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Mathematical Modeling Regulatory Mechanisms of Human Cellular Communities at Anomalies

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ABSTRACT

This paper considers the method for modeling regulatory mechanisms of cellular community, based on introducing the functional unit of cellular communities (FUES), consisting of dividing, growing, differentiated, carrying out the specific functions, ageing cellular groups functioning interconnected as a unit. Regulatorika of the interconnected activity between molecular-genetic systems of hepatocytes and hepatitis B viruses (HBV) taking into account miRNA action are considered. During computing experiments with the developed program complex it is established that there are the following regimes of the process, which depend on HBV miRNA concentration: clarification, symbiosis, regular and irregular fluctuations, sharp destructive changes which define various clinical forms of disease.

Keywords: *modeling, regulatorika, cellular communities, functional-differential equations with delay, miRNA, viral hepatitis, functional equation;*

INTRODUCTION

Worldwide development of the theory and practice of mathematical modeling of the regulatory mechanisms functioning (Regulatorika) of living systems at the main hierarchical levels of the organization is connected with successful application its to biology, medicine and agriculture, because it allows to choose the most effective ways for prophylaxis and treatment of number of diseases, for agricultural techniques of cultivation and plant selection, to creation various products of biotechnology. According to WHO forecasting, the number of cases of genetic diseases will continue to grow from 14 million in 2012 to 22 million in the next decade. In European countries adopted a national strategy on research of regulatory mechanisms of rare genetic diseases, and the program "Horizon 2020" running is considered as beginning of new era in the financing of scientific research in the EU. The budget of "Horizon 2020" for the period 2014-2020 is 80 billion euros in the prices of 2011. If the funds index allotted in 2013 for the study of regulatory mechanisms of cells are 6.7% of the total EU budget, according to estimates, the index will increase to 8.5% in 2020. Since 2014 International research consortium of genetic diseases have already embarked on unprecedented scale of international scientific cooperation in the study of the regulatory mechanisms of living systems.

After discovering regulatory micro-RNA molecules at the beginning of this century there exist intensively growing number of works devoted to the development and practical application of mathematical modeling methods of different regulatory mechanisms of the cell [1-11]. Although large-scale international studies on cell's regulatory mechanisms are expanded (the budget of the "Human Genome" project was more than 3 billion dollars), the interpretation of genome data is still not carried out, its regulatory mechanisms are not clarified in detail.

In this regard, it is especially actuial to analyze hierarchical inter connection of cellular communities of living systems at different levels of its organization; to develop conceptual model of regulatory mechanisms of cellular communities; to analyze possible formation laws of functional communities; revealing the basic association regularities of multicellular organisms, cells in the cell community to perform specific functions of the organisms; to develop model to ensure the population dynamics of the major research

cellular groups that make up the cellular community; development of cell's simulation models based on the spatio-temporal organization of cells and intracellular processes, to create mathematical models of quantitative relationships of cells on the basis of a system of differential equations with delayed argument; a qualitative and comparative analysis of mathematical models of cell division and cell differentiation, taking into account the dynamics of the volume; elimination of the quantitative relationship between the parameters of the model of cell division and the change in volume; study of mechanisms of sustainable functioning of organs and tissues as a whole in the performance of specific functions.

The problems of creation and improvement of models that take into account complex regulatory processes of living organisms to solve theoretical and practical tasks on development of information technology tools for regulatory mechanism of living systems cellular communities, applying the theory of linear programming, a stoichiometric modeling technology, methods of discrete, stochastic and hybrid approaches based on ordinary differential equations, partial differential equations, differential-functional equations are considered by scientisis such as Leon Glass (Centre for Nonlinear Dynamics), Bernhard Palsson (Systems Biology Research Group), James D. Murray (University of Oxford), Andreas Gisel (Institute for Biomedical Technologies), Wojciech Karlowski (Institute of Molecular Biology and Biotechnology), Andrey Kajava (Macromolecular Biochemistry Research Center), Rubem P. Mondaini (BIOMAT Consortium) and others.

