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Mathematical Modeling of Glioma Development Considering Regulatory MicroRNAs

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ABSTRACT: The paper presents the results of mathematical modeling of the regulatory mechanisms of the division of glial cells of the nervous system based on the analysis of mitotic cell division during the sequential implementation of phases G_0, G_1, S, G_2, M, taking into account regulatory microRNAs and the dynamics of the cellular community of nerve glial cells, consisting only of dividing and buffer cells.The results of a series of computational experiments have shown that the developed functional differential equations of the regulatory mechanisms of glial cell division make it possible to consider the principal modes of functioning of nerve cell communities: extinction (death), stationary state, self-oscillations, dynamic chaos (cancerous growths) and a sharp destructive change - the "black hole" effect (metastasis) depending on various external and internal influences.

KEYWORDS: Mathematical modeling, nonlinear dynamics, regulators, living systems, nervous system, functional differential equations, self-oscillations, chaos, the "black hole" effect.

I. INTRODUCTION

Gliomas are highly invasive cancers and the most common (~ 80%) primary tumors in the human central nervous system [1]. The nervous system is comprises two different cells: nerve cells (neurons) and glial cells. Glial cells are also called glia or neuroglia [2]. In the central nervous system, glial cells surround neurons. They maintain homeostasis, produce myelin, and protect neurons. There are several types of glial cells in the central nervous system and peripheral nervous system. These include astrocytes, ependymal cells, microglia, satellite cells, oligodendrocytes, and Schwann cells.

Glia cells make up 80-90% of human brain cells and are the main regulator of the development of the nervous system, its functioning and health. It has long been known that glial cells play an important role in the development, metabolism, and isolation of neurons, but recent research has shown that there is a two-way, not one-way, relationship between astrocytes and neurons. All glial cells should meet three criteria, which do not belong to non-glial cells: they are always physically connected with glial neurons, glia does not form presynaptic structures (although a connection between neuronal synapses and glia is noted), glia and neuron are linearly interconnected. Astrocytes are actively involved in the processing of information in the brain and are one of the important elements in the physiology of the nervous system. An increase in intracellular calcium in astrocytes promotes the formation of glutamate from astrocytes by modulating the presynaptic and postsynaptic activity of neurons through depolarization of the neuronal flow [3].

According to the World Health Organization, malignant gliomas account for over 50% of primary brain tumors. Statistical analysis shows that the incidence of malignant glioma is 5-8 cases per 100,000 people. Despite improved diagnostics, the mortality rate in patients with brain tumors remains high and the treatment outcomes are poor. The average life expectancy of patients with glioblastoma, which is a dangerous glioma with the use of modern methods of treatment, is 14 months after diagnosis, despite surgery, radiation therapy and chemotherapy [4]. In the course of the functioning of the human body in oncopathologies, molecular genetic regulatory mechanisms play a very important role, ensuring the performance of vital functions of organs [5]. Violations of normal molecular genetic regulatory mechanisms can be the cause of oncopathologies, for example, in glioblastoma (a very malignant form of brain cancer), a 100-fold increase in the expression of miR-21 miRNA was observed [5-6]. Despite a huge number of works on the analysis of the patterns of vital activity of the systems of the human body in oncopathologies, the main mechanisms of the onset and course of cancer diseases, the mechanism of microRNA action at the molecular genetic level are still not

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clear [5-9]. Disclosure of the regulatory mechanisms of microRNA action will significantly help to determine the mechanisms of formation and development of pathological conditions in cancer. The development and implementation of information technologies in medicine, which makes it possible to improve the methods of early diagnosis, planning treatment processes for brain tumors, the lack of generally accepted methods for quantitative research of the regulatory mechanisms of the onset and development of tumor pathologies determines the relevance of research to identify new regulatory mechanisms for the onset of tumor processes in the central the human nervous system.

II. RELATED WORK

Mathematical modeling is the most powerful and universal theoretical method in biology and medicine. Existing models, which do not take into account temporal relationships, cooperativity of processes and feedback, have shortcomings and cannot be called universal models to describe the functioning of glial systems in norm and pathology.

Glial ensembles have oscillatory activity. When modeling on the basis of functional-differential equations of lagged type, the modeled system has an innate tendency to the presence of oscillatory mode of solutions.

