Mathematical modeling of molecular-genetic systems regulatory mechanisms activity in malignant neoplasms

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Abstract. The paper presents the method for constructing systems of nonlinear functional-differential equations with delay of a cellular regulator in norm and in cancerous formations. The existence of stable stationary as well as self-oscillatory solutions to the regulator equations, chaotic solutions and the "black hole" effect is established. The results of the quantitative analysis of the developed equations show the possibility of existence of chaotic behavior (the emergence of various types of chromosomal aberrations), the effect of failure of solutions on the trivial attractor - the effect of "black hole" (metastasis). The opportunity for forecasting the basic modes characteristics allows establishing molecular-genetic bases in oncologic pathogenesis, carrying out diagnostics and predicting characteristic stages of malignant neoplasms current.

1. Introduction

Extensive studies on oncology carried out in recent years have not developed a significant progress in improving early diagnosis and reducing mortality due to malignant neoplasms. The current area of modern interdisciplinary research is the study of the regulatory mechanisms of the appearance of malignant tumors. The discovery of the genetic structure of DNA (J. Watson and F. Crick) and the development of the operons theory in bacteria (M. Jacob and J. Monod) allowed starting the study of the patterns of gene activity during ontogenesis. This also allows identifying the mechanisms of genetic regulation of biological processes at the molecular level of the organization of living systems and studying the mechanisms of gene cooperative activity, i.e. dynamic characteristics of genes activity. I.I. Schmalhausen points out that "genes are regulators of the processes of individual development". B. Goodwin, B. Sendov and R. Tsanev have developed methods for mathematical modeling of the mechanisms of intracellular processes based on the regularities of molecular interactions of the main "parts" of the transcription process: nucleic acids, repressors and inducers and cellular functions based on the interrelated activity of genetic systems. There were also developed methods for studying the mechanisms of evolution of macromolecules based on mathematical models of hypercycles (M. Eigen), created the theory of molecular evolution on the basis of analysis "molecular genetic control systems" (V.A. Ratner), investigated the mathematical model of “sizers” (V.V. Shamim). These developments have led to extensive quantitative studies of the molecular-genetic mechanisms of living systems [1-10].
Mathematical modeling provides additional opportunities for experimentation, providing the researcher with an analogue of a living cell or organ, which is more accessible for manipulation than its prototype. Relatively independent behavior of the model, as well as distraction from its prototype, suggest new hypotheses, appent and verification experiments. Functional computer models can serve as a certain criterion for the correctness of the propositions and theories implemented in them, since their invalidation either does not allow the model to perform its functions, or it will quickly lead to results that clearly differ it from the prototype. Moreover, the model is a unity of theory and practice; therefore, it effectively stimulates formalization and elaboration of data on the research subject, facilitating the construction and testing of several advanced hypothesis. Finally, an effectively functioning computer model, reflecting the processes of internal interconnection and depicting the final effects of such interaction, can be used in practice for scientific research. It is used in the clinic to predict the "behavior" of the molecular-genetic system of a cell in response to a drug or another influences.

2. Materials and methods

As it is known, in early development, the organism develops on the basis of the products of the maternal molecular-genetic system. Although the corresponding system of genes always exists in the genome due to its function, providing autonomous reproduction of cells (normally necessary only for the embryo in early development), only their copies in the form of i-RNA stored as informosomes are used. Recording and organizing the storage of genetic information about autonomous development occur during the development of gamic cells (at the lambrush stage) in specially organized, exceptionally special conditions. Model studies have shown that the genes system of the considered functions consists of initiating, structural, organizing storage and blocking groups of genes [9]. It should, however, be assumed that under certain exceptional conditions, this system of genes can become functioning. Currently, there are protein-enzymes (the so-called oncoproteins) and genes (oncogenes) that are involved in the regulation of processes during uncontrolled reproduction of cells. Our research is based on the theory of regulatorika (by B.N. Hidirov’s definition - regulatorika is the science that involves the study of interconnected activity of regulatory mechanisms based on the ORASTA concept which consists of the oscillator-regulator OR (capable to accept, recycle and transfer signals) and ASTA (active regulatorika is the science that involves the study of interconnected activity of regulatory mechanisms based on the ORASTA concept which consists of the oscillator-regulator OR (capable to accept, recycle and transfer signals) and ASTA (active mechanisms). The functional-differential equations taking into account stimulating and inhibiting interactions, temporal relations, combined feedback and cooperativity in the regulatory mechanisms of molecular-genetic systems during considered processes are developed [9,10]:

\[ \frac{dx_i(t)}{dt} = A^N_i(X(t-1)) \exp(- \sum_{k=1}^{N} \delta_{ik} x_k(t-1)) - b_i x_i(t) \]  

(1)

with

\[ A^N_i(X(t-1)) = \sum_{j=1}^{N} \left( \sum_{k_1,...,k_j=1}^{N} \prod_{m=1}^{j} x_{ik_1,...,k_j}(t-1) \right) \]

Initial conditions

\[ x_i(t) = \varphi_i(t) \text{ at } t_0 - h \leq t \leq t_0 \quad (t_0 > h); \]

\[ i, j, k_j = 1, 2, ..., N. \]

Here \( x_i(t) \) is a quantity characterizing the amount of i-RNA transcribed from the \( i \)-th gene at the time moment \( t \); \( h \) is the feedback time in the considered molecular-genetic system; \( \delta_{ik_1,...,k_j} \) are elements of
the induction matrix and $\delta_k$ are the elements of the repression matrix of inter-genic relationships; $i_{k_1,...,k_j}$, $i, j, k_l = 1,2,...,N$.

