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4. МАТЕМАТИЧЕСКИЕ МОДЕЛИ ЭКОНОМИКИ, ЭКОЛОГИИ

STABILITY OF MATHEMATICAL MODELS OF IMMUNOLOGY

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Introduction

Recently there has been an increasing interest in constructing mathematical models to study dynamics of spread of bacterial and virus infections in a human organism, with the aim of predicting viral progression upon infection and bacterial and virus decline after drug treatment. In this item we give a shot review of some mathematical models in immunology constructed on employing different ideas.

The model that distinguished between susceptible uninfected cells x, infected cells y, and a free virus v is considered by Anderson and May [1] , De Boer and Perelson [5], Nowak and May [20], Wodarz [23].

The model is described with ordinary differential equations

$$\begin{aligned} \frac{dx}{dt} &= \lambda - dx - \beta xv, \\ \frac{dy}{dt} &= \beta xv - \alpha y, \\ \frac{dv}{dt} &= ky - uv. \end{aligned} \qquad (1)$$

Uninfected cells are produced with a rate λ, and die with a rate d. When susceptible cells meet free virus particles they become infected with a rate β. The infected cells die with a rate α. Infected cells produce new virus particles with a rate k and the free virus particles are destroyed with a rate u.

The model (1) has two types of equilibrium (Wodarz[23]). Failure to establish an infection is described by $x^* = \lambda / d,\ y^* = 0,\ v^* = 0.$ Successful establishment of infection is described by $x^* = \alpha u / (\beta k),$ $y^* = (\lambda\beta k - d\alpha u) / (\alpha\beta k),\ \ v^* = (\lambda\beta k - d\alpha u) / (\alpha\beta u).$

Studding this model Anderson and May [1] introduced the basic reproductive ratio of the virus $R_0 = \lambda\beta k / (d\alpha u)$. This is the average number of newly infected cells produced by a single infected cell at the beginning of the infection. If $R_0 > 1$ then one cell infects more than one infected cells and the infection can spread. If $R_0 < 1$ then the virus population goes extinct.

Similarly the dynamics of cytotoxic T lymphocytes (CTL) can be modeled following De Boer and Perelson [5], Nowak and Bangham [19]. Following Wodarz [23] we consider a single population of CTL that fights the infection and denote it by z. Let the population of uninfected cells be x and the population of infected cells be y. Dynamical processes among the populations x, y, z are described with the following system of ordinary differential equations [23]

$$\begin{aligned} \frac{dx}{dt} &= \lambda - dx - \beta_1 xv, \\ \frac{dy}{dt} &= \beta_1 xv - \alpha y - pyz, \\ \frac{dz}{dt} &= cyz - bz. \end{aligned} \tag{2}$$

The CTL proliferate in response to antigenic stimulation with a rate c, and die in the absence of antigenic stimulation with a rate b. CTL kill infected cells with a rate p. In this model one assumes that the number of free virus v is proportional to the number of infected cells.

The model of CTL dynamics (2) was modified by Wodarz and Nowak [24] on the assumption that the rate of CTL expansion has saturation:

$$\begin{aligned} \frac{dx}{dt} &= \lambda - dx - \beta_1 xy, \\ \frac{dy}{dt} &= \beta_1 xv - \alpha y - pyz, \\ \frac{dz}{dt} &= \frac{cyz}{cz+1} - bz. \end{aligned} \tag{3}$$

Here the level of CTL saturation is expressed in the variable s.

Criteria of Liapunov's stability of solutions of equations (1) and (2) under some conditions were given in the book [23]. The generalization of these models on the mathematical model that includes two different effectors responses (CTL and antibodies) was proposed by Wodarz [23]. The model contains five variables: susceptible host cells x, infected cells y, free virus v, an antibody response w, and a CTL response z. The time dynamics of these populations can be described by the following system of ordinary differential equations

$$\begin{aligned}
\frac{dx}{dt} &= \lambda - dx - \beta xv, \\
\frac{dy}{dt} &= \beta xv - \alpha y - pyz, \\
\frac{dw}{dt} &= gvw - hw, \\
\frac{dz}{dt} &= cyz - bz.
\end{aligned} \tag{4}$$

Susceptible host cells are produced at a rate λ, die at a rate dx and become infected by virus at a rate βxv. Infected cells die at a rate ay and are killed by the CTL response at a rate pyz. Free virus is produced by infected cells at a rate ky, decays at a rate uv, and is neutralized by antibodies at a rate qvw. Antibodies develop in response to free virus at a rate gvw and decay at a rate hw. CTL expand in response to viral antigen derived from infected cells at a rate cyz, and decay in the absence of antigenic stimulation at a rate bz.

In the absence of immune responses, the system converges to the following equilibrium:

$$x^{(0)} = \alpha u / \beta k,\ y^{(0)} = (\lambda\beta k - d\alpha u) / \alpha\beta k,$$

$$v^{(0)} = ky^{(0)} / u,\ w^{(0)} = 0, z^{(0)} = 0.$$

If both CTL and antibody responses have been developed, the equilibrium is described by

$$x^{(1)} = \lambda g / (dg + \beta h),\ y^{(1)} = b / c,$$

$$v^{(1)} = h / gu,\ w^{(1)} = (ky^{(1)} - uv^{(1)}) / qv^{1},$$

$$z^{(1)} = (\beta x^{(1)} v^{(1)} - \alpha y^{(1)}) / py^{(1)}$$

Computer simulation of solution of the system of equations (4) was studied by Wodarz [23]. The generalization of models (1) − (3) is proposed by Iwasa et al. [15], where x is the set of uninfected cells, y_i is the set of cells infected with the i virus, $i = 1, 2, \ldots, n$, z_i is the set of immune cells specific to i, $i = 1, 2, \ldots, n$, virus. Note that a cell can be infected by only one type of viruses.

Uninfected cells are supplied at a constant rate λ, and die of a rate proportional to their quantity dx. The infection rate is proportional to the quantity of uninfected and infected cells, $\beta_i x_i y_i$. Infected cells die at the rate $a_i y_i$ and are killed with immune response z_i at the rate p_i. Immune activity increases at a rate proportional to $c_i y_i$, and decreases at a rate $b_i z_i$.

The first model, which is generalization of (1), has the form [15]

$$\begin{aligned}
\frac{dx}{dt} &= \lambda - dx - \sum_{i=1}^{n} \beta_i x y_i, \\
\frac{dy_i}{dt} &= (\beta_i x - \alpha_i - p_i z_i) y_i, i = 1, 2..n, \\
\frac{dz_i}{dt} &= c_i y_i - b_i z_i, i = 1, 2..n.
\end{aligned} \tag{5}$$

The second model, which is generalization of (2), has the form [15]

$$\begin{aligned}
\frac{dx}{dt} &= \lambda - dx - \sum_{i=1}^{n} \frac{\beta_i x y_i}{1 + \eta_i z_i}, \\
\frac{dy_i}{dt} &= \left(\frac{\beta_i x y_i}{1 + \eta_i z_i} - \alpha_i y_i \right), i = 1, 2..n, \\
\frac{dz_i}{dt} &= c_i y_i - b_i z_i, i = 1, 2..n.
\end{aligned} \tag{6}$$

The third model, which is generalization of (3), has the form [15]

$$\begin{aligned}
\frac{dx}{dt} &= \lambda - dx - \sum_{i=1}^{n} \beta_i x y_i, \\
\frac{dy_i}{dt} &= \left(\beta_i x - \alpha_i - p_i z_i\right) y_i, i = 1, 2..n, \\
\frac{dz_i}{dt} &= (c_i y_i - b_i) z_i, i = 1, 2..n.
\end{aligned} \tag{7}$$

For each of the models (5), (6), (7) Iwasa et al [15] found the equilibrium points and studied Lyapunov's stability in (5), (6), (7) under certain constraints.

