MATHEMATICAL AND COMPUTER MODELLING ORGANISM'S CELLULAR COMMUNITIES REGULATORIKA AT ANOMALIES

Mahruy Saidalieva

Received January 31, 2008

Abstract. The mathematical and computer modelling of *functioning regulatory mechanisms* (regulatorika) of cellular communities is actual at solving the many biological problems which are connected with the quantitative evaluation of an organism's cells behaviour, united by performing some general functions. In this work we consider the mathematical modelling method for the regulatorika of cellular communities based on the functional-differential equations of a function unit of cellular communities in multicellular organisms. Results, obtained applying this approach to the quantitative analysis of CD4 lymphocytes number regulatorika in HIV/AIDS, as well as thyroid gland follicles cellular communities in malignant neoplasms are given.

1 Introduction The quantitative study of an organism's cellular community regulatorika is conducted, basically, in three directions. In the first direction the biosystem is considered as a system of uniform cell groups, possessing existence feature in some discrete conditions and researchers have interest in the quantitative correlations of cells in different uniform groups [1, 2, 3, 4]. In this works, results, obtained in the field of population's mathematical theories, are widely used. In the second and the third directions, attempts are made to take into account of the intracellular processes in modelling the regulatorika of cellular communities [5, 6, 7]. Herewith, in the models of the second direction the main attention is devoted to regulatory mechanisms of cellular functions, while in the models of the third direction the cell's space-temporary organization on the considered area of multicellular organism is taken into account.

In the first direction, in the models studying the regulatorika of cellular communities for rapidly regenerating cellular systems, the following three groups of uniform cells are usually taken into account [8, 9]:

- the proliferative pool is the set of cells , which will inevitably divide by mitosis, if at the division moment they will be in the given cellular system;
- the fixed pool is the set of cells, which do not enter in mitosis, being in same conditions, as the cells from the first group;
- the ballot pool is the set of cells , which go either in the first group with probability p, or in the second group with probability $1 - p$.

The main parameter of the given modelling variant is the probability of daughter cells entering in the division cycle. V.G. Tyajelova conducts cell population partition on dividing, ripening and functioning pools in proliferative cell systems [10, 11]. The given direction models are suitable for the analysis of quantitative correlations between different cells in the considered organ (or process). In modelling infectious processes in the organism the

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

Key words and phrases. Living systems, cellular communities, regulatory mechanisms, differential-delay equations, chaos, "black hole", control, anomalies, HIV/AIDS.

number of normal and infected cells and some features of their habitat are often taken into account. Let us consider character equation system of these models, developed in respect to the virus disease [12]:

$$\begin{aligned} \frac{dX}{dt} &= \lambda - dX - \beta XV; \\ \frac{dY}{dt} &= \beta XV - aY; \\ \frac{dV}{dt} &= kY - uV, \end{aligned} \tag{1}$$

where X is the number of non-infected cells; Y is the number of infected cells; V is the number of free virus particles; λ, d, β, a, k, u are non-negative constants. In some models in this direction the temporal factors in mutual relations between cells and virus are taken into consideration [13]:

$$\begin{aligned} \frac{dT(t)}{dt} &= s - \mu_T T(t) + rT(t)\left(1 - \frac{T(t)+I(t)}{T_{\max}}\right) - k_1 T(t)V(t); \\ \frac{dI(t)}{dt} &= k_1^{'} T(t-\tau)V(t-\tau) - \mu_I I(t); \\ \frac{dV(t)}{dt} &= N\mu_b - k_1 T(t)V(t) - \mu_V V(t), \end{aligned} \tag{2}$$

where $T(t)$ represents concentration of healthy CD4$^+$ T-cells at time t; $I(t)$ represents the concentration of infected CD4$^+$ T-cells, and $V(t)$ the concentrations of free HIV at time t; s is the source of CD4$^+$ T-cells from precursors; μ_T is the natural death rate of CD4$^+$ T-cells; r is CD4$^+$ T-cells growth rate (thus, $r > \mu_T$ in general); $T_{\max}$ is CD4$^+$ T-cells carrying capacity; k_1 represents the rate of infection of T-cells with free virus; $k_1^{'}$ is the rate at which infected cells become actively infected; μ_I is a blanket death term for infected cells; N represents source for free virus; μ_b is the lytic death rate for infected cells; μ_V is the lass rate natural of virus.

