MATHEMATICAL AND COMPUTER MODELLING REGULATORIKA OF HIERARCHICAL MOLECULAR-GENETIC SYSTEMS

Bahrom Nabievich Hidirov

Received January 31, 2008

Abstract. The progress achieved in biology during the last century has led to development of mathematical and computer modelling of *functioning regulatory mechanisms* (regulatorika) in molecular-genetic processes in living systems. In this work we consider one of the possible methods for mathematical and computer modelling of molecular-genetic systems regulatorika. The corresponding equations (in the class of delay functional-differential equations) are developed, using the approaches by B.Goodwin, Bl. Sendov, M. Eigen, B.A. Ratner, and taking into account of temporary relations, presence of multifunctional feedback and cooperative nature of processes in cell's regulatory loops. Results on the regulatorika for uniform molecular-genetic systems, as well as the problem of the origin and development of hierarchical molecular-genetic systems are considered. Results of using the considered method for analyzing cell's molecular-genetic systems in the presence of the alien genes (on the example of hepatic cell infections by hepatitis B virus) are given.

1 Introduction The analysis of main protein-ferments participating in the specific functioning of cells in a multicellular organism shows, that each cell contains different complex of protein molecules, though all cells have the same set of chromosomes and, consequently, identical genetic information [1, 2, 3]. It happens because in eukaryotic cells there is mechanism of hierarchical organizations of molecular-genetic system, regulating genes activity: which groups of genes at the moment must be active and which genes should be in the inactive condition. Existence of biochemical properties and processes, inherent all cells of the organism (syntheses of energy proteins, amino acid, to maintain and build membrane, etc) shows that there are universal groups of genes functioning in all cells regardless of specialization. Remaining part of genes consists of groups of general genes (its operation depends on activity conditions in universal groups of genes), containing information on general functions characteristic for many, but not all cells and groups of specific genes (its functioning depends on activity conditions of universal and general genes groups), keeping information on strictly specific functions of concrete cells [4]. Under such approach, the whole cell genome of multicellular organism works as evolutionary established hierarchical system of universal, general and specific genes groups (Figure 1).

Hierarchical organization of molecular-genetic systems is of the utmost importance in regulatorika of intracellular processes and cellular functions. Their account makes it possible to carry out studying mechanisms of origin, existence and development of living systems when quantitatively analyzing activity patterns of molecular-genetic systems. In this work we develop the mathematical modelling of genes activity (section 2), possible equations of molecular-genetic systems regulatorika (sections 3,4) and certain problems concerning the mathematical and computer modelling of hierarchical molecular-genetic systems (sections 5,6).

2000 *Mathematics Subject Classification.* 34K35, 34K60.

Key words and phrases. Hierarchical molecular-genetic systems, regulatorika, differential-delay equations, chaos, "black hole", hepatitis B.

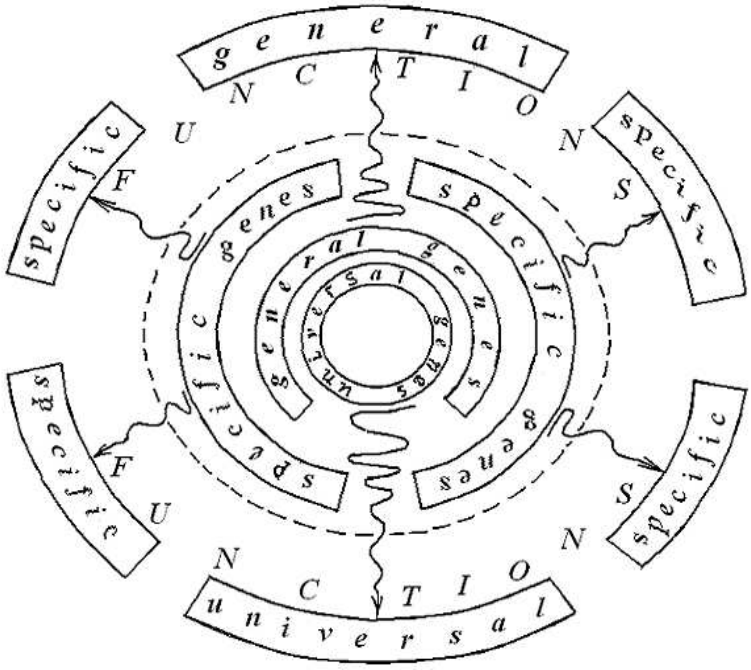
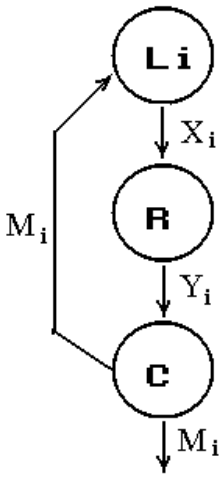


Figure 1: Structural-functional organization of cell genome.