III. MATERIALS AND METHODS

The development of effective quantitative methods for the analysis of the emergence and development of malignant neoplasms of the nervous system, allowing early diagnosis, the choice of possible preventive and therapeutic measures, involves the creation of model and software support for quantitative studies of the mechanisms of the emergence and development of cancer at the molecular genetic and cellular levels of organization. The importance of the role of genetic processes and fission disorders in the emergence and development of cancerous neoplasms can be considered generally recognized. The process of division and reproduction of eukaryotic cells (mitosis) comprises four phases: prophase, metaphase, anaphase and telophase. Before mitosis, the cell goes through a phase of preparation (interphase) for division. Mitosis and the period of cell preparation for division forms the mitotic cycle. Below is a brief description of the steps in the cycle. Interphase comprises three phases: presynthetic or postmitotic - G_1, synthetic - S, postsynthetic or premitotic - G_2. During the interphase process, DNA, protein and ATP are synthesized. As a result, the amount of DNA in chromosomes doubles. This process is called replication.

Glial cells create a unique microenvironment for neurons, this creates conditions for the generation and transmission of nerve impulses. Glial cells keep the ability to divide. The regulation of the functional state of the glial cell, which performs mitotic division, can be expressed by the following equations:

$$
\begin{aligned}
&\frac{dC_i(t)}{dt} = \frac{\varepsilon\varepsilon_i a_i D(t) Mir(t-\tau)}{1+\sum_{j=1}^{3} d_{ij} R_j(t-\tau_2) Mir(t-\tau)} - \frac{T+T_{C_i}}{TT_{C_i}}(\ln 2) C_i(t);\\
&\frac{dX_i(t)}{dt} = \nu_i C_i(t-\tau_1) - \frac{T+T_{C_i}}{TT_{C_i}}(\ln 2) X_i(t);\\
&\frac{dMir(t)}{dt} = kP_r(t) C_r(t) Mir(t-\tau);\\
&\frac{dP_1(t)}{dt} = g_1 X_1(t) - \frac{T+T_{X_i}}{TT_{X_i}}(\ln 2) P_1(t);\\
&\frac{dP_r(t)}{dt} = g_r(t) X_r(t) - \frac{T+T_{X_r}}{TT_{X_r}}(\ln 2) P_r(t);\\
&\frac{dP_m(t)}{dt} = g_m X_m(t) - \frac{T+T_{X_m}}{TT_{X_m}}(\ln 2) D(t) P_m(t);\\
&\frac{dR_1(t)}{dt} = g_1 X_1(t) - h_1(R_1(t) - R_e(t-\tau_3));
\end{aligned}
\qquad (1)
$$

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$$\frac{dR_m(t)}{dt} = g_m X_m(t) - \frac{T + T_{X_m}}{TT_{X_m}}(\ln 2)R_m(t);$$

$$\frac{dR_e(t)}{dt} = h_1(R_1(t) - R_e(t)) - \frac{T + T_{X_e}}{TT_{X_t}}(\ln 2)R_e(t);$$

$$\frac{dD(t)}{dt} = k_D(1-\varepsilon)(2D_0 - D(t))t_s;$$

$$\varepsilon = \begin{cases} 0 & in\ \ S\ \ and\ \ M\ \ \text{periods;} \\ 1 & \text{in the rest;} \end{cases} \qquad \varepsilon_1 = \begin{cases} 0 & \text{at} \quad R_m(t) > A_1; \\ 1 & \text{at} \quad R_m(t) \le A_1; \end{cases}$$

$$\varepsilon_r = \begin{cases} 0 & \text{at} \quad R_1(t) > A_r; \\ 1 & \text{at} \quad R_1(t) \le A_r; \end{cases} \qquad \varepsilon_m = \begin{cases} 0 & \text{at} \quad R_1(t) > A_m; \\ 1 & \text{at} \quad R_1(t) \le A_{1m}. \end{cases}$$

Index $i = 1, r, m$ values correspond to functional, plastic and mitotic polyoperons; $C_i(t)$, $X_i(t)$, $P_i(t)$, $R_i(t)$, $Mir(t)$ are i-RNA concentration indicators, primary groups of proteins, protein-enzymes, repressors and microRNA, respectively; $R_e(t)$ is a concentration of the repressor in the external environment; T_Z is a half-life of a substance of Z; τ, τ_1, τ_2 are timing parameters; t, t_S, T are the current time, the time counted from beginning of *S*-period and duration of mitosis in general; *D(t)* is a amount of DNA; D_0 is premitotic amount of DNA; $\varepsilon, \varepsilon_i$ are binary parameters characterizing the state of the cell during the division period; all coefficients are positive constants.

