristics. The contact zone can be relatively small. In this case, one can and should consider the coefficients of the conductivities to be small and consistent with the parameter λ. Now let us turn to the system of (2.2.1) and (2.2.2).

Thus, model representations about electric synapses explain their role in the synchronization of neurons. This is consistent with biological facts. Neurophysiologists have considered that "electric conducting is more convenient in cases when it is necessary to synchronize the electrical activity of some nerve cells or to encompass excitation of several cells" (cited in [172], p. 175).

Let $g_1 = d_1 \exp(-\lambda\sigma), g_2 = d_2 \exp(-\lambda\sigma)(\sigma > 0)$ and assume that $u_1 = \varphi(s) \in S$ and $u_2 = \psi(s) \in P_r$. We consider that constant r, allocating the class P_r, satisfies the inequality $r > \sigma$. Denote the start of the second spike of a neuron by ξ. We restrict ourselves to the case when $0 < \sigma < \alpha_1$, where $\alpha_1 = f_K(0) - 1$ [given by formula (1.6.3)], and $\alpha < \alpha_1$ [α is given by formula (1.5.8)]. Because $\lambda \to \infty$ is a valid asymptotic representation, $\xi = \sigma/\alpha_1 + o(1)$. If under the same assumptions we consider the model of electrical synapse, as described by the system of Eqs. (2.2.3) and (2.2.4), then at $\lambda \to \infty$, the moment of the start of a spike of the second neuron is $\xi = \sigma/\alpha + o(1)$.

In such a way, a spike of the second neuron occurs across time, which renders it practically independent of the state in which it was before the action of the first spike of the neuron. According to model representations, the electrical synapse has been proven to be very reliable in signal transmission. The same argument, based on experimental data, is given by J. Eccles [170].

We give an example of numerical study of the system of Eqs. (2.2.1) and (2.2.2). Write $f_{Na}(u) = R_1 \exp(-u^2), f_K(u) = R_2 \exp(-u^2)$, thus concretizing the entrance of the system functions. With such choice as theirs for the equation of a single neuron, the conditions of Theorem 1.6.1 are fulfilled if, of course, $\alpha = R_2 - R_1 - 1 > 0$. Take $R_2 = 2.2, R_1 = 1, \lambda = 3$. Even with this relatively small value of λ, the solutions of the equation of the individual neuron have a pulse structure as shown in Fig. 1.2. We note that the value of the period of the solution is in good agreement with the statement of Theorem 1.6.1. Numerical calculation gives the value of a period of approximately 12, and by Theorem 1.6.1 we obtain 13.2.

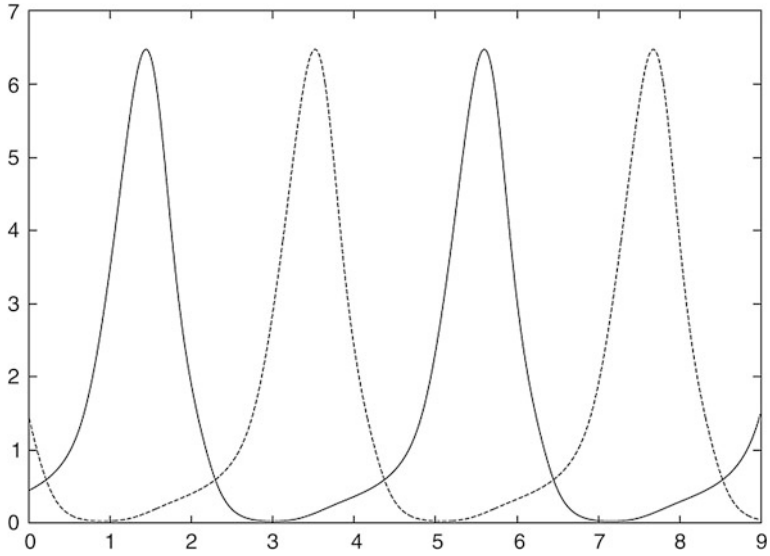

Fig. 2.1 Symmetric mode of system (2.2.1) and (2.2.2) for $G = 0.03, \lambda = 3, R_1 = 1, R_2 = 2.2$. The period of functions $u_1(t), u_2(t)$ is considerably less than that at $G = 0$.

Write (2.2.1) $g_1 = g_2 = G$. At fixed values of the parameters R_1, R_2, λ in (2.2.1) and (2.2.2), we vary the coupling coefficient G. For its small values (G of the order 0.01–0.1), the homogeneous solution $(u_1(t) \equiv u_2(t))$ of systems (2.2.1) and (2.2.2) is unstable, or perhaps the domain of its attraction is small. Solutions with nonoverlapping time pulses are stable formations. Graphs $u_1(t)$ and $u_2(t)$ for $G = 0.03$ are shown in Fig. 2.1. It is easy to see that the period of these functions is much less than that at $G = 0$. The corresponding phase trajectory $(u_1(t), u_2(t))$ on the plane (u_1, u_2) is shown in Fig. 2.2. It is located at the first quadrant, and it is symmetric with respect to its bisector. Later, the existence of such modes will be shown by asymptotic methods.

With an increase of the coefficient G from the symmetric modes, two nonsymmetric modes arise. The phase trajectory of one of them at $G = 0.1$ is shown in Fig. 2.3. In this case, the symmetric mode itself loses stability and possibly disappears. In this situation, the pulse of one neuron precedes for a time the spike of another neuron, i.e., there is a causal relationship between discharges. The period of the nonsymmetric modes is also much smaller than the period of the solution of the equation of the isolated neuron. This is due to two factors that have biological meaning. Let the spike of the first neuron anticipate the spike of the second neuron, which is induced and therefore begins earlier. Simultaneously, the spike of the second neuron falls on the descending part of the spike of the first neuron and increases the minimum of its membrane potential (i.e., it prevents the membrane's strong polarization). As a result, the next spike of the first neuron occurs earlier.

