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### Cover Page Footnote

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### Erratum

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## NONLINEAR DYNAMICS WITH CHAOTIC PROCESSES IN BIOTECHNOLOGY AND GENETIC ENGINEERING

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**Abstract:** This paper deals with modeling genetic systems activity during manipulation of an organism's genes using biotechnology. Computational experiments show that at certain values of internal and external cellular conditions there are exist the following regimes: stationary state, auto-oscillations and chaotic behavior of gene regulatory network linkages.

**Keywords:** biotechnology, genetic engineering, chaotic processes, chaos, nonlinear dynamics, functional-differential equations, modeling.

### Introduction

Intensive development of quantitative methods for analyzing regulation mechanisms of genetic systems during manipulation of an organism's genes using biotechnology [1-3], observed in last decade, is basically conditioned by outstanding achievements in studying structural-functional organization of processes what is going in cell's molecular-genetic system, wide intrusion of cybernetical concepts, mathematical ideas and methods into molecular biology. Objects formalization in mathematical and computer modeling of molecular-genetic system is realized within the bounds of mathematical biology, biocybernetics and bioinformatics. There are many different approaches for quantitatively studying functioning regularities of molecular-genetic systems. Mathematical and computer modeling of molecular-genetic systems using ODE is probably routine method. B. Godwin's work is one of the first works, based on the operon idea by F.Jakob and J.Monod and contains elementary differential

equations of cellular functions regulatory system. Bl. Sendov and R. Tsanev [4] have shown a possibility for making a models, which imitate acting regulatory system of cellular functions, tissue's cells groups using systems of nonlinear ODE. J. Smith has modified the considered equation with taking into account delay in regulation loop of cells biosynthetic processes. Relations in cell regulatorika system with taking into account cooperativity, end product inhibition and temporal mutual were applied for quantitative analyzing gene control mechanisms, cell's malignant growth, cell function regulatorika and cellular communities [5-10]. In the following sections we consider possible method for modeling molecular-genetic system activity in class of functional-differential equations and its application for quantitative studying during manipulation of an organism's genes using biotechnology.

### 1. Statement of a problem

B.N. Hidirov developed methodology for modeling the regulatory mechanisms of living systems, taking into account the nonlinear mechanisms of interaction between the regulator and the molecules of the repressor and effector, regulating enzyme activity based on end product inhibition, which makes it possible to consider from one point of view a wide range of phenomena combined by the presence of a regulatory system, regulation and complex

feedback. He introduced the concept of ORASTA, consisting of an Oscillator-Regulator (OR), capable of receiving, processing and transmitting signals of a certain nature, and ASTA (Active System with Time Average), allowing to implement a feedback loop in the system for finite time [5]. Mathematical modeling regulatory mechanisms for living systems is realized based on quantitative analyses of element complex behavior functioning in certain medium and capable to respond to determined external influences. The basic equations for cell division model with taking into account the concentration influence of carbohydrates, amino acids and fats on the biosynthetic activity regulation, cell volume changes, gene reconstructions during genetic manipulations, have the following form [5]:

$$\frac{dC_i(t)}{dt} = \begin{cases} me^{-C_i(t-\tau)} - \frac{T+T_{C_i}}{TT_{C_i}}(\ln 2)C_i(t) & \text{at } Y(t) < Y_1; \\ \frac{\varepsilon\varepsilon_i a_i D(t)}{1 + \sum_{j=1}^3 d_{ij} \tilde{R}_j(t-\tau_2)} - \frac{T+T_{C_i}}{TT_{C_i}}(\ln 2)C_i(t) & \text{at } Y(t) \geq Y_1; \end{cases}$$

$$\frac{dX_i(t)}{dt} = \begin{cases} -\frac{T+T_{C_i}}{TT_{C_i}}(\ln 2)C_i(t) & \text{at } Y(t) < Y_2; \\ v_i C_i(t-\tau_1) - \frac{T+T_{C_i}}{TT_{C_i}}(\ln 2)C_i(t) & \text{at } Y(t) \geq Y_2; \end{cases} \quad (1)$$

$$\frac{dP_n(t)}{dt} = \begin{cases} -\frac{T+T_{P_n}}{TT_{P_n}}(\ln 2)P_n(t) & \text{at } Y(t) < Y_3; \\ g_n X_n(t) - \frac{T+T_{P_n}}{TT_{P_n}}(\ln 2)P_n(t) & \text{at } Y(t) \geq Y_3; \end{cases}$$