2 Development of modelling molecular-genetic systems regulatorika by ordinary differential equations (ODE) The intensive development of quantitative methods for the analysis of regulation mechanisms of genetic systems [5, 6, 7, 8], observed in the last decade, is basically conditioned by outstanding achievements in studying structural-functional organization of processes which occur in a cell's molecular-genetic system [9, 10, 11], as well as by a wide intrusion of cybernetical concepts, mathematical ideas and methods into molecular biology. Objects formalization in the mathematical and computer modelling of regulatorika of molecular-genetic system is realized within the bounds of mathematical biology, biocybernetics and bioinformatics. There are many different approaches for quantitatively studying the functioning regularities of molecular-genetic systems [12, 13, 14]. The mathematical and computer modelling of regulatorika of molecular-genetic systems using ODE is probably by now a routine method. B. Goodwin's work [15] is one of the first works, based on the operon idea by F. Jakob and J. Monod [9] and contains elementary differential equations of cellular functions regulatory system (Figure 2). In Figure 2, L_i denotes genetic locus, where there occurs the RNA molecules (X_i) synthesis, incoming in the cellular organoid R - ribosome, where there occurs the specific protein (Y_i) synthesis. On a certain section C in the cell this protein regulates metabolism degree, acting as ferment. Under ferment activity the metabolite M_i, which closes the feedback loop, is produced, as its parts return to the genetic locus L_i and operate there as a repressor [15]. Based on ODE, M. Eigen, B.A. Ratner and their followers [16, 17] describe the dynamics of informational macromolecules community in the course of evolution - hypercycles and sysers. These models propose that the macromolecules synthesis is far from steady state, and occurs only in complex of matrix and ferments carrying out this synthesis. In general view the dynamics of informational macromolecules community can be described by the following system [16]:



$$\frac{dX_i}{dt} = \frac{a_i}{A_i + k_i M_i} - b_i X_i \; ;$$

$$\frac{dY_i}{dt} = \alpha_i X_i - \beta_i Y_i \; ; \qquad (1)$$

$$\frac{dM_i}{dt} = r_i Y_i - s_i M_i \; .$$

Figure 2: Diagram of elementary regulatory system of cellular functions - systems of protein synthesis - and its simple equations (by B. Goodwin [15]).

$$\frac{dX_i}{dt} = (A_i Q_i - D_i) X_i + \sum_{k \neq i} \omega_{ik} X_k + F_i, \qquad (2)$$

$$\sum_k X_k = const \equiv C.$$

Here X_i is a concentration of i-th informational macromolecules community; $A_i Q_i X_i$ and $D_i X_i$ expresses formation and decay of i-th informational macromolecules community, accordingly; ω_{ik} denotes individual rate of mutations; F_i determines outflow velocity of reactions products $(i, k = 1, 2, .., N)$.

The mathematical models of molecular-genetic systems based on ODE were repeatedly improved [18, 19, 20, 21, 22, 23] in the sequel. Bl. Sendov and R. Tsanev [18] 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 like (1). J. Smith has modified the equation (1) by taking into account the delay in the regulation loop of cell biosynthetic processes [21]. Using the considered models, the mechanisms of malignant growth in liver [19], regulation of biosynthetic functions [20], metabolic systems [24], rhythmical processes [25] have been quantitatively investigated; mechanisms of probionts, phages's molecular-genetic systems have been studied and similar evolutionary problems have been considered [16, 17]. Improved versions of equations (1) taking into account the cooperativity, end product inhibition and temporal mutual relations in cell regulatorika system were applied for quantitative analyzing gene control mechanisms [21], cell's malignant growth [26], cell function regulatorika and cellular communities [26, 27, 28, 29]. In the following sections we consider a possible method for modelling molecular-genetic system regulatorika in the class of functional-differential equations and its application for quantitative studying of hierarchical molecular-genetic systems regulatorika.