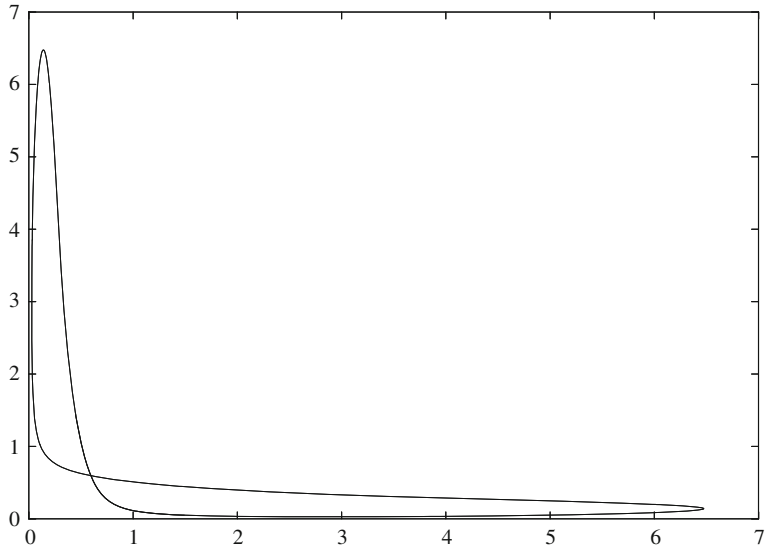

Fig. 2.2 Phase trajectory of the symmetric mode of the system (2.2.1) and (2.2.2) for $G = 0.03, R_1 = 1, R_2 = 2$

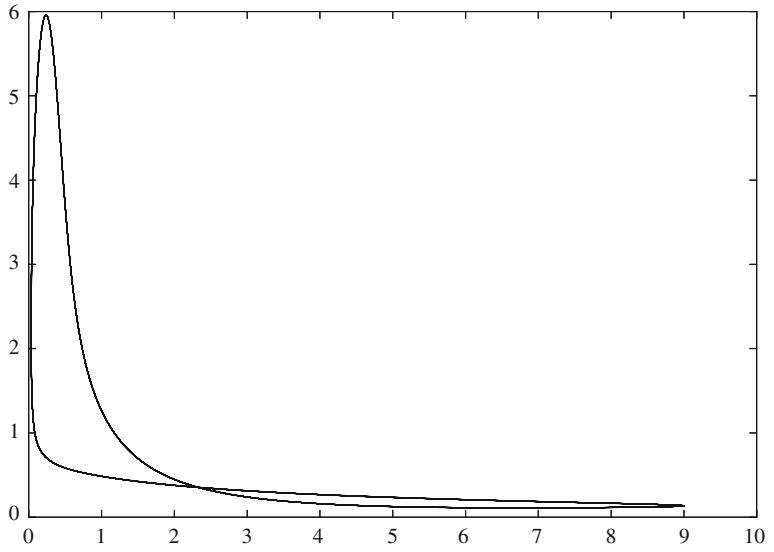

Fig. 2.3 Phase trajectory of the nonsymmetric mode of the system (2.2.1) and (2.2.2) at $G = 0.1(\lambda = 3, f_{Na}(u) = R_1 \exp(-u^2), f_K(u) = R_2 \exp(-u^2)$, where $R_1 = 1, R_2 = 2.2)$

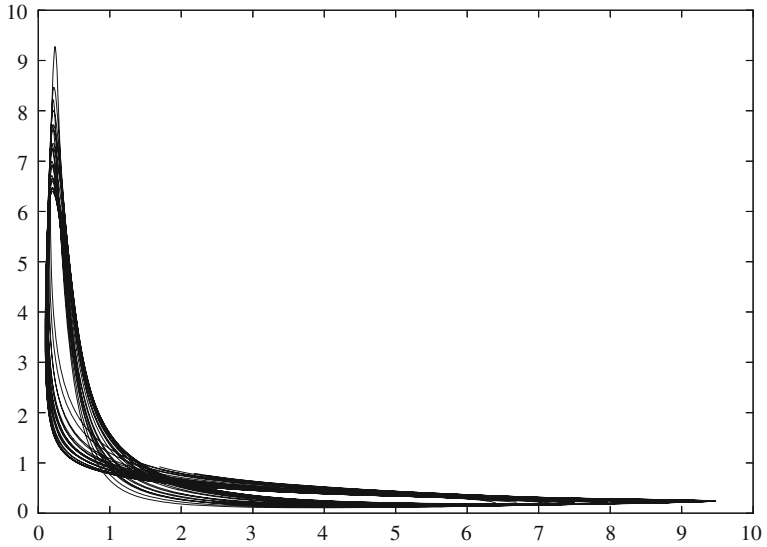

Fig. 2.4 Phase portrait on the plane u_1, u_2 of multi-winding attractor of system (2.2.1) and (2.2.2) at $G = 0.2(\lambda = 3, f_{\mathrm{Na}}(u) = R_1 \exp(-u^2), f_{\mathrm{K}}(u) = R_2 \exp(-u^2)$, where $R_1 = 1, R_2 = 2.2)$

A further increase of G leads to the fact that the causal mode impulses undergo a series of transformations and give rise to a multi-winding attractor, the phase portrait of which is shown for the value $G = 0.2$ in Fig. 2.4. Visually, this attractor can be described as follows. Let the spike of the second neuron immediately follow the spike of the first neuron. At the next cycle of pulses, the time between the maxima peaks will be longer, but after a series of cycles the pulse of the second neuron anticipates the discharge of the first neuron, and thus the cause and effect are exchanged. Then the process goes in the reverse direction. Note that at large values of the parameter $\lambda(\lambda \approx 5)$, a multi-winding attractor can not be detected. Apparently, its existence is the effect of a finite parameter.

The described attractor at $G = 0.2$ coexists with a stable homogeneous mode. The increase of the coefficient G (for example, $G = 0.3$) leads to the attractor, thus becoming part of the transition process to a stable homogeneous mode.

