Dynamics of Regulatory Mechanisms of the Human Organism on the Basic Hierarchical Levels of the Organization

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Abstract. Based on the methodology of the regulatory, the main methods of mathematical modeling of the regulatory mechanisms of living systems at the molecular-genetic, cellular and organ-tissue levels are presented. The constructed mathematical models of the regulatory of the cardiovascular system, the liver and the thyroid gland are presented in the form of systems of functional-differential equations with delay arguments, and also results of qualitative analysis for these models are obtained. Computer models have been developed for quantitative analysis and assessment of the state of biological systems. The most common regularities in the functioning of systems and various behavioral regimes, such as stationary, self-oscillating, dynamic chaos and a "black hole" are revealed.

1. Introduction

Using methods of mathematical modeling and computational experiment in the development of scientifically based on methods of controlling the functional activity of living systems in norm and in anomalies provides: objective, operational, environmentally friendly and resource-saving information technology for quantitative analysis of the patterns of living systems functions; identification of effective influence points in the system of regulatorika and development of ways for optimally manage the functional activity of biosystems in order to achieve pre-defined regimes of their vital activity. It should be noted that regulatorika is the science that involves the study of interconnected activity of regulatory mechanisms based on the ORASTA concept which consists of the operator-regulator OR (capable to accept, recycle and transfer signals) and ASTA (active system with time average, carrying out a feedback loop in system for finite time) [1].

The development of a system for analyzing the state of the human body, taking into account the basic levels of organization (molecular genetic, cellular, organ-tissue), involves the creation of appropriate biological and mathematical models of the regulator of organs and tissues, and the organization of a clinical sequence of data (Figure 1). In this paper, the most basic regulatory mechanisms of the cardiovascular system, liver and thyroid gland are adopted as objects.

2. Molecular-genetic level

Molecular genetic mechanisms are of paramount importance for the vital activity of the cell and should form the basis of any theory describing its structural and functional organization in dynamics. The analysis of mathematical models of genetic systems shows insufficient consideration of the temporal and cooperative properties of molecular genetic processes in them. The analysis of the peculiarities of the space-time organization of the processes of transcription, translation and realization of genetic information, and the possible way of taking them into account in model studies, make it possible to attempt to develop a model of molecular genetic mechanisms with allowance for temporal
relationships in the system of regulation of intracellular processes. Let's have a set of universal, general and specific genes that functions in a certain environment (an organoid containing its own genetic system, cell, tissue, organ or organism as a whole). Such a set of genes can be called functioning genes of the considered biosystem. In the future, we will mainly use the term genes in relation to such, functioning genes. Effective functioning of the functioning genes requires environment conditions favorable for their activity (pH, energy, material resources, etc.), created by protein structures, which, in turn, are products of genetic systems. In order to analyze the regulation of molecular genetic processes, all acting factors at the DNA level can be divided into repressor and inductive effects. The first is repressor proteins, and the second is effectors acting at the level of transcription, nucleic acid precursors, nucleotides, polymerases, tRNA, etc. In the analysis of specific molecular genetic systems, the activity of a certain number of genes can be considered to be at a stationary level and to take into account the dynamics of activity of only those genes whose interrelated activity by the feedback system ensures the implementation of the process or phenomenon in the biosystem. Such a set of genes together with the environment providing their activity on the basis of the feedback principle can be called a molecular genetic system (MGS). In relation to such systems, model studies based on the methods of analysis of dynamic systems used by researchers in the modeling of gene activity are possible. Equations for the analysis of the functioning laws of the MGS, taking into account all possible subsystems, on the basis of equations B.N. Hidirov [1] have the form

\[
\frac{dX_i(t)}{dt} = A_i^N (X(t-h)) e^{-\sum_{k=1}^{n} \delta_{ik} X_k(t-h_k)} - b_i X_i(t); \quad (1)
\]

where

\[
A_i^N (X(t-h)) = \gamma_{i0} + \sum_{j=1}^{N} \left[ \sum_{k_1,\ldots,k_j=1}^{N} \gamma_{ik_1,\ldots,k_j} \prod_{m=1}^{j} X_{k_m} (t-h_{ik_m}) \right].
\]

\(X_i(t)\) – a quantity that characterizing the amount of the signal corresponding to the \(i\)-th OR at time \(t\); \(h_k\) – time distance from \(k\)-th OR to \(i\)-th OR; \(\gamma_{ik_1,\ldots,k_j}\), \(\delta_{ik}\), \(b_i\) – constants; \(\gamma_k\) – parameter of signal generation (\(i\)-th kind) of the medium; \(i, k_j = 1, 2, \ldots, N\).