In the second direction of model studying cellular communities regulatorika the main attention is given to mathematical modelling separate cellular functions regulatorika, realizing the process in consideration. M. Eigen and P. Shuster [5], V.A. Ratner and other [6] simulated cell's self-reproducing function by means of "information box" notions. Concentration change in macro-molecules and proteins communities in "information box" is quantitatively described by the ordinary differential equation system. Mathematical models of cellular functions regulatorika can be constructed by quantitative description regulation mechanisms for corresponding molecular-genetic systems [14, 15] with taking into account temporal relations in intracellular processes regulation loops [16, 17]. In the third direction of model investigating cellular communities regulatorika it is observed attempt to imitate cells spatial organizations with the account of intracellular processes [14, 15, 16].

In this work we consider a method for mathematical modelling cellular communities regulatorika based on the notion of function units of cellular communities for multicellular organisms (section 2), its method application to analyzing CD4 lymphocytes count dynamics in an immune system to HIV/AIDS (sections 3, 4 and 5) and to the quantitative study of thyroid gland follicles cellular communities regulatorika at the norm and anomalies (section 6). In the section 7 the problems on controlling cellular communities regulatorika at anomalies are considered.

2 The method of mathematical modelling cellular community regulatorika at anomalies The notion of function units of cellular communities which is introduced in the works [16, 17, 18] allows to realize the mathematical and computer modelling cellular community regulatorika with taking into account the main uniform groups of multicellular organism cells and temporal relations in its regulation system. According to this notion, the cells of multicellular organism in the course of performing the general functions are united in structural-functional formation, consisting of character cells groups, fulfilling the following functions: dividing - M, growing - B_1, specialization - D, fulfilling the specific functions - S_1, S_2, ..., S_n and aging - B_2 (Figure 1), i.e. united in Cellular Communities Functional Units (CCFU), its spatial and functional formation forms organs and tissues of multicellular organism.

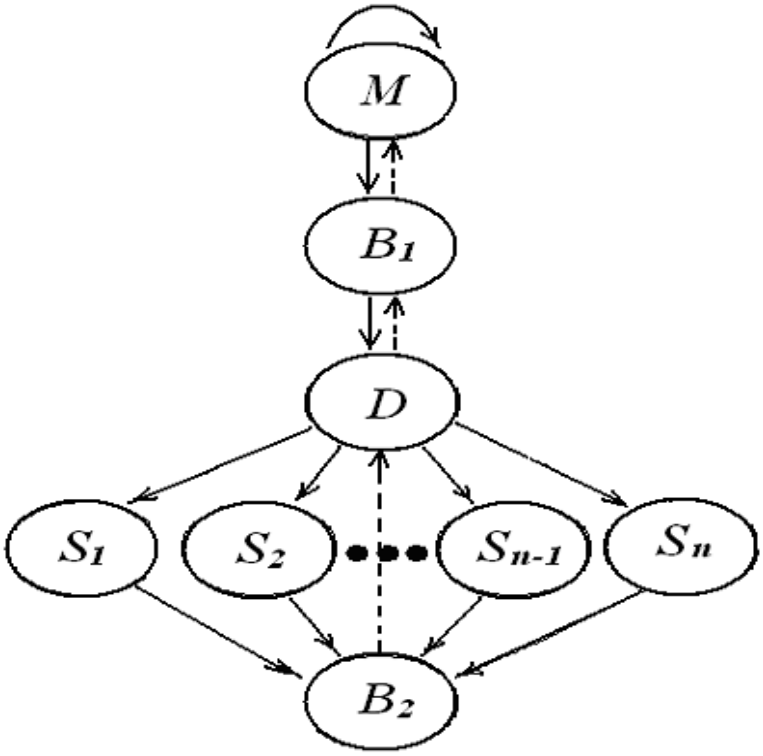

Figure 1: Scheme of cellular transitions in CCFU.