3 Functional-differential equations of molecular-genetic systems regulatorika

The main equations of molecular-genetic systems, in the most general aspects, have the

following form

$$\frac{dx_i(t)}{dt} = a_i F_i(x_1, x_2, ..., x_n) - b_i x_i, \quad i = 1, 2, ..., n \tag{3}$$

where $x = (x_1, x_2, ..., x_n)$ is a vector of molecular-genetic system products concentrations; $F_i = (x_1, x_2, ..., x_n) : R^n \to R$ are functions which express activity degree by i-th molecular-genetic elements; a_i, b_i are nonnegative constants of "synthesis" and "decay" for i-th molecular-genetic element products, $i = 1, 2, ..., n$.

Since the equations of type (3) appeared in B. Goodwin's work [15], the functions F_i ($i = 1, 2, ..., n$) are the most subject to improvement. In choosing the functions F_i, starting from functioning regularities for the considered class of molecular-genetic systems, the influence from stimulating and inhibitory factors on molecular-genetic systems functioning in different cases are taken into account [18, 19, 22, 25, 26, 28, 30]. One of the possible variants (3)-like-equations, applying for mathematical and computer modelling regulation mechanisms of molecular-genetic systems, can be general regulatorika equations [22, 26, 28, 30]. In this case, with taking into account the following characteristics for molecular-genetic systems:

- the biologically reasonable genetic text's appearance in the cells, without the participating living system's genetic apparatus, is absent;
- the genetic processes in the cells are subordinated to a united regulation system: initiations, transcriptions and translations of genes; forming the active protein -ferments and their operation; forming effector complexes and repressors;
- genetic process regulation, occurring in cells, can be realized autonomously

the mathematical and computer models for molecular-genetic systems regulatorika can be based (in accordance with (3)) on the following equations:

$$\frac{\theta_i}{h}\frac{dx_i(t)}{dt} = A_i^N(X(t-1)) \exp\left(-\sum_{k=1}^{N} \delta_{ik} x_k(t-1)\right) - x_i(t) \tag{4}$$

with

$$A_i^N(X(t-1)) = \sum_{j=1}^{N} \left(\sum_{k_1,...,k_j=1}^{N} \gamma_{i_{k_1,...,k_j}} \prod_{m=1}^{j} x_{k_m}(t-1) \right),$$

where $x_i(t)$ is the value which characterizes m-RNA count, transcribed from i-th gene at time t; θ_i express average time of genes products vital activity; h is the feedback time in considered molecular-genetic systems; $\gamma_{i_{k_1,...,k_j}}$ are the induction matrix elements and δ_{ik} are repression matrix elements of intergenic mutual relations; $i_{k_1,...,k_j}, i, j, k_j = 1, 2, ..., N$.

Elements of the vector $M_c(C_1, C_2, ..., C_N)$ of the molecular-genetic systems relationships with external medium are calculated by the formula

$$C_i = \int_0^{\infty} ... \int_0^{\infty} A_i^N(S) \exp\left(-\sum_{j=1}^{N} \delta_{ik} S_j\right) dS_1 ... dS_N - 1. \tag{5}$$

This vector outlines the boundaries of admissible values for equation coefficients of genetic processes regulatorika. System (4) belongs to the class of delayed functional-differential equations and if we have continuous functions on initial time segment, then its continuous solution can be obtained by consequent integration method [31, 32].

4 Regulatorika equations of homogeneous molecular-genetic systems As expected, the evolutionary development of molecular-genetic system regulatorika began from homogeneous molecular-genetic systems. Let us consider the equations of a possible homogeneous (associative, inter-conjugate and self-conjugate) molecular-genetic system based on (4) and (5). For qualitative studying of the functioning of associative molecular-genetic system we offer the following equations on the basis of (4)

$$\frac{\theta_i}{h}\frac{dX_i(t)}{dt} = \sum_{j=1}^{n} a_{ij}X_j(t-1)\exp\left(-\sum_{k=1}^{n} X_k(t-1)\right) - X_i(t) \tag{6}$$

with vector elements M_c (see (5))

$$C_i = \sum_{j=1}^{n} a_{ij} - 1.$$

$$i = 1, 2, ..., n$$

In (6), θ_i expresses the average vital activity time of gene products; h is the feedback time of molecular-genetic systems regulatorika; a_{ij} are parameters describing the i-th product formation by j-th gene.