As it is well known, the molecular genetic system, during functioning, covers the processes of transcription (copying of the necessary genetic programs from the hereditary apparatus in the form of a nucleic sequence) with the formation of \(i\)-RNA, translation (translation of the nucleic sequence into a chain of amino acids - elements of protein-enzymes) to the form of polypeptides and the formation of protein-enzymes (the main building and functional elements of biosystems).

In studying the interrelated activity of molecular genetic systems of hepatocyte and hepatitis viruses, was considered the following system of equations of Goodwin's type

\[
\frac{dX_i(t)}{dt} = \frac{\alpha_i \prod_{l=1}^{m} X_{l}(t-h)}{1 + \sum_{l=1}^{n} c_{il} X_{l}^{n+m}(t-h) + \sum_{l=1}^{m} c_{2il} Y_{l}^{n+m}(t-h)} - \frac{1}{\tau X_i} X_i(t); \quad (2)
\]

\[
\frac{dY_j(t)}{dt} = \frac{\beta_j \left( \prod_{i=1}^{n} Y_{i}(t-h) \right) \left( \prod_{k=1}^{m} X_{k}(t-h) \right)}{1 + \sum_{p=1}^{n} d_{jp} X_{p}^{n+m}(t-h) + \sum_{p=1}^{m} d_{2jp} Y_{p}^{n+m}(t-h)} - \frac{1}{\tau Y_j} Y_j(t),
\]

where \(X_i(t), Y_j(t)\) – values that characterize the activity of hepatocyte and viral molecular genetic systems at time \(t\); \(h\) – the time radius of the cell (the time necessary for carrying out the feedback of molecular genetic systems); \(\{\alpha, \beta\}\) и \(\{c,d\}\) – non-negative parameters expressing levels of resource
availability and inhibition of the considered systems of genes; \( \{\tau\} \) - "lifespan" of products of gene activity; \( n, m \) - respectively, the number of considered genetic systems of hepatocyte and hepatitis virus; \( i = 1, 2, ..., n \); \( j = 1, 2, ..., m \).

Figure 1. Diagram of the model system for diagnosing the state of the body's diseases

Qualitative analysis for determining the most general laws of solutions and investigating the behavior of the system (2) is complex. This leads to the relevance of the development of model systems of the equations of the regulator of living systems, which are much simplified with the preservation of the most general properties of the behavior of solutions at a qualitative level. Model system of equations of regulatorika of the interrelated activity of genetic systems of hepatocyte and hepatitis viruses for (2) was adopted in the following form

\[
\begin{align*}
\mathcal{E}_1 \frac{dX(t)}{dt} &= \frac{aX^2(t-h)}{1 + X^2(t-h) + cY^2(t-h)} - X(t); \\
\mathcal{E}_2 \frac{dY(t)}{dt} &= \frac{bX(t-h)Y(t-h)}{1 + dX^2(t-h) + Y^2(t-h)} - Y(t);
\end{align*}
\]

where \( X(t), Y(t) \) - values that characterize the activity of molecular genetic systems of hepatocyte and hepatitis B virus, respectively; \( \mathcal{E}_1 = \tau_1 / h, \mathcal{E}_2 = \tau_2 / h \); \( \tau_1, \tau_2 \) - parameters characterizing the "lifespan" of products of molecular genetic systems of hepatocyte and hepatitis viruses; \( h \) - time required for feedback in the considered system; \( a, b \) - constant rates of formation of products of the considered genetic systems; \( c, d \) - parameters expressing the repression degree of molecular genetic systems of hepatocytes and hepatitis viruses; all parameters are positive.

Analysis of the characteristic behavior of the solutions of equations (3) using the mathematical and computer models of the body's regulatorika, methods for qualitative investigation of functional-differential equations shows the presence modes of stable steady state (B), stable self-oscillation behavior (C), irregular functioning (D), and the effect of sudden destructive changes (E) - the "black hole" effect (Figure 2).
Figure 2. The effect of a "black hole" in the system (3)

\[
(\varepsilon_1 = 0.21, \varepsilon_2 = 0.04, a = 4.2, b = 2.45, c = 2.6, d = 0.12 \text{ and } X_0 = 3, Y_0 = 6).
\]

3. Cell level

Modeling of regulatorika of cellular communities leads to the necessity: to identify the laws of their existence and development; a critical analysis of the existing main directions of model studies of cellular communities; revealing the main laws of the unification of cells of multicellular organisms into cellular communities for performing specific functions of the organism; development of model for studies of the dynamics of the number of major cellular groups that components the cellular community; development of a complex of mathematical models of the regulator of the basic cellular functions; software development for computational experiment for analyzing the regulatorika of living systems at the cellular and supra-cellular levels of their organization [2].

