Quantitative Study of Cellular Mechanisms of HIV Infection's Pathogenesis

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***Abstract*— CD4 lymphocyte affection underlies in HIV/AIDS infection pathogenesis. In this work we consider some questions of quantitative analysis of CD4 lymphocyte activity at the norm and HIV infection by mathematical modeling. Functional-differential equations for studying regulatory mechanisms of dynamics of CD4 lymphocyte's cellular communities' number have been developed. Results of the qualitative analysis, illustrating possibility of using the developed equations for studying mechanisms of HIV infection's pathogenesis without attraction of the "Hayflick limit" concept are presented. Some questions concerning choice of control ways of dynamics behavior of CD4 lymphocyte's cellular communities' number during HIV infection's pathogenesis are considered.**

Index Terms— HIV infection, CD4 lymphocyte, mathematical model, qualitative analysis, irregular oscillations, "black hole" effect.

I. Introduction

It is notorious that cellular communities of immune system take active participation in preventing the virus infections. HIV infection, affecting CD4 lymphocytes, led to sharp weakening of immunity (AIDS) and in the end to organism death. Mechanisms cognition to maintain CD4 lymphocytes number on the normal level and analysis of possible ways to disturb this mechanism under heavy virus infection is one of the actual problems in struggle against AIDS.

Coordination of structural-functional organization of large number of cells in immune system is reached by means of regulatory mechanisms. Important parts in given regulatory mechanisms are systems of proliferation and well-timed removing the cells - apoptosis. Intuitive understanding the activity of these regulatory mechanisms during activity regulation of multicomponental cellular system combined by mean of complex interaction mechanisms between positive and negative feedback loops is very difficult. It is necessary formal mathematical methods and computer tools for imitation and modeling corresponding regulatory mechanisms.

At present, the methods for quantitative analysis are successfully used for studying HIV infection's mechanisms [1-3]. These methods allow to evaluate different sides of regulation between HIV and immune system cells and to investigate realization mechanisms for main stages during HIV infection. However, main mechanisms, which regulate balance of cells number in immune system and save ways from HIV infection not yet determined. In this work results of using methods for mathematical modeling regulatory mechanisms functioning (regulatorika) of cellular communities [4] for studying mechanisms of HIV infection's pathogenesis are considered.

II. Equations of Cellular Communities Regulatorika..

Cells of multicellular organisms during fulfilling mutual functions are united in structural-functional formation, which consist of characteristic cell's group carrying out the functions of renovation, specialization, substance exchange with environment, fulfilling specific functions and aging, i.e. united in Functional Unit of Cellular Communities (FUCC), spatial and functional formation from which forms organs and tissues of multicellular organisms.

Definition: coherent set (on space or (and) on time) of cells is called FUCC if there are dividing (M), growing (B_1), differentiating (D), carrying out the specific functions (S_1, …, S_n) and aging (B_2) cells, functioning interconnected us a whole (n is the quantity of amount specific functions of FUCC) [4]. On Figure 1 there is scheme of FUCC for n = 2. Assuming for simplicity that there are only two specific functions (S_1 and S_2) we consider one of the possible variants for studying regularity mechanisms for cells number in separate groups (M, B_1, D, S_1, S_2, B_2) of FUCC using differential equations. Let $Xi(t)$ (i=1,..., 6) be the values, expressing the number of cells in homogeneous groups M, B_1, D, S_1, and S_2 at the time moment t. Let us consider equations for the quantitative description changing cell's number in concrete FUCC groups. In the functional meaning the most important group in FUCC is cells group duplicating by division. Reproduction velocity depends on cells number, potentially capable to dividing, on substance, promoting division (effectors) and on nutrients [4].

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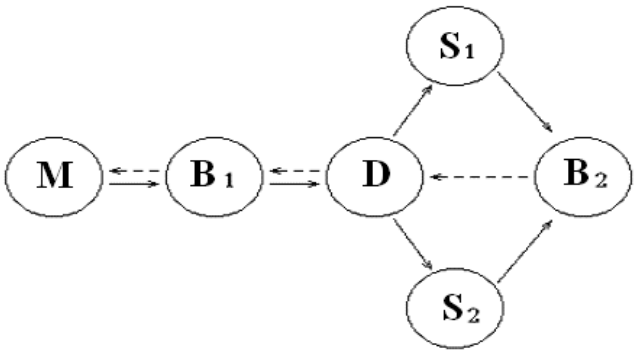

