Mathematical modeling of regulatory mechanisms of neuronal functioning and stem cell neurogenesis

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Abstract. The article is dedicated to the mathematical modeling of the regulatory mechanisms of the functioning of nerve cells and the dynamics of the transformation of stem cells into brain cells. Following modes have been revealed according to the results of the investigation: state of calm stem cells, stationary mode, activation of transformation into neuronal cells, self-oscillatory mode of neurogenesis, uncontrolled, chaotic process and a sharp loss of newly formed neurons due to apoptosis - the “black hole” effect. The revealed conditions of disturbances in the regulation of transformation of nerve cells, depending on external and internal factors, will help to develop new strategies for the treatment of diseases of the human central nervous system. Research data can be useful in creating strong artificial intelligence.

Keywords: Mathematical modeling, regulator, functional differential equations, nervous system, self-oscillations, chaos, black hole effect.

1 Introduction

Neurobiology had dogmas about the nervous system, comprising nerve cells devoid of the ability of neurogenesis, about the immobility of the mature brain for a long time. The end of the 19th century was marked by the discovery of new knowledge about the process of transformation of nerve stem cells and the birth of new neurons [1-3]. At the same time, the regulatory mechanisms of neurogenesis are not fully understood. An increase in the rate of propagation of excitation in nerve structures may be evidence in favor of neurogenesis. The modern method of quantitatively describing nervous and cerebral processes originates from the investigations of Hodgkin-Huxley in 1952. They made a very successful attempt at a mathematical analysis of the processes of excitation of nervous tissue. The mathematical model of excitation of Hodgkin-Huxley determines the total current I through the cell membrane through conduction in relation to ions of potassium, sodium and others [5]:

$$
\begin{aligned}
&I = c\frac{du}{dt} + \overline{g}_K n^4 (u - u_k) + \overline{g}_{Na} m^3 h(u - u_{Na}) + g_e (u - u_e);\\
&\frac{dn}{dt} + (\alpha_n + \beta_n) n = \alpha_n;\\
&\frac{dm}{dt} + (\alpha_m + \beta_m) m = \alpha_m;\\
&\frac{dh}{dt} + (\alpha_h + \beta_h) h = \alpha_h,
\end{aligned}
\tag{1}
$$

where V – transmembrane potential; $\overline{g}_K n^4$ – membrane conductivity regarding potassium ions; $\overline{g}_{Na} m^3 h$ – membrane conductivity regarding sodium ions; c – membrane specific capacity; E_k, E_{Na}, E_e – equilibrium potentials for the corresponding ions, measured from the rest potential; $\{a\}$, $\{\beta\}$ – coefficients of differential equations; n, m, h – additional dimensionless variables for a more accurate approximation of experimental data. According to the Hodgkin-Huxley model, based on equations (1), during a nerve impulse, a local response of the system under consideration is formed, due to the flows of salt ions, which open conduction channels for sodium ions. Sodium enters the cell and the membrane potential changes its sign. The permeability to potassium ions slowly increases, the sodium current is turned off, and the inner surface of the membrane is again charged negatively relative to the outer one. Here, the analysis of information processes in the body is carried out mainly with the help of a quantitative study of the mechanism of distribution and transfer of potentials or spikes in nerve cells.

It should be noted that the main tasks of mathematical modeling of processes in the human nervous system are knowledge of the patterns of the structural and functional organization of the nervous system at various levels of the hierarchy, the investigation of the complexity of regulatory mechanisms both within the nervous system and in the interaction of the nervous system with the environment. Revealing the regulatory mechanisms of neurogenesis, the interconnected functioning of human neurons is an urgent task due to the fact that the issues of self-organization, self-regulation and adaptation of the body have not yet been studied in detail to achieve stable functioning in the process of processing external and internal information flows in the learning process. For a more realistic reflection of the regulatory mechanisms of neurogenesis, a complete understanding of intracellular regulation in health and in the case of anomalies, it is important to take into account the temporal relationships in the feedback system, the cooperative nature of the course of biological processes. and an inhibition effect by the final product.