Murray [18] investigated the model of drug therapy for human immunodeficiency virus (HIV). Murray's model includes the equation for uninfected T-cells T, productively infected T-cells T*, (not all infected T-cells produce the virus), infectious viruses V_1, and noninfectious V_{N_1}:

$$\begin{aligned}
\frac{dT}{dt} &= s + pT\left(1 - \frac{T}{T_{\max}}\right) - d_T T - kV_l T, \\
\frac{dT^*}{dt} &= (1 - n_{ri}) kV_1 T - \delta T^*, \\
\frac{dT_1}{dt} &= (1 - n_p) N \delta T^* - cV_1, \\
\frac{dV_{N_1}}{dt} &= n_p N \delta T^* - cV_{N_1},
\end{aligned} \tag{8}$$

where k, s, p, T_{max}, d_T are positive constants. Here the logistic term T^2 is introduced.

Murray [18] also studied a delay model. Assumed that uninfected T-cells remain constant $T = T_0$. Then

$$\begin{aligned} \frac{dT^*}{dt} &= kT_0V_1(t-\tau) - \delta T^*, \\ \frac{dV_1}{dt} &= (1-n_p)N\delta T^* - cV_l, \\ \frac{dV_{N_1}}{dt} &= n_pN\delta T^* - cV_{N_l}, \end{aligned} \tag{9}$$

where the term $V_l(t-\tau)$ allows for the time delay between contact and viral production.

Dynamics of (8), (9) was presented in [18]. In a reality the delay is a distributed function. Immune responce model with distributed function of delay was proposed by Guardiola and Vecchio [14]:

$$\begin{aligned} P(t) &= \int_0^t F(t-x)e^{-\delta(t-x)}k_ik_sV(x)dx\,, \\ V(t) &= V_0e^{-ct} + \int_0^t e^{-c(t-x)}P(x)dx, t\in[0,t_f], \\ S(t) &= S_0e^{-\beta t} + \int_0^t e^{-\beta(t-x)}[\alpha - k_sV(x)S(x)]dx, t\in[0,t_f], \end{aligned} \tag{10}$$

where P is the population of infected cells that produce viruses, V is the population of viruses, S is the population of cells susceptible to the infection or target cells. The function F is a continuously distributed intracellular delay,

$$F(x) = 1 - e^{-x/b}\sum_{j=0}^{n-1}\frac{x^j}{j!b^j}$$

$\alpha > 0$ is the renewal rate of susceptible cells, β is the rate of clearance of susceptible cells, k_s is the rate of infection, $S_0 \geq 0$, $c > 0$ is the rate of clearance of viruses, $p > 0$ is the rate of virus production, $V_0 \geq 0$, $\delta > 0$ is the rate of clearance of productive cells, $k_i > 0$ is the rate of transition from infected to productively infected cells, $b > 0$ is the scale parameter of the Gamma function, $N \in N^+$ is a shape parameter of the Gamma function.

Guardiola and Vecchio [14] have performed the analysis of the qualitative behavior of the solution of system (10) by proving its positivity and roundedness.

The great number of models of an immune system behavior upon different external effects has been proposed and studied by Marchuk [16], [17].

The basic (primary) model of an immune reaction was constructed by Marchuk [16], [17]. Marchuk [16], [17] and Belykh [3] proved some basic re-

sults about the model. Some modification of this model were developed by Asachenkov [2], Bodnar and Forys [12], Forys [13].

The basic model is described with the system of differential equations

$$\begin{aligned}
\frac{dV(t)}{dt} &= (\beta - \gamma F(t))V(t), \\
\frac{dC(t)}{dt} &= \varepsilon(m)\alpha V(t-\tau)F(t-\tau) - \mu_c(C(t) - C^*), \\
\frac{dF(t)}{dt} &= \rho C(t) - (\mu_f + \eta\gamma V(t))F(t), \\
\frac{dm(t)}{dt} &= \sigma V(t) - \mu_m m(t),
\end{aligned} \tag{11}$$

where *V(t)* is the antigen concentration at the time *t*, F(t) is the antibody concentration at the time t, C(t) is the concentration of plasma cells at the time t, m(t) is the characteristic of the damage of the antigens organ-target. The function m(t) is defined as follows: $m(t) = (M_0 - M_1(t))/M_0$, where M_0 is the characteristic of healthy organ and $M_1(t)$ is the characteristic of healthy part of this organ at time t. Model parameters are determined as follows: β is the coefficient of reproduction of antigens ; γ is the coefficient of neutralization of antigens by antibodies at their meeting; μ_c is the coefficient, determining dynamic of the number of plasma cells with respect to C^*; C^* is the permanent level of plasma cells in a healthy organism; τ is the time during which the formation of plasma cells cascade takes place; α is the coefficient considering probability of meeting of antibodies with antigens and defining the speed of new cells formation.

The organ damage depends on the antigen damage possibilities (with the coefficient σ) and the organ recovery rate μ_m (where μ_f^{-1} is equal to the mean organ recovery time). By definition, $0 \le m(t) \le 1$. Therefore if *m(t)* reaches the level 1 for some $\tilde{t} > 0$, then m(t) = 1 for all $t > \tilde{t}$, which means the lethal outcome of the disease.

The number of antibodies depends on their reproduction rate (with the production rate coefficient *q*) per one plasma cell and the suppression due to immune reactions (with the coefficient γ of neutralization of antigens by antibodies at their meeting and the coefficient η of the rate of antibodies necessary to suppress one antigen) and ageing, where μ_f is the mortality coefficient.

The function $\xi(m)$ is the coefficient of renewal of organism activity and defined by [16], [17]

$$\xi(m) = \begin{cases} 1 \; for \; m \in [0, m^*], \\ \dfrac{m-1}{m^*-1} \; for \; m \in [m^*, 1] \end{cases}$$

where $m^* \in (0,1)$ is a certain level of damage. This means that initially immune processes do not depend on an organ damage rate, but for large damage, ξ tends to zero reflecting the rapid decrease of defense possibilities.

The system (11) has various fixed points. The condition of a healthy organism is described by the fixed point as follows

$$v(t_0) = 0, C(t_0) = C^*, F(t_0) = F^* = \rho C^* / \mu_f, m(t_0) = 0. \tag{12}$$

Stability of the fixed points in (12) has been studied under some conditions in [17].