The clear organization of structural and functional processes in the body presupposes the existence of regulatory mechanisms for the proliferation of glial cells. In this case, the temporal relationships existing in the feedback loop of the system of regulation of the body's nerve cells are of great importance. The number of divisions directly depends on the number of cells capable of division and on the total amount of incoming nutrients. Lack of nutrient intake is a limiting mechanism for cell division. The limiting factor of cell proliferation, in addition to the level of nutrients, may be the total number of cells capable of reproduction. Let us assume that the cellular community of nerve glial cells consists only of dividing (M) and buffer cells (B). B cells grow, can go back to M, or end their life here. Analysis of the features of the functioning of the proliferative pool (M) shows that it is the main regulator of the number of glial cells. In M, the necessary number of cells is born for the normal functioning of the nervous tissue. A deviation from the norm in the number of dividing cells leads to the launch of regulatory mechanisms to eliminate pathologies. For example, if the number of divisions decreases, then regulatory mechanisms at the level of the body through the level of nutrition, biologically active substances activate cell division in M. Consequently, the regulation of the rate of multiplication of glial cells occurs through a feedback system. It should be noted that this feedback stimulates cell division at a low level of the number of dividing cells and inhibits in the opposite case. The functioning of the proliferative pool of glial cells can be described based on the methodology for modeling the regulation of living systems in tumor processes:

$$\frac{dM(t)}{dt} = \frac{a_1 M^n(t-\tau)B^m(t-\tau)}{c + qM^k(t-\tau) + rB^l(t-\tau)} - b_1 M(t);$$

$$\frac{dB(t)}{dt} = a_2 M(t-\tau) - b_2 B(t), \qquad (2)$$

with initial conditions

$$\begin{cases} M(t) = \alpha(t); \ \ t \in [0;\ h], \\ B(t) = \beta(t); \ \ t \in [0;\ h]. \end{cases}$$

where *M(t), B(t)* are quantities expressing the number of dividing and buffer cell groups of glia; a_1 expresses the rate of cell division in M; b_1 is the rate of decrease of dividing cells into the buffer zone скорость; a_2 is the rate of residence of cells in the buffer zone; b_1 is the decreasing rate of buffer cells. τ is the time parameter (average feedback loop time); k, l are the positive constants expressing the degree of repressiveness towards the regulator, n, m are the positive constants, expressing the level of resource supply of the proliferative pool. The values of all coefficients are nonnegative, which provides biologically reasonable – nonnegative solutions to the system of equations (1).

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The equations of mathematical models of the regulatory mechanisms of division of glial cells of the nervous system and the dynamics of the cellular community of nerve glial cells at the molecular-genetic, cellular levels of organization are nonlinear functional differential equations with a lagging argument. Computer studies make it possible to quickly assess the general pattern, characteristic features and basic modes of decision behavior. They allow one to obtain approximate solutions of nonlinear functional differential equations of models of regulatory mechanisms of division of glial cells of the nervous system and the dynamics of the cellular community of nerve glial cells, to evaluate the behavior of irregular solutions and the level of their "chaos", to analyze the patterns of functioning of glial cells by means of "computational experiments" of numerical methods and their practical application, a technique based on the ideas of separating the finite-dimensional and infinite-dimensional phase components, constructing from finite-dimensional components full analogs of methods known for systems without delay, and interpolation with specified properties of discrete history to take into account implicit methods apply extrapolation with specified properties.