Consider the mathematical modeling of the regulatorika of the cellular community of the thyroid follicle. Assuming the presence of two specific functions \( C_1 \) and \( C_2 \), associated with the formation of iodine-containing hormones (thyroxine -T4 and triiodothyronine -T3), we consider one of the possible variants of studying the mechanisms of regulating the number of thyroid follicle cells in separate phases of their vital activity (division – \( M \), growth and development – \( B_1 \), differentiation – \( D \), the performance of specific functions of the formation of hormones – \( C_1, C_2 \), aging – \( B_2 \)) (Figure 3) with the help of functional-differential equations of cellular communities regulatorika [3].

![Figure 3. Scheme of cell transitions in the follicle of the thyroid gland](image)

Let \( X_i(t) (i=1,2,...,6) \) be the quantities characterizing the numbers of fissile, growing, differentiating, performing specific functions and aging follicle cells at time \( t \), respectively. We will compose equations for a quantitative description of changes in the numbers of follicle cells in specific phases of life. The most important, in a functional sense, phase is the fission phase, in which the multiplication of the cells of the follicle occurs. The rate of multiplication of cells, in general, depends
on the number of potentially dividable cells, on substances that contribute to the division (effectors), and on nutrients.

Since follicles with the functions of hormone production, which are useful for the body, were formed during evolution, it is easiest to assume that the number of effectors and the nutrients entering the fission zone depends on the degree of performance of the specific functions by the cellular community, i.e. depends on the number of cells in the C_1 and C_2 phases. On the basis of the regulatorika equations, taking into account the effect of "medium pressure" (inhibition by the final product) and the possibility of the transition of the M phase cells to the growth phase, we can write the following equation

\[ \frac{dX_1(t)}{dt} = a_1 \left( \prod_{k=1}^{4,5} X_k(t-\tau_k) \right) e^{-\sum_{j=1}^{6} \delta_j X_j(t-\tau_j)} + b_1 X_2(t-\tau_1) - a_2 X_1(t), \] (4)

where \( a_1 \) – propagation speed constant; \( b_1, a_2 \) – constant rates of transition of cells of phase M into a phase of growth; \( \delta_i \) – coefficient characterizing the pressure of the medium; \( \tau_i \) – transition time (\( i = 1,2,...,6 \)).

Taking into account cell transitions from one phase of vital activity to another, it is possible to propose, based on (4), the following system of linear functional-differential equations for changing cell numbers in phases B_1, D, C_1, C_2 and B_2:

\[ \frac{dX_2(t)}{dt} = a_3 X_1(t-\tau_1) + b_2 X_3(t-\tau_2) - (b_1 + a_3) X_2(t); \]
\[ \frac{dX_3(t)}{dt} = a_3 X_2(t-\tau_2) + b_3 X_6(t-\tau_6) - (b_2 + a_4 + a_5) X_3(t); \]
\[ \frac{dX_4(t)}{dt} = a_4 X_3(t-\tau_3) - a_6 X_4(t); \]
\[ \frac{dX_5(t)}{dt} = a_5 X_3(t-\tau_3) - a_6 X_5(t); \]
\[ \frac{dX_6(t)}{dt} = a_6 (X_4(t-\tau_5) + X_5(t-\tau_5)) - (a_7 + a_6) X_6(t). \] (5)

Equations (4) and (5) constitute a closed system of functional-differential equations. The created software product, upon startup, organizes the working field of the display (Figure 4) with a chain of dependencies \( \text{M} \rightarrow \text{B}_1 \rightarrow \text{D} \rightarrow \text{C}_1 \rightarrow \text{C}_2 \rightarrow \text{B}_2 \) (from cell division to aging), and it is possible to correct the numerical parameters controlling the speed of signals responsible for both transitions of cells to the following (or previous) stages of differentiation, and for the exit of cells beyond the considered cellular community (cell death).

4. Organic-tissue level

The most basic organs of the body are the brain, lungs, heart, skin, liver, spleen, stomach, intestinal system, kidneys, etc. Blood provides nutrients and oxygen to the organs and tissues of the body. Provision occurs by dividing large arterial vessels into small capillaries. It should be noted the complexity of the processes associated with the movement of blood through arterial and venous vessels, capillaries and tissue spaces. Effective quantitative research in this field requires taking into account the properties of the blood and walls of blood vessels, the laws of blood passage through tissue cells, etc. Occurs that taking into account modern concepts of the main laws of the ongoing processes, simplest, composite models can be models of cardiac activity, blood movement along the vessels and the model of tissue transfer [4].