Figure 1. FUCC scheme (continuous arrows are determined transitions and dotted arrows are a probable return transitions)

If we may assume that during evolution FUCC are formed only with functions, which useful for organisms, then we can take that amount of effectors and nutrients depends on execution degrees of specific functions by cellular communities, i.e. depends on cell's amount in S_1, and S_2 groups. Taking into account "environment pressure" effect (end product inhibition) and possible cell's transfer from M to B_1, based on method for modeling regulatory mechanisms of living system [5] we have

$$\frac{dX_1(t)}{dt} = a_1\left(\prod_k^{1,4,5} X_k(t-\tau_k)\right)e^{-\sum_{j=1}^{6}\delta_j X_j(t-\tau_6)} + b_1X_2(t-\tau_1) - a_2X_1(t) \quad (1)$$

where a_1 is non-negative constant, expressing duplication rate; b_1, a_2 are constants, expressing cells exchange velocities between M and B_1; δ_i are coefficients, characterizing medium pressure; τ_i are transition time $(i = \overline{1,6})$.

Taking into account cell's transitions from one FUCC groups to another we obtain following system of linear functional-differential equations for changing cell's number in B_1, D, S_1, S_2 and B_2 groups:

$$\frac{dX_2(t)}{dt} = a_2X_1(t-\tau_1) + b_2X_3(t-\tau_2) - (b_1+a_3)X_2(t);$$

$$\frac{dX_3(t)}{dt} = a_3X_2(t-\tau_2) + b_3X_6(t-\tau_6) - (b_2+a_4+a_5)X_3(t);$$

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

$$\frac{dX_5(t)}{dt} = a_5X_3(t-\tau_3) - a_6X_5(t); \quad (2)$$

$$\frac{dX_6(t)}{dt} = a_6(X_4(t-\tau_5) + X_5(t-\tau_5)) - (a_7+a_6)X_6(t)$$

Equations (1) and (2) form a closed system of functional-differential equations for dynamics of cells number in FUCC. Theorems of existence and unique for continue solutions can be proved and approximate solutions of this equation can be defined using computer, based on the methods of consequent integration by Bellman-Cooke at given initial functions on the interval of length $\tau = \max_i(\tau_i)$ $(i = \overline{1,6})$ [4-5]. Possible variant for demonstration main characteristics of functional-differential equations using this method for model system (1)-(2) is given in following section.

III. Modeling dynamics of CD4 lymphocytes number at the norm.

For the analysis of dynamics regulatorika for CD4 lymphocytes number we can simplify the system (2), considering only one cells group S, carrying out specific function (CD4 lymphocytes). We have interest in most common mechanisms for CD4 lymphocytes homeostasis during organism life. In this connection, here we suppose that changing cells number in B_1, D, S and B_2 have stable nature. In this case systems (1), (2) can be simplified to one equation. Then dynamics of CD4 lymphocytes number can be investigated based on following functional-differential equation:

$$\frac{\theta}{h}\frac{dX(t)}{dt} = \rho X^2(t-1)e^{-X(t-1)} - X(t), \quad (3)$$

where $X(t)$ is the function, expressing number of thymus proliferative cells, which reproduce CD4 lymphocytes; θ is average time for live for this proliferative cells; h is the time interval requiring for feedback realization in organism's immune system; ρ is a parameter of "virus pressure", expressing velocity of cells division in proliferative pool in immune system.

Let us consider questions on studying characteristic solutions of equation (3). We will show:

- existence of continue, unique solution for (3) at given initial function which is continuous on initial interval;
- solutions are in the first quadrant of phase space at non-negative values of parameters and initial conditions;
- unstability of infinite points;
- existence possibility for trivial and positive equilibrium..

For demonstration of first formulated feature for solutions of (3) we assume that on initial interval $[t_0,t_0+1]$ we have continuous function $\varphi(t) \geq 0$. Then equation (3) on interval $(t_0+1,t_0+2]$ has following form:

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

Solution has form

$$X(t)=\frac{h}{\theta}e^{-\frac{\theta}{h}(t-t_0-1)}\left(\frac{\theta}{h}\varphi(t_0+1)+\rho\int_{t_0+1}^{t}\varphi^2(\tau)e^{-\varphi(\tau)}d\tau\right) \quad (4)$$

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

This solution is continuous on $(t_0+1,t_0+2]$. If we take solution (4) as initial function, we get solutions for the interval $(t_0+2,t_0+3]$ etc. Such integration allows to obtain the continuous solution at $t > 0$.