2.3 Model of Chemical Synapse

A classic presentation of the mechanisms of interaction of neurons is associated with processes taking place in the chemical synapses. In contrast to electrical synapses, chemical synapses have a unidirectional effect. As already noted, the neuron is a distributed formation. A spike, relatively speaking, is generated in the

central part of the neuron, i.e., the body (in soma). A spike, born by the neuron and propagating along the axon and its branches, reaches the synapses, i.e., the intervals of contacts with other neurons. A neuron-transmitter is called the "presynaptic transmitter" and the receiver the "postsynaptic transmitter." Synapses are classified according to their location relative to the postsynaptic neuron (see Pappas and Waxman 1973; Eckert et al. 1991; Green et al. 1993). Axosomatic, axodendritic, and axoaxonic synapses are selected. The dendrodendritic synapses are selected separately. The role of the latter is not clear, and they will not be considered here. Synapses also differ in their structure (Kositsyn 1976, 1993): Two main types are "button hole like" and "spinulose." The extension of the end of the axon, which forms a relatively large area of contact, is typical for a button hole like synapse. In the case of a spinulose synapse, the end of the axon looks as if it has been placed on the postsynaptic ledge (these are usually axodendritic synapses), which increases the contact area. This description cannot be considered in detail, but it points to the difficulties of the simulation of chemical signaling. The mechanisms taking place in the synapses are even more complex.

The action of the incoming spike on the presynaptic side starts the entire cascade of electrical and biochemical responses. As a result, chemical mediators called "neurotransmitters," which are enclosed in the vesicles, are liberated (see Pappas and Waxman 1973; Eckert et al. 1991; Green et al. 1993). The most widespread neurotransmitter is acetylcholine. The amount of neurotransmitter, liberated in the presynaptic side in response to a spike, rapidly increases, relatively stabilizes, and then is rapidly destroyed. Vesicles of neurotransmitters cross the synaptic cleft and act on the membrane of a postsynaptic neuron, which starts a new cascade of biochemical responds activating (or inactivating) ion channels. This results in local changes of the membrane potential of a postsynaptic neuron. These deviations influence the dynamics of the membrane potential in general.

Experiments (and their interpretation) are usually performed on biological neurons, the membrane potential of which is at rest u_0. Arising as a result of neurotransmitter action, currents shift the postsynaptical membrane potential to the new level, the so-called "reversal potential" u_{rev} (see Eckert et al. 1991). In experiments, the equilibrium potential u_0 can be controlled. It has long been clear that regardless of the sign $u_0 - u_{\text{rev}}$, the shift of the membrane potential occurs in the direction of u_{rev}, which is completely determined by the mechanism of the neurotransmitter's action.

To avoid misunderstanding, we note once more that we count the potential value of u from the minimum possible value, which is negative and large in absolute value. Thus, at $u > 0$, u indicates a decrease in the polarization of the membrane, and an increase indicates depolarization. If the value is $u_{\text{rev}} < u_0$, then the neurotransmitter's action polarizes the membrane. If $u_{\text{rev}} > u_0$, membrane depolarization, which can cause a spike, takes place. In accordance with this, the neurotransmitter's action is classified as inhibitory or excitatory. It is easy to see that the same mechanism of the neurotransmitter (one and the same u_{rev}) can lead to the inhibition of both neurons as well as the generation of spikes depending on the sign of the difference $u_0 - u_{\text{rev}}$. This has been observed in protozoa. For some neurons, the

neurotransmitter acetylcholineis excitatory, and for others it is inhibitory (see Eckert et al. 1991). One of the nearest tasks is to explain the described phenomena in the context of the model. Before doing so, it is also necessary to cite a series of facts reflecting the peculiarities of neurotransmitter action. It is believed that during a spike, a neurotransmitter has almost no influence on the dynamics of the membrane potential of the postsynaptic neuron. The view of several researchers (Katz 1968; Blum et al. 1988; Eckert et al. 1991; Plonsi and Barr 1992) on the role of the neurotransmitter after a spike is different. Some believe that the presence of the neurotransmitter at a certain time interval after the spike does not influence the dynamics of the potential. Others say that as a result of the action of the neurotransmitter, a new spike of the neuron can begin. The time interval in which the neuron is not sensitive to the action of neurotransmitter is called the "zone of refractoriness." By unanimous opinion, it is considered that at the time of spike generation, the neuron enters a zone of refractoriness. It is possible that the answer to the question of refractoriness of a neuron after a spike depends on the type of neuron involved.

Note that the functioning of the mechanism of neurotransmitter action assumes the presence of delays. However, from biological data (Eccles 1966), these delays are usually not large. It is not difficult to take into account the synaptic delays in the model.

We also note that in the opinion of several researchers (Pappas and Waxman 1973; Eckert et al. 1991), small presynaptic fibers can excite large postsynaptic cells at chemical transmission of the signal. Regarding this connection, even in a model of the simplest situation, the action of one neuron on another through a single synapse is of interest.

Let us turn to the model of synaptic action. Consider two neurons, one of which acts on the second through a single synapse. Let the membrane potential of the postsynaptic neuron be denoted by u and that of the presynaptic one by ω. For simplicity, we assume that the evolution of the membrane potential ω of presynaptic neuron is given as $\lambda \to \infty$ by the asymptotic formulas of Theorem 1.6.1. We neglect the propagation delay of the nerve impulse along the axon. For the neurotransmitter, we could write one more equation, but this would complicate the model. We proceed differently. As already mentioned, the amount of neurotransmitter released from the presynaptic neuron spike on some torus-time interval is relatively stable. We assume that on this interval with the duration T_v the amount of neurotransmitter is constant. This is the usual method of replacing the variable value with some effective value. Represent the amount of the neurotransmitter $V(t)$ in the functional form $V(t) = \ell(\omega(t+s))$, where $s \in [-T_v, 0]$, $\ell(*)$ is a continuous nonlinear functional defined on the space of continuous functions $C[-T_v, 0]$. We describe the functional $\ell(*)$, corresponding to the essence of the problem. Choose the constant ω_0, i.e., the level of potential of the presynaptic neuron, the exceedance of which begins the release of the neurotransmitter. Associate the start and end of a spike of the presynaptic neuron with moments of time when the potential $\omega(t)$ also crosses the value is ω_0, respectively, with positive and negative speed. According to Theorem 1.6.1, the duration of the spike is close as $\lambda \to \infty$ to T_1. From the

viewpoint of asymptotic theory, in this case the number ω_0 is arbitrary, and we can write $\omega_0 = 1$.