Let $X_1(t)$ be a value, characterizing dividing cells number; $X_2(t)$ - growing cells; $X_3(t)$ - differentiating cells; $X_4(t)$, $X_5(t)$, ..., $X_{n+3}(t)$ (n is integer and ≥ 1) performing specific functions and $X_{n+4}(t)$ aging cells number at time t. Then, using method for constructing equations for quantitative description of changing the cells number in CCFU concrete groups [16, 17, 18], we can offer (under certain simplifications) the following system of functional-differential equations for regulatorika of cellular communities number

$$\frac{dX_1(t)}{dt} = a_1 \left(\prod_{k=1(k\neq 2,3)}^{n+3} X_k(t-1) \right) e^{-\sum_{j=1}^{n+4} \delta_j X_j(t-1)} + b_1 X_2(t-1) - a_2 X_1(t);$$

$$\frac{dX_2(t)}{dt} = a_2X_1(t-1) + b_2X_3(t-1) - (b_1+a_3)X_2(t);$$

$$\frac{dX_3(t)}{dt} = a_3X_2(t-1) + b_3X_{n+4}(t-1) - \left(b_2 + \sum_{k=4}^{n+3} a_k\right) X_3(t); \tag{3}$$

$$\frac{dX_k(t)}{dt} = a_kX_3(t-1) - a_{n+4}X_k(t);$$

$$k = 4, 5, ..., n+3;$$

$$\frac{dX_{n+4}(t)}{dt} = a_{n+4}\sum_{k=4}^{n+3} X_k(t-1) - (b_3+c)X_{n+4}(t),$$

where a_1 is rate constant of cells division in M; a_i $(i = 2, ..., n+4)$ are rate constants of direct transitions; b_k $(k = 1, 2, 3)$ are rate constants of inverse transitions; δ_j $(j = 1, 2, ..., n+4)$ are the repression parameters of proliferative pool M; c are the death rate constant of aged cells.

Equations (3) form a closed system of functional-differential equations for regulatorika of cells number of cellular communities. Unique existence theorems of continuous solutions, as well as approximate solutions to the given equations on PC can be obtained using the method of consequent integrating by Bellman-Cooke if we have the initial functions on the unit length segment [17, 18, 19].

3 Equations of CD4 lymphocytes number dynamics in an immune system CD4 lymphocytes lesion in immune system underlies HIV/AIDS pathogenesis [4, 20, 21, 22]. In the event that we use the method for mathematical modelling cellular communities regulatorika, CD4 lymphocytes number dynamics in immune systems can be investigated based on the functional-differential equations (3). For the simplicity we can consider proliferative pool and other uniform groups in immune system concerning CD4 lymphocytes only. Then (3), with taking into consideration only one specific cellular function (S), have the form

$$\frac{dX_1(t)}{dt} = a_1X_1(t-1)X_4(t-1)e^{-\sum\limits_{j=1}^{5}\delta_jX_j(t-1)} + b_1X_2(t-1) - a_2X_1(t);$$

$$\frac{dX_2(t)}{dt} = a_2X_1(t-1) + b_2X_3(t-1) - (b_1+a_3)X_2(t);$$

$$\frac{dX_3(t)}{dt} = a_3X_2(t-1) + b_3X_5(t-1) - (b_2+a_4)X_3(t); \tag{4}$$

$$\frac{dX_4(t)}{dt} = a_4X_3(t-1) - a_5X_4(t);$$

$$\frac{dX_5(t)}{dt} = a_5X_4(t-1) - (b_3+c)X_5(t),$$

where $X_1(t)$ is the function, expressing thymus proliferative cells number; $X_2(t)$, $X_3(t)$, $X_4(t)$ and $X_5(t)$ are growing, differentiating, fulfilling the specific function and aging CD4 lymphocytes, accordingly; the other parameters are similar to such designations in (3).