For the functioning of inter-conjugated molecular-genetic systems it is necessary to have all the genes products. We have

$$\Lambda_i^n(X(t-h)) = a_i \prod_{j=1}^{n} X_i(t-h);$$

$$\frac{\theta_i}{h}\frac{dX_i(t)}{dt} = a_i\left(\prod_{j=1}^{n} X_i(t-h)\right)\exp\left(-\sum_{k=1}^{n} X_k(t-h)\right) - X_i(t); \tag{7}$$

$$C_i = a_i - 1.$$

$$i = 1, 2, ..., n$$

If there is balance with the external medium ($C_i = 0; i = 1, 2, ..., n$) then the right part of (7) doesn't have arbitrary constants. In some cases for functioning molecular-genetic systems it is necessary to have n products of the same gene (here n can be associated with the Hill coefficient). Then all genes have identical activity and

$$\frac{\theta_i}{h}\frac{dX_i(t)}{dt} = a_i X_j^n(t-1)\exp\left(-\sum_{k=1}^{n} X_k(t-1)\right) - X_i(t);$$

$$C_i = a_i \int_0^{\infty} S_j^n \exp\left(-\sum_{k=1}^{n} S_k\right) dS_1 ... dS_n - 1.$$

$$i, j = 1, 2, ..., n$$

This leads to the following regulatorika equations for self-conjugated molecular-genetic system (n is the self-conjugate degree)

$$\frac{\theta}{h}\frac{dX(t)}{dt} = aX^n(t-1)e^{-nX(t-1)} - X(t); \tag{8}$$

$$C = a \int_0^\infty S^n e^{-nS} dS - 1.$$

Here θ, h are the parameters of average vital time for molecular-genetic system products and feedback system; a, n are the parameters of resource-provision and self-conjugate of molecular-genetic system. The equations (6), (7) and (8) were used for model studying the concrete molecular-genetic systems which accordingly have the following properties: additivity, inter-conjugate and self-conjugate [21, 26, 27, 28, 29, 30, 33]. In the following sections possible applicability of the equations (7) and (8) for analyzing main regularities in regulatorika of uniform and hierarchical molecular-genetic systems will be considered.

5 Qualitative analyzing uniform self-conjugated molecular-genetic systems Based on the results of the analyzing regulatorika systems [28, 33] we suppose that initial development of molecular-genetic systems regulatorika is realized from associative to inter-conjugate and hereinafter to self-conjugate systems. In this case the studying general regularities of further evolutionary developments of molecular-genetic systems can be realized using equations (8).

Within the framework of the given problem the value h is defined by means of feedback common time in the considered biosystem population with given type of molecular-genetic system and consequently $\theta \ll h$. Then, qualitative analyzing characteristic solutions (8) can be realized by the following functional equations [28, 29, 33]

$$X(t) = aX^n(t-1)e^{n(1-X(t-1))} \tag{9}$$

and its discrete analogue

$$X_{k+1} = aX_k^n e^{n(1-X_k)}. \tag{10}$$

If the analyzed molecular-genetic system is in equilibrium with the external medium, then we have

$$X_{k+1} = (n^n/(n-1)!)X_k^n e^{n(1-X_k)}.$$

When $n \gg 1$ using Stirling's approximation [33] we have

$$X_{k+1} = \sqrt{n/2\pi} X_k^n e^{n(1-X_k)}, \tag{11}$$

where X_k expresses product count, outputting by molecular-genetic system on k-th step. Analyzing (11) solutions behavior we show [28, 33] that the solutions are in the first quadrant of phase space when parameters values and initial conditions are non-negative; infinitely distant points are unstable; it is possible that there exist stable trivial steady state - trivial attractor (for all $n \geq 1$), unstable positive steady state (α) and positive attractors (β) if $n \geq 6$. The basin β-attractor is area of possible regulatorika for hierarchical molecular-genetic systems. Results of the qualitative studying solutions (10)-(11) in the β-attractor basin have shown that there is sufficiently complex behavior of the considered models for regulatorika of self-conjugated molecular-genetic systems (Figure 3). Besides periodic functioning regimes there can exists irregular oscillations (where Lyapunov exponent $L(\beta) > 0$; see Table 1) and "black hole" effect [28, 29, 33]. In this case, the last effect consists of appearance the destructive changes in the system and is expressed by oscillations failure [34] - solutions tend into the trivial attractor.