Let t_v be the time of the start of a spike of the presynaptic neuron and the effective time of the presence of the neurotransmitter be $T_v > T_1$. Let on the interval $t \in [t_v, t_v + T_*]$, where $T_* > T_v$ is not observed, be a new spike of the presynaptic neuron. The functional $\ell(\omega)$ is written out from simple considerations: For the time moment $t \in [t_v, t_v + T_*]$, its value is equal to V_0 (effective constant) if on the interval $[t - T_v, t]$ there are points t_*, where $\omega(t_*) > 1$ but in the absence of such points the value of functional is $\ell(\omega) = 0$. The specific form of the functional may be different. Let us consider, for example, the following method of presentation. As in Sect. 2.2 of this chapter, introduce the function $\chi(\omega)$ with the following properties: $\chi(\omega) = 0$ as $\omega < 0$, $\chi(\omega) = \omega$ at $0 < \omega < 1$ and $\chi(\omega) = 1$ as $\omega \geq 1$. Denote $\chi_\varepsilon(\omega) = \chi(\omega/\varepsilon)$ by $\chi_\varepsilon(\omega)$, where positive ε is sufficiently small. Note that pointwise $\varepsilon \to 0$, function $\chi_\varepsilon(\omega) \to \theta(\omega)$, where $\theta(\omega)$ is the function of Heaviside. Now we write:

$$\begin{aligned} l(\omega) = V_0 \chi_\varepsilon(\chi_\varepsilon(\omega(t) - 1) + \chi_\varepsilon(\omega(t - (T_1 - \varepsilon_1)) - 1) \\ + \cdots + \chi_\varepsilon(\omega(t - k(T_1 - \varepsilon_1)) - 1) - 0.5), \end{aligned} \tag{2.3.1}$$

where $0 < \varepsilon_1 < T_1$. For $T_v > T_1$, integer k and real ε_1 can be ordered so that $\ell(\omega) = V_0$ at $t \in [t_v + \delta, t_v + T_v - \delta]$ and $\ell(\omega) = 0$, if $t_v + T_v < t < T_*$. Here, δ is an arbitrarily small number. It is sufficient to require $(k+1)T_1 + k\varepsilon_1 = T_v$.

If the effective time of action of the neurotransmitter $T_v < T_1$ (T_1 is asymptotic for the duration of spike), then we can take:

$$\ell(\omega) = V_0 \chi_\varepsilon(\omega(t) - 1)\chi_\varepsilon(1 - \omega(t - T_v)). \tag{2.3.2}$$

In model representations (2.2.1) and (2.2.2), the stabilization of the amount of neurotransmitter released in response to the spike of the presynaptic neuron occurs in time $O(\varepsilon/\lambda)$, i.e., it occurs quickly. One can pass to the limit as $\varepsilon \to 0$. As a result, we obtain the expression for the functional $\ell(\omega)$ by way of the Heaviside function $\Theta(*)$:

$$\begin{aligned} \ell(\omega) = V_0 \Theta(\Theta(\omega(t) - 1) + \Theta(\omega(t - (T_1 - \varepsilon_1)) - 1) \\ + \cdots + \Theta(\omega(t - k(T_1 - \varepsilon_1)) - 1) - 0.5), \end{aligned} \tag{2.3.3}$$

$$\ell(\omega) = V_0 \Theta((\omega(t) - 1)\Theta(1 - \omega(t - T_v)), \tag{2.3.4}$$

respectively, for the cases $T_v > T_1$ and $T_v < T_1$. Below we assume that $V_0 = 1$ and that the presentation

$$V(t) = \ell(\omega) \tag{2.3.5}$$

considers the presence of the neurotransmitter as the indicator of the presence of a mediator. In case of necessity, we introduce normalization factors.

Consider the postsynaptic neuron in the time interval of the effective presence of the neurotransmitter $(V = 1)$. In the balanced equation, we should add the following term taking into account the currents initialized by neurotransmitter:

$$c\dot{u} = I_{\mathrm{Na}} + I_{\mathrm{K}} + I_v, \tag{2.3.6}$$

where $c\dot{u}$ is the capacitive current, I_{Na} is the sodium current, and I_{K} is the potassium current. Finally, I_v is the current flowing through ion channels activated by the neurotransmitter. In full analogy with Sect. 1.5, we write $I_v = \chi^*(u, V)u$. Because the neuron during a spike is refractory to the effects of neurotransmitter, then $\chi^*(u, V) \to 0$ as $u \to \infty$. If there is no neurotransmitter, current I_v is not observed, i.e., $\chi^*(u, 0) = 0$. Following the steps described in Sect. 1.5, change Eq. (2.3.6) of the current balance to the following form:

$$\dot{u} = \lambda[-1 - f_{\mathrm{Na}}(u) + f_{\mathrm{K}}(u(t-1)) + \chi_v(u, V)]u, \tag{2.3.7}$$

where $\chi_v(u, V) = \chi^*(u, V)(h/c(b-a))$. The meaning of all other parameters and functions, as well as their expected properties, are explained in the analysis of Eq. (1.5.7).