The condition of a chronicle disease is defined by

$$\begin{aligned} \bar{V} &= \mu_c \mu_f (\beta - \gamma F^*) / (\beta(\rho\xi(\bar{m})\alpha) - \eta\mu_c\gamma), \\ \bar{C} &= (\mu_f \beta\alpha\xi(\bar{m}) - \gamma^2 \eta\mu_c C^*) / (\gamma\rho\xi(\bar{m}) - \eta\mu_c\gamma^2), \\ \bar{F} &= \beta / \gamma, \\ \bar{m} &= \sigma\bar{V} / \mu_m \end{aligned} \tag{13}$$

Asymptotical stability of the fixed point in (11) for $\alpha \to \infty$ has been studied in [17]. If does not tend to ∞, the criteria of asymptotical stability of the fixed point (13) were derived by Boykov et al. [11].

Theorem 2.1. Suppose that there exists a positive number $\chi, \chi > 0$ that satisfies the conditions $\beta - \chi\bar{F} < -\chi$, $\bar{F}\alpha\xi(\bar{m}) - \mu_c < -\chi$, $\eta\gamma\bar{F} + \rho - \mu_f < -\chi$, $\sigma - \mu_m < -\chi$. Then the equilibrium point (13) of system (11) is asymptotical stabile.

Mathematical models of immune response on bacterial and virus infection was constructed by Marchuk [16], [17].

The model of immune response on virus infection is described by system of equations

$$\frac{dV_f}{dt} = vC_V + nb_{CE}C_v E - \chi_{VF}FV_f - \chi_{VM}MV_f - \chi_{VC}(C^* - C_V - m)V_f,$$

$$\frac{dM_V}{dt} = \chi_{MV}MV_f - \alpha_M M_V,$$

$$\frac{dH_E}{dt} = b_H^{(E)}\left[\xi(m)\rho_H^{(E)}M_V(t - \tau_H^{(E)}) - M_V H_E\right] -$$

$$-b_p^{(H_E)}M_V H_E E + \alpha_H^{(E)}(H_E^* - H_E),$$

$$\frac{dH_B}{dt} = b_H^{(B)}\left[\xi(m)\rho_H^{(B)}M_V(t - \tau_H^{(B)}) - M_V H_B\right] -$$

$$-b_p^{(H_B)}M_V H_B B + \alpha_H^{(B)}(H_B^* - H_B),$$

$$\frac{dE}{dt} = b_p^{(E)}\left[\xi(m)\rho_E M_V(t-\tau_E)H_E(t-\tau_E)E(t-\tau_E) - M_V H_E E\right] -$$

$$-b_{EC}C_V E + \alpha_E(E^* - E),$$

$$\frac{dB}{dt} = b_p^{(B)}\left[\xi(m)\rho_B M_V(t-\tau_B)H_B(t-\tau_B)B(t-\tau_B) - M_V H_B B\right] + \alpha_B(B^* - B),$$

$$\frac{dP}{dt} = b_p^{(P)}\left[\xi(m)\rho_P M_V(t-\tau_P)H_B(t-\tau_P)B(t-\tau_P) - M_V H_E E\right] + \alpha_P(P^* - P),$$

$$\frac{dF}{dt} = \rho_F P - \gamma_{FV} V_f F - \alpha_F F,$$

$$\frac{dC_y}{dt} = \sigma V_f(C^* - C_V - m) - b_{CE}C_V E - b_m C_V,$$

$$\frac{dm}{dt} = b_{CE}C_V E + b_m C_V - \alpha_m m, \tag{14}$$

where $V_f(t)$ is the number of free viruses, $M_V(t)$ is the number of stimulated macrophages, $H_E(t)$ is the number of $T-$ lymphocytes helpers to cell- mediated immunity, $H_B(t)$ is the number of T − lymphocytes helpers to humoral immunity, E(t) is the number of T − effectors cells (killers), $B(t)$ is the number of B− lymphocytes, $P(t)$ is the number of plasma cells, $C_v(t)-$ the number of cells of a target organ infected with a virus, Here v, nb_{CE}, $\gamma_{V\ F}$, $b_H^{(E)}, b_H^{(B)}, \rho_H^{(E)}, b_p^{H_E}, \alpha_H^B, \rho_H^B, b_p^{H_B}, \gamma_{VM}, \gamma_{VC}, \gamma_{MV}, \alpha_M, \alpha_H^{(B)}, b_p^{(E)}, \rho_E, \rho_P, b_{EC}, b_p^{(p)}, \alpha_E, b_p^B, b_p^p, \rho_B, \alpha_B, \alpha_P, \rho_F, \gamma_{FV}\ \alpha_F, \sigma, b_{CE}, \alpha_m$ are the parameters characterizing the dynamics of processes going on in a human organism.

The description of these parameters is given in [16], [17].

Stimulation of mM_V -cells by free virus is a trigger of a plasma cell production process. The H_E, H_B, E, B, P cell productions are delayed with different delays $\tau_H^{(E)}, \tau_H^{(B)}, \tau_E, \tau_B, \tau_P$.

It is natural to take the condition of a healthy human organism which has not been infected with a virus as initial values

$$V_f(t_0) = 0, M_V(t_0) = 0, H_E(t_0) = H_E^*, H_B(t_0) = H_B^*\ E(t_0) = E^*, B(t_0) = B^*,$$

$$P(t_0) = P^*, F(t_0) = \frac{\rho_F P^*}{\alpha_F}, C_V(t_0) = 0, m(t_0) = 0. \tag{15}$$

The mathematical model of immune response on bacterial infection was constructed by Marchuk [16], [17]. It is described with the system of ordinary differential equations

$$\frac{dK}{dt} = \beta K - \gamma_{KM} MK - \gamma_{KF} FK,$$

$$\frac{dM_K}{dt} = \gamma_{MK} M_K K - \alpha_M M_K,$$

$$\frac{dH_B}{dt} = b_H^{(B)}[\varepsilon(m)\rho_H^{(B)} M_K(t-\tau_H^{(B)})H_B(t-\tau_H^{(B)}) - M_K H_B] -$$

$$-b_p^{(H_B)} M_K H_B B + \alpha_H (H_B^* + H_B),$$

$$\frac{dB}{dt} = b_p^{(B)}[\varepsilon(m)\rho_B M_K(t-\tau_B)H_B(t-\tau_B) - M_K H_B] + \alpha_B(B^* - B),$$

$$\frac{dP}{dt} = b_p^{(P)}[\varepsilon(m)\rho_P M_K(t-\tau_P)H_B(t-\tau_P)B(t-\tau_P) + \alpha P(P^* - P), \quad (16)$$

$$\frac{dF}{dt} = \rho_F P - \eta_F \gamma_{FK} KF - \alpha_F F,$$

$$\frac{dm}{dt} = \sigma K - \alpha_m m,$$

where *K(t)* is a quantity of pathogenic bacteria in target organ; $M_K(t)$ is the quantity stimulated macrophages of lymphoid tissue of target organ $H_B(t)$ is the quantity of T − cell-assistants of the given specificity; *B(t*) is the quantity of B− lymphocytes of the given specificity; *P(t*) is the quantity of the plasmatic cells developing antibodies of given specificity; *F(t)* is the quantity of specific antibodies; *m(t)* is the characteristic of damage of viruses of organ-target. The description of the parameters are used in this model is given in [16], [17]. Stimulation of MK-cells by free virus is a trigger of a plasma cell production process. The M_K, H_B, B, P cell productions are delayed with different delays $\tau_H^{(B)}, \tau_B, \tau_P$.

