SIMULATION OF CELLULAR COMMUNITIES MECHANISMS

Mahruy Saidalieva

Received February 27, 2006

Abstract. The age model of cellular communities is considered. Delay-differential equations and their model systems for cellular communities are constructed and quantitatively analyzed. It is determined that there are the following states: rest, stationary state, Poincaré type limit cycles, dynamic chaos and "black hole" effect. Regularities for the origin of dynamic chaos, "r-windows" regions and prediction problems for the determination of destructive changes - "black hole" effect, are investigated. The results of the developed approaches are applied to the quantitative analysis of cellular communities and the delay-differential equations of animal and plant organisms are considered.

1 Introduction. In the study of many biological problems the quantitative estimation of the behavior of communities of cells is required. Such communities of cells generally fulfill mutual functions necessary to a system activity [1, 2]. Especially, this is important for model investigations of regulatory mechanisms for cellular communities of an organism. Based on the principles of biological epimorphism [3] and the block structurally-functional organization of living systems [4, 5], the concept of Functional Unit of Cellular Communities (FUCC) as connected cells set (on space or (and) on time) with dividing (M), growing (B_1), differentiating (D), carrying out the specific functions ($S_1, S_2, ..., S_n$; n is the quantity of amount specific functions and usually, $n = 2$) and aging (B_2) cells has been developed. During FUCC functioning, its elements consistently pass from one homogeneous group to another consecutive homogeneous group of cells (Figure 1). Cells leave from homogeneous group (B_2) by a natural death or (if necessary) by a transition into homogeneous cells in D group, where cells are de-differentiated, preparing for repeated fulfilment of the specific functions. Cells transitions are carried out with some time delay and we get a temporal mutual relations in FUCC (Figure 2). Organs and tissues of the multicellular organisms can be considered as a system in which an elementary component is FUCC.

2 Delay-differential equations of FUCC. The method application for mathematical description of the regulatory mechanisms for living systems functioning (regulatorika) [6, 7, 8] allows carrying out the following formal system of delay-differential equations for FUCC regulatory mechanisms:

$$\begin{aligned}
\frac{dX_1(t)}{dt} &= f_1\left(X_1(t-\tau), X_2(t-\tau_1), X_4(t-\tau), X_5(t-\tau)\right) - a_1 X_1(t);\\
\frac{dX_2(t)}{dt} &= f_2(X_1(t-\tau_1), X_2(t), X_3(t-\tau_2)) - a_2 X_2(t);\\
\frac{dX_3(t)}{dt} &= f_3(X_2(t-\tau_2), X_3(t), X_6(t-\tau_5)) - a_3 X_3(t);
\end{aligned} \tag{1}$$

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

Key words and phrases. simulation, cellular communities, regulatory mechanisms, differential-delay equations, chaos.

$$\frac{dX_4(t)}{dt} = f_4(X_3(t-\tau_3), X_4(t)) - a_4X_4(t);$$

$$\frac{dX_5(t)}{dt} = f_5(X_3(t-\tau_3), X_5(t)) - a_5X_5(t);$$

$$\frac{dX_6(t)}{dt} = f_6(X_4(t-\tau_4), X_5(t-\tau_4)X_6(t)) - a_6X_6(t),$$

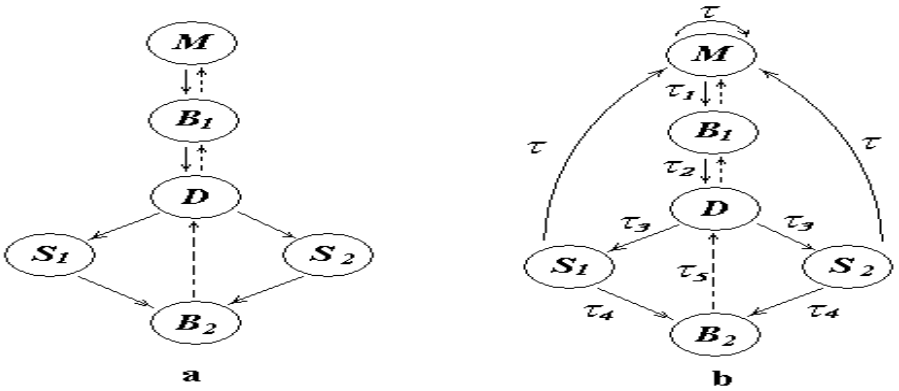

Figure 1: spatial-temporal organization of FUCC: **a** is the transitions scheme (continuous arrows are the determined transitions and dotted arrows are a probable return transitions); **b** is the temporal relations.