Explain within the framework of Eq. (2.3.7) the appearance of the above-mentioned reversal of potential under the neurotransmitter's action. Physiological experiments [172] to study the neurotransmitter's action can be interpreted as follows. Special agents inhibit the potentially dependent (i.e., controlled by the membrane potential of the neuron) sodium and potassium channels, which ensure the functioning of the neuron under normal conditions. At the same time, the neurotransmitter-dependent ion channels are not influenced. In the presence of the neurotransmitter, the membrane potential achieves some stable level u_{rev}. In the situation reflecting the experimental conditions, Eq. (2.3.7) takes the form:

$$\dot{u} = \lambda\chi_v(u, V)u$$

and it must have stable equilibrium state $u_{\mathrm{rev}} > 0$. Then in some neighbourhood of the equilibrium state, $\chi_v = g_v(u_{\mathrm{rev}} - u)$, where g_v is the coefficient of conductivity.

In the absence of a neurotransmitter $(V = 0)$, let Eq. (2.3.7) have a stable equilibrium state u_0, i.e., the membrane potential is at rest. In the presence of the neurotransmitter, Eq. (2.3.7) takes the form:

$$\dot{u} = \lambda[-1 - f_{\mathrm{Na}}(u) + f_{\mathrm{K}}(u(t-1)) + g_v(u_{\mathrm{rev}} - u)]u.$$

If $u_{\mathrm{rev}} < u_0$, then $1 - f_{\mathrm{Na}}(u_0) + f_{\mathrm{K}}(u_0) + g_v(u_{\mathrm{rev}} - u_0) < 0$. As a result, the equilibrium state of this equation shifts toward u_{rev}. As noted, this phenomenon has been observed in biological experiments. If $u_{\mathrm{rev}} > u_0$, then the equilibrium state increases shifting to u_{rev} or disappearing, thus leading to the generation of a spike. This is also consistent with biological data. Thus, the reversal potential is explained in terms of Eq. (2.3.7).

Discuss other aspects of Eq. (2.3.7) of the model neuron, which is under neurotransmitter action. It is necessary to clarify the properties of function $\chi_v(u, V)$. We state here a biological fact: If the membrane is strongly polarized (i.e., u is small), then the neurotransmitter has almost no effect on the neuron. In this connection, we write:

$$\chi_v(u, V) = GV(t)f_v(u)\chi_\varepsilon((u - u_*)/u_*), \tag{2.3.8}$$

where $\chi_\varepsilon(*)$ is the function defined before formula (2.3.1), and u_* is the critical value of the membrane potential such that at $u < u_*$ the neurotransmitter has no effect on the neuron. We consider that the threshold value is exponentially small for $\lambda : u_* = \exp(-\lambda p)$. Here, $0 < p < \alpha_2$, where the number $\alpha_2 = f_{\mathrm{Na}}(0) + 1$ (formula (1.6.3)). Assume that in (2.3.8), the positive function $f_v(u) \to 0$ occurs as $u \to \infty$. One can consider that $f_v(0) = 1$. Coefficient G characterizes the efficiency of the synapse. Call it the "synaptic weight." Below we find out that at $G > 0$, we naturally consider the synapse to be excitatory; if $G < 0$, we consider the synapse is called inhibitory. Note that in (2.3.8), instead of function $\chi_\varepsilon((u - u_*)/u_*)$, in some cases we can take the Heaviside function: $\Theta(u - u_*)$.

Assume that in Eq. (2.3.7), functions $f_{\mathrm{Na}}(u)$ and $f_{\mathrm{K}}(u)$ are positive and quickly become $f_{\mathrm{Na}}(u) \to 0$ and $f_{\mathrm{K}}(u) \to 0$ as $u \to \infty$. For Eq. (2.3.7), in the absence of action $(V = 0)$, the conditions of Theorem 1.6.1 are fulfilled. In the determination of class S of the initial functions, number $\gamma > 0$ is arbitrary. Associate the start and end of a spike with moments of time when the membrane potential crosses the value γ with both positive and negative speed, respectively.

Denote by $u_v(t, \varphi)$ the solution of Eq. (2.3.7) with the initial condition $u_v(s, \varphi) = \varphi(s) \in S$. Let t_v be the beginning of the release of the neurotransmitter, i.e., function $V(t) = 1$ at $t \in [t_v, t_v + T_v]$ and $V(t) = 0$ at $t \notin [t_v, t_v + T_v]$.

Suppose that $t_v \le 0$ and $t_v + T_v > T_1 + A (A > 0)$, i.e., the transmitter appeared later than the spike began and decays later (let significantly A ≥ 1), which should end the spike. Then because $\lambda \to \infty$ uniformly with respect to $\varphi \in S$, the specified time intervals are valid asymptotic formulas:

$$u(t, \varphi) = \exp \lambda\alpha_1(t + o(1)), \quad t \in [\delta, 1 - \delta],$$

$$u(t, \varphi) = \exp \lambda(\alpha_1 - (t - 1) + o(1)), \quad t \in [1 + \delta, T_1 - \delta],$$

coinciding with formulas (1.6.6) and (1.6.7) from Theorem 1.6.1. As expected, in the the interval of spike generation, the neurotransmitter practically does not act on the neuron.

For $T_1 - \delta < t < t_v + T_v$ the situation strongly varies. Let $G > 0$. The asymptotics for solution $u_v(t, \varphi)$ are defined mainly from following equation:

$$\dot{u} = \lambda[-1 - f_{\mathrm{Na}}(u) + Gf_v(u)\chi_\varepsilon((u - u_*)/u_*)]u. \tag{2.3.9}$$

It may happen that this equation has no positive equilibrium states or that there may be no such states. It is easy to see that the latter case occurs, for example, if $G > \alpha_2 = 1 + f_{\mathrm{Na}}(0)$.

First, let us consider the case when there are no positive equilibrium states. Additionally, let $\alpha_2 > G > \alpha_2 - p$. Then, on that part of the interval $t \in [T_1 + \delta, t_v + T_v]$, where $u_v(t, \varphi) < \gamma$, the following formula is valid:

$$u_v(t, \varphi) = u(t, \varphi) \exp(\lambda G(t - T_1 + 0(1))).$$

Here, $u(t, \varphi)$ is the solution of Eq. (1.5.7) for the neuron without external action (the asymptotics of this solution reveal Theorem 1.6.1). Function $u(t, \varphi)$ on the considered interval is exponentially large in comparison with $u(t, \varphi)$. The action should be called "excitatory." The picture is consistent with biological data: In some cases, excitatory synapses after a spike prevent hyperpolarization of the membrane, i.e., they have a residual depolarizing action. Note also that the solution $u(t, \varphi)$ was cross-linked from several exponentials. This corresponds to the ideology of the exponential model of approximation.