From the formula (4) we see that non-negativity of initial function, values of θ, h and ρ provide non-negativity of solutions (3).

Note, that for $X(t) \to \infty$ equation (3) has the form

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

whence we see that infinite points are unstable i.e. solutions of equation (3) are limited.

It can easily be checked that (3) has steady trivial state (trivial attractor). Existence of non-trivial equilibrium (P) depends on values of parameter ρ (Figure 2). From the equation

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

we see that if $\rho \geq e$ then there is non-trivial equilibrium P = 1, which splits into P_1, P_2 as parameter ρ increases and

$$0 < P_1 < 1 < P_2 < \infty . \quad (5)$$

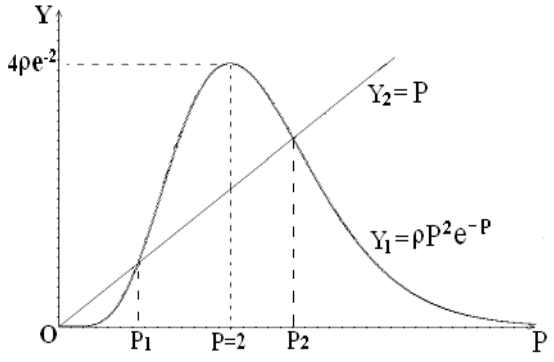

Figure 2. Existence of non-trivial equilibrium of (3)

Results of the qualitative research show that O and P_2 are attractors with $(0, P_1)$ and (P_1, ∞) basins.

Stability nature of equilibrium we evaluate by studying solutions neighbourhood of equilibria. Using $X(t) = P + y(t)$, where P = O, P_1, P_2 and $y(t)$ is small, for $y(t)$ we have

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

We see that trivial attractor is stable. For non-trivial attractors P_1, P_2 we have

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

The characteristic equation has the form

$$(\theta\lambda + h)e^{\lambda} + h(P-2) = 0 . \quad (6)$$

Using Hayse criterion [6] we can see that the roots of equation (6) have the negative real part if

$$P > 1, \quad (7)$$

$$h(P-2) < \theta\xi\sin\xi - h\cos\xi, \quad (8)$$

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

(5) and (7) show that P_1 is unstable. For non-trivial attractor P_2 condition (8) is true and (8) defines diapason of parameters values for stable stationar state of CD4 lymphocytes population. The fact that the diapason is not empty follows from non-negativity of right part of (8) and possible values of P_2 (see (5)). For instance, inequality (8) fulfillment for $1 < P_1 < 2$ is evident.

Thereby, when (8) is true we have stable attractor and solutions of (3) can be identified as normal behavior in dynamics of CD4 lymphocytes number. If (8) is not true, then there is Hopf bifurcation accompanied by the occurrence Poincare type limit cycles in neighbourhood of P_2. Apparently, we can consider small regular oscillations of CD4 lymphocytes number as normal state too. However, quantitative study on PC shows that under certain parameter's value attractor P_2 can transform into strange attractor with the appearance of irregular oscillatory solutions.

IV. Modeling Dynamics of CD4 Lymphocytes Number at Anomalies

Suppose, that average time for division of thymus proliferative cells more lesser that time interval, required for feedback realization in immune system of organism, i.e. $\theta << h$. Then, for studying dynamics of CD4 lymphocytes number we have following functional equations as model system for (3):

$$X(t) = \rho X^2(t-1)e^{-X(t-1)} \quad (9)$$

and its discrete analogue

$$X_{k+1} = \rho X_k^2 e^{-X_k}, \ k = 0,1,\ldots, \quad (10)$$

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

It is necessary to note that equation (10) is the most suitable equation for analysis of dynamics of CD4 lymphocytes number. Solutions of (10) can be visually evaluated using Lamerey diagram construction and calculation of Kolmogorov entropy and Lyapunov number on PC.

Results of studying solutions (10) behavior show that besides irregular oscillations there is effect of "black hole" (solutions

failure to trivial attractor). Usually, irregular oscillations and "black hole" effect are identified as biosystem anomalies [4-6].