where $X_1(t), X_2(t), X_3(t), X_4(t)$ and $X_5(t), X_6(t)$ are the values, expressing the number of cells in homogeneous groups M, B_1, D, S_1 and S_2, B_2; $f_1(\cdot), f_2(\cdot)$,..., $f_6(\cdot)$ are homogeneous, continuous, non-negative functions of their arguments; $\{a\}$ are non-negative constants, expressing rate of change in number of cells in homogeneous groups, t is parameter of temporal relations (Figure 1). The uniformity and continuity of the given functions do not allow the appearing "ex novo" of elements in the considered community (elements can arise only in M group by duplication) and we have the well-known Virhov's principle as "each cell from cell". The non-negativity of considered functions provides that there is no negative number of cells during quantitative researches.

Within the framework of the assumptions, the first terms in the right hand side of (1) express rate of cell growth (due to duplication in M and cells transition in the others) in homogeneous group of community, and the second terms are velocities of their decrease due to transition into other groups and the natural destruction of cells in the B_2 group.

Stimulatory and inhibitory factors have a simultaneous effect on cell reproduction. Stimulatory factors for increase in number of cells in homogeneous M group are set of dividing cells and, probably, number of elements carrying out specific functions. This is FUCC sustenance during carrying out the specific functions necessary for FUCC community (for multicellular organism). Inhibiting factors can be quantitatively described using biological principle of "end-product inhibition" taking into account method for modelling regulatory mechanisms of living systems [6, 8]. Considering possible cell's transfer from M to B_1 (Figure 1) we have:

$$\frac{dX_1(t)}{dt} = aX_1(t-\tau)X_4(t-\tau)X_5(t-\tau)e^{-\sum\limits_{j=1}^{6}\delta_j X_j(t-\tau)} + \varepsilon_1 X_2(t-\tau_1) - a_1X_1(t) \qquad (2)$$

For other homogeneous groups, on the basis of the accepted assumptions, for transitions and temporal relations, in the elementary case, we obtain

$$\frac{dX_2(t)}{dt} = a_1X_1(t-\tau_1) + \varepsilon_2X_3(t-\tau_2) - (\varepsilon_1 + a_3)X_2(t);$$

$$\frac{dX_3(t)}{dt} = a_3X_2(t-\tau_2) + \varepsilon_3X_6(t-\tau_5) - (\varepsilon_2 + a_4 + a_5)X_3(t);$$

$$\frac{dX_4(t)}{dt} = a_4X_3(t-\tau_3) - a_6X_4(t); \tag{3}$$

$$\frac{dX_5(t)}{dt} = a_5X_3(t-\tau_3) - a_7X_5(t);$$

$$\frac{dX_6(t)}{dt} = a_6X_4(t-\tau_4) + a_7X_5(t-\tau_4) - (\varepsilon_3 + a_8)X_6(t),$$

where $\{a\}$ are positive values of the determined transitions, $\{\varepsilon\}$ are probable return transitions and δ_j are repression parameters ($j = 1,...,6$).

3 Model systems for FUCC equations. (2), (3) are the closed system of delay-differential equations. If we have continuous initial functions on a time interval equal to $\max(\tau, \tau_1,...,\tau_5)$ there exists a unique continuous solution obtained by a method of consecutive integration [9, 10]. For the analysis general regularities for FUCC dynamics we can assume that the number of dividing, fulfilling specific functions and aging elements is proportional to the total number of FUCC elements, $\tau_j = 0 (j = 1,...,5)$ and

$$X(t) = \sum_{j=1}^{6} X_i(t), X_1(t) = k_1X(t), X_4(t) = k_2X(t),$$

$$X_5(t) = k_3X(t), X_6(t) = k_4X(t);$$

$$0 < k_i < 1; i = 1, 2, 3, 4.$$

Summing (2) and (3) we obtain

$$\theta\frac{dY(t)}{dt} = pY^3(t-1)e^{-Y(t-1)} - Y(t), \tag{4}$$

where

$$Y(t) = X(\tau t); \theta = \frac{1}{\tau k_4 a_8}; p = \frac{ak_1k_2k_3}{k_4a_8}$$

and $\theta, p > 0$.