As initial conditions Marchuk [16], [17] assumed a condition of a healthy organism

$$K(0) = 0, M_K(0) = 0, H_B(0) = H_B^*, B(0) = B^*, P(0) = P^*, F(0) = F^* = \frac{\rho_F P^*}{\alpha_F}$$

$$m(0) = 0; M_K(T)H_B(t) = 0, -\tau_H^{(B)} \le t < 0,$$

$$M_K(t)H_B(t)B(t) = 0, -\tau \le t < 0, \tau = \max(\tau_B, \tau_P).$$

Detail study of mathematical models of immune response on bacterial and virus infection was given by Marchuk [16], [17], Belykh [3], Bocharov and Romanyukha [4], Romanyukha et al. [21], Romanyukha [22]. The literature review presented in [21], [22].

Generalizations of a basic model of immunology and models of immune response on bacterial and virus infections were derived by Boykov et al. in [8], [9], [10]. The authors studied stability of these models with variable coefficients which are depended at the time. Study of mathematical models in immunology with parameters that depend on time is of interest because of the following reasons. It is known that the state of a healthy human organism varies for a period of time depending on various conditions such as the external environment, physical activity, nervous loading, etc. Also, necessity of this study is stipulated of the change of organism state during the ill and under drug therapy. Therefore it is essential to study mathematical models with variable parameters. Thus the problem is formulated as follows. Without loss of generality we consider the basic problem (11) which coefficients depend on time. Assume that its solution is described by a vector $V_*(t), C_*(t), F_*(t), m_*(t),$ that defines the state of a healthy human organism. Let an organism be infected with a certain amount of antigen V_0 at the moment $t_0 = 0$. It is necessary to study stability of the model with respect to V_0.

In the papers [8], [9], [10] Liapunov's stability and asymptotical stability criteria of solutions of the basic model of immunology and models of immune responses on bacterial and virus infections with time depend coefficients were presented. These criteria have place in regular and singular cases when eigen values of linearized models can lay on image axis.

Below we show criteria of stability for the models (11), (14), (16) where all coefficients depend on time.

Theorem 2.2 [8] Let us consider the model (11). Suppose that the following conditions occur:

1) coefficients of the system (11) are continuous in interval $[0, \infty)$,

2) exists a positive number χ, $\chi > 0$, that

$$\beta(t) - \gamma(t)F(t_0) - \left|\gamma_3(t)\right|\delta \le -\chi,$$

$$\left|\varepsilon(m)\right|\left|\alpha(t)\right|\delta + \left|\varepsilon(m)\right|\left|\alpha(t)\right|F(t_0)\right| - \mu_c(t) \le -\chi,$$

$$-\mu_f^0 + \left|\eta(t)\gamma(t)\right|\delta + \left|\eta(t)\gamma(t)F(t_0)\right| + \left|\rho_0\right| \le$$

$$\le -\chi, -\mu_m(t) + \left|\sigma(t)\right| \le -\chi) \text{ if } 0 \le t \le \tau \text{ and } \beta(t) - \gamma(t)F(t_0) - \gamma(t)\delta \le -\chi,$$

$$-\mu_C + \left|\varepsilon(m)\alpha(t)(\delta + F(t_0))\right| \le -\chi, -\mu_f^0 + \left|\eta(t)\gamma(t)\delta\right| + \left|\eta(t)\gamma(t)F(t_0)\right| + \left|\rho_0\right| \le -\chi$$

$$-\mu_m(t) + \left|\sigma(t)\right| \le -\chi \text{ for } t \in [0;\infty)$$

Then the solution of the Cauchy task (11), (12) is exponential stable.

Theorem 2.3 [9] Let us consider the model (14). Suppose that the following conditions are occurred:

1) coefficients of the system (14) are continuous in interval $[0, \infty)$,

2) there exists a positive number

$$\chi, \chi > 0 \; that - \gamma_{VE}(t)F(0) - \gamma_{VE}(t)C^* + \left(\left|\gamma_{VE}(t)\right| + 2\right)\left|\gamma_{VC}(t)\right| + \left|nb_{CE}(t)\right|$$

$$+ \left|nb_{CE}(t)\right|\left|E^*\right|\delta_0 + \left|v(t)\right| \le -\chi; \gamma_{MV}(t)\delta_0^2 - \alpha_M(t) <\le -\chi; \left|b_p^{H_E}(t)\right|(\delta_0 + \left|E^*\right|) +$$

$$+ \left|b_H^E(t)\right|(\delta_0 + \left|H_E^*\right|) - \alpha_H^E(t) \le -\chi; (\delta_0 + \left|H_B^E(t)\right|)(\left|b_H^E(t)\right| + \left|b_p^{H_B}(t)\right|(\delta_0 + \left|B^*\right|)) -$$

$$-\alpha_H^B(t) \le -\chi; (\delta_0 + \left|E^*\right|)(\left|b_p^E(t)\right|(\delta_0 + \left|H_E^*\right|) + \left|b_{EC}(t)\right| - \alpha_E(t) \le -\chi;$$

$$\left|b_p^B(t)\right|(\delta_0 + \left|B^*\right|)\delta_0 - \alpha_B(t) <\le -\chi; -\alpha_P(t) <\le -\chi;$$

$$\left|\rho_F(t)\right| + \left|\gamma_{FV}(t)\right|(\delta_0 + \left|F(0)\right|) - \alpha_F(t) <\le -\chi;$$

$$\left|\sigma\right|(\left|C^*\right| + 2\delta_0) + \left|b_{CE}(t)\right|\left(\delta_0 + E^*(t)\right) - b_m(t) <\le -\chi;$$

$$\left|b_{CE}(t)\right|(\delta_0 + E^*) + \left|b_m(t)\right| - \left|\alpha_m(t)\right| <\le -\chi.$$

Then the solution of the Cauchy problem (14), (15) is exponential stability in the time interval $[0, \tau*]$, $\tau* = min(\tau_H^{(E)}, \tau_H^{(B)}, \tau_E, \tau_B, \tau_P)$.