The studying solutions (11) conducted on PC using Lamerey diagrams construction, calculations of Lyapunov exponent, Hausdorff and high dimensions (based on [34]) show the existence of irregular oscillations when $n \geq 11$ and the appearance of a "black hole" effect when $n > 12$. Consequently, stable self-conjugated molecular-genetic systems, which

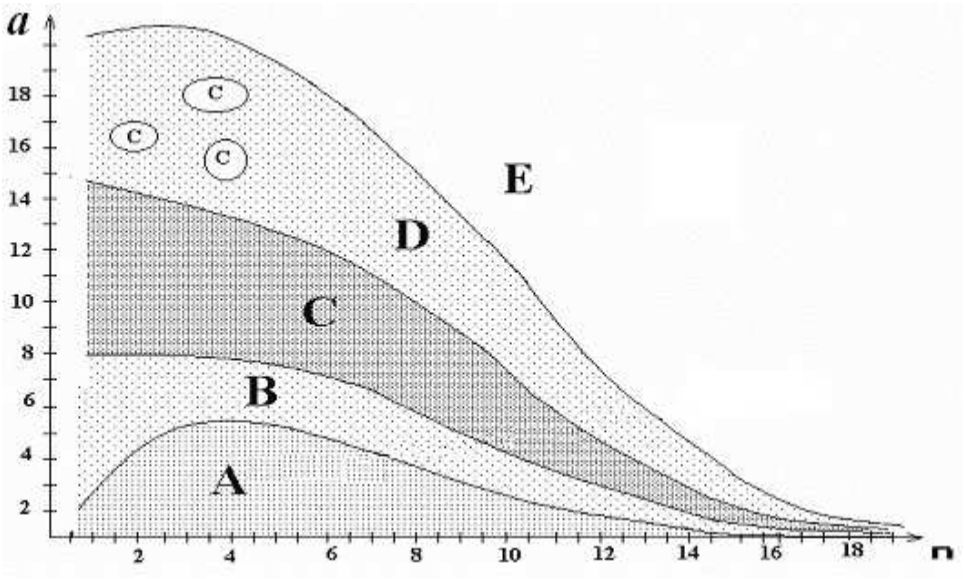


Figure 3: Parametric portrait (10). A is the trivial attractor area, B is the area of stationary modes, C is the auto-oscillations area, D is the area of irregular oscillations, E is the "black hole" area.

Table 1: Positive steady states and Lyapunov exponent self-conjugated molecular-genetic systems calculated based on (11).

n	6	7	8	9	10	11	12
α	0.7197	0.6989	0.6937	0.6936	0.6955	0.6987	0.7020
β	0.9637	1.0379	1.0859	1.1184	1.1416	1.1585	1.1714
$L(\beta)$	-1.3945	-1.3265	-0.3747	-0.1614	-0.1113	+0.3794	+0.6806

are in the equilibrium with the external medium, can exist under $6 \leq n \leq 12$ only, moreover under $6 \leq n < 9$ their regulatorika is characterized by stable stationary behavior, under $9 \leq n < 11$ regulatorika is characterized by stable regular oscillations, if $11 \leq n \leq 12$ there are irregular oscillations.

Thereby, within the framework of the accepted suggestions, based on the studies results we can get the following effects comparatively evolutionary stable molecular-genetic systems: they have genes from six to twelve in number, if genes in number are greater than twelve then the systems are organized by the hierarchical type, if genes in number are less than eight then the systems basically have stable stationary activity, if genes in number are greater than eight then we have behavior in the manner of irregular oscillations.

6 Modelling regulatorika of hierarchical molecular-genetic systems In general cases the regulatorika of hierarchical molecular-genetic systems can be investigated using (4). The equations of inter-conjugate molecular-genetic systems type (7) are elementary equations and available for modelling hierarchical molecular-genetic systems. When constructing the regulatorika equations of hierarchical molecular-genetic systems it is necessary to take into account consequent dependence molecular-genetic systems activity of primitive hierarchical level on molecular-genetic systems activity of higher hierarchical level. Let us

consider this on the example of constructing elementary regulatorika equations of eukaryotic cells genome with taking into account common hierarchical levels (universal, general and specific genetic systems). For the simplicity we present each level as one genetic system. Then as the simplest regulatorika equations for considered molecular-genetic system we have

$$\begin{gathered}\frac{\theta_1}{h}\frac{dX(t)}{dt} = aX(t-1)e^{-\omega(t)} - X(t);\\ \frac{\theta_2}{h}\frac{dY(t)}{dt} = bX(t-1)Y(t-1)e^{-\omega(t)} - Y(t);\\ \frac{\theta_3}{h}\frac{dZ(t)}{dt} = cX(t-1)Y(t-1)Z(t-1)e^{-\omega(t)} - Z(t);\\ \omega(t) = X(t-1) + Y(t-1) + Z(t-1),\end{gathered} \tag{12}$$

where $X(t), Y(t), Z(t)$ are values, characterizing common m-RNA count for universal, general and specific genetic systems products at time t; θ_1, θ_2, θ_3 are parameters, expressing "lifetime" for molecular-genetic systems products; h is the time, necessary for fulfilling feedback in cell; a, b, c are rate constants of product formation for considered genetic systems.