Let us assume that the virus load influence for immune system is realized in the end to this that immune system proliferative function is increased. As far as we have interest in most commonly mechanisms for CD4 lymphocytes homeostasis maintenance within the organism lifespan we suppose that in this model in B_1, D, S and B_2 groups the cells number changing occurs more quickly than in the M group. For the qualitative study we assume that

there is equilibrium nature in quantitative changing the cells in B_1, D, S and B_2 areas. In this case the system (4) can be simplified up to one equation. Then characteristic dynamics of CD4 lymphocytes number can be investigated using the following functional-differential equation

$$\frac{\theta}{h}\frac{dX(t)}{dt} = \rho X^2(t-1)e^{-X(t-1)} - X(t), \tag{5}$$

where $X(t)$ is the function, describing thymus proliferative cells number reproducing CD4 lymphocytes; θ is the average "lifetime" for the proliferative cells; h is the time duration, necessary for fulfilling feedback in organism's immune system; ρ is the virus load parameter, expressing rate of cell division in immune system proliferative pool.

4 Characteristic solutions of equation (5) Let us consider problems of studying characteristic solutions of equations for CD4 lymphocytes number dynamics in immune system. We will show that

- there are continuous, unique solutions of (5) under given continuous function on initial time segment;
- solutions are in the first quadrant of phase space if the parameter values and initial conditions are non-negative;
- infinitely remote points are unstable;
- there are trivial and positive steady states.

In order to prove the first formulated feature for (5) we assume that on $[t_0,t_0+1]$ we have continuous initial function $\varphi(t) \geq 0$. Then the system (5) on $(t_0+1,t_0+2]$ has the following form

$$\frac{\theta}{h}\frac{dX(t)}{dt} = \rho\phi^2(t)e^{-\phi(t)} - X(t)$$

and its solution has the form

$$X(t) = \frac{h}{\theta}e^{-\frac{\theta}{h}(t-t_0-1)}\left(\frac{\theta}{h}\varphi(t_0+1) + \rho\int\limits_{t_0+1}^{t}\varphi^2(\tau)e^{-\varphi(\tau)}d\tau\right). \tag{6}$$

$$t \in (t_0+1, t_0+2]$$

This solution is continuous on $(t_0+1, t_0+2]$. Taking the computed solution as initial function we obtain continuous solution on $(t_0+2, t_0+3]$ by stated method and etc. In such manner we can construct continuous solution of (5) at $t > 0$. Uniqueness is implied by accepted constructive methods for obtaining solutions to (5). Formula (6) shows that non-negativity of the initial function, θ, h and ρ ensures non-negativity of solutions to (5).

Note that if $X(t) \to \infty$ then (5) has the form

$$\frac{\theta}{h}\frac{dX(t)}{dt} = -X(t),$$

we have unstability of infinitely remote points, i.e. equation (5) solutions are bounded.

It is obvious that there is a trivial steady state for (5). Nontrivial steady state existence (P) depends on parameter ρ value. From equation

$$\rho S e^{-S} = 1$$

we see that if $\rho \geq e$, then we have nontrivial steady state P = 1 which splits into P_1 and P_2 when parameter increases, at that

$$0 < P_1 < 1 < P_2 < \infty. \tag{7}$$

Results of qualitative studying solutions (5) behavior have shown that trivial steady state and P_2 are attractors with (0, P_1) and (P_1, ∞) basins. Stability nature for steady states we evaluate by studying solutions (5) near their neighbourhood, entering $X(t) = P + y(t)$, where $P = O$, P_1, P_2 and $y(t)$ is small. From (5) for $y(t)$ we have

$$\frac{\theta}{h}\frac{dy(t)}{dt} = \rho P(2-P)e^{-S}y(t-1) - y(t),$$

whence we see that trivial attractor is stable. For nontrivial steady states P_1, P_2 we have

$$\frac{\theta}{h}\frac{dy(t)}{dt} = (2-P)y(t-1) - y(t).$$

Its characteristic equation has the form

$$(\theta\lambda + h)e^{\lambda} + h(P-2) = 0. \tag{8}$$

Using Hayse criterion [23] we found that equation (8) roots have negative parts if

$$P > 1, \tag{9}$$

$$h(P-2) < \theta\xi\sin\xi - h\cos\xi, \tag{10}$$

where ξ is the root of equation ξ =-$(h/\theta)\tan\xi$ $(0 < \xi < \pi)$.

