MODELLING OF REGULATION MECHANISMS OF CELLULAR COMMUNITIES

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ABSTRACT. Quantitative study of regulation mechanisms of living systems assumes to take into account the hierarchical interconnection of the different involved organization levels, which is not methodologically designed and is met extremely seldom in the concrete cases. This clearly emerges when we are modelling the regulation mechanisms of cellular communities. In spite of great successes achieved by molecular biology, genetics and cytology, which allow to build sufficiently motivated mathematical models of cellular regulation mechanisms, modelling their interconnected activity causes great difficulties. In the paper possible variant of models and the software for quantitative study of cellular communities regulation mechanisms are discussed.

Quantitative study of regulation mechanisms of a living system supposes taking into account of the hierarchical interconnection of the different levels of its organization which is not methodologically designed and at the practical modelling is met extremely seldom [1-3]. This first of all concerns to modelling of the regulation mechanisms of cellular communities. Despite great successes of molecular biology, geneticists and cytology, which are allowed to the build sufficiently motivated mathematical models of regulations mechanisms of cells functioning, modelling of their interconnected activity causes the greater difficulties. In the work, a possible variant of a model and a software for quantitative study of cellular communities' regulation mechanisms are considered. Cells of multicellular organisms, during performing their general functions, are united to structured-functional formations which consist of distinctive areas. They form a universal subsystem of organs and tissues of the organism and fulfil main collection of an elementary function of living systems (renovation, specialization, metabolism with an environment, fulfilling of specific functions and aging). These universal subsystems are Functional Units of Cellular Communities (FUCC), spatial and functional formation from which organs and tissues of a multicellular organism are forming [4-6]. Principle of biological epimorphism [7] is the theoretical base of FUCC, and the principles of a block organizations [8] can be used for the construction of cellular systems of organs and tissues on the basis of interconnected FUCC. Definition: a connected cells set (on space or (and) at the time) is called FUCC, if in the set there are dividing (M), growing (B_1), differentiating (D), fulfilling of specific functions ($C_1, ..., C_n$) and aging (B_2) cellular groups, functioning interconnected, as a unit whole (n is a quantity of specific FUCC function) [9]. Organs and tissues are considered as a system in which an elementary component is FUCC in the given approach. Used methods of functional units modelling depend on their worked-out degree, the usual traditions at research of the given class of the phenomena and concrete features of a considered functional unit. We developed two approaches for quantitative research the regulation mechanisms of cellular communities on the basis of FUCC: research of the most common laws of a cellular groups dynamics in

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community and simulation of cellular communities taking into account the mechanisms of intracellular processes regulation [8-10]. For simplicity, let us suppose the presence of two specific function (C_1 and C_2) and consider one of the possible variants for research of the regulation mechanisms of cells amount in FUCC separate zones (M, B_1, D, C_1, C_2, B_2) using functional-differential equations. Let $X_i(t)$ $(i = 1..., 6)$ be the sizes, describing number dividing, growing, differentiating, fulfilling of specific functions and aging cells; t is the current time. Let us suppose, that a change law for dividing cells amount depends on cells sizes which are in M, C_1, C_2 and in B_1 FUCC zones [6,8,11]. Taking into account the time mutual relation in FUCC and cells migrations from proliferation zones, we can write the equation for $X_1(t)$

$$\frac{dX_1(t)}{dt} = a_1(\prod_{k=1}^{1,4,5} X_k(t-\tau_k))e^{-\sum_{j=1}^{6}\delta_j X_j(t-\tau_6)} + b_1 X_2(t-\tau_1) - a_2 X_1(t), \tag{1}$$

which is basic in FUCC model and its choice is determined by the concrete analysis of influence character of each cell kinds to generation speed. On the basis of interrelation between FUCC zones, we offer the following equations system for changing of the homogeneous groups of FUCC cells:

$$\begin{aligned}
\frac{dX_2(t)}{dt} &= a_2 X_1(t-\tau_1) + b_2 X_3(t-\tau_2) - (b_1 + a_3)X_2(t);\\
\frac{dX_3(t)}{dt} &= a_3 X_2(t-\tau_2) + b_3 X_6(t-\tau_6) - (b_2 + a_4 + a_5)X_3(t);\\
\frac{dX_4(t)}{dt} &= a_4 X_3(t-\tau_3) - a_6 X_4(t);\\
\frac{dX_5(t)}{dt} &= a_5 X_3(t-\tau_3) - a_6 X_5(t);\\
\frac{dX_6(t)}{dt} &= a_6(X_4(t-\tau_5) + X_5(t-\tau_5)) - (a_7 + b_3)X_6(t).
\end{aligned} \tag{2}$$

Equations (1) and (2) are the closed system of the functional-differential equations for FUCC cells dynamics. Taking into account that