Now let $0 < G < \alpha_2 - p$. Introduce the following numbers:

$$T_p^1 = T_1 + p/(\alpha_2 - G), \quad T_p^2 = T_1 + 1 + \alpha_2(1 - p/(\alpha_2 - G))/\alpha.$$

If the time duration of the presence of the neurotransmitter is sufficiently long, then as $\lambda \to \infty$, the asymptotic formulas hold true:

$$u_v(t, \varphi) = \exp[-\lambda(\alpha_2 - G)(t - T_1 + o(1))], \quad t \in \left[T_1 + \delta, T_p^1 - \delta\right],$$

$$u_v(t, \varphi) = \exp\left[-\lambda\left(p + \alpha_2\left(t - T_p^1\right) + o(1)\right)\right], \quad t \in \left[T_p^1 + \delta, T_1 + 1 - \delta\right],$$

$$u_v(t, \varphi) = \exp \lambda \begin{bmatrix} \alpha(t - T_1 - 1) - \\ -p - \alpha_2\left(T_1 + 1 - T_p^1\right) + o(1)) \end{bmatrix}, \quad t \in \left[t_1 + 1 + \delta, T_p^2 - \delta\right].$$

Furthermore, at $T_p^2 + \delta < t < t_v + T_v$, as $u_v(t, \varphi) < \gamma$, holds representation

$$u_v(t, \varphi) = \exp \lambda\left[(\alpha + G)\left(t - T_p^2\right) - p + o(1)\right].$$

As before, the neurotransmitter stimulates action: The values of function $u_v(t, \varphi)$ are exponentially greater as $\lambda \to \infty$ in comparison with $u(t, \varphi)$. However, the ratio $u_v(t, \varphi)/u(t, \varphi)$ has become smaller. This is natural because the synaptic weight of G is less. Note that at moments of time $T_p^1 + o(1)$ and $T_p^2 + o(1)$, solution $u_v(t, \varphi)$ crosses the threshold value $u_* = \exp(-\lambda p)$, respectively, with both negative and positive speed. In the interval of time $t \in [T_p^1 + o(1), \in [T_p^2 + o(1)]$, the neurotransmitter does not influence the membrane potential as shown by the above-mentioned formulas. They do not include the synaptic coefficient G for this

interval. We note the obvious fact that the excitatory action approximates the start of the next spike of the neuron.

Consider now the second case when Eq. (2.3.9) has positive stable equilibrium states. Let u_v be the largest of these. Let now assume that the number γ, which singles out the zone of spike, is larger than u_v.

In the interval of time $t \in [T_1 + \delta, T_1 + 1 - \delta]$, the solution $u_v(t, \varphi)$ of Eq. (2.3.7) is close to the equilibrium state u_v of Eq. (2.3.7). In turn, for $t \in [T_1 + 1 + \delta, T_1 + 2 - \delta]$, the solution $u_v(t, \varphi)$ asymptotically differs little from the solution of the following equation

$$\dot{u} = \lambda[-1 - f_{\mathrm{Na}}(u) + f_{\mathrm{K}}(u_v) + Gf_v(u)]u \tag{2.3.10}$$

with initial condition $u + (T_1 + 1) = u_v$. We assume that the solution $u(t)$ grows without limit when $t \to \infty$. In addition, let number

$$\alpha_v = f_{\mathrm{K}}(u_v) - 1 > 0.$$

Then Eq. (2.3.10) asymptotically integrates as $\lambda \to \infty$ for $t \in [T_1 + 1 + \delta, T_1 + 2 - \delta]$. Such step-by-step actions can easily be continued further. Let us formulate the results of the calculations as follows.

Lemma 2.3.1 *Under these conditions, uniformly with respect to t from the specified periods, and $\lambda \to \infty$ hold the formulas:*

$$u_v(t, \varphi) = u_v + o(1), \quad t \in [T_1 + \delta, T_1 + 1 - \delta],$$
$$u_v(t, \varphi) = u_v \exp[\lambda\alpha_v(t - T_1 - 1 + o(1))], \quad t \in [T_1 + 1 + \delta, T_1 + 2 - \delta],$$
$$u_v(t, \varphi) = u_v \exp[-\lambda(t - T_1 - 2 - \alpha_v + o(1))], \quad t \in [T_1 + 2 + \delta, T_1 + 2 + \alpha_v - \delta],$$
$$u_v(t, \varphi) = u_v + o(1), \quad t \in [T_1 + 2 + \alpha_v + \delta, T_1 + 3 + \alpha_v - \delta].$$

This lemma proves the existence of solutions of a specific type for Eq. (2.3.7), which are the result of sufficiently long and intensive external actions. For this type, it is characteristic that the time interval between the end of one spike and the start of the next spike is close to one. Thus, the pulses follow often and form the burst. Therefore, this type of activity has been named "above bursting." In the burst, the amplitude of the spikes, beginning with the second spike, is asymptotically close to $\exp(\lambda\alpha_v)$. In general, it differs from the amplitude of the first spike, which is close to $\exp(\lambda\alpha_1)$. The duration of the spikes starting from the second spike asymptotically differs little from the number $T_1^v = \alpha_v + 1$, which also differs from the asymptotic duration $T_1 = \alpha_1 + 1$ of the first spike in the burst. For nerve cells, the bursting type of response to stimulation often takes place (Khodorov 1975).

The existence of the bursting type of activity is associated with the length of the refractory period. According to some biologists (Khodorov 1975), a neuron has a short interval of increased excitability after a spike, which leads to the emergence of the burst response. Other investigators (Green et al. 1993) consider that there is no such period of increased excitability. A spike plus a certain time interval after it

form the zone of refractoriness. It is possible that we are talking about different types of neurons. The model of the synapse, in which the refractory period continues after the spike, will be considered here and used in subsequent chapters.