The equations for regulating glial cells can be written as a system of functional differential equations

$$\frac{dX(t)}{dt} = f(X(t), X(t-\tau))$$

with initial conditions

$$X(t) = \phi(t) \quad t \in [0, t_0].$$

Let us assign to $[t_0,\ t_0+\theta]$ a time grid $t_l = t_0 + l\Delta,\ l = 0, 1, ..., N$ with a uniform step $\Delta = \theta / N$, where N is an integer. For simplicity, we will assume that $\tau / \Delta = m$ is an integer.

$$X_{k+1}^{(0)} = X_k + \Delta f(X_k, X(t_k - \tau))$$

$$X_{k+1}^{(\nu+1)} = X_k + \frac{\Delta}{2}\left(f(X_k, X(t_k - \tau)) \right) + f(X_{k+1}^{(\nu)}, X^{(\nu)}(t_{k+1} - \tau))$$

The end of the process of successive approximations occurs when the required absolute accuracy of the solution is reached ε

$$\left| X_{k+1}^{(\nu+1)} - X_{k+1}^{(\nu)} \right| < \varepsilon$$

The method converges if

$$\max_{1 \le l \le N} \left\| X_l - X(t_l) \right\| \to 0 \quad \text{при} \quad N \to \infty.$$

Mathematical models of the regulatory mechanisms of glial cell division (1) and the dynamics of the cellular community of nerve cells (2) have been implemented on PC (Delphi 7). The block diagram of the corresponding computer model (1) is shown in Figure 1. In the model, after entering the values of the coefficients of the equations and initial conditions, the current state of the cell is determined by the amount of DNA, the values of ε_n and ε_m. Next, the new values of the variables are calculated and the completion of the individual stages of division is determined ($G_0 \to G_1 \to S \to G_2 \to M$).

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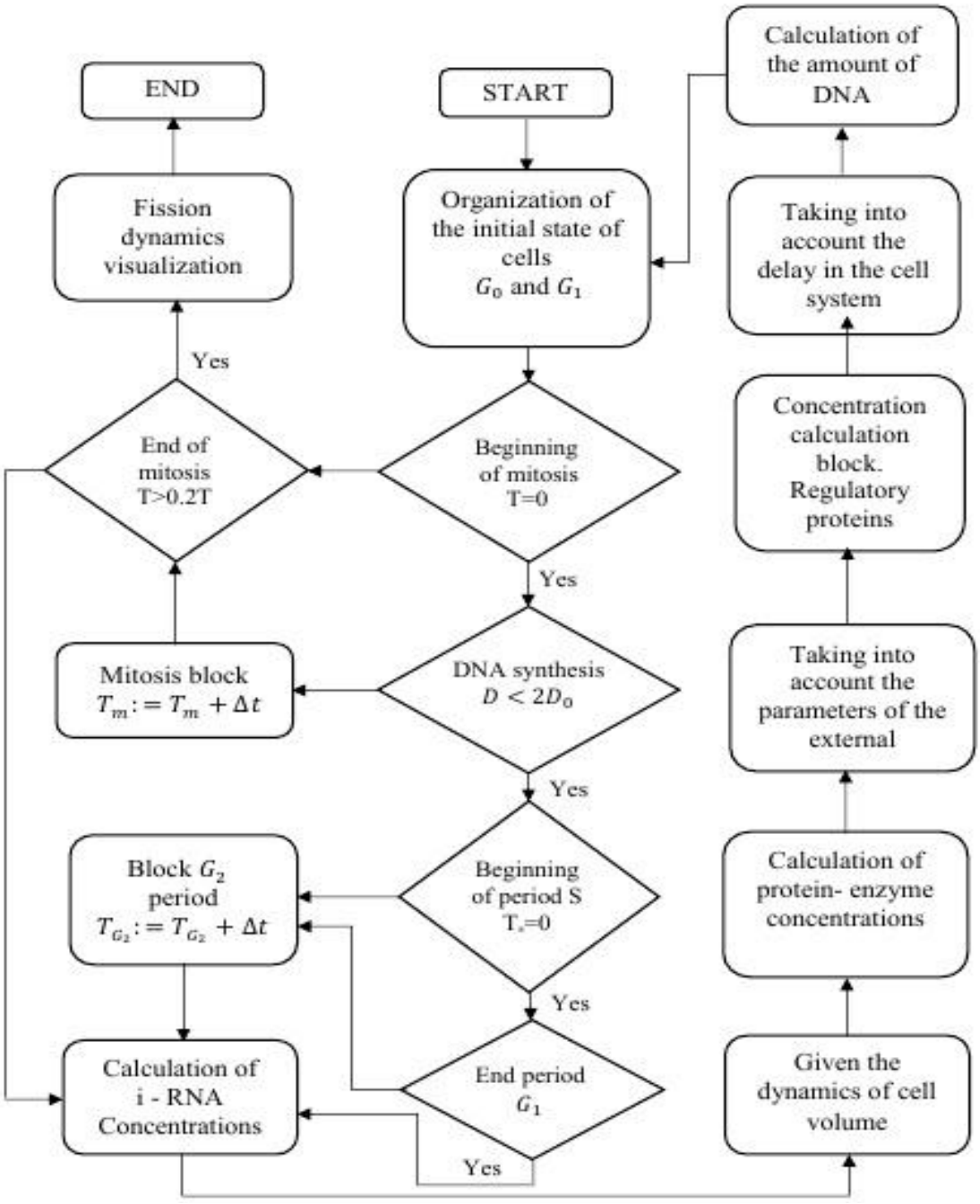