Theorem 2.4 [9] Let us consider the model (14). Let $\tau_H^E \le \tau_H^B \le \tau_E \le \tau_B \le \tau_P$. *Let* $\tau_H^E < \tau_H^B$. *Put* $\tau_1^* = \tau_H^E$ *and* $\tau_H^B = \tau_2^*$, Suppose that the following conditions occur:

1) coefficients of the system (14) are continuous in interval $[0, \infty)$,
2) for $t \in [0;\infty)$

$$-\gamma_{VE}(t)F(0) - \gamma_{VE}(t)C^* + \left(\left|\gamma_{VE}(t)\right| + 2\right)\left|\gamma_{VC}(t)\right| + \left|nb_{CE}(t)\right| +$$

$$+ \left|nb_{CE}(t)\right|\left|E^*\right|\delta_0 + \left|v(t)\right| < 0; \gamma_{MV}\delta_0 - \alpha_M(t) < 0;$$

$$\left|b_p^{H_E}(t)\right|[\varepsilon(m)]\left|\rho_H^{(E)}(t)\right|(\delta_0 + \left|H_E^*\right|) +$$

$$+(\delta_0 + \left|H_E^*\right|)] + \left|b_P^{H_E(t)}\right|\left|\delta_0 + E^*\right| + \left|\delta_0 + H_E^*\right| - \alpha_H^{(E)}(t) < 0\,(-\chi),$$

$$(\delta_0 + \left|H_B^E(t)\right|)(\left|b_H^E(t)\right| + \left|b_p^{H_{B(t)}}\right|(\delta_0 + \left|B^*(t)\right|) - \alpha_H^B(t) < 0;$$

$$(\delta_0 + \left|E^*(t)\right|)(\left|b_p^E(t)\right|\delta_0 + \left|b_p^E(t)\right|\left|H_E^*(t)\right|) + \left|b_{EC}(t)\right|(\delta_0 + \left|E^*(t)\right|) - \alpha_E(t) < 0;$$

$$\left|b_p^B(t)\right|(\delta_0 + \left|B^*(t)\right|)(\delta_0 + H_B^*(t)) - \alpha_B(t) < 0;$$

$$-\alpha_P(t) < 0; \left|\rho_F(t)\right| + \left|\gamma_{FV}(t)\right|(\delta_0 + \left|F(0)\right|) - \alpha_F(t) < 0;$$

$$\left|\sigma(t)\right|(\left|C^*\right| + 2\delta_0) + \left|b_{CE}(t)\right|(\delta_0 + E^*) - b_m < 0; \left|b_{CE}(t)\right|(\delta_0 + E^*) + \left|b_m\right| - \alpha_m < 0.$$

Then the solution of the Cauchy problem (14), (15) is stability in the time interval $[\tau_1^*, \tau_2^*]$.

The similar statements have place for other time intervals.

Theorem 2.5 [9] Let us consider the model (16). Let $\tau^* = \min(\tau_H^{(B)}, \tau_B, \tau_B)$

1) coefficients of the system (16) are continuous in interval [0, ∞),
2) there exists a positive number

$$\chi, \chi > 0 \; that \; \beta(t) - \gamma_{KF}(t)F(0) + (|\gamma_{KM}(t)|) +$$

$$+ \; \gamma_{KF}(t))\delta_0 < -\chi, -\alpha_M(t) + |\gamma_{KF}(t)|\delta_0 < -\chi,$$

$$\left|b_H^{(B)}(t)\right|(\delta_0 + \left|H_B^*\right|) + \left|b_p^{H_B(t)}\right|(\delta_0 + \left|H_B^*(t)\right|) *$$

$$*(\delta_0 + B^*(t)) - \alpha_M(t) < -\chi, \left|b_p^{(B)}\right|(\delta_0 + H_B^*)(\delta_0 + \left|B^*\right|) - \alpha_B < -\chi, -\alpha_P(t) < -\chi,$$

$$|\rho_F(t)F(0)| + |\eta_E(t)\gamma_{FK}(t)|(\delta_0 + |F(0)|) +$$

$$+|\rho_F(t)| - \alpha_F(t) < (-\chi), |\sigma(t)| - \alpha_m(t) < (-\chi)$$

Then the solution of the Cauchy problem (16), (17) is exponential stability in the time interval $[0, \tau^*]$.

Theorem 2.6 [9] Let us consider the model (16). Let $\tau_H^{(B)} \le \tau_B \le \tau_B$. *Put* $\tau_1^* = \tau_B$ *and* $\tau_B^H = \tau_2^*$.Suppose that the following conditions occur:

1) coefficients of the system (16) are continuous in interval [0, ∞),
2)

$$\beta(t) - \gamma_{KF}(t)F(0) + (|\gamma_{KM}(t)|) + \; \gamma_{KF}(t))\delta_0 < 0,$$

$$-\alpha_M(t) + |\gamma_{KF}(t)|\delta_0 < 0, \left|b_H^{(B)}(t)\right|(\delta_0 + \left|H_B^*(t)\right|) + \left|b_p^{H_B(t)}\right|(\delta_0 + \left|H_B^*(t)\right|) *$$

$$*(\delta_0 + B^*(t)) - \alpha_H(t) < 0,$$

$$\left|b_p^{(B)}(t)\right|(\delta_0 + H_B^*(t))(\delta_0 + \left|B^*(t)\right|) - \alpha_B(t) < 0, -\alpha_P(t) < 0,$$

$$|\rho_F(t)F(0)| + |\eta_E(t)\gamma_{FK}(t)|(\delta_0 + |F(0)|) + |\rho_F(t)| - \alpha_F(t) < 0, |\sigma(t)| - \alpha_m(t) < 0$$

Then the solution of the Cauchy problem (16), (17) is stability in the time interval $[\tau_1^*, \tau_2^*]$.

The similar statements have place for other time intervals.

Generalizations of the basic model of immunology, taking into account interspecies competition, are investigated in [24].

Stability of solutions of mathematical models of immunology with parameters depending on time

At first we give two Theorems devoted to stability and asymptotical stability of solutions of ordinary differential equations without delay and with delay (also see [7], [6]).

Let us consider the following Cauchy task

$$\frac{dx(t)}{dt} = A(t)x(t) + B(t, x(t)), \tag{20}$$

$$x(0) = x_0, \tag{21}$$

where

$$x(t) = (x_1(t),..,x_n(t))^{\tau}, x_0 = (x_1^0,..,x_n^0)^T, A(t) = \{a_{ij}(t)\}, i, j = 1,2..n,$$

$$B(t, x(t)) = (b_1(t, x(t)),..,b_n(t, x(t)).$$

Let $a_{ij}(t), i, j = 1,2..n,$ be a continuous function, $B(t,0) = 0$ *for* $t \in [0,\infty)$. We shall assume that a solution of the system (20) exists on interval $[0,\infty)$.

The stability the Cauchy task (20).(21) we shall investigate in the space R_n of vector $x = (x_1,..,x_n)$ with the norm $\|x\| = \max|x_k|$. Let $S(a,r) = \{x \le R_n, a \in R_n : \|x - a\| = r\}$; $B(a,r) = \{x \in R_n, a \in R_n : \|x - a\| \le r\}$; $\Lambda(A)$ is logarithmic norm of the matrix A: $\Lambda(A) = \lim_{h \downarrow 0}(\|I + hA\| - 1)/h.$

Theorem 3.1 Let the following conditions are occurred: 1) for each $t, t \in [0,\infty)$, $\Lambda(A(t)) \le -\alpha, \alpha > 0$, 2) $\|B(t, x(t)\| \le \beta\|x(t)\|$, 3) $-\alpha + \beta < 0$.

Then the trivial solution of the system (20) is asymptotical stability.

Proof. At first we prove stability of trivial solution of the system (20). The proof we conduct by contradiction.