Quantitative study of living systems, using the methods of modeling cellular communities, cellular functions, studies related to the definition of regulation mechanisms of molecular-genetic systems, conducted by number of scientists, including J.F. Bailey; AB Ruby; I. Prigojin; VA Ratner; VN Novosel; OG Chorayan; P.J. Murray shows that to date, developed mathematical models on the level of phages, cell functions, cell communities of organisms and populations. Also achieved a certain degree of positive results by such as scientists Strohman; J.E. Bailey; R. Ramakrishna; JL Gordeeva in biotechnology, D.R. Wada; D.W.A. Bourne; S. Neuhoff in medicine, C. Cobelli, D.M. Foster, M .; Hakman, Groth T .; D. Noble in pharmacology and RA Polouektov; D. G. Rossiter; G. Alexandre, VV Petrenko in agriculture.

The works devoted to different types of mathematical modeling of living system regulatory mechanisms, B. Goodwin, J.Smith, M. Eigen, V.A. Ratner, E.E. Selkova, D.S. Chernavsky (subcellular level); Antomonov, Sendov, R. Tsanev (cellular level); L.I. Lischetovich, Y. Kibardin, K.K. Dzhanseitov (organ-tissue level); N. Rashevsky, AM Molchanov, GI Marchuk (organismal level) and other are discovered basics mechanisms of biosystem regulation at considered levels, given the use of mathematical modeling to solve medical and biological problems, and analysis of biological processes. However, to date, there is no single approach to the creation of a system of mathematical models and effective methods for the quantitative analysis of the functioning of the regulatory mechanisms of cellular communities, taking into account spatial and temporal organization, practically there are not research on the study of non-linearity and cooperative biological processes on the basis of allocation of functional unit of cell communities.

METHODS

The analysis of literary data (A. Hem, D. Kormak; K.A. Zufarov with co-authors; P. Kemp, K. Arms; L.N. Seravin and others) shows, that complexity of the organization of multicellular organisms is caused by evolutionary developed "work division" between cells and fulfillment of special systems of organs bodies for performance of the basic vital functions. Research of the cellular organization of multicellular organisms shows existence of certain subcellular elements of tissues and organs - the cellular communities which are carrying out their elementary functions. Cellular communities consist of many thousand the cells united in homogeneous groups interconnected with each other of cells. Each cellular community provides the existence by proliferation, differentiation and fulfillment of specific functions. In cellular community there are exist growing (after division), buffer (after performance of specific functions) and growing age cells.

From the point of view of theoretical biology, epimorphism sets of biological functions of organisms (N.Rashevski) and identity of their components at existence of the big variety of the spatial organization and functional activity of organs and tissue of vegetative and animal

organisms leads to thought on existence of a universal subsystem of organs and tissues which are carrying out the basic set of elementary functions of living organisms (renovation, specialization, metabolism with environment and fulfillment of specific functions) - a functional unit of cellular communities (FUES), spatial and functional formation from which makes organs and tissues of multicellular organisms.

Following definition is entered**:** multiplying, growing, differentiating, carrying out specific functions, ageing cellular groups which are closely functioning, as an unit, is called functional unit of cellular communities - FUES (Figure 1). Introduction of FUES concept allows to effectively investigate control mechanisms in cellular communities using method of mathematical modeling. Here, as well as in case of the concrete cellular communities considered in chapter 1, three ways of mathematical modeling when it is considered number dynamics of homogeneous groups of cells, regulation mechanisms of cellular functions and spatio-temporal organization of FUES are possible.

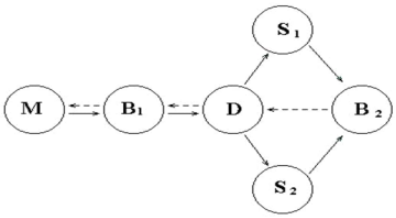

Figure1. *The basic scheme of cellular mutual relations in FUES. M is the group of divided cells; B_1 is the growing cells; D is the differentiated cells; S_1 S_2 is the cells which are fulfilling specific functions; B_2 is the ageing cells; arrows designate transitions in normal conditions, and dotted arrows are transitions under certain stressful conditions*