2 Problem statement

The brilliant work of Hodgkin-Huxley, crowned with the Nobel Prize, inspired entire teams and led to the powerful development of quantitative research on cells of the nervous system. Here, the analysis of information processes in the body is carried out mainly with the help of a quantitative study of the mechanism of distribution and transfer of potentials or spikes in nerve cells. In this article, the modeling of the regulatory mechanisms of the interconnected functioning of neurons is based on the concepts of ***OR*** (Oscillator-Regulators) - elements of the regulatory system capable of perceiving and synthesizing signals of a certain nature, and ***ASTA*** (***Active System*** with ***Time Average***) - the signaling environment of the regulatory system, in which the interconnected the activity of the elements is carried out, on the basis of feedback, with some average time (the time elapsed from the moment of formation of signals until the moment of their (or their products) impact on the activity of the elements). ***OR*** together with ***ASTA*** constitute the ***ORASTA*** regulatory system. The geometry of such control systems is dynamic, in which the concept of a fixed point loses its meaning. The functioning of the regulatory mechanisms of such systems, for brevity, is designated by the term "regulation" [5]. As defined by B.N.Hidirov– regulation *is the science that involves the study of interconnected activity of regulatory mechanisms* [5].

The structural and functional unit of the nervous system is a neuron, which is a miniature nervous system. Each neuron consists of a body (inside which there is a nucleus, a molecular genetic system, and regulation and synthesis of proteins necessary for the formation and functioning of memory, thought processes (*P*) ***OR***), an axon hillock (main generator of nerve impulses, trigger (*T*) or mini-***OR***) and dendritic processes diverging from the body in different directions (***ASTA***). The short branches are called dendrites (*D*) and the long branches are called axons (A). A neuron receives signals from other neurons through their branches, which form contacts-synapses on the body of the neuron or on its dendrites. The cell collects, integrates these signals and transmits them along the axon and its branches to other cells or executive organs. The equations of the model of regulatory mechanisms of neuron functioning, built taking into account cooperativity, temporal relationships in ***ORASTA***, taking into account past events, predictive abilities and the possibility, in some cases, of signaling in ***ASTA*** without the participation of ***OR*** have the form:

$$\begin{aligned}
&\frac{dT(t)}{dt} = \frac{a_1 A^2(t-\tau_1)P(t-\tau_1)D(\mathrm{t}-\tau_1)}{1+a_2 A(t-\tau_1)P(t-\tau_1)D(\mathrm{t}-\tau_1)} + a_3 P(t-\tau_1) + a_4 P(t+\tau_1) - b_1 T(t);\\
&\frac{dA(t)}{dt} = a_5 T(t-\tau_2) - b_2 A(t);\\
&\frac{dD(t)}{dt} = d_1 A(t-\tau_3) - b_3 D(t);\\
&\frac{dP(t)}{dt} = \frac{p_0 T^2(t-\tau_4)}{p_1 + T^5(\mathrm{t}-\tau_4)} + p_2 D(t-\tau_4) + p_3 D(t+\tau_4) - b_4 P(t),
\end{aligned} \tag{2}$$

with the initial conditions:

$$\begin{aligned}
&T(t)=\varphi(t), \qquad t\in[-\tau,0)\\
&A(t)=\varphi_1(t), \qquad t\in[-\tau,0)\\
&D(t)=\begin{cases}\varphi_2(t), t\in[-\tau,0)\\ \varphi_2^*(t), t\in(t_k, t_k+\tau]\end{cases}\\
&P(t)=\begin{cases}\varphi_3(t), t\in[-\tau,0)\\ \varphi_3^*(t), t\in(t_k, t_k+\tau]\end{cases}\\
&\tau=\max(\tau_1,...,\tau_4)
\end{aligned} \tag{3}$$

where *P, T, D, A* are variables expressing the activities of the molecular genetic system, axonal hillock, dendrite and axon of the neuron, respectively. All parameters are positive. The developed mathematical model of a neuron will make it possible to analyze the interconnected activity of conjugated neurons in order to identify regulatory mechanisms for a clear organization of the implementation of information processes in brain activity, to determine functional disorders and possible ways to prevent and treat anomalies. The problem of analyzing the dynamics of stem cell neurogenesis is of great interest. To consider methods for solving this problem, we assume the presence of some average value of the feedback implementation time (h). This means that the process of formation of new neuronal cells is carried out for the considered stem cell in the time interval h. Then, to describe the dynamics of the activity of the i-th element of the nervous system, the following equation can be proposed:

$$\frac{dX_i(t)}{dt} = a_i f_i(X_1(t-h), X_2(t-h),...,X_n(t-h)) - b_i X_i(t), \tag{4}$$

where $X_i(t)$ – neural stem cell count, a_i – the rate of transformation of new cells, $f_i(\cdot)$ – feedback function, b_i – neuronal death rate, i=1,2,...,n.