The results formulated previously allow us to understand the model the role of the exciting action. In its absence of an exciting action ($G = 0$), a neuron rarely spontaneously generates spikes. Relatively weak excitatory action only decreases interspike intervals. Strong excitatory action gives rise to burst activity. All of this follows from the above-presented analysis of the model adopted by us, but simultaneously it is fully consistent with biological data.

Thus, the considered model of the neuron has the properties of the neuron as detector, which is the result of functioning, the expression of which is burst activity. Detection proceeds according to the force and the duration of the external action. At the same time, excitation must enroll on quite definite stage of the internal processes of the neuron for it to start functioning. The neuron should capture the spike zone. If a neurotransmitter is released in a moment of time t_v when $u(t_v) < u_*$, then initially the neuron would not feel the presence of the neurotransmitter. Thus, the neuron follows the time of the appearance of the signal.

A burst response to a sufficiently strong excitatory action is observed if the solution $u(t)$ of Eq. (2.3.10) with initial condition $u(T_1 + 1) = u_v$ grows unboundedly with increasing t. If this solution is bounded, then as $\lambda \to \infty$, it tends very rapidly to the equilibrium state of Eq. (2.3.10). The solution $u_v(t, \varphi)$ of Eq. (2.3.7) for $t \in [T_1 + 1 + \delta, T_1 + 2 - \delta]$ will be close to the same equilibrium state. In such a way, we will observe the process of the walking of the membrane potential according to the system of ledges. On each ledge, the membrane potential will be delayed during the time interval close to one.

In the case when the functions $f_{\mathrm{Na}}(u)$ and $f_{\mathrm{K}}(u)$ in Eq. (2.3.7) satisfy the conditions of Theorem 1.6.2, the result of action of the exciting neurotransmitter is, in many respects, analogous to that already described. The interval of spike generation is the zone of refractoriness. All of the above formulas are saved on the interval of time after the spike, and these are valid conclusions to draw from them. Lemma 2.3.1, which describes burst neuron activity observed at sufficiently large value of synaptic weight G, is held. Differences arise during the interval of time in which, in the absence of mediator action, the membrane potential walks the system of ledges. The presence of the neurotransmitter changes the system of steps and can cause a premature spike. Here, the specific type of functions $f_{\mathrm{Na}}(u)$, $f_{\mathrm{K}}(u)$ and $f_v(u)$. are important. The sequence of steps is defined recurrently in the same way as in Theorem 1.6.2, of course taking into account that changes that have appeared on the right side of equation.

Note that simulation of the exciting action of a neurotransmitter occurs when in Eq. (2.3.7) instead of $\chi_\varepsilon((u - u_*)/u_*$, we use the Heaviside function $\Theta(u - u_*)$.

Let us turn to the simulation results of the action of an inhibitory neurotransmitter on the neuron. Let in Eq. (2.3.7) the positive functions $f_{\mathrm{Na}}(u)$ and $f_{\mathrm{K}}(u)$ sufficiently and rapidly tend to zero as $u \to \infty$. Number $\alpha = f_{\mathrm{K}}(0) - f_{\mathrm{Na}}(0) - 1 > 0$. As before, we assume that $f_v(u) > 0, f_v(0) = 1$ and $f_v(u) \to 0$ as $u \to \infty$; however, unlike in the previous equation, the synaptic weight is $G < 0$. Let the

beginning of the release of the neurotransmitter be $t_v < 0$, and let the time of its effective action T_v be sufficiently long. Recall that in Eq. (2.3.7) $V(t) = 1$ at $t \in [t_v, t_v + T_v]$,; otherwise, this function takes the value zero.

In the problem of action of the inhibitory neurotransmitter, we consider a number of different cases. Let, as above, P_r be the class of continuous on the interval $s \in [-1, 0]$ of functions $\psi(s)$, for which $\psi(s) \leq \exp(-\lambda r)$, where $r > 0$, i.e., these functions are uniformly exponentially small as $\lambda \to \infty$. Denote by $u_v(t, \psi)$ the solution of Eq. (2.3.7) with the initial condition $u_v(s, \psi) = \psi(s) \in P_r$.

Lemma 2.3.2 *Let $G < 0$ and $|G| > \alpha$. Then as $\lambda \to \infty$ for all $t \in [0, t_v + T_v]$, we have the inclusion $u_v(t + s, \psi) \in P_r$. If the time of the effective action of neurotransmitter $T_v \to \infty$, then $u_v(t, \psi) \to u_*(1 + \varepsilon\alpha/|G|)$ as $t \to \infty$.*

From a biological point of view, the meaning of Lemma 2.3.2 is clear. If the membrane is sufficiently strongly polarized, the presence of a highly active inhibitory neurotransmitter does not allow the membrane to leave this state. Moreover, if the action of the inhibitory neurotransmitter is continuous, then an equilibrium state of the membrane potential is established. This is caused by a compromise between the neural processes leading to depolarization as well as by external inhibition. Effective braking action, according to Eccles (1971), can be quite continuous.