Let us consider functional-differential equations for regulatorika of inter-conjugate molecular genetic systems (7) and (12) for investigating the hepatitis B development mechanism, which is one of the actual medical problems in viral hepatology [35]. The analysis of possible equations variants and preliminary studying its behavior using mathematical and virology viewpoints shows [36] that it is necessary to take into account specific aspects of interconnected activity between hepatocyte and hepatitis virus molecular-genetic systems. Especially, we must take into consideration independent functioning hepatocyte, hepatitis B virus genome adoption ability into hepatocyte genome and dependence of hepatitis B virus activity on conditions of hepatocyte intracellular medium.

Subject to aforesaid, the elementary system of regulatorika equations for interconnected activity between hepatocyte and hepatitis B viruses molecular-genetic systems on the basis of (7) has the form

$$\begin{gathered}\frac{\theta_1}{h}\frac{dX(t)}{dt} = aX^2(t-1)e^{-X(t-1)-cY(t-1)} - X(t);\\ \frac{\theta_2}{h}\frac{dY(t)}{dt} = bX(t-1)Y(t-1)e^{-dX(t-1)-Y(t-1)} - Y(t),\end{gathered} \tag{13}$$

where $X(t)$, $Y(t)$ are values, characterizing hepatocyte and hepatitis B virus molecular-genetic systems activity, accordingly; θ_1, θ_2 are parameters, expressing products "lifetime" of hepatocyte and hepatitis B virus molecular-genetic systems; h is the time necessary for feedback fulfilment in the considered systems; a, b are velocity constants of product formation in the considered genetic systems; c, d are parameters, expressing repression degree in hepatocyte and hepatitis B virus molecular-genetic systems; all parameters are positive. Qualitative study (13) shows that there are stable trivial and complex positive attractors. Analysis of character solutions (13), using the methods for qualitative analyzing functional-differential equations and results of computer studies, shows that there is parameters values ensemble under which there exists hepatocyte genome domination. The most interesting case when there is joint activity regime between hepatocyte and hepatitis B virus genomes (chronic hepatitis B) (Figure 4). Under certain values of the functional-differential equations system parameters (13) the positive attractor is stable (Figure 4) and its stability loss is realized by Hopf bifurcations by beginnings of stable, regular oscillations. Results of

computer studies have shown that in the interconnected symbiotic activity between hepatocyte and hepatitis B virus there are irregular oscillation regimes(dynamic chaos) and "black hole" effect (Figure 5). In the last case, there exist oscillations failure and solutions (13) tend to trivial attractor (Figure 5: c, d).

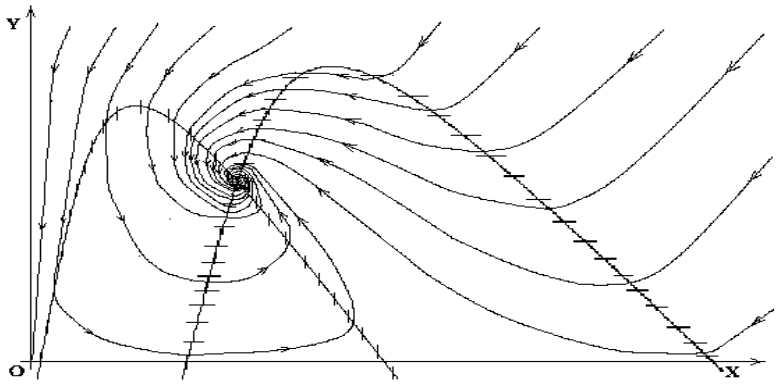


Figure 4: Symbiotic regime in "hepatocyte-hepatitis B virus" system (13).

Our research using PC showed that in dynamic chaos area there are small regions (r-windows), in which the solutions (13) behavior have regular character. That indicates that there exists possibility for effective controlling hepatocyte molecular-genetic systems regulatorika for the purpose of getting its normal functioning. Entry in the area of irregular oscillations can be forecasted: splash series of Lyapunov exponents (Hopf bifurcations by Feigenbaum scenario) precede this occurrence [34]. Splash can be fixed by analyzing solutions using PC. This allows to forecast a coming the destructive changes in hepatocyte under the hepatitis B virus influence, to realize a diagnostics and forecasting specific stages in disease current under infection by hepatitis B virus.