Let the trajectory of Cauchy task (20), (21) in the moment T leave the ball $B(0,r_1), r = 2r_0, r_0 = \|x_0\|$ *and* $x(T) \in S(0,r_1)$. We can rewrite the system (20) in the following way:

$$\frac{dx(t)}{dt} = A(T)x(t) + (A(t) - A(T))x(t) + B(t, x(t)). \tag{22}$$

The solution of the Cauchy task (22), (21) is

$$x(t) = e^{A(T)(t-T)}x(T) + \int_T^t e^{A(t)(t-s)}((A(s) - A(T))x(s) + B(s, x(s))ds. \tag{23}$$

Going over to norm in the equation (23), we have

$$\|x(t)\| \le e^{\Lambda(T)(t-T)}\|x(T)\| + \int_T^t e^{\Lambda(T)(t-s)}(\|A(s) - A(T)\|\|x(s)\| + \|B(s, x(s)\|)ds \tag{24}$$

The functions $a_{ij}(t), i, j = 1,2..n,$ are continuous. So, for $\varepsilon < |\alpha| - \beta$ the such time interval $[T, T + \Delta T]$ exists that $\|A(s) - A(T)\| < \varepsilon, s \in [T, T + \Delta T]$.

Let $\varphi(t) = e^{-\Lambda(T)t}\|x(t)\|$. The inequality (24) can be represented as

$$\varphi(t) \le \varphi(T) + \int_T^t e^{\Lambda}(\varepsilon + \beta)\varphi(s)ds .$$

Using the Gronwall- Bellman inequality we have

$$\varphi(t) \le e^{(\varepsilon+\beta)(t-T)}\varphi(T).$$

So,

$$\|x(t)\| \le e^{(\Lambda(T)+\varepsilon+\beta)(t-T)}\|x(T)\| < \|x(T)\|.$$

We receive contradiction and the trajectory of Cauchy task (20), (21) do not leaved the ball $B(0,r_1)$ in the moment T. The Lyapunov stability of trivial solution of the system (20) is proved.

Let us prove the Lyapunov asymptotical stability of the trivial solution of the system (20).

Let $0 < \varepsilon < (|\alpha| - \beta)/2$. We have proved that a time interval $[T,\ T + \Delta T]$ exists in which $\|A(t) - A(T)\| < \varepsilon$. Let $T_1 = T + \Delta T$. By similar way we can prove that a time interval $[T_1, T_1 + \Delta T_1]$ exists in which $\|A(t) - A(T_1)\| < \varepsilon$

Continuing this process we have the sequence $T_0, T_1 ..., T_n ...., (T_0 = T)$ with the following properties: $\|A(t) - A(T_k)\| < \varepsilon$ *for* $t \in [T_k, T_{k+1}], k = 0.1....$

So for $t \in [T_k, T_{k+1}], k = 0,1..n,$

$$\|x(t)\| \le e^{-(\alpha-\varepsilon-\beta)(t-T_k)}\|x(T_k)\| \le e^{-(\alpha-\beta)(t-T_k)/2}\|x(T_k)\| \qquad (25)$$

For the sequence $T_0, T_1, ..., T_n,$ it exists two possibilities:

1) $\lim_{t->\infty} T_n = \infty$ 2) $\lim_{t->\infty} T_n = T_* < \infty$.

In the first case, using the inequality (25), we have

$$\|x(t)\| \le e^{-(\alpha-\beta)(t-T)/2}\|x(T)\|$$

So, $\lim_{t->\infty}\|x(t)\| = 0$ and asymptotical stability is proved.

Let us consider the second case. We see that

$$\|x(t)\| \le e^{-(\alpha-\beta)(t-T)/2}\|x(T)\| \ for\ t \in [T, T_*).$$

Now we have two new cases $\|x(T_*)\| = 0,\ 2)\|x(T_*)\| = c = const > 0.$

In the first case the asymptotical stability is proved. In the second case we can take $x(T_*)$ as initial conditions and repeat the previous arguments. In result we see that a interval $[T_*, T_{**}]$ exists in which

$$\|x(t)\| \le e^{-(\alpha-\beta)(t-T_*)/2}\|x(T_*)\| \le e^{-(\alpha-\beta)(t-T)/2}\|x(T)\|$$

It easy to see that the last inequality is realized for $t \in [T, \infty)$. So, $\lim_{t \to \infty} \|x(t)\| = 0$ and asymptotical stability of the trivial solution of the equation (20) is proved. We have assumed that a solution of the system (20) exists on interval $[0, \infty)$ is proved.

The Theorem is proved.

Let us consider the ordinary differential equations with delay

$$\frac{dx(t)}{dt} = A(t)x(t) + B(t, x(t-\eta)), \tag{26}$$

with initial condition

$$x(t) = \psi(t),\ t \in -\eta \le t \le 0,$$

where

$$x(t) = (x_1(t), ..., x_n(t))^T; A(t) = \{a_{ij}(t)\}, i, j = 1, 2, ..., n;$$

$$\psi(t) = (\psi_1(t), ..., \psi_n(t))^T;\ B(t, x) = (b_1(t, x), ..., b_n(t, x)). \tag{27}$$

Theorem 3.2 Let the following conditions are occurred: 1) for each $t, t \in [0, \infty), \Lambda(A(t)) \le -\alpha, \alpha > 0$. 2) $\|B(t, x(t))\| \le \beta \|x(t)\|$, 3) $-\alpha + \beta < 0$. Then the Cauchy task is asymptotical stability.

Proof. Let us prove the Lyapunov stability of Cauchy task (26), (27). The proof is given by contradiction. Assume that the trajectory $x(t, \psi)$ of the Cauchy task in the moment T leaves the ball $B(0, r_1)$, where $r_1 > \max_{1 \le i \le n} \|\psi_i(t)\|_{C[-\eta, 0]}$

So, $\|x(T, \psi)\| = r_1$. For determination we shall assume that $|x_1(T, \psi)| = r_1, |x_i(T, \psi)| < r_1, i = 2, 3, ..., n.$

Let us rewrite the system (26) in the following form:

$$\frac{dx_i(t)}{dt} = \sum_{j=1}^{n} a_{ij}(T)x_j(t) + B_i(T, x(T-\eta))\frac{x_1(t)}{x_1(T)} + f_i(t),$$

where

$$f_i(t) = \sum_{j=1}^{n} (a_{ij}(t)) - a_{ij}(T)x_j(t) - B_i(T, x(T-\eta))\frac{1}{x_1(T)} \times$$

$$\times (x_1(t) - (x_1(T) + B_i(t, x(T-\eta)) - B_i(T, x(T-\eta)) +$$

$$+ (B_i(t, x(t-\eta)) - B_i(t, x(T-\eta))),\ \ i = 1, 2, ..., n.$$

or, in the operator form,

$$\frac{dx(t)}{dt} = A(T)x(t) + B^*(T, x(T-\eta))x_1(t) + F(t). \qquad (28)$$

The designations $A(T), B^*(T, x(T-\eta)), F(t)$ are obviously. The solution of the equation (28) with initial condition $x(T) = x(T, \psi)$ is

$$x(T) = e^{A(T)(t-T)}x(T) + \int_T^t e^{A(T)(t-s)}(B^*(T, x(T-\eta))x_1(s) + F(s))ds.$$