The same type of the equation can be obtained, if we assume that the processes are stationary in homogeneous groups of cells B_1, D, S_1 and S_2, B_2 of FUCC. Then the number of elements in these groups is proportional to the number of cells in homogeneous group M that leads to the equation such as (4) for number of cells in M. In the paper [11] it is shown the opportunity for approximation of delay-differential equation like (4) by the functional and discrete equations, if θ is small. Hence, if θ is small, then dynamics (4) can be qualitatively investigated on the basis of the functional

$$Y(t) = pY^3(t-1)e^{-Y(t-1)} \tag{5}$$

and the discrete equations

$$Y_{k+1} = pY_k^3e^{-Y_k}. \tag{6}$$

The condition is usually true for most of real biological communities (due to large values of feedback time and constant velocity of elements renovation in an organism) and the quantitative analysis for dynamics of considered cellular communities on the basis (6) is effective. The equation (6) is a very convenient equation for the qualitative analysis of FUCC dynamics due to its realization easiness on computer using the method of Lamerey diagram construction [12], calculations of Lyapunov parameter, Hausdorff, information and high dimensions [7].

4 Analysis the general regularities of FUCC dynamics. On the basis of the admitted assumptions it is possible to conclude, that solutions of (4)-(6) are in the first quadrant if initial conditions are positive. Using the standard technique for the analysis of critical points of delay-differential equations [13, 14, 15], for equilibrium points (ξ) of considered equations (4)-(6) we have

$$\xi = p\xi^3 e^{-\xi}. \tag{7}$$

It is obvious that there is a steady trivial attractor. Results of the qualitative analysis shows, that if

$$0 < p < e^2/4$$

then the equations (4)-(6) have only a trivial equilibrium, and if $p = e^2/4$ we have a non-trivial equilibria which is hardly appeared if $\xi = 2$. The further increase in value p ($p > e^2/4$) leads to its splitting on two non-trivial equilibria ξ_2, ξ_3

$$0 < \xi_2 < 2 < \xi_3 < \infty. \tag{8}$$

.

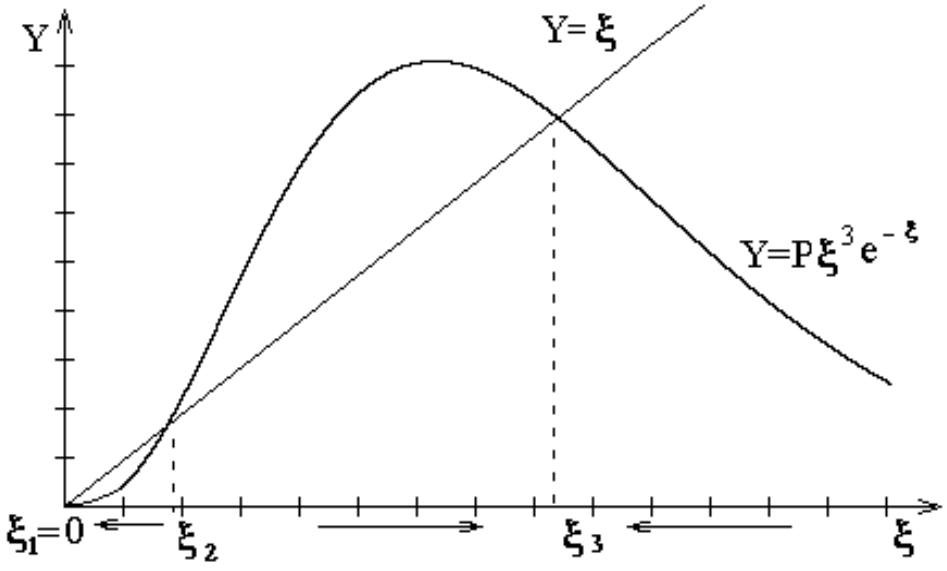

Figure 2: Attractors existence in the equations (7).