(7) and (9) have shown that P_1 is unstable. For nontrivial attractor P_2 the inequality (9) is true and (10) defines parameters values diapason for stable stationary regime of CD4 lymphocytes population. That fact that given diapason is not empty, follows from positiveness of right part (10) and possible values P_2 (see (7)). For instance, performing inequality (10) is obvious for $1 < P_1 < 2$.

Thereby, at fulfilling (10) we have stable attractor and solutions (5) express normal behavior CD4 lymphocytes number dynamics. If (10) is not true then there is Hopf bifurcation with becoming Poincaré type limit cycles around P_2. It seems that small regular oscillations of CD4 lymphocytes number can be considered as normal condition. However, quantitative study on PC shows that under certain parameter's values, attractor P_2 transforms into strange attractor with the appearance of irregular oscillatory solutions.

5 Modelling CD4 lymphocytes number dynamics at anomalies Anomalies in cells number regulatorika in immune system, connected with the virus load, lead to increasing rate constant of corresponding proliferating cells (in this instance the parameters values ρ in (5)) and the feedback systems disturbances. For the accounting last case, we suppose that average time for division of thymus proliferative cells is more less than time interval required for feedback realization in organism's immune system, i.e. $\theta \ll h$ in (5). Then, for analyzing CD4 lymphocytes number dynamics we can use the model systems for (5) in the following form

$$X(t) = \rho X^2(t-1)e^{-X(t-1)}, \tag{11}$$

and its discrete analogue

$$X_{k+1} = \rho X_k^2 e^{-X_k}, \tag{12}$$
$$k = 0, 1, ...$$

where X_k is the value, expressing proliferative cells number in immune system on k-th step of organism's vital activity.

It is necessary to note that (12) is the most suitable equation for the analyzing CD4 lymphocytes number dynamics. Its solutions can be visually evaluated using Lamerey diagrams construction and calculating Kolmogorov entropy and Lyapunov exponent on PC.

Results of the studying solutions (12) behavior show that there are stationary, periodic solutions, irregular fluctuations (dynamic chaos) and effect of solutions failure to trivial attractor - "black hole" effect. Usually, irregular oscillations and "black hole" are identified as biosystems anomalous conditions [23, 24].

Origin and developments regularities of irregular oscillations and "black hole" were investigated using (12) by the analyzing Lyapunov exponent values dynamics Lamerey diagrams construction (under different parameter values of equations (11), (12)) on PC using the special program "SW-FDE-3" [25]. In the Table 1 the main features of solutions (12) behavior are presented.

Table 1: The boundaries of main behavior regimes of solutions (12).

Value	(0, e)	[e, 6.7)	[6.7, 11)	[11, 19.6)	≥ 19.6
Solutions (12) behavior	Rest (α)	Stationary state (β)	Limit cycles (γ)	Irregular oscillations (δ)	"Black hole" (μ)

Thus, consecutive increase in the virus load parameter, observing under HIV infections, leads to consequent transition from the stationary conditions mode (β) to the regular oscillations mode (γ), hereinafter to the irregular oscillations (δ) of CD4 lymphocytes number, completing by sharp destructive reducing CD4 lymphocytes reproduction (μ).

In the field of irregular oscillations CD4 lymphocytes population number has unpredictable pattern, but in the field of "black hole" there occurs sharp destructive change. This changes end in division failure of thymus proliferative cells, reproducing CD4 lymphocytes. In the given method of model studies for arising AIDS disease the "Hayflick limit" concept attraction is not obligatory.