Going over to the norm we have

$$\|x(t)\| \le e^{\Lambda(A)(t-T)}\|x(T)\| +$$

$$+\int_T^t e^{\Lambda(A)(t-s)}(\|F(s)\| + \|B^*(T, x(T-\eta)\|x_1(s))ds. \qquad (29)$$

Let ε be a real number, $0 < \varepsilon < |\alpha| - \beta$. It is easy to see that it exists so time interval $[T, T+\Delta T]$ that for $t \in [T, T+\Delta T]$ $\|F(t)\| \le \varepsilon\|x(t)\|$ and

$$\|B^*(T, x(T-\eta))\| \le \frac{\beta\|x(T-\eta)\|}{|x_1(T)|} \le \frac{\beta\|x(T)\|}{\|x(T)\|} = \beta.$$

From the last inequalities we have

$$\|x(t)\| \le e^{\Lambda(A)(t-T)}\|x(T)\| + \int_T^t e^{\Lambda(A)(t-s)}(\varepsilon + \beta)\|x(s)\|ds. \qquad (30)$$

Let $\|\varphi(t)\| = e^{-\Lambda(A)t}\|x(t)\|$. Using this function we can rewrite the inequality (30) as

$$\varphi(t) \le \varphi(T) + \int_T^t (\varepsilon + \beta)\varphi(s)ds.$$

Applying the Gronwall-Bellman inequality we have $\varphi(t) \le e^{(\varepsilon+\beta)(t-T)}\varphi(T)$.

So, $\|x(t)\| \le e^{(\Lambda(A)+\varepsilon+\beta)(t-T)}\|x(T)\| \le e^{-(\alpha-\varepsilon-\beta)(t-T)}\|x(T)\| < \|x(T)\|$.

From this inequality follows that the trajectory $x(t, \psi)$ do not leave the ball $B(0, r_1)$ in the moment *T*. We receive the contradiction. From this contradiction Lyapunov stability of Cauchy task (26), (27) follows.

Now we return to investigation stability of mathematical models of immunology with coefficients depended on time *t*. This is realistic supposition because parameters of immune system are changed during the time of immune response.

This investigation we start from the model (5). Let $\left\{x^*(t), y_i^*(t), z_i^*(t), i=1,2,...,n\right\}$ is the solution of the system (5) under initial conditions $\left\{x^0, y_i^0, z_i^0, i=1,2,...,n\right\}$, which describe a state of healthy organism or chronic ill. Let the initial conditions are exited in the time $t_0 = 0$. We investigate the stability of the solution $x^*(t), y_i^*(t), z_i^*(t), i=1,2,...,n$, of the model (5) assuming that the coefficients depend on time. We make the substitution of variables such that

$$x(t) = x^*(t) + \bar{x}(t), y_i(t) = y_i^*(t) + \bar{y}_i(t), z_i(t) = z_i^*(t) + \bar{z_i}(t), i=1,2,...,n.$$

In result we obtain the system of equations

$$\frac{d\bar{x}(t)}{dt} = -d(t)\bar{x}(t) - \sum_{i=1}^{n}\beta_i(t)x^*(t)\bar{y}(t) - \sum_{i=1}^{n}\beta_i(t)\bar{x}(t)\bar{y}_i(t); \qquad (31)$$

$$\frac{d\bar{y_i}(t)}{dt} = \beta_i(t)\bar{x}(t)y_i^*(t) + (\beta_i(t)(x^*(t) + \bar{x}(t) - a_i(t) -$$

$$-p_i(t)(z_i^*(t) + \bar{z_i}(t))\bar{y_i}(t) - p_i(t)y_i^*(t)\bar{z_i}(t), i=1,2,...,n;$$

$$\frac{d\bar{z_i}(t)}{dt} = c_i(t)\bar{y_i}(t) - b_i(t)\bar{z_i}(t), i=1,2,...,n.$$

Applying the statement of the Theorem 3.1 to the system (31) we obtain the following assertion.

Theorem 3.3 Suppose that for all $t(t \geq 0)$ *the following conditions hold:*

1) $d(t) \geq 0, \beta_i(t), a_i(t), p_i(t), b_i(t), c_i(t) \geq 0, i=1,2,...,n,$

2) $x^*(t), y_i^*(t), z_i^*(t) \geq 0, i=1,2,...,n;$

3) $d(t) + \sum_{i=1}^{n}\beta_i(t)y_i^*(t) - \sum_{i=1}^{n}\beta_i(t)x^*(t) \geq \gamma_1 > 0, i=1,2,....,n,$

4) $a(t) + p_i(t)z_i^*(t) - \beta_i(t)x^*(t) - \beta_i(t)y_i^*(t) - p_i(t)y_i^*(t) \geq \gamma_2 \geq 0,$
$i=1,2,...,n,$

5) $b_i(t) - c_i(t) \geq \gamma_3 \geq 0, i=1,2,...,n.$

Then the solution $x^*(t), y_i^*(t), z_i^*(t), i=1,2,...,n$ of the system (5) is asymptotically stable with respect to initial perturbations.

Let the system (6) with coefficients depended on time has the solution $\left\{x^*(t), y_i^*(t), z_i^*(t), i=1,2,...,n\right\}$ under initial conditions $\left\{x^0, y_i^0, z_i^0 i=1,2,...,n\right\}$. Let the initial conditions are exited in the time $t_0 = 0$. Let the perturbation values are equal $\bar{x}(0)$ for variable $x(t), \bar{y_i}(0), \bar{z_i}(0)$ for variables

$y_i(t), z_i(t), i = 1,2,...,n.$ We investigate the stability of the solution $x^*(t), y_i^*(t), z_i^*(t), i = 1,2,...,n$, of the model (6) under the assumption that the coefficients depend on time. We make the substitution of variables $x(t) = x^*(t) + \bar{x}(t), y_i(t) = y_i^*(t) + \overline{y_i}(t),\ z_i(t) = z_i^*(t) + \overline{z_i}(t), i = 1,2,...,n.$

In result we obtain the system of equations

$$\frac{d\bar{x}(t)}{dt} = -d(t)\bar{x}(t) - \sum_{i=1}^{n} \frac{\beta_i(t)x^*(t)y_i^*(t)}{1+\eta_i(t)z_i^*(t)} \sum_{i=1}^{\infty} (-1)^l (\eta_i(t)\bar{z_i}(t))^l -$$

$$- \sum_{i=1}^{n} \frac{\beta_i(t)(x^*(t)\overline{y_i}(t) + \bar{x}(t)y_i^*(t) + \bar{x}(t)\overline{y_i}(t))}{1+\eta_i z_i^*}(1 + \sum_{l=1}^{\infty} (-1)^l (\eta_i(t)\overline{z_i}(t))^l),$$

$$\frac{d\overline{y_i}(t)}{dt} = \frac{\beta_i(t)x^*(t)y_i^*(t)}{1+\eta_i(t)z_i^*(t)} \sum_{i=1}^{\infty} (-1)^l (\eta_i(t)\bar{z_i}(t))^l +$$

$$+ \frac{\beta_i(t)(x^*(t)\overline{y_i}(t) + \bar{x}(t)y_i^*(t) + \bar{x}(t)\overline{y_i}(t))}{1+\eta_i z_i^*}(1 + \sum_{l=1}^{\infty} (-1)^l (\eta_i(t)\overline{z_i}(t))^l) -$$

$$-a_i(t)\overline{y_i}(t), i = 1,2,...,n,$$

$$\frac{d\overline{z_i}(t)}{dt} = c_i(t)\overline{y_i}(t) - b_i(t)\overline{z_i}(t), i = 1,2,...,n, \qquad (32)$$

Applying the statement of the Theorem 3.1 to the system (32) we obtain the following assertion.