In the given chapter the general equations of quantitative ratio of FUES cells presented, questions of its qualitative and quantitative research are considered. If we have interest in pattern change of cells quantity in FUES separate zones, then supposing certain assumptions (constancy of transitions time from a zone to zone, dependence of FUES condition at present only from the previous condition etc.) we can use methods of discrete analysis. Choosing the transitions operator from one condition of FUES to another, we can consistently receive all dynamics of FUES conditions during the discrete moments of time from the initial condition of FUES expressing cells quantity in separate zones. Imposing certain conditions on FUES dynamics, we can define values area of transitions operator, i.e. a structural portrait of model, which will allow us to reveal a possible class of mutual relations between separate FUES zones. Further, we can define area of acceptable initial conditions from an observance condition that elements sets in concrete FUES zones at $T_0 < T$ are not empty (T is existence time of FUES, T_0 is a threshold of FUES maturity). The area of transitions operator values form one FUES condition into another together with area of admissible initial values allow to investigate regularities of FUES existence and functioning in various biosystems using methods of discrete analysis and to use its for getting practical results under the admitted conditions. If we consider big FUES class then conditions of transitions time constancy and dependence of FUES condition at present only from the previous condition may not be observed. In such cases, effective methods of FUES research are methods of mathematical modeling based on the functional equations.

Fundamental preconditions of researches on mathematical modeling of cellular functions are works by N. Rashevski, J. Watson and F. Crik, F.Jakob and Z. Mono, L.N. Seravin, B. Sendov, R. Tsanev, B. Goodwin, B.N. Hidirov, etc. in which the structurally functional organization of hereditary units, regulatory mechanisms of intracellular activity and possible ways of their quantitative description are sequentially opened. Meaning importance of biosynthetic processes in functioning of biosystems, considering time mutual relations in system of cells regulation, B.N.Hidirov has developed advanced system of the equations of protein synthesis [12]

$$\frac{dC_i(t)}{dt} = \frac{-\sum_{j=1}^{n} a_{ij} P_j^{n_j}(t-\tau_2)}{1+\sum_{j=1}^{n} d_{ij} R_j^{m_j}(t-\tau_2)} - \frac{\ln 2}{T_{C_1}} C_i(t) \quad ;$$

$$\frac{dP_i(t)}{dt} = q_i C_i(t-\tau_3) - \frac{\ln 2}{T_{P_i}} P_i(i) \quad ; \qquad (1)$$

$$\frac{dR_i(t)}{dt} = \rho_i P_i(t-\tau_3) - \frac{\ln 2}{T_{R_i}} R_i(t) \quad ,$$

where C_i (t), P_i (t), R_i (t) are the values characterizing concentration RNA information, protein-enzymes and repressors; T_x is the value characterizing time of half-decay of substance X; $\{a\}$, $\{d\}$, $\{q\}$, $\{p\}$ are non-negative constants; t_1, t_2 are the value characterizing times of transitions of biomolecules in nuclear-cytoplasm systems; t_3 is the time necessary for repression activation; n is quantity of functioning genes. The equations (1) used for the quantitative

description of regulation of cellular functions during modeling of cellular communities.

Modeling homogeneous cellular groups functioning based on of equilibrium models of regulatory mechanisms of cells, along with introduction of scale multipliers, allows developing comprehensible imitating models of cellular communities of multi cellular organisms.

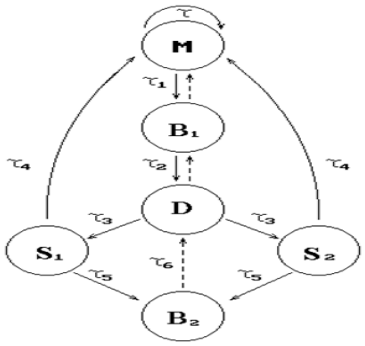

Figure2. *Basic scheme of time mutual relations in FUES*

The concrete equations describing cells quantities dynamics in separate FUES zones are considered. Let $X_1(t), X_2(t)..., X_6(t)$ be the sizes characterizing quantity of dividing, growing, differentiated, carrying out specific function (for simplicity in FUES performance of two specific functions is provided) and ageing cells at the time moment t, accordingly.