6 Quantitative studying thyroid gland follicles cellular communities regulatorika at the norm and anomalies The main function unit of thyroid gland is a follicle [26]. Mathematical and computer modelling thyroid gland follicles cellular communities regulatorika allows to research quantitative regularities in functioning follicular system in the syntheses process of its main hormones and failure mechanisms in thyroid gland regulatorika, what lead to appearance the different types of malignant growths. Supposing that there are two specific functions S_1 and S_2, connected with iodine-containing hormones formation (thyroxin - T4 and triiodothyronine - T3) thyroid gland follicles cellular communities regulatorika can be investigated using the following equations based on (3)

$$\frac{dX_1(t)}{dt} = a_1 \left(\prod_k^{1,4,5} X_k(t-1) \right) e^{-\sum\limits_{j=1}^{6} \delta_j X_j(t-1)} + b_1 X_2(t-1) - a_2 X_1(t);$$

$$\frac{dX_2(t)}{dt} = a_2 X_1(t-1) + b_2 X_3(t-1) - (b_1 + a_3) X_2(t);$$

$$\frac{dX_3(t)}{dt} = a_3 X_2(t-1) + b_3 X_6(t-1) - (b_2 + a_4 + a_5) X_3(t); \qquad (13)$$

$$\frac{dX_4(t)}{dt} = a_4X_3(t-1) - a_6X_4(t);$$
$$\frac{dX_5(t)}{dt} = a_5X_3(t-1) - a_6X_5(t);$$
$$\frac{dX_6(t)}{dt} = a_6(X_4(t-1) + X_5(t-1)) - (b_3 + c)X_6(t),$$

where $X_i(t)$ (i=1,...,6) are the value, characterizing numbers of dividing, growing, differentiating, fulfilling specific functions and aging follicles cells at time t, accordingly; the other parameters are similar to such designations in (3) and (4).

Such reasoning that in the modelling CD4 lymphocytes number regulatorika leads to possibility for quantitative studying the thyroid gland follicles cells number regulatorika on the basis of the following functional-differential equation

$$\frac{\theta}{h}\frac{dX(t)}{dt} = \rho X^3(t-1)e^{-X(t-1)} - X(t), \tag{14}$$

where $X(t)$ is the function, expressing dividing thyroid gland follicles cells number; θ is the average lifetime of these cells; h is the time interval necessary for fulfilling feedback in organism's hormonal systems; ρ is the parameter, expressing division rate of thyroid gland follicles cells. In case of feedback system failure we can use the following model systems for (14) in the form of functional equation

$$X(t) = \rho X^3(t-1)e^{-X(t-1)} \tag{15}$$

and its discrete analogue

$$X_{k+1} = \rho X_k^3 e^{-X_k}, \tag{16}$$
$$k = 0, 1, ...$$

where X_k is the value, expressing number of dividing thyroid gland follicles cells on k-th step of its vital activity.

Analysis of solutions (13)-(16) character behavior using the methods for qualitative studying functional-differential equations has shown that in models of thyroid gland follicles cellular communities regulatorika there are stationary, periodic solutions, irregular fluctuations (dynamic chaos) and effect of solutions failure to trivial attractor - "black hole" effect. Irregular oscillations and "black hole" can be identified as uncontrolled reproduction (malignant growth) and sharp destructive change in thyroid gland follicles cellular communities (metastasis).

7 Problems on controlling cellular communities regulatorika at anomalies If biosystem regulatorika is in the anomalies area (irregular oscillations and sharp destructive change) then there appears the question on carrying off in the area of regular oscillations and (or) in the area of stationary regime. Analysis of anomalies areas in considered model studying regulatorika of CD4 lymphocytes number and thyroid gland follicles cells shows that the irregular oscillations area is heterogeneous (Figure 2) and "black hole" area has high rate. Quantitative study of solutions (12) and (16) on PC shows that in the field of dynamic chaos there are small regions with regular behavior - r-windows , i.e. in the diseases field there exist the small "windows" with normal system condition (Figure 2).