3 Results and Discussions

The algorithm for solving problem (1) is based on the use of a modified method of steps, which is reduced to sequential solution of the problem on time intervals equal to the values of the lag and lead. The developed mathematical model of the regulatory mechanisms of the functioning of a neuron, built taking into account cooperativity, temporal relationships depending on past events and predictive abilities, and a simulation computer model of the interaction of conjugated neurons created on its basis, allows: comparison of the results with experimental facts, the main regularities of the functioning of neural networks in health and disease. Recently, the decisive role of newly formed neurons in the pathology of strokes and other diseases of the human nervous system has been noted. To identify the regulatory mechanisms of brain plasticity, that is, in an increase in the number of cells involved in the structural rearrangement of neural networks, consider an exponential feedback function, then the minimum basic equation for the dynamics of stem cell neurogenesis based on (2) has the following form:

$$\frac{\theta}{h}\frac{dX(t)}{dt} = \alpha X(t-1)e^{-X(t-1)} - X(t). \tag{5}$$

Determination of the laws of solution behavior, analysis of the presence and dynamics of critical points, determination of the nature of their stability allow in advance, without starting quantitative studies, to determine the degree of suitability of the equations for describing the dynamics of transformation. New cells, the nature of the decrease in the number of stem cells due to apoptosis and determination of the ranges of parameter values used in mathematical modeling [6-8]. The presence of a trivial and functional attractor in the equation for the dynamics of neurogenesis makes it possible to use it to describe the states of calm stem cells and activate transformation into neuronal cells. Let us proceed to consider the nature of stability of the equilibrium positions of the functional differential equation of the dynamics of neurogenesis (5). The results of a qualitative analysis show that for $0 \le a \le 1$ we have a unique, trivial equilibrium position. Point $a = 1$ is a bifurcation point and for $a > 1$ we have two (trivial and positive) equilibrium positions (Figure 1).

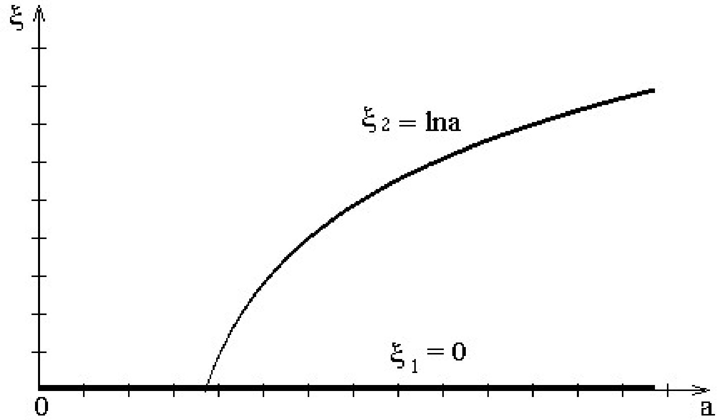

Fig. 1. Bifurcation diagram of equilibrium positions (3)

Linearization with respect to the equilibrium position X leads to a linear differential-difference equation:

$$\frac{\theta}{h}\frac{dX(t)}{dt} = -\alpha(\xi - 1)Z(t-1) - Z(t) \tag{6}$$

(where $Z(t) = X(t) - \xi$ few) which has the following characteristic equation:

$$\frac{\theta}{h}\lambda = -\alpha e^{-\xi}(\xi - 1)e^{-\lambda} - 1 \tag{7}$$

Or:

$$\left(\lambda + \frac{h}{\theta}\right)e^{\lambda} + \frac{ha}{\theta}(\xi - 1)e^{\xi} = 1 \tag{8}$$

A detailed analysis of (8) can be carried out on the basis of the following theorem, due to N.D. Hayes [9]. Hayes's theorem. All roots of the equation:

$$(Z + \alpha)e^{z} + \beta = 0, \tag{9}$$

where α and β are real numbers, have negative real parts if and only if:

$\alpha > -1;$

$\alpha + \beta > 0;$

$\alpha < \eta \sin\eta - \alpha \cos\eta,$

where η – root of the equation $\eta = -\alpha atg\eta$; $0 < \eta < \pi$, if $\alpha \neq 0$ and $\eta = \pi/2$, if $\alpha > 0$. Consider first the trivial equilibrium $\xi = 0$. Then $\alpha = h/\theta$, $\beta = h/\theta$ and the first Hayes condition is satisfied. The second and third conditions are as follows:

$$h/\theta(1-a) > 0$$

$$-h/\theta\, a < \eta \sin\eta - h/\theta \cos\eta$$

where η – root of the equation

$$\eta = -tg\eta\pi, \qquad 0 < \eta < \pi \tag{10}$$

It should be noted that equation (6) has only one root (Figure 2) located at (π/2, π).