Figure 1: Block diagram of a computer model of glial cell division.

This mathematical model makes it possible to understand the regulatory mechanisms of the transition of an uncontrolled process of cell division to another stable state, to a cancerous tumor of the cells of the central nervous system. Detection of the corresponding violations of the mitotic cycle, changes in the duration of the phases of transitions $G_0 \rightarrow G_1 \rightarrow S \rightarrow G_2 \rightarrow M$ can be an early diagnostic sign of precancerous processes in the central nervous system.

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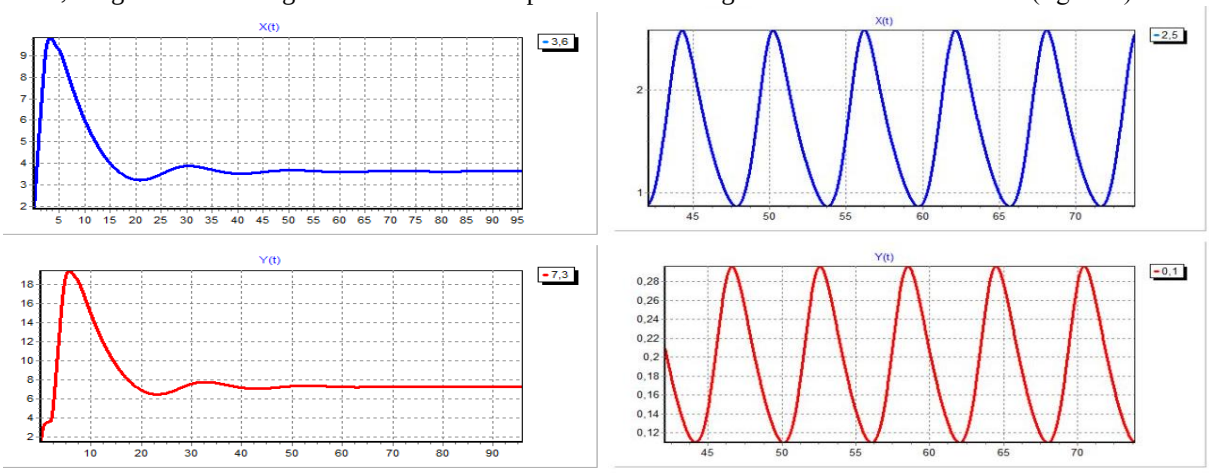
IV. RESULTS AND DISCUSSION

The results of quantitative studies of mathematical models of the regulatory mechanisms of division of glial cells of the nervous system (1) show that models of the system, taking into account temporal relationships, make it possible to effectively investigate the main regularities of the occurrence of glial tumor processes, which are carried out on the basis of disturbances in oscillatory processes [10]. Thus, the beginning process of tumor progression shows that the transformed cell has passed the stages of inhibition of its division and death, and an increase in the concentration of microRNA leads to "escape" from the system of antitumor surveillance. A further consequence of tumor development is the synthesis of specific factors by the tumor itself, which suppress the response to tumor agents and deprive the system of the ability to fight the pathological state of the body. From the standpoint of the genetic instability of tumor cells, a qualitatively new development of the tumor is also assessed, in particular, the activation or inactivation of apoptosis and proliferation (division), as a result of which the biological progression of the tumor and its acquisition of new clinical properties, such as aggressiveness and high malignancy, occurs. The area of irregular fluctuations is characterized by a violation of the body's regulatory system with a consequent deterioration in functional activity. The research results allow us to determine the state of the norm, the range of regular and irregular fluctuations and the critical level of microRNA, to develop effective measures to improve the state of the nervous system as a whole.