Regularities for origin and development of irregular oscillations and "black hole" effect were investigated using (10) by means of analysis of Lyapunov number value dynamics (Figure 3.) and construction of Lamerey diagram (under different values of parameter ρ in equation (10)) on PC using special program "SW-FDE-3". Main features of solutions (1) behavior given in the table [7].

ρ values	(0, e)	[e, 6.7)	[6.7, 11)	[11, 19.6)	≥ 19.6
Features for solutions of (10) behavior	Rest mode (α)	Statio-nar state (β)	Limit cycles (γ)	Irregular oscil-lations (δ)	"Black hole" (μ)

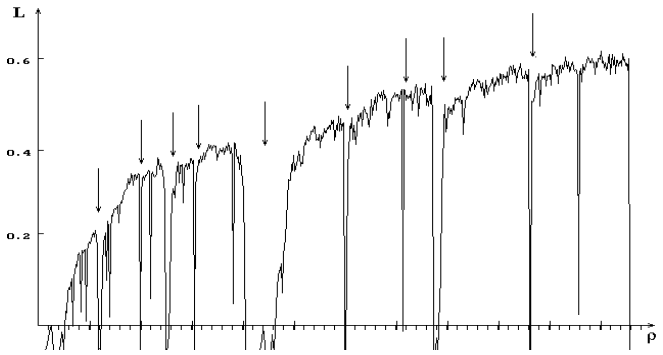

Figure 3. The graph for dynamics of Lyapunov parameter in the field of deterministic chaos δ (arrows specify small areas with regular solutions)

Thereby, when parameter of "virus pressure" ρ increases (this fact is observed during HIV infection) then there are consequent transitions $\beta \to \gamma \to \delta \to \mu$, concluding with sharp destructive diminution of CD4 lymphocytes reproduction.

In area of irregular oscillations the number of CD4 lymphocytes population has unpredictable behavior, but in area of "black hole" there are sharp destructive changes, finishing with division failure of thymus proliferative cells, reproducing CD4 lymphocytes. In this method for model studies attraction of "Hayflick limit" concept for understanding AIDS origin and development is not necessary.

If CD4 lymphocytes population is in anomalies area (δ and μ) then there exists a question on moving out the system from area of the deterministic chaos and "black hole" into area of regular oscillations (γ) or (and) area of stationar state (β).

Results of quantitative studies (10) on PC have shown that in area of deterministic chaos there are small regions with regular oscillations (r-windows) (Figure 3.). Existence of r-windows in area δ allows temporarily to solve the problem by entering the system to the nearest r-window to take out the system from area δ. It follows that a construction of a path for moving out the system from area δ into area γ by using r-windows series is effective.

The fleeting destructive changes in the "black hole" area complicate the problems for control of the system behavior. It is required the estimation of the time during which the system is in the functional attractor basin and development of the effective (on time) ways for moving out the systems to area of the deterministic chaos and then to area of the regular oscillations.

Note that the control must be "sparing" with the minimally possible level of the pressure. The acceptance in the capacity of the pressure value of an irregularity level (H) of the dynamical system conditions is natural in the field of anomalies. H can be calculated on the base of Kolmogorov entropy or Lyapunov number. "The principle of the minimal pressure" can be reached by minimization of $H(t)$ during control

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

where $K(x(\theta),u(\theta))$ is Kolmogorov entropy at concrete values for functions of state $x(\theta)$ and control $u(\theta)$ at the time moment θ; t_0 is the initial time on control, $t \geq t_0$..

Thus based on method for modeling regulatory mechanisms of living systems and equations for regulatorika of cellular communities, the functional-differential (3), functional (9) and discrete (10) equations for quantitative studying dynamics of CD4 lymphocytes number at the norm and anomalies are developed. Main parameters of developed equations express time for division of thymus proliferative cells, feedback time in immune system and value of "virus pressure". Model investigations show that chronic increase of "virus pressure" parameter's value led to anomal behavior of CD4 lymphocytes number. Stationar state is broken, appear auto-oscillations with transition to irregular oscillations, hereinafter to "black hole" effect (sharp reducing CD4 lymphocytes number) and to AIDS development. From the generality characteristic for model studies follows that such picture must be observed for any anomalies in immune system with the chronic growing value of "virus pressure".

Questions analysis for control of CD4 lymphocytes number for moving out the system into area of norm (area of auto-oscillations and stationar state) shows that scenario of moving out by using r-windows series with observance of "the principle of the minimal pressure" is expedient.

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