If $|G| < \alpha$, then sooner or later, even in the presence of the inhibitory neurotransmitter, the membrane of the neuron will be released from the state of strong polarization. This means that with time, the value is $u_v(t, \psi) = O(1)$. Let in Eq. (2.3.7) the functions $f_{\mathrm{Na}}(u)$ and $f_{\mathrm{K}}(u)$ be positive and monotonically tend to zero as $u \to \infty$. For the neuron in the absence of action, the case is covered by Theorem 1.6.1. Introduce number $\alpha_* = \alpha - |G| > 0$ and arbitrary number $\gamma > 0$. Associate the spike with the interval of time where $u_v(t, \psi) > \gamma$. Denote by S_* the set of continuous on the interval $s \in [-1, 0]$ functions $\varphi_*(s)$, for which $\varphi_*(0) = \gamma$ and $\psi(s) \leq \gamma \exp(\lambda\alpha_* s/2)$. Consider the solution $u_v(t, \varphi_*)$ of Eq. (2.3.7) with the initial condition $u_v(s, \varphi_*) = \varphi_*(s) \in S$ (i.e., the spike starts at zero time). Let its end be in a moment of time $t_1\varphi_*$, and $t_2\varphi_*$ be the beginning of the next spike. Denote by $t_p^1(\varphi_*)$ and $t_p^2(\varphi_*)$ the moments of time when the solution $u_v(t, \varphi_*)$ crosses the value $u_* = \exp(-\lambda p)(0 < p < \alpha_2$ with both negative and positive speeds. Consider the time of the effective action of the neurotransmitter T_v to be sufficiently continuous. Write:

$$T_p^1 = T_1 + p/(\alpha_2 + |G|),$$

$$T_p^2 = T_1 + 1 + \alpha_2(1 - p/(\alpha_2 + |G|))/\alpha,$$
$$T_{2v} = T_p^2 + p/(\alpha - |G|).$$

Lemma 2.3.3 *As $\lambda \to \infty$ hold asymptotic equalities:*

$$t_1(\varphi_*) = T_1 + o(1), \quad t_2(\varphi_*) = T_{2v} + o(1), \tag{2.3.11}$$

$$t_p^1(\varphi_*) = T_p^1 + o(1), \quad t_p^2(\varphi_*) = T_p^2 + o(1), \tag{2.3.12}$$

$$u_v(t, \varphi_*) = \exp \lambda \alpha_1 (t + o(1)), \quad t \in [\delta, 1 - \delta], \tag{2.3.13}$$

$$u_v(t, \varphi_*) = \exp \lambda (\alpha_1 - (t-1) + o(1)), \quad t \in [1 + \delta, T_1 - \delta], \tag{2.3.14}$$

$$u_v(t, \varphi_*) = \exp[-\lambda(\alpha_2 + |G|)(t - T_1 + o(1))], \quad t \in [T_1 + \delta, T_p^1 - \delta], \tag{2.3.15}$$

$$u_v(t, \varphi_*) = \exp\left[-\lambda\left(\alpha_2(t - T_p^1) + p + o(1)\right)\right], \quad t \in \left[T_p^1 + \delta, T_1 + 1 - \delta\right], \tag{2.3.16}$$

$$u_v(t, \varphi_*) = \exp \lambda \begin{pmatrix} \alpha(t - T_1 - 1) - \\ -\alpha_2\left(T_1 + 1 - T_p^1\right) - p + o(1) \end{pmatrix}, \quad t \in \left[T_1 + 1 + \delta, T_p^2 - \delta\right], \tag{2.3.17}$$

$$u_v(t, \varphi_*) = \exp \lambda \left[(\alpha - |G|)\left(t - T_p^2\right) - p + o(1))\right], \quad t \in [T_p^2 + \delta, T_{2v} - \delta]. \tag{2.3.18}$$

From formulas (2.3.13) and (2.3.14) in Lemma 2.3.3, it follows that inhibitory action on the part of a spike does not influence the membrane potential. Immediately after the spike, the presence of the the inhibitory neurotransmitter, by virtue of formula (2.3.15), accelerates the process of polarization (i.e., it increases the absolute value of the negative indicator of the exponent). Time interval $t \in \left[t_p^1(\varphi_*), t_p^2(\varphi_*)\right]$, according to formulas (2.3.16) and (2.3.17), is the interval of resistance to the inhibitory action. In view of formula (2.3.18), the process of polarization is sloweron the interval $t \in [T_p^2 + \delta, T_{2v} - \delta]$, i.e., it decreases the indicator of the exponent approximating the solution. As a result of the inhibitory action, the new spike of the neuron begins later than in the absence of a neurotransmitter. At intervals of susceptibility, the result of the neurotransmitter's action agrees with the ideology of the model of exponential approximation.

Let us now turn briefly to individual aspects of the influence of the inhibitory action when the functions $f_{\mathrm{Na}}(u)$ and $f_{\mathrm{K}}(u)$ in Eq. (2.3.7) satisfy the conditions of Theorem 1.6.2. Let in Eq. (2.3.7) $f_v(v) > 0, f_v(0) = 1, G < 0$, and the number $\alpha_* = \alpha - |G| < 0$, i.e., the synaptic weight of the action, not be too large. We assume that the beginning of the neurotransmitter's release is $t_v < 0$ and that the effective time of action is sufficiently large.

Under the conditions of the assumptions made about the functions $f_{\mathrm{Na}}(u), f_{\mathrm{K}}(u), f_v(u)$ and the synaptic coefficient G, equation

$$\dot{v} = \lambda[-1 - f_{\mathrm{Na}}(v) + f_{\mathrm{K}}(0) + Gf_v(v)]v$$

has a positive equilibrium state v_1^* and a domain of attraction that is always adjacent to zero. Here $v^* < v_1$, where v_1 is the first term of the sequence in Theorem 1.6.2. Recall that the solution of Eq. (1.5.7) for the neuron without external action on the time interval $[\delta, 1 - \delta]$ is close to v_1.

In determining the set S_* of initial conditions for the solutions $u_v(t, \varphi_*)$ of Eq. (2.3.7), choose the number $\gamma < v_1^*$. Then, on the interval of time $t \in [\delta, 1 - \delta]$ as $\lambda \to \infty$, the solution is $u_v(t, \varphi_*) = v_1^* + o(1) < u(t, \varphi)$. Thus, the neurotransmitter exhibits inhibitory properties. From step v_1^* begins the process of the walking of the membrane potential on the system ledges, which is enforced by external action. The process of the walk can be completed or not completed by the spike. This depends on the specific type of functions in Eq. (2.3.7). The algorithm of asymptotic construction of the solution $u_v(t, \varphi_*)$ is completely analogous to that used in the construction of the approximation of the solution of Eq. (1.5.7) in the conditions of Theorem 1.6.2.

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