7 Conclusion Mathematical and computer modelling cell's molecular-genetic systems regulatorika of multicellular organisms supposes accounting their hierarchical organizations. This can be reached by constructing the equations of molecular-genetic systems regulatorika based on the general functional-differential equations of regulatorika.

The obtained equations allow conducting the quantitative studying hierarchical molecular-genetic systems origin and developments, mathematical and computer modelling regulatorika of concrete molecular-genetic systems at the norm and at the interaction with alien genes.

Mathematical and computer modelling regulatorika of interconnected activity between hepatocytes and hepatitis B virus molecular-genetic systems shows possibility to quantitatively diagnose consequent regimes of this hierarchical process development.

Acknowledgements This research was partially supported by scientific funds of Uzbekistan (grants No F-1.3.1, FA-F1-F011, A-14-010 and A-9-152).

References

[1] E.B. Popov. *Under seven seals of heredity.* Agropromizdat, 1991. (in Russian).

[2] M. Ptashne. *Pereklyuchenie genov. Regulyaciya gennoy aktivnosti i fag D.* Mir, 1988. (in Russian).

[3] E.H. Davidson. *Gene activity in early development.* 3rd ed. New York, 1986.

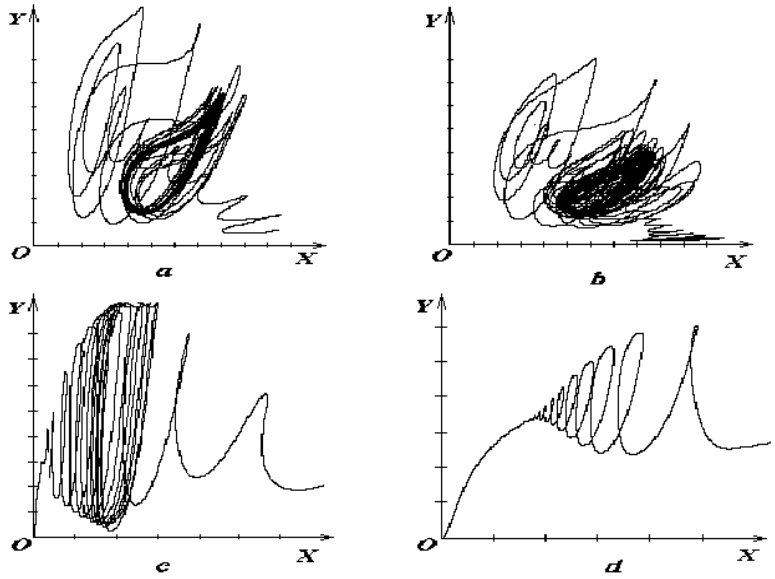


Figure 5: Characteristic phase trajectories (13) are obtained using PC (a is the auto-oscillation, b is the irregular oscillation (chaos), c, d are the "black hole" variants (trajectories go right to left)).

[4] B.N. Hidirov. Mathematical model of temporal regulation of cells. *"Mathematical theory of biological processes", Kaliningrad*, pages 166–167, 1976. (in Russian).

[5] H. Salgado, A Santos, and et all. Regulondb (version 2.0): A database on transcriptional regulation in escherichia coli. *Nucl.Acids Res*, 27(1):59–60, 2000.

[6] F.A Kolpakov, E.A. Ananko, G.B. Kolesov, and N.A. Kolchanov. Genenet: A gene network database and its automated visualization. *Bioinformatics*, 14(6):529–537, 1999.

[7] M. G. Samsonova, E. G. Savostyanova, V. N. Serov, A. V. Spirov, and J. Reinitz. Genet: A database of genetic networks. In *First Int. Conf. Bioinformatics Genome Regul. Struct., BGRS'98*. Novosibirsk, 1998.

[8] N. Friedman, M. Linial, I. Nachman, and D. Pe'er. Using bayesian networks to analyze expression data. *J. Comput. Biol.*, 7:601–620, 2000.

[9] F. Jacob and J. Monod. Genetic regulatory mechanisms in the systems of proteins. *J.molec. Biol.*, 3:318, 1961.

[10] J.D. Watson and F.H.C. Crick. *The structure of DNA*. Cold.Spring Harb Symp, 1953.

[11] B. Devis. *Telenomical values of biosynthesis regulatory mechanisms//Cells regulatory mechanisms*. Mir, 1964. (in Russian).