The most important in functional sense zone in FUES is the division zone where cells multiplying by mitosis. Reproduction velocity depends on cell quantity which potentially capable to division, effectors and nutrients. If we admit, that during evolution FUES were formed with functions useful for an organism then we can assume, that the effectors quantity and nutrients arriving in division zone depends on performance degree cellular community of specific functions, i.e. from quantity of cells in zones S_1 and S_2. Account of "pressure of environment" effect (end-product inhibition or analogue of Novak-Stsillard-Umberger effect) and time mutual relations $\{\tau\}$ on the basis of FUES basic scheme (Figure 2) assumes a choice as a mathematical apparatus of system nonlinear differential-delay equations during quantitative research of cellular mutual relations in functional unit of cellular communities of multicellular organisms.

The developed equations of mathematical model of number dynamics FUES homogeneous cellular groups have the following form:

$$\begin{aligned}
\frac{dX_1(t)}{dt} &= a_1\Big(\prod_{k=1}^{1,4,5} X_k(t-\tau_6)\Big)e^{-\sum_{j=1}^{6}\delta_j X_j(t-\tau_6)} + b_1 X_2(t-\tau_1) - a_2 X_1(t);\\
\frac{dX_2(t)}{dt} &= a_2 X_1(t-\tau_1) + b_2 X_3(t-\tau_2) - (b_1+a_3)X_2(t);\\
\frac{dX_3(t)}{dt} &= a_3 X_2(t-\tau_2) + b_3 X_6(t-\tau_4) - (b_2+a_4+a_5)X_3(t);\\
\frac{dX_4(t)}{dt} &= a_4 X_3(t-\tau_3) - a_6 X_4(t);\\
\frac{dX_5(t)}{dt} &= a_5 X_3(t-\tau_3) - a_6 X_5(t);\\
\frac{dX_6(t)}{dt} &= a_6\big(X_4(t-\tau_5) + X_5(t-\tau_5)\big) - (a_7+b_3)X_6(t).
\end{aligned} \qquad (2)$$

Here a_1 is the parameter expressing resource insurance in proliferative zones; a_i, b_1, b_2, b_3 are specific velocities of cells migration ($i = 2..., 7$); d_j ($j = 1, 2, \ldots, 6$) are the parameter expressing closeness level in cells group of j-th zones ($d_j \geq d > 0$); τ_j ($j = 1,2..., 6$) are time mutual relations (the factors expressing times, necessary for cells migration from a zone in a zone). Next section is devoted to analyzing the interconnected activity between molecular-genetic systems of hepatocytes and hepatitis B viruses taking into account microRNA action.

RESULTS

Infection with the hepatitis B virus (HBV) remains a global health problem and it is estimated that about 2 billion people worldwide are infected with this virus, more than 350 million people are sick. Chronic HBV infection can lead to primary carcinoma of the liver. The genome of the hepatitis B virus encodes microRNA. These viral microRNAs can participate in suppressing the expression of own viral genes. The regulatory mechanisms of microRNA action have not been studied in detail. Disclosure of the regulatory mechanisms of the microRNA action will help to determine the mechanisms of formation and development of the infectious process at viral hepatitis B at the molecular genetic level and will allow finding effective ways for targeted therapeutic and preventive influence on the molecular-genetic system of the liver cells. Taking into consideration that the hepatitis B virus by its microRNA affects the cell, suppressing it (see Figure 3), then equations of minimal mathematical model based on (1)-(2) for interconnected regulatorika between hepatocyte and viral

microRNA molecular-genetic systems have the following kind

$$\frac{\theta_1}{h}\frac{dX_1(t)}{dt} = a_1 X_1(t-1)e^{-X_1(t-1)-X_2(t-1)} - X_1(t);$$
$$\frac{\theta_2}{h}\frac{dX_2(t)}{dt} = a_2 X_1(t-1)X_2(t-1)e^{-X_1(t-1)-X_2(t-1)} - X_2(t), \quad (3)$$

where $X_1(t)$ is the concentration of hepatocyte mRNA; $X_2(t)$ is the concentration of the hepatitis B virus microRNA; θ_1, θ_2 are corresponding average activity durations of hepatocyte and hepatitis B virus molecular-genetic systems, respectively; h is the time radius of the cell (the time required for carrying out the feedback of molecular genetic systems); a_1, a_2 are non-negative constants, expressing the resource availability for considered genes systems and products.