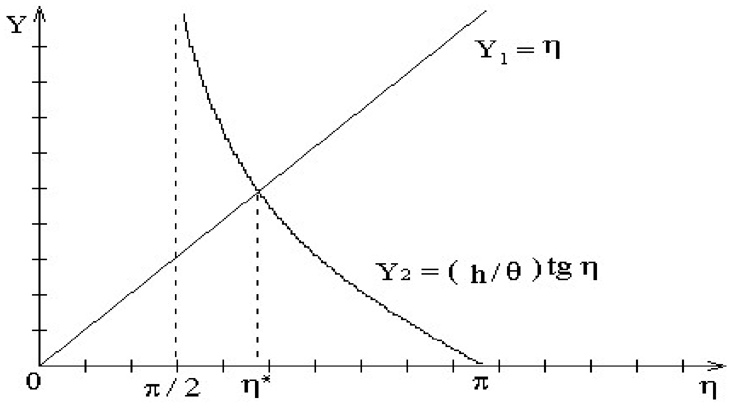

Fig. 2. Existence of a root of equation (6)

Consequently, the right-hand side of the inequality of the third Hayes condition is positive (since $\sin\eta^* > 0, \cos\eta^* < 0$)) and for the trivial equilibrium to be stable, *a <1* must hold.

The emergence of a nontrivial equilibrium position will lead to the loss of stability of the trivial equilibrium position.

Let us proceed to consider the stability condition for a nontrivial equilibrium position. For him, the first two conditions are satisfied, and the third condition is reduced to:

$$\ln a < 1 + (\theta/h)\eta^* \sin\eta^* - \cos\eta^* \tag{11}$$

Consequently, the parametric portrait of equation (3) consists of three regions (Figure 3).

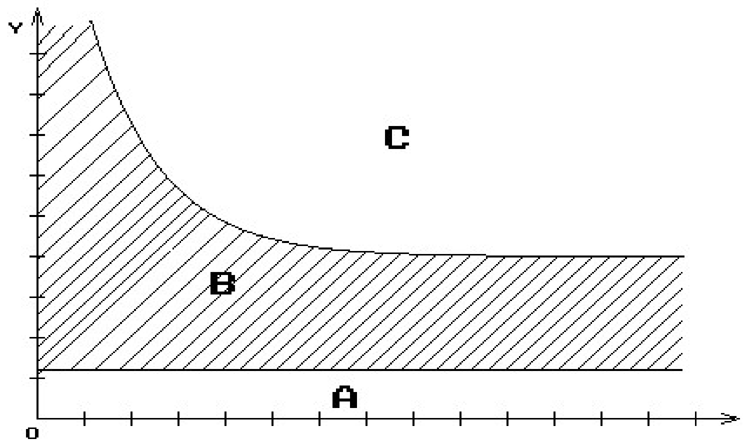

Fig. 3. Parametric portrait of equation (3)

Domain A has a single stable trivial root. Upon transition to B, its stability is lost and the so-called "soft excitation" arises, at which a smooth change (in this case, the emergence of a nontrivial equilibrium position) of the rest position to a stable mode occurs. Upon transition to region C, the nontrivial equilibrium position loses its stability and oscillations arise around it (Figure 4).

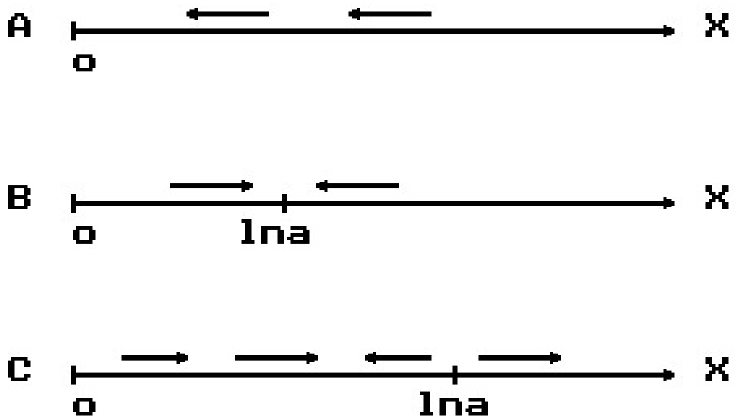

Fig. 4. Typical phase portraits (3), arrows express velocity vectors. A, B, C are the areas of the parametric portrait