The dependence of the change in the number of dividing cells on the number of cells in the buffer zone is due to the ability of buffer cells to replace the cells of the proliferative pool, since under certain circumstances the cells of the buffer zone can enter the division cycle. The values of the variables at the initial moment of time make it possible to set the starting value of the number of the considered cellular community, i.e. use the initial number of glial cells for further modeling. The values of the parameter a_1 can be used to control the rate of cell multiplication in M. These values are important for an adequate analysis of the behavior of the cell population in each specific case. The values of the parameters b_1 andb_2 allow one to take into account the rate of cell loss from the modeled system. The introduction of these parameters makes it possible to assess the rate and degree of cell death under various characteristics of variable transitions (from cell division to a buffer state), as well as to predict the development of the cell community under pathological conditions and changes in external regulatory signals. Thus, for a separate virtual experiment, a real basic premise is created, which makes it possible to obtain numerical data (during the simulation) that correlate with the quantitative characteristics of the distribution of glial cells. An analysis of the characteristic behaviors of solutions (2) using methods for obtaining approximate solutions of functional differential equations shows the presence in the regulation's model of cellular communities of glial cells of modes of a stable stationary state, stable self-oscillatory behavior, irregular functioning and the effect of sharp destructive changes – the "black hole" effect (figure 2).



a)
(a1=60, a2=10, b1=0.2, b2=5)

b)
(a1=40, a2=0.6, b1=0.8, b2=5)

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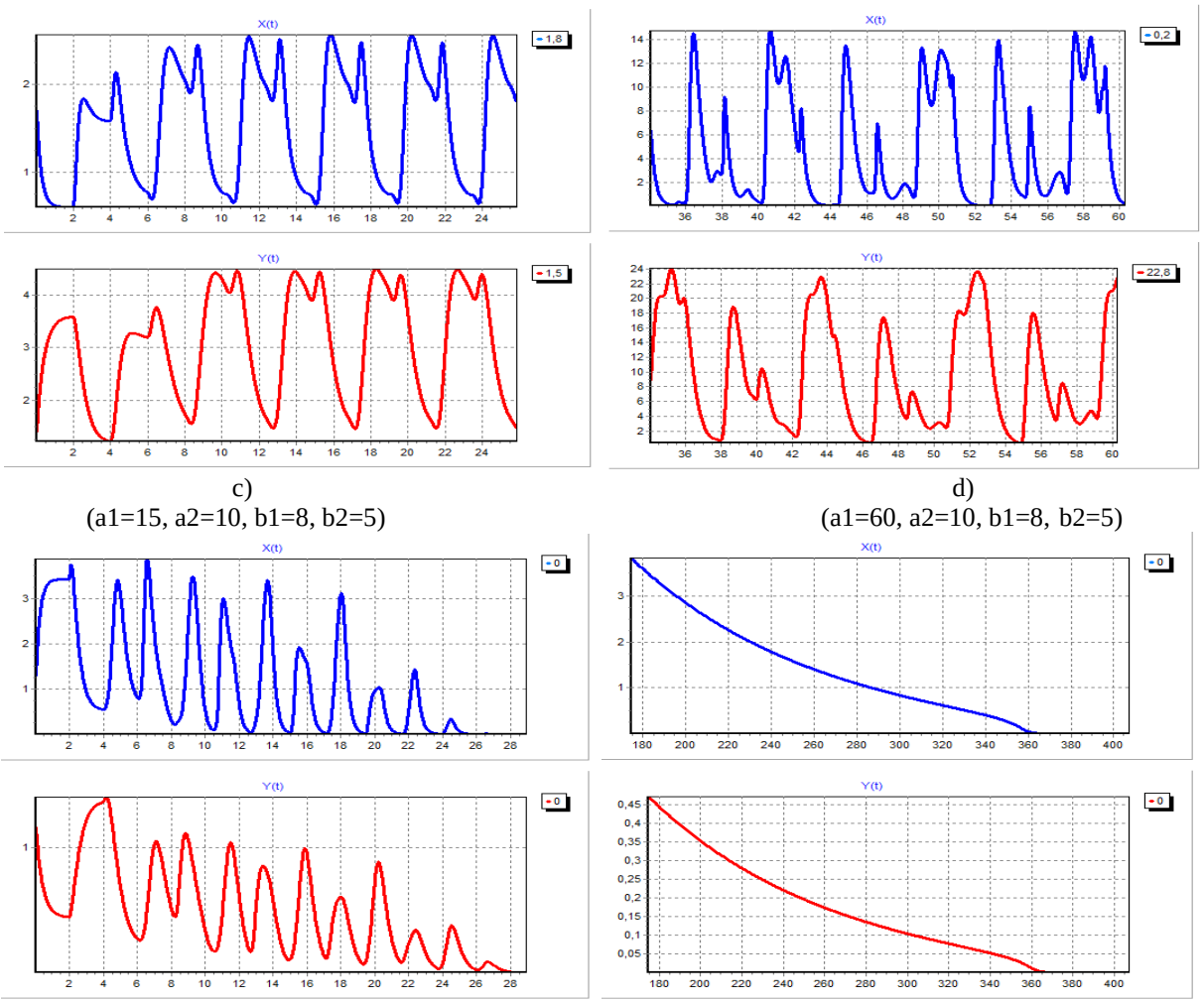