Qualitative analysis of (4)-(6) solutions shows, that in considered case the α-set consist of one element (ξ_2), and the ω-set has two elements - (ξ_1, ξ_3) (Figure 2). Non-trivial attractor ξ_3 has basin (ξ_2, ∞), and trivial attractor has basin (ξ_1,ξ_2) . Hence, attractor ξ_2 is called

the functional attractor. In the basin of ξ_2 we can carry out the quantitative analysis of FUCC dynamics.

For the analysis of non-trivial attractor stability we can use (if (8) is fully justly) the Lyapunov method of linearisation. Near ξ, for small $y(t)(Y(t) = \xi + y(t)$ at $(t))$, we have

$$\theta \frac{dy(t)}{dt} = (3 - \xi)y(t-1) - y(t). \tag{9}$$

The characteristic equation for (9) can be written in the form

$$(1 + 1/\theta)e^{\lambda} + (\xi - 3)/\theta = 0. \tag{10}$$

Real parts of roots of the transcendental equation (10) must be negative for stability of considered equilibria. We use the Hayse theorem [13]: the equation like (10) has a negative real parts if

$$1/\theta > -1;$$

$$\xi - 2 > 0;$$

$$(\xi - 3)/\theta < \rho \sin\rho - \cos\rho,$$

where ρ is a root of the equation

$$\rho = -\frac{1}{\theta}\tan\rho,$$

$0 < \rho < \pi$.

First condition is true for both non-trivial equilibria. According (8), the second condition is correct only for ξ_3. Hence, the non-trivial equilibrium point ξ_2 is unstable. Stability character of the second non-trivial equilibrium point ξ_3 is defined by third Hayse condition. The third condition may not always be satisfied. We consider the case $\theta = 1$. Then the condition for stability ξ_3 has the form

$$\xi < 3 + \rho \sin\rho - \cos\rho,$$

where ρ is a root of the equation

$$\rho = -\tan\rho$$

$(0 < \rho < \pi)$. This equation has the approximate numerical solution: $\rho = 2.03(\sin\rho = 0,896; \cos\rho = 0,443)$. Then third Hayse have the form: $\xi < 4.376$. According (7), if ρ grows, then ξ_3 monotonously increases. Hence, there are such values ξ_3 that the considered condition is not true and non-trivial attractor ξ_3 loses stability. It is accompanied by the occurrence Poincaré type limit cycles in neighbourhood of ξ_3.

5 FUCC dynamics at small θ. The case when q is small deals with rapidly reborn cellular communities with large feedback time ($a_8 \gg 1$, $\tau \gg 1$ in (4)). Then (5) and (6) can be used for the qualitative analysis of FUCC dynamics. Equation (6) is especially convenient due to an evident realizability of the solution (using method of Lamerey diagram construction), self-oscillations, irregular fluctuations and characteristics calculation of the deterministic chaos [12, 10]. On the basis of quantitative researches we show that (6) has the following states: rest, steady stationary state, self-oscillations, deterministic chaos and "black hole"effect (Figure 3). The "black hole"effect denotes that there is solution failure from functional attractor basin into trivial attractor. Note, that before direct solution failure we have quick maximal growth of number of FUCC elements.

Results of the quantitative analysis of Lyapunov number dynamics shows that in the field of the deterministic chaos there are small regions with regular fluctuations are called r-windows (Saidalieva, 1998).