- in the growth (B_1),differentiating (D), fulfilling of specific functions (C_1, C_2) and ageing (B_2) zones, there are not cell "birth";
- in time aspect, in these zones change of cells sizes occur faster, than in a division zone (M),

we can admit equilibrium nature of cells quantitative changes in considered zones for qualitative research. Then concrete values of cells size in considered zones can be calculated by size values of dividing cells and the equations system (1), (2) can be simplified. Here, under certain conditions on parameter values of the considered equations, it is possible to use known A.I. Tihonov's theorem [12] about a reduction of the differential equations systems

and biophysical methods for reduction of the equations number of mathematical models for biological processes [13]. Then the characteristic behaviour of FUCC near stable state can be investigated based on the following functional-differential equation

$$\frac{dX_1(t)}{dt} = PX_1^3(t-h)e^{-dX_1(t-h)} - \rho X_1(t), \tag{2}$$

functional equation

$$X_1(t) = \frac{P}{\rho}X_1^3(t-h)e^{-dX_1(t-h)} \tag{3}$$

and discrete equation

$$X_{1k+1} = \frac{P}{\rho}X_{1k}^3 e^{-dX_{1k}}, \tag{4}$$

where X_{ik} is a value characterising a size of dividing cells on k^{th} step of functioning (the size of a step corresponds to average time of cells maturing for specific functions performance); r is a value characterising duplication speed of FUCC cells; parameter values P, d, ρ can be calculating based on the appropriate factors values of the equations (1) and (2) [10, 14]. Analyses results of the characteristic solutions (3) - (5) using methods of qualitative research for the delay-differential equations [14,15] have shown presence of trivial equilibrium state and an existence opportunity of nontrivial equilibrium state A, B $(A \leq B)$, instability A and various behaviour of solution near B: a steady stationary state, Pouncare type limit cycles and irregular fluctuations; existence (at the consideration (5)) of an effect of the oscillatory solutions failure to the trivial equilibrium state ("black hole" effect) [14, 16]. Regularities for an origin and development of the dynamic chaos for (5) were analyzed by calculation of Lyapunov's number and construction of Lamerey's diagrams [6,14,16]. Developed based on the given approach, the software for the quantitative research of regularities of cells number's dynamics in the cellular community (FUES) allows to carry out a computing experiments with the concrete cellular communities of organs and tissues of vegetative and animal organisms [17]. Let us consider the second approach for quantitative research of regulation mechanisms of cellular communities. On the basis of entered FUCC we developed a model provision and a software "Imitating Cellular Model of Development (ICMD)" for modelling of regulation mechanisms of cellular communities of vegetative and animal organisms. At models construction for regulation mechanisms of the concrete cellular functions (division, growth, differentiation, fulfilling of specific functions and ageing) based on the Jacob-Mono's regulation schemes, B. Goodwin, B. Sendov, R. Tsanev, B.N. Hidirov approaches are used [9,10,18]. Characteristic construction particularities of equations for regulation mechanisms of cellular functions are visible from the following model equations

for regulation mechanisms of cellular division (mitosis) [18,19]:

$$
\begin{gathered}
\frac{dC_i(t)}{dt} = \frac{\epsilon\epsilon_i a_i D(t)}{1 + \sum\limits_{j=1,m,r} \sigma_{ij} R_j(t-\tau_2)} - \frac{T + T_{C_i}}{TT_{C_i}}(ln2)C_i(t); \\
\frac{dX_i(t)}{dt} = \nu_i C_i(t-\tau_1) - \frac{T + T_{X_i}}{TT_{X_i}}(ln2)X_i(t); \\
\frac{dr(t)}{dt} = kP_r(t)C_r(t); \\
\frac{dP_1(t)}{dt} = g_1 X_1(t) - \frac{T + T_{P_1}}{TT_{P_1}}(ln2)P_1(t); \\
\frac{dP_r(t)}{dt} = g_r X_r(t) - \frac{T + T_{P_r}}{TT_{P_r}}(ln2)P_r(t); \\
\frac{dP_m(t)}{dt} = g_m X_m(t) - \frac{T + T_{P_m}}{TT_{P_m}}(ln2)D(t)P_m(t); \\
\frac{R_1(t)}{dt} = g_1 X_1(t) - h_1(R_1(t) - NR_e(t-\tau_3)); \\
\frac{dR_m(t)}{dt} = g_m X_m(t) - \frac{T + T_{R_m}}{TT_{R_m}}(ln2)R_m(t); \\
\frac{dR_e(t)}{dt} = h_1(R_1(t) - NR_e(t)) - \frac{T + T_{R_e}}{TT_{R_e}}(ln2)R_e(t); \\
\frac{dD(t)}{dt} = k_D(1-\epsilon)(2D_0 - D(t))t_S;
\end{gathered}
\tag{6}
$$

$$
\epsilon = \begin{cases} 0- & \text{in} \quad S, M \\ 1- & \text{in} \quad G_1, G_1 \end{cases} \qquad \epsilon_1 = \begin{cases} 0 & \text{at} \quad R_m(t) > A_1 \\ 1 & \text{at} \quad R_m(t) \le A_1 \end{cases}
$$

$$
\epsilon_r = \begin{cases} 0 & \text{at} \quad R_1(t) > A_r \\ 1 & \text{at} \quad R_1(t) \le A_r \end{cases} \qquad \epsilon_m = \begin{cases} 0 & \text{at} \quad R_i(t) > A_m \\ 1 & \text{at} \quad R_i(t) \le A_m \end{cases}
$$