Figure 2: Characteristic phase trajectories (1): a – stationary mode; b – limit cycle; c – violation of regular vibrations, d – irregular oscillations (chaos), e – the "black hole" effect, f – extinction mode.

The areas of normal behavior are generally considered being the area of stable equilibrium and the area of regular fluctuations (stable periodic mode). It can be assumed that the region of the stationary regime is the region of functional activity of cells, and the region of limiting cycles is the region of mitotic activity of cells. The regions of anomalies are the region of dynamic chaos and the region "black hole". The area of dynamic chaos is characterized by irregular fluctuations in the performance of nerve cells and can be identified as a loss of regulation in the system under consideration and the onset of a tumor process. It borders, on the one hand, with the region of limit cycles of the Poincaré type (where the behavior of the system is characterized by bilaterally stable periodic oscillations), and on the other hand, with the region of sharp destructive changes - a "black hole". The region of extinction can be identified with the region of programmed cell death by apoptosis, and the region "black hole" - with cancer metastasis. If external influences are harmful to cells or in internal environments and abnormalities appear in the mechanisms, the cell moves to the region of extinction, where apoptosis occurs. Here, there is a genetically determined, evolutionarily fixed sequence of intracellular processes of dismantling nuclear and cytoplasmic structures to elementary blocks suitable for plastic and functional systems of neighboring normal cells. Uncontrolled multiplication (malignant neoplasm) and a sharp destructive change in regulating cell communities of glial cells of the nervous system (metastasis can identify irregular behavior and the "black hole" effect).

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Thus, it is especially important to study the structural features of the area of regular behavior, the degree of chaos and the area of sharp destructive changes due to the relevance of early diagnosis of cancer.

V. CONCLUSION

Thus, the existing biological experimental data and theoretical provisions on the structural and functional organization of cellular communities of glia make it possible to construct mathematical models for quantitative analysis of regulating the number of glia in normal conditions and in case of anomalies based on the method of modeling the regulatory mechanisms of living systems and equations for regulating cellular communities. An extremely important role in the functioning of the human body in normal conditions and in cancer diseases belongs to molecular-genetic regulatory mechanisms that ensure the fulfillment of vital functions of organs: they maintain stable states in the body, characterized by constant concentrations of substances; provide periodic undamped fluctuations in the concentration of certain groups of substances; control irreversible processes: development, growth, differentiation, apoptosis. When investigating the pathological states of glial cells, especially malignant cells, prognostic data on the proliferative behavior of cells are very important, especially when external signals change due to therapeutic actions. Quantitative studies show the presence of extinction modes, stable stationary state, stable self-oscillatory behavior, irregular functioning and the effect of abrupt destructive changes - the “black hole” effect in the regulator of glial cell communities.

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