Presence of r-windows in the field of irregular fluctuations allows temporarily solving normalization problem in cellular communities regulatorika by entering the system in the nearest r-window in order to remove the system from the area of irregular oscillations. Consequently system withdrawal path from the irregularity area into the area of regular

oscillations by the chain, consisting of r-windows is efficient. Results of the qualitative studying regulatorika equations for the considered biosystems have shown that there are ensemble of such paths. Choice of optimum from these paths can be realized based on the minimization of control load at the path passage. In the anomalies field we accept irregularity level of dynamic system condition (H) as value of control load.

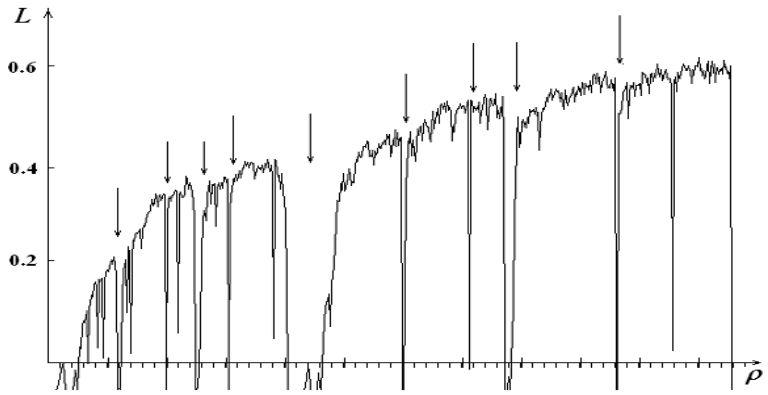

Figure 2: Lyapunov exponent dynamics in the field of irregular oscillations (arrows specify r-windows).

"H" value can be calculated based on the Kolmogorov entropy or Lyapunov exponent. Compliance with this "principle of minimum load" can be reached by minimization $H(t)$ in the course of the control

$$H(t) = \int_{t_0}^{t} K(x(\theta), u(\theta))d\theta,$$

where $K(x(\theta), u(\theta))$ is the Kolmogorov entropy under concrete function values of condition $x(\theta)$ and control $u(\theta)$ at time θ; t_0 is the time from beginning the control process, $t \geq t_0$. Destructive changes fleetingness in the event of "black hole" effect complicates questions on controlling behavior of CD4 lymphocytes populations. Here is required the time evaluation for staying the system in the basin of functional attractor and designing efficient (on a time) measures on the system transfer in the area of deterministic chaos, in the sequel in the area of regular oscillations.

8 Conclusion Considered model studies show a possibility for using the developed functional-differential equations of cellular community's regulatorika (3) at quantitative studying the number dynamics regularities of concrete cellular communities in the norm and anomalies. Constructed functional-differential equations of cellular communities regulatorika, their model systems in the forms of functional and discrete equations are applied for the quantitative studying CD4 lymphocytes count regulatorika and also at analyzing dynamics regularities of thyroid gland follicles cellular communities at the norm and anomalies. Model investigations show that chronic growing parameter value at virus load leads to anomalous behavior of CD4 lymphocytes number. The stationary condition is violated, here appears auto-oscillation with transition to irregular fluctuations, hereinafter to the "black hole" effect - sharp reducing CD4 lymphocytes number and AIDS development. It is necessary to note that for the explanation of AIDS disease the attraction of "Hayflick limit" concept is not required. Quantitative study of thyroid gland follicles cellular communities dynamics based on the developed functional-differential equations for cellular communities

regulatorika shows the possibility for arising malignant neoplasms at breaking organism's hormonal regulation in the system.

Analyzing questions on optimal controlling cellular communities number behavior for the considered biosystems for the purpose of its rapidly withdrawal in the normal area (modes of auto-oscillations and stationary state) we show that the following scenario for takeaway by the chain, consisting of small regions with normal behavior (r-windows) with adhearance to the "*principle of minimal load*" is more appropriate.

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

References

[1] A.A. Romanyukha. Data analysis and modelling of infectious diseases. *Rus.J. Numer. Anal. Math. Modelling.*, (3-4):297–331, 2000. (in Russian).