The vector $M_i(C_1, C_2, ..., C_N)$ of the relationship between the molecular-genetic system and the external environment outlines the boundaries of acceptable values for the coefficients of the regularization equations of genetic processes. The vector elements are calculated by the formula:

$$\int_0^\infty \int_0^\infty A_i^N(S) \exp(-\sum_{j=1}^N \delta_{ik} S_j) dS_1...dS_N = b_i .$$

System (1) belongs to the class of functional-differential equations with delay and, when specifying continuous functions on the initial time interval of length $h (h = (i, j = 1,2, ..., n))$, its continuous solution can be obtained by sequential integration. Created on the basis of (1) taking into account (2), the information technology tools for gene activity, cell engineering and biotechnology are constructed for preliminary quantitative studies, targeted computational experiments to determine possible effects at the genes level in compliance with ecological, genetic purity and normal homeostasis.

3. Simulation of regulatory molecular-genetic systems

Molecular-genetic processes occurring in living systems are very complex, involving the interaction of the effector and repressor molecules with DNA, the functioning of RNA polymerases, nucleotides, etc. As a result, the general equations of mathematical models for regulatory mechanisms of molecular-genetic processes are nonlinear functional-differential equations with delay (1). Exact solutions to the nonlinear functional-differential equations with delay type (1) do not exist, and detailed analysis of the general characteristics of solutions for computer implementation presents certain difficulties and requires a lot of time. It is important to obtain model systems for the considered basic equations with saving the qualitative picture of the behavior of the original system (1). During qualitative research, the most common patterns of solutions behavior are revealed: the existence of stationary states, the nature of homogeneous solutions, the stability of stationary modes, the existence of limit cycles and its stability, etc. The study of model systems (1) shows a rich variety of behaviors of its solutions. In the established models for the regulatory mechanisms of molecular-genetic systems, autonomous development gene systems are activated if in a mature organism there are products of the parent molecular-genetic system. Let us consider the regulatory structure of the molecular-genetic system of the organism with the constant presence of the products of the autonomous development gene system. In the most simplified form (taking into account the inability of the considered organism’s genome to self-induction), the model equations have the following form:

$$\frac{\theta}{h} \frac{dX(t)}{dt} = (A + aX^2(t-1))e^{-X(t-1)} - X(t)$$

where $X(t)$ is a value expressing the activity of the molecular-genetic system of the organism or its part, which in this case can be identified with the number of cells; $A$ is constant, expressing the activity of the autonomous development gene system; $a$ is resource availability of the considered molecular-genetic system; $h$ is the time required for the feedback loop; $\theta$ is the average lifetime of gene products. Taking into consideration that the $\theta$(seconds) is small that $h$ (hours) for a qualitative analysis of the most general laws of the considered process, we can to analyse solutions to the equation:

$$X(t) = (A + aX^2(t-1))e^{-X(t-1)}$$

and its discrete analog:

$$X_k = (A + aX_{k-1}^2)e^{-X_k}. $$

The set of equilibrium positions for the considered equations is determined from:

$$\xi = (A + a\xi^2)e^{-\xi}. $$
The condition for the stability of this equilibrium position is:
\[
\xi < \frac{a}{2} \left( \sqrt{1 + \frac{A}{a}} + 1 \right),
\]
which is not performed for small values of the resource provision parameter. Then oscillations arise around the point \( \xi \), with increasing amplitude. Comparison with the nature of the model behavior shows that in the absence of \( A \), increasing values of \( X(t) \) lead to a breakdown of solutions in such models. Here (for sufficiently large \( A \)) this controlling mechanism is absent and cell multiplication can occur on a large scale. Based on the constructed equations, a set of programs has been developed for analyzing the regulatory mechanisms for the oncopathology [11]. The performed computational experiments show the possibility of identifying possible ways of diagnostics (based on the analysis of products synthesis patterns of initiating gene systems), prevention and treatment (based on the study of the functioning laws of genes autonomous development) cancer.

4. Conclusion
Application of the developed computational tools for experiments in the quantitative studying the regulatory mechanisms of living systems at the molecular-genetic level allows revealing the appearance laws of functionally active states for biological systems: a steady stationary state, oscillation in the form of a Poincare-type limit cycle, dynamic chaos and destructive change mode - "black hole" effect. Specific studies based on structural and phase portraits of the basic equations for the regulatory model of living systems showed the presence of general patterns in irregularities development during stable behavior of the biological system: stability loss of the equilibrium state, self-oscillation, transition to unpredictable behavior with further occurrence of destructive changes - its entry into the "black hole" mode. The results of the quantitative analysis of the developed equations show the possibility of the existence of chaotic behavior (the emergence of various types of chromosomal aberrations), the effect of solutions failure to the trivial attractor - the effect of "black hole" (metastasis).

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