The system equation (3) has a trivial equilibrium position, has instability of infinitely distant points in the first quadrant of phase space and a nonnegative solution for nonnegative initial values of the functions. The coordinates of the equilibrium position $\xi(\xi_1, \xi_2)$ are determined from equations

$$a_1\xi_1 e^{-\xi_1-\xi_2} - \xi_1 = 0;$$
$$a_2\xi_1\xi_2 e^{-\xi_1-\xi_2} - \xi_2 = 0. \quad (4)$$

Researching equation (4) solutions we find that when

$$a_1 > 1, \quad a_2 > e$$

There are non-trivial equilibrium positions for equation (3).

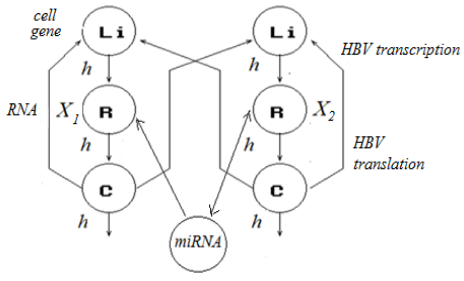

Figure3. *Interconnected regulatorika between hepatocyte and viral microRNA molecular-genetic systems*

Let us analyze the stability nature of equilibrium positions for equation (3).

Introducing small $z_1(t)$, $z_2(t)$ near $\xi(\xi_1, \xi_2)$ we have

$$X_1(t) = \xi_1 + z_1(t), \quad X_2(t) = \xi_2 + z_2(t).$$

After linearization we have

$$\frac{\theta_1}{h}\frac{dz_1(t)}{dt} = \alpha(1-\xi_1)z_1(t-1) - \alpha\xi_1 z_2(t-1) - z_1(t);$$
$$\frac{\theta_2}{h}\frac{dz_2(t)}{dt} = \beta\xi_2(1-\xi_1)z_1(t-1) - \beta\xi_1(1-\xi_2)z_2(t-1) - z_2(t),$$

Where

$$\alpha = a_1 e^{-\xi_1-\xi_2}; \quad \beta = a_2 e^{-\xi_1-\xi_2}.$$

In the case of a trivial equilibrium position, we have $\alpha = a_1 e$; $\beta = a_2$ and

$$\frac{\theta_1}{h}\frac{dz_1(t)}{dt} = a_1 z_1(t-1) - z_1(t);$$
$$\frac{\theta_2}{h}\frac{dz_2(t)}{dt} = -z_2(t). \quad (5)$$

Analysis equation (5) shows that there is stability for trivial equilibrium position at $a_1 < 1$. Near non-trivial equilibrium positions we have the following characteristic equation

$$\left(\frac{\theta_1}{h}\lambda - 1 + (1-\xi_1)e^{-\lambda}\right) - \left(\frac{\theta_2}{h}\lambda - 1 - e^{-\lambda}\right) = 0. \quad (6)$$

Analysis equation (6) shows that there is the stability by X_1 and there is the instability possibility for given equilibrium position by X_2 at, $\ln a_1 > 1 + \frac{\theta_1}{h}\eta\sin\eta - \cos\eta,$

Where η is the root of the following equation?

$$\eta = -\frac{h}{\theta_1}tg\eta, \quad 0 < \eta < \pi.$$

The presence of a trivial attractor means that for the elements activation of the regulatory system, it is required a certain threshold influence that removes the system from the basin of the trivial attractor. The existence of non-trivial equilibrium positions means that considered system has a potential functional activity with an infinite attractor basin. In addition for regulatorika equations we can use approximated functional-differential equations and its discrete analogy when we consider the concrete biological systems [13-24]. It is necessary to note that discrete recurrent equations as model systems for equation (3) are especially useful, because, in this case we can apply such methods as Lamerey diagrams construction, calculation of Lyapunov number, definition of "chaotic degree".