The results of targeted computational experiments based on the developed program showed the possibility of analyzing the dynamics of the number of brain cells and revealed the presence of the following modes: state of calm stem cells, stationary mode, activation of transformation into neuronal cells (Figure 5), self-oscillatory mode of neurogenesis (Figure 6), loss self-oscillation mode (Figure 7), an uncontrolled, chaotic process (Figure 8) and a sharp loss of newly formed neurons due to apoptosis — the “black hole” effect (Figure 9).

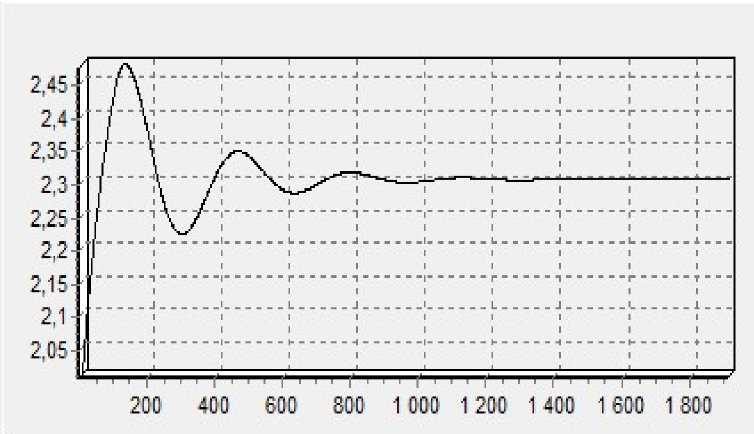

Fig. 5. Formation of a stationary state

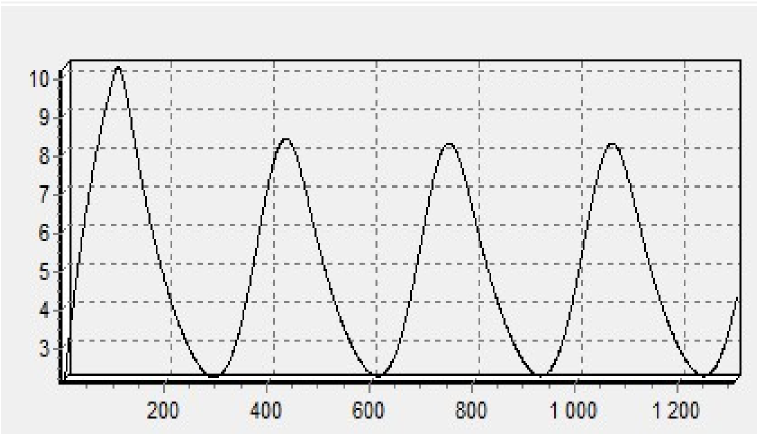

Fig. 6. Fluctuations in the number of newly formed brain cells

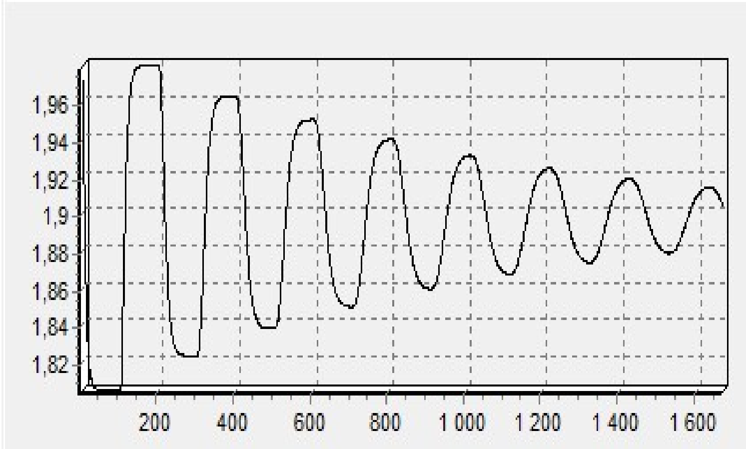

Fig. 7. Loss of self-oscillations

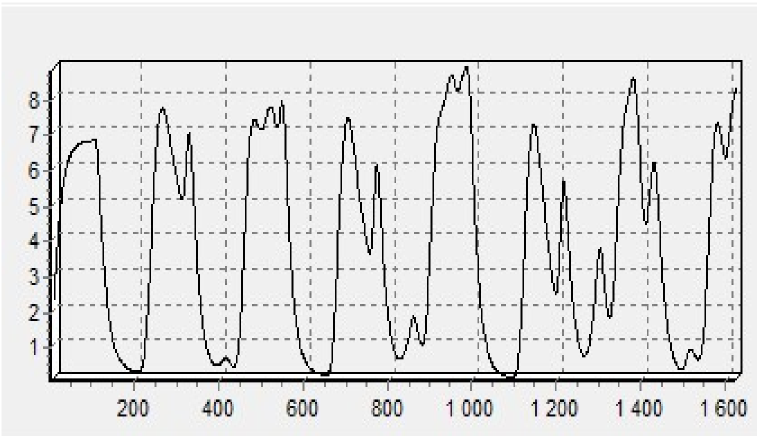

Fig. 8. Uncontrolled, chaotic process

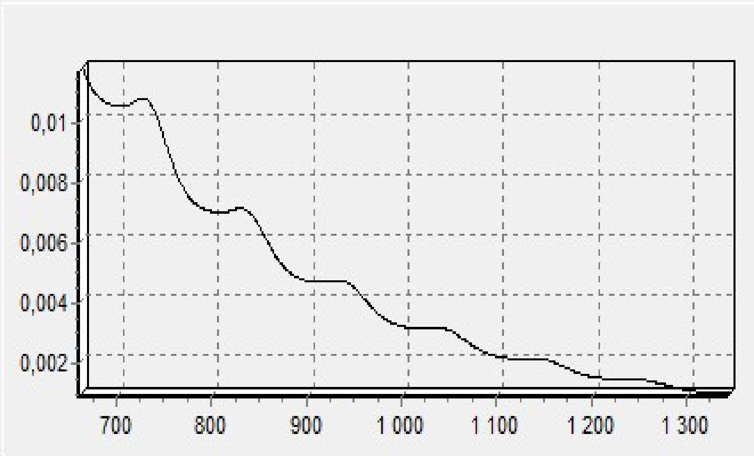

Fig. 9. Apoptosis of newly formed neurons - the “black hole” effect

One of the mechanisms for stabilizing the processes of neurogenesis is programmed cell death, that is, apoptosis. Programmed cell death is biologically reasonable as an effective way to remove non-viable and pathological nerve cells from the body. In the brain cell that has received the death signal, important processes of decision-making about apoptosis take place. This results in either continuation of normal operation or in the launch of the self-destruct program. Modeling the regulation of neurogenesis makes it possible to analyze the behavior of a model based on possible modes of normal behavior or transition to a "black hole" mode.

4 Conclusion