The following system of equations describes the propagation of wave excitation and the level of activity of the heart parts. The heart rhythm driver is a sinus node that located in the upper corner of
the right atrium. An electrical impulse is generated at the sinus node and transmitted to the right and left atria, which causes the atria of the heart to be excited and contracted. The electrical signal will reach the atroventricular node and through the bundle the His is transmitted to both ventricles and contracted. After the contraction, the relaxation phase begins. All these processes are repeated as a cycle our whole life.

\[ \frac{dx(t)}{dt} = \frac{a_1 \Theta(t-h) \eta(t-h)}{(1 + \sigma_1^2 \Theta^2(t-h))(1 + \sigma_2^2 \eta^2(t-h))} - b_1 x(t) \]

\[ \frac{dy(t)}{dt} = a_2 x(t-h) - b_2 y(t) \]

\[ \frac{dz(t)}{dt} = a_3 x(t-h) - b_3 z(t) \]

\[ \frac{dv(t)}{dt} = \frac{a_4 x(t-h) y(t-h) z(t-h)}{1 + \sigma_3^2 x^2(t-h) y^2(t-h) z^2(t-h)} - b_4 v(t) \]

\[ \frac{d\Theta(t)}{dt} = a_5 v(t-h) - b_5 \Theta(t) \]

\[ \frac{d\eta(t)}{dt} = a_6 v(t-h) - b_6 \eta(t) \]

where \( x(t), y(t), z(t), v(t), \Theta(t), \eta(t) \) – are the quantities characterizing the degree of excitation of the sinus node, right and left atrium, atroventricular node and ventricles, respectively; \( a_i, b_i (i = 1,\ldots,6) \) –
the rate of activation and deactivation of cardiac excitation, respectively; \( h \) – feedback time; all parameters are positive.

Finding solutions to this system is complex and because there are several unknown parameters, we simplify this system by reduction and scaling. The discrete analogue (6) of the system has the following form:

\[
\begin{align*}
v_j &= \frac{a_2a_3a_4}{b_2b_3b_4} \frac{x_j^3}{1 + (\sigma_3 \frac{a_5}{b_5} x_j^3)^2} \\
x_{j+1} &= \frac{a_5a_6v_j^2}{b_5b_6(1 + (\sigma_1 \frac{a_5}{b_5} v_j)^2)(1 + (\sigma_2 \frac{a_6}{b_6} v_j)^2)}
\end{align*}
\]

(7)

On the basis of (7) a computer model of the Lamérea diagram was developed to analyze the chaotic degree of heart activity.

![Diagram](image)

**Figure 5.** The degree of chaotic functioning of the heart

In figure 5 has shown the various degrees of chaotic behavior of the considered system and the "black hole" effect.

Based on the results of qualitative and quantitative studies of the system of equations (1) - (6), taking into account the models of cardiac activity, blood flow through the vessels and the model of tissue transfer, a parametric portrait of the model systems of the human body's regulatorika system was constructed, with the identification of specific areas of the same behavior: the trivial attractor, stationary regime, limit cycles of Poincare type, dynamic chaos, destructive changes – a "black hole". The domains of normal behavior are generally considered to be the region of stable equilibrium - B and the region of regular oscillations – C (stable periodic regime). It can be assumed that region B is a
region of functional activity of cells, and region C is a region of mitotic activity of cells. The area of dynamic anomalies is considered to be the region of dynamic chaos - D and the "black hole" region – E. The area of dynamic chaos is characterized by irregular fluctuations in the functioning of dynamic systems and can be identified as a loss of regulation the considered system and the onset of diseases. It borders on the one hand with the region of limit cycles of the Poincare type (where the behavior of the system is characterized by two-sidedly stable periodic oscillations), and on the other hand with the region of sudden destructive changes, the "black hole". The fading region can be identified with the area of programmed cell death – apoptosis, and the "black hole" region – with necrosis [5-10].

Thus, the knowledge of the dynamics of regulatory mechanisms of the emergence and development of anomalies at the main hierarchical levels of the organization make it possible to assess the patterns of the structural and functional organization of biological processes in norm and in pathologies, the potentialities of living systems, to determine the regulatory mechanisms of their interconnected existence and development under normal conditions and under stressful conditions, purposefully introduce changes at the genetic, metabolic and cellular levels, to identify the conditions of occurrence of diseases of organisms, to develop scientific recommendations for their treatment and prevention.

5. References

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