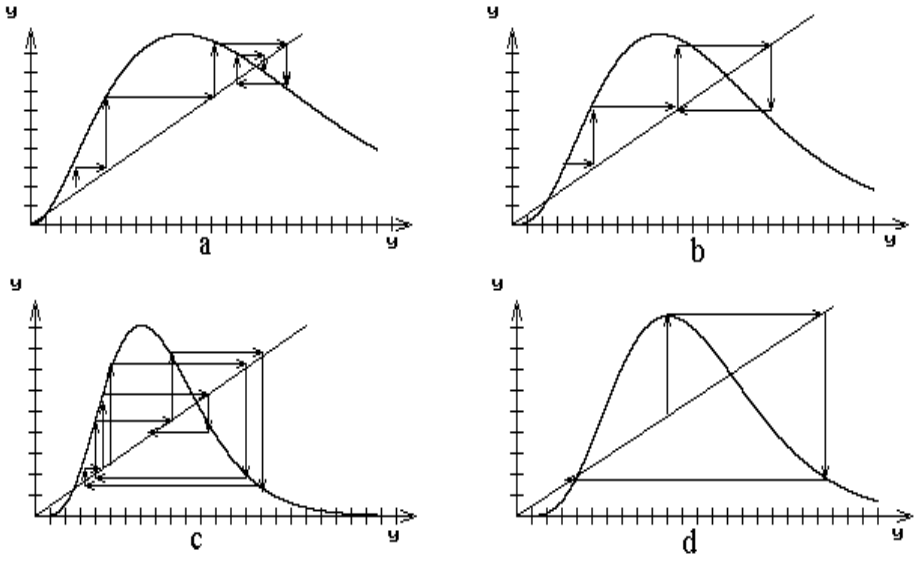

Figure 3: Lamerey diagrams, describing the basic states of (6) solutions behavior: **a** is a steady stationary state ($1.85 < p < 3.41$);**b** is a self-oscillation ($3.41 < p < 4.39$); **c** is an irregular fluctuation ($4.39 < p < 6.99$); **d** is a destructive change, "black hole" effect ($p > 6.99$).

6 Mini-FUCCs and their dynamics. In biological systems, in addition to the basic circuit for interactions between elements (Figure 1), there are a short regulation circuits; among these are stable or particularly stable structures in concrete cases. It can be appeared as the normal phenomenon like the adaptive answer to stressful influences, and as an abnormal pathological condition. This partial or fractal FUCCs is called a mini-FUCCs. Let us consider a few mini-FUCCs.

Such cells are observed in rapidly reborn cells at early development of an organism, in the animal epithelial tissues and in the cambial cells of plants. Using (2) and (3), for generative mini-FUCC (Figure 4, a) we get (for simplicity, we consider the case when $\tau_1 = 0$) :

$$\begin{gathered}\frac{dX_1(t)}{dt} = aX_1(t-\tau)e^{-\sum\limits_{j=1}^{2}\delta_j X_j(t-\tau)} - a_1X_1(t);\\ \frac{dX_2(t)}{dt} = a_1X_1(t) - a_2X_2(t),\end{gathered} \tag{11}$$

where all parameters are similar to parameters in (2), (3), however a_2 expresses the constant velocity of natural cells dying in homogeneous group B_1. The qualitative research (11) shows, that there are steady non- trivial stationary state and there appears Poincaré type limit cycles near non-trivial equilibria (ξ_1, ξ_2) :

$$\xi_1 = (1 + (a_1/a_2)/(\delta_2/\delta_1))^{-1}\ln(a/a_1);$$
$$\xi_2 = (a_1/a_2)\xi_1.$$

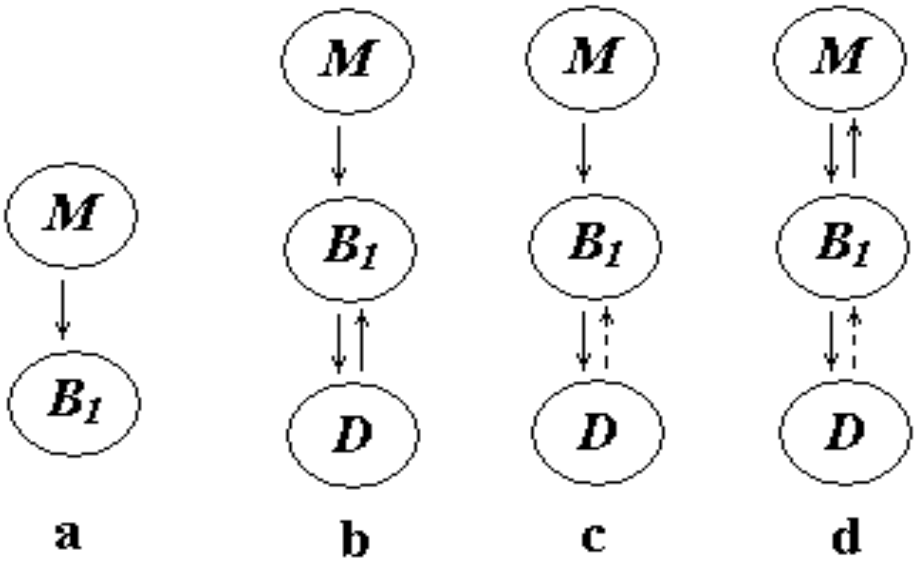

Figure 4: Generative mini-FUCCs.