[2] L.N. Belyh. *Analyzing mathematical models in immunology.* Nauka, 1988.

[3] M. A. Nowak and C. R. M. Bangham. Population dynamics of immune responses to persistent viruses. *Science*, (272):74–79, 1996. (in Russian).

[4] M.D. Mascio and et all. Naive t-cell dynamics in human immunodeficiency virus type 1 infection: Effects of highly active antirefroval therapy provide insights into the mechanisms of naive t- cell depletion. *Journal of Virology.*, (6):2665–2674, 2006.

[5] M. Eygen and P. Shuster. *Gipercikl. Principy samoorganizacii makromolekul.* Mir, 1982. (in Russian).

[6] V.A. Ratner and V.V. Shamin. Sayzery': modelirovanie fundamental'ny'h osobennostey molekulyarno-biologicheskoy organizacii. *Matematicheskie modeli evolyucionnoy genetiki.*, pages 60–82, 1980. (in Russian).

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

[8] A.Ya. Monichev. Modelirovanie dinamiki postradiacionnogo krovetvoreniya s uchetom terapevticheskih vozdeystviy i specifiki techeniya luchevoy bolezni. *Dinamika biologicheskih popylyaciy. Gor'kiy, GGU*, (9):55–62, 1988. (in Russian).

[9] V.V. Smolyaninov. *Matematicheskie modeli biologicheskih tkaney.* Nauka, 1980. (in Russian).

[10] V.G. Tyajelova. Obsch'nost' dinamiki processov vosstanovleniya v proliferiruyusch'ih sistemah organizma. *Dinamika biologicheskih sistem*, pages 3–14, 1977. (in Russian).

[11] V.G. Tyajelova, V.A. Selivanov, and V.N. Lanan. *Regulyaciya megakariocitopoeza.* Puschino,ONTI Puschinskogo NC, 1991. (in Russian).

[12] M.G.M. Gomes and G.F. Medley. *Dynamics of multiple strains of infectious agents coupled by cross-immunity: a comparison of models in Mathematical Approaches for Emerging and Reemerging Infectious Diseases: Models, Methods and Theory.* Springer Verlag, New York, 2002.

[13] R.V. Culshaw and S. Ruan. A delay-differential equation model of HIV infection of $CD4^+$ T-cells. *Math Biosci.*, (14.May;165(1)):27–39, 2000.

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

[15] Bl. Sendov, R. Tsanev, and B. Mateeva. Issledovane na edin matematicheski model na regulyaciyata na klet'chnogo razmnojenie v epidermisa. *Izvestiya na matematicheskiya institut "Bolgarska Akademiya na naukite"*, (XXI):221–235, 1966.

[16] M. Saidalieva. Modeling cellular communities. *Voprosy kibernetiki*, (103):89–103, 1978. (in Russian).

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

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

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

[20] A.S. Perelson and P.W. Nelson. Mathematical analysis of HIV-1 dynamics in vivo. *SIAM Review*, (41(1)):3–44, 1999.

[21] D. Wick. On T-cell dynamics and hyperactivation theory of HDV pathogenesis. *Mathematical of Biosciences*, (158):127–144, 1999.

[22] R.B. Effros. Replicative senescence in the immune system: impact of the hayflick limit on t cell function in the elderly. *Am.J.Hum.Gen.*, (62):1003–1007, 1998.

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

[24] B.N. Hidirov. Regulation mechanisms of living systems. *Scientiae Mathematicae Japonicae*, 64(2):497–504, 2006.

[25] B.N. Hidirov and M.B. Hidirova. Program for qualitative analysis of functional-differential equations "SW-FDE-3". *Patent certificate DGU 00720*, 2004.

[26] F. Bernier-Valentin, S. Trouttet-Masson, R. Rabilloud, S. Selmi-Ruby, and B. Rousset. Three-dimensional organization of thyroid cells into follicle structures is a pivotal factor in the control of sodium/iodide symporter expression. *Endocrinology*, 147(4):2035–2042, 2006.

Mahruy Saidalieva
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`