In connection with the successful implementation of the achievements of information technologies in various fields of science and the creation of strong artificial intelligence, the development and application of highly reliable mathematical methods for quantitative research of the abilities of perspective thinking, including brain research. plasticity is relevant [10-11]. The developed mathematical models of regulatory mechanisms of the functioning of neurons and neurogenesis of stem cells make it possible to quickly, in detail, in an environmentally safe way to analyze the functionality of the brain at the accepted level of modeling in various conditions of the external and internal environment, acting factors and biologically active substances. Effective mathematical modeling of the regulatory mechanisms of the interconnected functioning of human neurons under normal conditions and with anomalies requires the determination of the main stages, functioning factors and the most significant parameters of the functioning of the neural network. The results of targeted computational experiments based on the developed program showed the possibility of analyzing the interrelated activity of conjugated neurons in order to identify regulatory mechanisms for the precise organization of the implementation of information processes in the brain activity, to determine functional disorders and possible ways to prevent and treat anomalies. The developed equations of stem cell neurogenesis allow simulating the regulatory mechanisms of the main modes of functioning of the number of brain cells: rest, stationary mode, self-oscillations, irregular oscillations and breakdown of the oscillatory mode - the “black hole” effect. Identification of violations in the regulation of neural cell transformation will help the development of new strategies in the treatment of human nervous diseases.

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