If there is not the time factor in a feedback (it means that $\tau = 0$) then system of the equations (11) has not self-oscillations. Indeed, linearizing (11) near (ξ_1, ξ_2) at $t = 0$ we have the following characteristic equation

$$(\lambda + a_1\xi_1)(\lambda + a_2) + a_1^2\xi_2\delta_2/\delta_1 = 0.$$

The equation has only negative roots. Results of qualitative and quantitative research show that "black hole" effect is absent in the case of (11) and its model system has the form

$$Y_{k+1} = pY_k e^{-Y_k}, p = a/a_1.$$

Mini-FUCCs without dividing function

Such cells can exist in the blood, bone tissues, nervous system and in aging plants tissues at the norm, and in the liver, cardiac tissues, pancreas and in some other animal tissues at a pathology.

The analysis of the appropriated equations for the mini-FUCCs shows that the non-trivial equilibria is absent and number of mini-FUCC elements is gradually reduced.

7 Imitative modelling of cellular communities. Introduction of the concept and structural-functional organization of FUCC allow carrying out an operative quantitative research for realizing the imitative modelling of the cellular communities of an organism. In order to attain these goals, the mathematical and computer models of regulatory mechanisms of dividing, growing, differentiating and aging cells have been constructed on the basis of the established biological facts and theoretical attainments (Saidalieva, 1998). For example let us consider the equations of regulatory mechanisms for cellular differentiation constructed based on the competition of metabolic ways at genetic level, polynucleotide ensuring level and at level of the cytoplasm (Saidalieva, 1998)

$$\frac{dC_1(t)}{dt} = \frac{a_1 + a_2P_1(t-h)}{1 + b_1M_1(t) + b_2M_2(t)} - \frac{\ln\left[2\frac{V(t_0+T_{C_1})}{V(t_0)}\right]}{T_{C_1}}C_1(t);$$

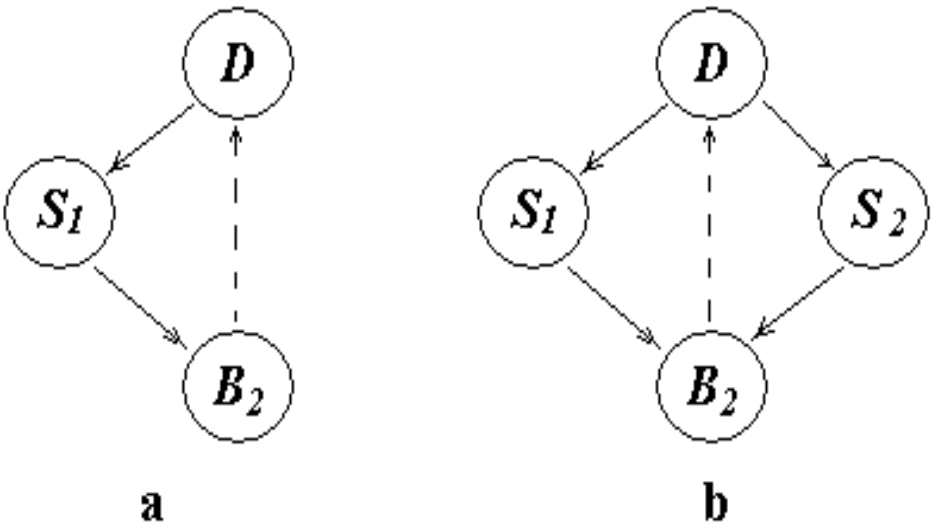

Figure 5: Mini-FUCCs without dividing function.