$$\frac{dP_m(t)}{dt} = \begin{cases} -\frac{T+T_{P_m}}{TT_{P_m}}(\ln 2)C_i(t) & \text{at } Y(t) < Y_3; \\ -\frac{T+T_{P_m}}{TT_{P_m}}(\ln 2)P_m(t) & \text{at } Y(t) \geq Y_m; \end{cases}$$

$$\frac{dR_n(t)}{dt} = g_n X_n(t) - h_n(R_n(t) - R_c(t-\tau_3));$$

$$\frac{dR(t)}{dt} = g_m X_m(t) - \frac{T+T_{R_m}}{TT_{R_m}} \tilde{R}_m(t);$$

$$\tilde{R}_n(t) = \frac{R_n(t)}{1 + \vartheta(t)R_n(t)}; \quad Y(t) = \sum_{i=1}^3 \alpha_i Y_i(t);$$

$$\varepsilon = \begin{cases} 0 & \text{in } S \text{ and } M \text{ cell cycles;} \\ 1 & \text{in others;} \end{cases}$$

$$\varepsilon_m = \begin{cases} 0 & \text{at } \tilde{R}_m \geq A_m; \\ 1 & \text{at } \tilde{R}_m < A_m; \end{cases} \quad \varepsilon_m = \begin{cases} 0 & \text{at } \tilde{R}_n \geq A_m; \\ 1 & \text{at } \tilde{R}_n < A_{1m}, \end{cases}$$

where  $a_i$ ,  $d_{ij}$ ,  $v_i$ ,  $g_n$ ,  $g_m$ ,  $\alpha_i$  are positive constants;  $A_i$  – threshold values for repressors;  $m$  is the concentration of non-coding RNA;  $Y_1$ ,  $Y_2$ ,  $Y_3$  – threshold values of the energy and material supply

function of the cell  $Y(t)$ ;  $T_Z$  – half-life of substance  $Z$ ;  $Y_1(t)$ ,  $Y_2(t)$ ,  $Y_3(t)$  are the concentrations of carbohydrates, amino acids and fats entering in the cell;  $R_n(t)$ ,  $R_m(t)$  – concentration values of active plastic and mitotic repressors;  $C_i(t)$ ,  $X_i(t)$ ,  $P_i(t)$ ,  $R_i(t)$  are the concentrations of m-RNA, primary proteins, protein-enzymes and repressors;  $\tau_1$ ,  $\tau_2$ ,  $\tau_3$  – time parameters;  $\vartheta(t)$  is the effector concentration;  $t$ ,  $t_s$ ,  $T$  – the current, counted from the beginning of the S-period and the total time of division, accordingly;  $i = n, m$  – plastic and mitotic polyoperones.

## 2. The concept of the problem decision

Considered functional differential equations (1) have an infinite number of basis functions. The method of sequential integration makes it possible to obtain a continuous solution for  $t > 0$ . Continuity follows from the continuity of the initial functions and the nature of the construction of the solution. When this method is implemented on modern computers, the problem arises of constructing solutions to given discrete values of the unknown variables, which is also relevant in the quantitative description of biological processes by delay-type functional-differential equations in the presence of only discrete experimental data. Depending on the method of specifying the initial data, various methods of sequential integration of functional-differential equations of a delayed type can be applied. If the initial data is given inside a segment of length  $h$  and their number is sufficient to characterize the behavior of the system at the initial segment, then the Bellman-Cook sequential integration method can be used. Sometimes the initial data can be specified not within a segment of length  $h$ , but scattered on a segment much larger than the length of  $h$ . Let us consider two variants of constructing solutions of functional-differential equations of delayed type related to the considered classes of specifying initial data. Suppose that for the equations the initial conditions are given in the form

$$X_i(t_k) = X_{ki}, \quad k=0,1,2,\dots,N; \quad t_N = t_0 + 1, \quad i=1,2,3 \quad (2)$$

To construct the solution of the considered equation, we use the "retarded" identifier –  $X_i[k]$ ,  $k = 1, 2, \dots, N$ . Before the implementation of the

decision procedure, a "lagging" identifier (2) is assigned initial conditions. The adoption of an integration step commensurable with  $1/N$  makes it easy to construct difference equations for the realization of the functional-differential equations of a delayed type. Cyclic assignment of the received solutions to the first element of the "lagged" identifier with a preliminary step of the elements, ensures the economical use of the working memory of the computer in the course of constructing solutions. The required accuracy is ensured by selecting the integration step, conducting qualitative research and comparing the nature of the expected solutions with the solutions received on the computer. The second case is rather complicated, since it is not possible to use difference equations. Here we can use the construction of approximate solutions in the neighborhood of the required point by linearizing the equations, since for a certain class of linear functional-differential equations with delay this problem is solvable and the corresponding results can be used to estimate the behavior of solutions in the considered region of the phase space.