Computer investigations with model equations for equation (3) have shown that the non-trivial attractor can lose own stability depending on various time delay and external influence according regulatorika laws and can have such solutions behavior that can be identified as normal functioning (stationary regime and regular oscillation mode or Poincare type limit cycles and as anomalous behavior (irregular oscillations and the "black hole" effect.

This allows to model the normal and anomalous states of real biological systems and to solve correction problems to improve their functioning.

Researches show that in chaos area there are small regions with normal behavior called "r-windows". Quantitative researches have shown that the basic characteristics of "r-windows" (quantity, the sizes and location) have nonlinear, difficult character. For example, if parameters of resource availability and aassociativity are increasing then it does not necessarily mean that number of "r-windows" must to increase. The organism, using adaptive mechanisms, can enter into the nearest region of regular decisions. It means normal activity of biosystem. Dynamics of Lyapunov number, calculated on PC for discrete analogy for model system (2), help to estimate "chaotic degree" and to investigate the small regions with normal regulatorika ("r-windows") in chaos area at various parameters values (Figure 4).

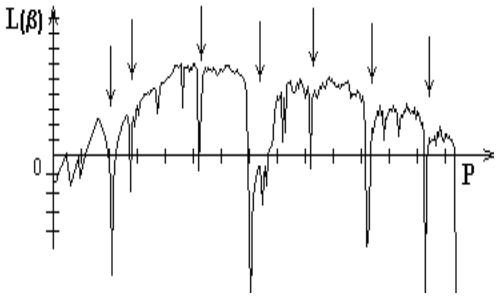

Figure4. *Dynamics of Lyapunov number in the model system for equation (2) (arrows show "r-windows").*

A common analysis of equation (3) and a series of computational experiments make it possible to determine that the hepatitis B virus's molecular-genetic system have an influence on the hepatocyte based on the *inhibition mechanism*. The functioning suppression of the hepatocyte molecular-genetic system is directly proportional to the activity level the virus's molecular genetic system (in particular, to the level of microRNA concentration). Moreover, suppression has an exponential nature. This means that the suppression intensification occurs not in a linear and not in a multiple, but exponential degree. Evidently, this mechanism determines the often observed transcendence of virus's molecular-genetic systems in mutual functioning.

The next mechanism of interaction between hepatocytes and hepatitis B viruses we can reveal by analyzing solutions behavior in dependence on the parameters changing. The solutions transition from the normal behavior into the area of unpredictable behavior and sharp destructive changes occurs with the increased growth of the resource parameter value. Consequently, the mechanism for the interaction between hepatocytes and hepatitis B viruses is the intensification mechanism of genes productivity in hepatocyte, which is imposed by hepatitis B viruses. The analysis results show that there is the mechanism of temporary improvement of the hepatocyte state in the field of unpredictable behavior. A hepatocyte, which is in area of unpredictable behavior, may enter inside a small region with "r-windows" and relatively improve its state, since the systems behavior inside the "r-windows" is regular. Researches results and defined regulatory mechanisms allows, at computer support of laboratory and clinical researches of infectious process at hepatitis B, to define molecular-genetic bases of pathogenesis at different level of microRNA concentration, to carry out diagnostics and forecasting of characteristic stages of disease course during hepatitis B.

CONCLUSION

The formulated basic structurally functional organization of the cells united by performance of the general cellular functions - a functional unit of cellular communities (FUES), allows carrying out the analysis of regulatory mechanisms of multicellular organisms cellular communities from uniform positions. FUES formulation opens wide opportunities at mathematical modeling of the most universal, peculiar to all real cellular communities, regulatory mechanisms of animal organisms at sub cellular level of its organization.

Results of scientific researches were applied for quantitative researches of mechanisms of the interconnected activity of genetic systems of liver cells and hepatitis B virus. Existence of the following regimes of regulatorika between molecular-genetic system of hepatitis B viruses and hepatocytes has been revealed: monotonous reduction, stationary condition, self-oscillations,

irregular fluctuations (chaos), sharp destructive chaos death ("black hole" effect).

Researches results show existence of the following regulatory mechanisms during diseases development: the inhibition mechanism, the mechanism of mobilization of potential possibilities of an organism at anomalies, the mechanism of temporal improvement of system.

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