$$\frac{dC_2(t)}{dt} = \frac{a_3 + a_4 P_2(t-h)}{1 + b_3 M_1(t) + b_4 M_2(t)} - \frac{\ln\left[2^{\frac{V(t_0+T_{C_2})}{V(t_0)}}\right]}{T_{C_2}} C_2(t);$$

$$\frac{dM_1(t)}{dt} = a_5 C_1(t) - \frac{\ln\left[2^{\frac{V(t_0+T_{M_1})}{V(t_0)}}\right]}{T_{M_1}} M_1(t);$$

$$\frac{dM_2(t)}{dt} = a_6 C_2(t) - \frac{\ln\left[2^{\frac{V(t_0+T_{M_2})}{V(t_0)}}\right]}{T_{M_2}} M_2(t);$$

$$\frac{dP_1(t)}{dt} = \frac{a_7 S_1 E_1(t)}{1 + b_5 E_1(t) + b_5' E_2(t)} - \frac{\ln\left[2^{\frac{V(t_0+T_{P_1})}{V(t_0)}}\right]}{T_{P_1}} P_1(t);$$

$$\frac{dP_2(t)}{dt} = \frac{a_8 S_2 E_2(t)}{1 + b_6 E_1(t) + b_6' E_2(t)} - \frac{\ln\left[2^{\frac{V(t_0+T_{P_2})}{V(t_0)}}\right]}{T_{P_2}} P_2(t);$$

$$\frac{dE_1(t)}{dt} = a_9 C_1(t-h) - \frac{\ln\left[2^{\frac{V(t_0+T_{E_1})}{V(t_0)}}\right]}{T_{E_1}} E_1(t);$$

$$\frac{dE_2(t)}{dt} = a_{10} C_2(t-h) - \frac{\ln\left[2^{\frac{V(t_0+T_{E_2})}{V(t_0)}}\right]}{T_{E_2}} E_2(t);$$

where $C_i(t), M_i(t), P_i(t), E_i(t)$ are values expressing concentration of m-RNA, multi-nucleotides, protein-enzymes, effectors for two alternative ways in specialization ($i = 1, 2$); $V(t)$ is cell volume; T_X is a time of the substance X half-decay; $\{a\}$, $\{b\}$ are the positive constants.

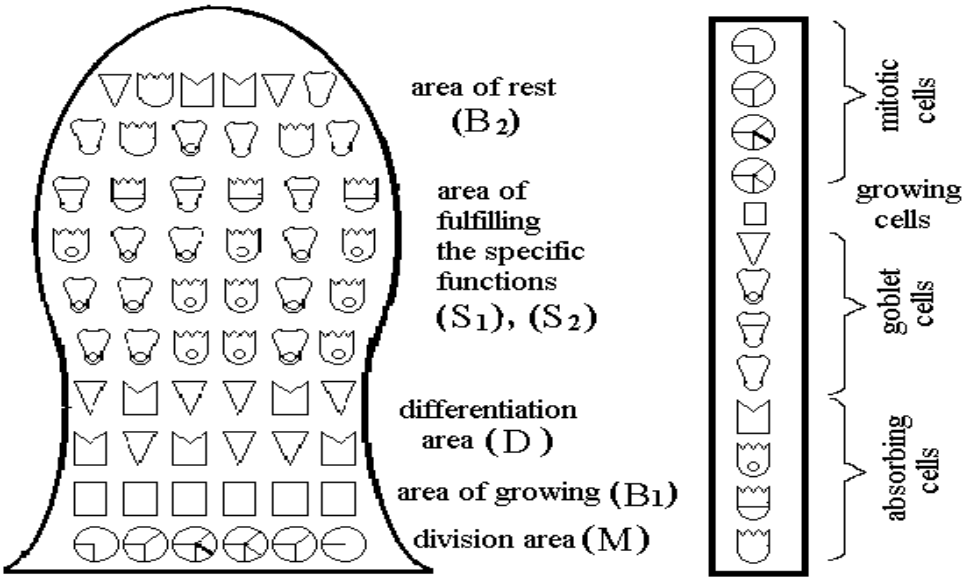

Figure 6: A schematic screen for the system of "crypt-nap"and its cells during computer imitation (the areas of the cells locations are shown).