Here $i = 1, r, m$ designates conformity to functional, plastic and mitotic genes group; $C_i(t), X_i(t), P_i(t), R_i(t), (i = I, r, m)$ are m-RNA concentrations indices, initial groups of proteins, protein-ferments and repressors accordingly; $R_e(t)$ is repressors concentration in the environment; $D(t)$ is DNA quantity; D_0 is DNA quantity before mitosis; t_s is the time counted from the S-period beginning; N is generated cells quantity at the time moment t; T is mitosis duration as a whole; T_x is the time of substance x half-decaying; all coefficients of (6) are positive constants; S, M, G_1, G_2 are mitosis periods.

ICMD allows to carry out the computing experiments with spatial architectonics dynamics of cellular communities and regulation laws for intracellular processes. Using ICMD for the analysis of interaction mechanisms between the cotton fruit cells and the fungus, causing the wilt, for plants transition to flowering and adaptive reactions of an organism digestive system to external influences have shown efficiency of regulation mechanisms modelling for the cellular communities of vegetative and animal organisms based on the FUCC [6,8,10,13].

Approbation of the concrete model and the software on regulation mechanisms imitating modelling for cellular communities was carried out during researches the mechanisms of the structurally functional organisation of nutrients absorption in an organism digestive system (together with employees from TGMI-1 faculty of histology and embryology). In the considered process the leading role belongs to the "kript-fiber" system is the basic functional unit of an organism digestive system [11, 20].

During the model construction for the "kript-fiber" cellular community, the concrete equations for proliferating, differentiating, secreting, absorbing cells and the software for computing experiments in a 10 x 6 area of model cells were developed. On this cell field the cellular structure were simulated and parameters of internal (blood) conditions and external (the intestinal gap) environments were represented by the appropriate matrixes. At modelling of the absorbtion process, the glycocalix layer activity, hidrolitic-transport and metabolic enzymes was imitated. A cells moving was modelled based on the pressure created by proliferous pul and speed of ageing cells husking in the intestines gleam. As a concrete object the kript-fiber of the lean gut [20] was considered.

During computing experiments, the external and internal conditions environments were considered: daily change of parameters of acting substances in an intestines gleam, various concentration of carbohydrates, amino acids and fats in blood system, loading an organism by fat and etc. The increase of dividing cells number at night was revealed, that caused to accumulation of reserve cells and significant speed increase of updating cells in the morning. Computing experiments with loading an organism with fat have shown consecutive strengthening of absorbed cells activity and cells migration due to reduction of differentiation time and cells existence in a growth zone, involving growing cells in division and increase of dividing cells in proliferation zone and, finally, due to reduction of cell division time in proliferation zone during increase process of fat concentration in the intestines gleam. Oscillatory character of cells number and fiber heights in wide limits (up to 25-30 percents) was observed, that is, apparently, a natural mode of "kript-fiber" system functioning. The carried out researches have shown the big sensitivity of model to external influences [20]. Based on the developed model for quantitative researches of regulatorika of cellular communities, together with the employees from HNC TSU faculty, the interaction laws between the cotton and the fungus V.dahliea causing wilt were analysed [21]. Interrelation mechanisms between imperfect fungus cells and higher plants cells at the norm and at some extreme influences, causing to the dynamic balance collapse of a complex of interconnected exchanging reactions were investigated. Results of computing experiments have shown that there is a symbiotic mode of functioning the cotton and the fungus. The collapse of this symbiotic regime lead to suppression of the cotton growth and development by the fungus. Preservation of a symbiotic mode prevents plants diseases by wilt and creates favorable living condition for coexisted kinds. During computing experiments the possible changes in regulation system of the symbiotic complex "the higher plant and the parasitic fungus" were investigated under stressful conditions. General characteristics of model behaviour of the interconnected activity between the cotton cells and the fungus in all cases of extreme influence were approximately identical. After the short latent period in a cotton fruit cells there was a formation braking of protein-enzymes, further - a metabolism failure and finally there came activity suppression of a cotton fruit cells [21]. The developed approaches for modelling regulation mechanisms of cellular communities were successfully applied at the analysis of cellular mechanisms of a cotton growth and development [22] and at revealing laws of a population dynamics [3,23]. The concept formulation for a functional unit of cellular communities - FUCC, development of mathematical and computer models for dynamics of homogeneous cellular groups will open, in our opinion, the big opportunities for modelling researches of regulation mechanisms of cellular systems of animal and vegetative

organisms at the norm and anomalies. The common qualitative and quantitative analysis of the FUCC equations allows to reveal cells dynamics laws in FUCC consecutive zones (divisions, growth, differentiation, fulfilling of specific functions and ageing), and imitation modelling researches allow to define quantitative laws for existence of concrete cellular structures in view of cells spatial architectonics and intracellular processes regulation. This research was partially supported by grants No 40-96 and No 61-2000 of Funds of Support of Basic Researches AS RUz.

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