Also, the analysis of the solutions is carried out by methods of qualitative investigation of functional-differential equations. Depending on the definition of finding the system in the sphere of influence of a particular attractor, one can determine the nature of the behavior of solutions. For example, if the system is in the sphere of influence of a trivial attractor, then the solutions will eventually tend to zero. The presence of oscillatory solutions is determined by the violation of the stability of the positive attractor: in this case, bifurcation of solutions occurs and around the positive attractor there appear (according to the Poincaré-Bendixson theorem) self-oscillatory solutions, limit cycles of Poincaré type. In many cases it is useful to build the corresponding reduced equations (the so-called "model systems") on the basis of biological, biophysical considerations and mathematical techniques. This allows us to effectively use computer methods to analyze the general patterns of behavior decisions. Preliminary analysis of the domains of homogeneous behavior in parametric space is

carried out their investigation in phase space using the theory of qualitative analysis of functional differential equations and developed special programs. It should be especially noted the effectiveness of model systems in the form of discrete recurrence equations. Analysis of the deformation of the phase space allows us to determine the nature of regular, bifurcational, irregular and destructive behaviors of the genetic system, which allows us to investigate the relationship between the frequency of chromosomal aberrations and polymorphic gene variants. To evaluate the stability of solutions, the existence of oscillatory solutions, the appearance of a strange attractor and irregular oscillations, we use bifurcation and fractal analysis methods, as well as methods for detecting the "black hole" effect-disruption of solutions to a trivial attractor. It should be noted the special importance of determining the mechanisms for the appearance of the "black hole" effect – the area of destructive changes.

### 3. Realization of the concept

We develop computer program based on developed equations system (1) for analyzing genome structural-functional reconstruction with taking into account biosynthetic activity regulation, cell volume changes and different values of carbohydrates, amino acids and fats concentration (see Figure).



Figure. Screenshot of computer program based on equations system (1).

Based on the results of qualitative research and quantitative calculations, a parametric portrait for model systems (1) was developed with the following behavior: the trivial attractor, the stationary regime, Poincare-type limit cycles, dynamic chaos, destructive changes – the "black hole" effect. The domains of normal behavior are generally considered as the region *B* with stable equilibrium (characterized by a constant concentration of substances (homeostasis, stationary states)) and the region *C* with regular oscillations (provide periodic undamped fluctuations in the concentrations of certain groups of substances (oscillations, cycles)). It can be assumed that region *B* is a region of cells functional activity, and region *C* is a region of cells mitotic activity. The area of dynamic anomalies is usually considered to be the region of dynamic chaos – *D* and the region of the "black hole" effect – *E*. The region of dynamic chaos is characterized by irregular fluctuations in the dynamic systems activity and can be identified as a regulation loss in the considered system and the onset of the pathological process. It borders on one side with the region of limit cycles of the Poincaré type (where the behavior of the system is characterized by two-sidedly stable periodic oscillations), and on the other hand with the region of sharp destructive changes-the "black hole" effect. The extinction area can be identified with the area of programmed cell death – apoptosis, and the "black hole" region – with necrosis.

### Conclusion

Thus, an extremely important role in the functioning of the human body at normal and diseases belongs to molecular genetic regulatory mechanisms that ensure the performance of vital organs functions: maintain stable states in the body characterized by a constant concentration of substances; provide periodic undamped fluctuations in the concentrations of certain groups of substances;

control irreversible processes: development, growth, differentiation, apoptosis. The obtained equations allow conducting the quantitative studying hierarchical molecular-genetic systems origin and developments, mathematical and computer modeling regulatorika of concrete molecular-genetic systems at the norm and at the interaction with alien genes. Computational experiments allowed to determine the main modes of gene activity during manipulation of an organism's genes using biotechnology: steady state, autooscillatory mode, irregular oscillation mode and a sharp decline in gene activity.

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