Models for the regulatory mechanisms of specific functions have been constructed in general view for flexible orientation in concrete cases. They have equations for protein-enzymes biosynthesis on the basis of genes regulation; substances transport from a medium, organoids development and functioning systems [16, 12]

Based on the models of regulatory mechanisms for cells activity in homogeneous groups of community and biologists assistance, the imitation models for plant and animal cellular communities; models for "crypt-nap" system (functional unit of digestive system) [16] (Figure 6) and "fruit cells of high plants and V.dahlie fungus" systems [17] have been constructed. The results of quantitative researches have shown opportunity for cells accumulation in growth zone in "crypt-nap" system as the adaptive mechanism and symbiosis between the high plants and fungus.

Imitative modelling researches allow defining quantitative regularities for functioning of a concrete cellular structures taking into account a spatial cellular architectonics and regulation of an intracellular processes. Results of the work are used for the regularities analysis of the cotton growing and development [18] and for the toolbox development for the information technology in gene, cellular engineering and biotechnologies [19].

8 Acknowledgements This work was partially supported by FSFR AS RUz (grant No. 41-98) and SST CM RUz (grant No. P-20.16).

References

[1] M. Saidalieva. Mathematical modeling of regulation mechanisms of cellular communities. In *International Scientific and Practical Conference "Innovation-2001"*, pages 167–169, Tashkent, 2001.

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

[3] N. Rashevski. *Mathematical Principles in Biology and Their Applications*. Springfield, Charler C Thomas, Publisher, 1961.

[4] L.N Seravin. Origin of eucaryotic cell: 4. the general hypothesis of unmutagenous origin of eucaryot. *Citologiya*, 28(9):899–910, 1986. (in Russian).

[5] F.M Ugolev. *Natural technologies for biological systems*. L., 1987. (in Russian).

[6] B.N. Hidirov. On one method of study an regulatorika living systems. *Voprosy Kibernetiki*, 76:42–51, 1984. (in Russian).

[7] B.N. Hidirov. Modelling of regulation mechanisms of living system. *Scientiae Mathematicae Japonicae*, 58(2):407–413, 2003. (in Russian).

[8] B.N. Hidirov. On one method of modeling the regulatory mechanisms of living systems. *Mathematical Modellin*, 16:77–91, 2004. (in Russian).

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

[10] B.N. Hidirov, M. Saidalieva, and M.B. Hidirova. Modelling of regulatorika of living beings. *Voprosy vych. i .prikl. matematiki*, (112):119–138, 2003.

[11] M.B. Hidirova. On solutions of functional-differential equation of living systems regulatorika. *Vestnik MGU*, (1):50–52, 2004. (in Russian).

[12] M Saidalieva. Control mechanisms for cellular communities: imitation modelling. *Problemy informatiki i energetiki*, (6):6–10, 1998. (in Russian).

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

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

[15] B.N. Hidirov and M. Saidalieva. Chaos research in autonomous regulating systems. In *WCIS-2000*. Quadrat Verlag, Kaufering, 2000.

[16] V.K. Kabulov, K.A. Zufarov, A.Yu. Yuldashev, and M. Saidalieva. Analises of processes of adaptiv mechanisms in the mucous shell of bowel by quantitative methods. *Doklady AN RUz*, (6-7):60–62, 1997. (in Russian).

[17] O.S. Otroshenko, M. Saidalieva, and N.N. Stepanichenko. Model studies of mechanism of structured and functional relationship of high plants and parasitic funguses (on example of wilt of cotton plant). *Voprosy Kibernetiki*, (111):42–51, 1980. (in Russian).

[18] M Saidalieva. Mathematical modeling of cotton plant with variable architectonics. *Izvestiya VUZov. Seriya tehnicheskih nauk*, (3):193–197, 2000. (in Russian).

[19] M Saidalieva. Toolbox of information technology in gene, cellular ingineering and biotechnologies. *Voprosy Kibernetiki.*, (165):125–132, 2003. (in Russian).

Saidalieva Mahruy
Institute of Informatics, Academy of Sciences of Uzbekistan
F.Khodjaeva, 34, Tashkent, 700187, Uzbekistan
E-mail: `regulatorika@yahoo.com`