[12] L. Glass. *Global analysis of nonlinear chemical kinetics. In B. Berne, ed. Statistical Mechanics, Part B: Time Dependent Processes*. Plenum Press, New York, 1977.

[13] H.M. McAdams and A. Arkin. Stochastic mechanics in gene expression. *Proc. Natl. Acad. Sci. USA*, 94:814–819, 1997.

[14] Endy D. and R. Brent. Modelling cellular behavior. *Nature*, 409:391–395, 2001.

[15] B.C. Goodwin. *Temporal organization in cells*. Academic Press, London and New York., 1963.

[16] M. Eigen and P. Schuster. Stages of emerging life-five principles of early organization. *J. Mol. Evol.*, 19:47–61, 1982.

[17] V.A. Ratner and V.V. Shamin. Sysers: modeling fundamental properties of molecular-biological organisations. i. sysers with non-conjunct matrix. *Mathematical models in evolutionary genetics, Novosibirsk, ITSiGSO AN SSSR*, pages 60–82, 1980.

[18] Tzanev R. and Bl. Sendov. A model of the regulatory mechanism of cellular multiplication. *J. Theoret. Biol.*, 12:327–341, 1966.

[19] Bl. Sendov and R. Tsanev. Computer simulation of the regenerative processes in the liver. *J. Theoret. Biol.*, 18:90, 1968.

[20] J. Smith. *Mathematical Ideas in Biology.* Cambridge, Cambridge Univ. Press, 1968.

[21] B.N. Hidirov. Gene control mechanisms: modeling associative molecular-genetic systems. *Problems of informatics and energetics*, 2:39–13, 1998. (in Russian).

[22] M. Saidalieva. Modelling of regulation mechanisms of cellular communities. *Scientiae Mathematicae Japonicae*, 58(2):415–421, 2003.

[23] J.D. Murray. *Lectures on nonlinear-differential equations. Models in biology.* Clarandon Press, Oxford, 1977.

[24] J. J. Tyson and H. G. Othmer. The dynamics of feedback control circuits in biochemical pathways. *Prog. Theor. Biol.*, 5:1–62, 1978.

[25] P. Ruoff, M. Vinsjevik, C. Monnerjahn, and L. Rensing. The goodwin model: Simulating the effect of light pulses on the circadian sporulation rhythm of neurospora crassa. *J. Theor. Biol.*, (209):29–42, 2001.

[26] B.N. Hidirov. Mathematical modeling of regulation mechanisms of living systems. In *International Scientific and Practical Conference "Innovation-2001"*, pages 156–158, Tashkent, 2001.

[27] M. Saidalieva. Simulation of cellular communities mechanisms. *Scientiae Mathematicae Japonicae*, 64(2):469–478, 2006.

[28] B.N. Hidirov. Living systems regulatorika: the main equations. *Doclady ANRUz*, 3:26–29, 1998. (in Russian).

[29] B.N. Hidirov. Modelling of regulation mechanisms of living system. *Scientiae Mathematicae Japonicae*, 58(2):419–425, 2003.

[30] B.N. Hidirov and M. Saidalieva. Chaos research in autonomous regulating systems. In *World Conference on Intelligent Systems "WCIS 2000"*, pages 138–140, Tashkent, 2000. b - Quadrat Verlag.

[31] R. Bellman and K. L. Cooke. *Differential-Difference Equations.* Academic Press,London, 1963.

[32] J.K. Hale. *Introduction to functional differential equations.* Springer-Verlag, 1993.

[33] B.N. Hidirov. On one method for analyzing living systems regulatorika. *Voprosy kibernetiki*, 128:41–46, 1984. (in Russian).

[34] L. Glass and M. Mackey. *From clocks to chaos: The rhythms of life.* Princeton University Press, 1988.

[35] B.R. Aliev and Z.A. Kushimov. Tissue markers of hepatitis b virus. *Pathology*, 3:32–33, 2003. (in Russian).

[36] Sh.Kh. Khodjaev, B.R. Aliev, B.N. Hidirov, and M. Saidalieva. Mathematical modeling molecular-genetic interaction mechanisms between liver cells and hepatitis viruses. *Problems of informatics and energetics*, 1:7–15, 2005. (in Russian).

Bahrom Nabievich Hidirov
Institute of Mathematics and Information Technologies, Academy of Sciences of Uzbekistan
F.Khodjaev, 25, 6 floor, room 12, 100125, Tashkent, Uzbekistan
E-mail: regulatorika@yahoo.com