Theorem 3.4. Suppose that for all $t(t \geq 0)$ *the following conditions hold:*

1) $d(t) \geq 0, \beta_i(t), a_i(t), b_i(t), c_i(t) \geq 0, i = 1,2,...,n,$

2) $x^*(t) \geq 0, y_i^*(t), x_i^*(t) \geq 0, i = 1,2,...,n;$

3)

$$d(t) + \sum_{i=1}^{n} \frac{\beta_i(t)y_i^*(t)}{1+\eta_i(t)z_i^*(t)} - \sum_{i=1}^{n} \frac{\beta_i(t)x^*(t)y_i^*(t)}{1+\eta_i(t)z_i^*(t)} - \sum_{i=1}^{n} \frac{\beta_i(t)x^*(t)}{1+\eta_i(t)z_i^*(t)} \geq \gamma_1 > 0, i = 1,2,....,n,$$

4) $a(t) + \dfrac{\beta_i(t)x^*(t)y^*(t)\eta_i(t) + x^*(t) + y^*(t)}{1+\eta_i(t)z_i^*(t)} \geq \gamma_2 \geq 0, i = 1,2,...,n,$

5) $b_i(t) - c_i(t) \geq \gamma_3 \geq 0, i = 1,2,...,n.$

Then the solution $x^*(t), y_i^*(t), z_i^*(t), i = 1,2,...,n$ *of the system (6) is asymptotically stable with respect to initial perturbations.*

Investigate the stability of the system (7) assuming that the coefficients depend on time. We make the substitution of variables $x(t) = x^*(t) + \bar{x}(t), y_i(t) = y_i^*(t) + \overline{y_i}(t),\ z_i(t) = z_i^*(t) + \overline{z_i}(t), i = 1,2,...,n.$

In result we obtain the system of equations

$$\frac{d\bar{x}(t)}{dt} = -d(t)\bar{x}(t) - \sum_{i=1}^{n} \beta_i(t)\bar{x}(t)y_i^*(t) - \sum_{i=1}^{n} \beta_i(t)x^*(t)\bar{y}(t) - \sum_{i=1}^{n} \beta_i(t)\bar{x}(t)\overline{y_i}(t),$$

$$\frac{d\overline{y_i}(t)}{dt} = \beta_i(t)\bar{x}(t)y_i^*(t) + (\beta_i(t)(x^*(t) + \bar{x}(t)) - a_i(t),$$

$$\frac{d\overline{z_i}(t)}{dt} = c_i(t)\overline{y_i}(t) - b_i(t)\overline{z_i}(t), i = 1,2,...,n, \tag{33}$$

Applying the statement of the Theorem 3.1 to the system (33) we obtain the following assertion.

Theorem 3.5. Suppose that for all $t(t \geq 0)$ *the conditions 1) - 4) of Theorem 3.3 are fulfilled and* $b_i(t) - c_i(t)(z_i^*(t) + y_i^*(t)) \geq \gamma_3 \geq 0, i = 1,2,...,n$, *is satisfied. Then the solution* $x^*(t), y_i^*(t), z_i^*(t), i = 1,2,...,n$, *of the system (7) is asymptotically stable.*

Investigation of stability of solutions of mathematical models with delay we demonstrate on mathematical model of immune response on biinfection. The mathematical model of immune response on biinfection was offered by Marchuk [17]. This model has great practical interest because almost each illness is taking with participation several antigens.

The mathematical models is described with the following system of differential equations with delays

$$\begin{aligned}
&\frac{dV_i}{dt} = (\beta_i - \gamma_i F_i)V_i, \\
&\frac{dF_i}{dt} = q_i(C_i)C_i - \eta_i\gamma_i F_i V_i - \mu_{f_i} F_i, \\
&\frac{dC_i}{dt} = \xi(m)p_S(V_i)\alpha_i F_i(t-\tau_i)V_i(t-\tau_i) - \mu_{c_i}(C_i - C_i^*), \\
&\frac{dm_i}{dt} = \sigma_i V_i - \mu_{m_i} m_i, i = 1,2,
\end{aligned} \tag{34}$$

where $q_i(C_i) = \rho_i C_i Q / \left(\sum_{i=1}^{2} \rho_i C_i \right)$, Q is total maximum possible performance plasma cells, $\xi(m) = \prod_{i=1}^{2} \xi_i(m_i)$ - function which characterizes the overall health organism, $p_S(V_i) = F_i V_i / \sum_{i=1}^{2} F_l V_l$. The model is based on the assumption that populations of antigens causing biinfection developed independently and each of them described by a basic model of immunology (7).

Stability of solutions of mathematical model (34) is studied for different initial conditions: 1) the simultaneous infection of a healthy body by two different viruses; 2) chronic patients infected by a new disease.

Let us investigate the stability of the system of equations (34) with initial conditions that describe the case of simultaneous infection by two different viruses. In this case, there exists a fixed point such that

$$\overline{V}_i = 0, \overline{C_i} = C_i^*, \overline{F_i} = F_i^* = (q_i(C_i)C_i) / \mu f_i = q_i(C_i)C_i^* / \mu f_i, \overline{m}_i = 0, i = 1,2. \quad (35)$$

Applying statements of the Theorems 3.1 we obtain.

Theorem 3.6. Let for $0 \le t \le \infty$ *the following conditions occur:*

$$\beta_i - \gamma_i \overline{F}_i < -\chi < 0, -\mu_c < -\chi < 0,$$

$$2q_i(C_i) - \mu f_i + \eta_i \gamma_i \overline{F_i} < -\chi < 0, \sigma - \mu_{m_i} < -\chi < 0, i = 1,2.$$

Then the fixed point (35) is stability.

Let us investigate the stability of the system (34) with initial conditions that describe a case when a chronic patient in the moment t_0 infected by a new disease. Let V_1 is a virus of a chronic disease, V_2 is a virus of a new disease. Fixed points for this case are

$$\begin{aligned}
&\overline{V}1(t_0) = \mu_{c_1}\mu_{f_1}(\beta_1 - \gamma_1 F_1^*) / (\beta_1(\rho_1\xi_1\alpha_1 - \eta_1\mu_{c1}\gamma_1),\\
&\overline{C}1(t_0) = (\mu_{f_1}\beta_1\alpha_1\xi_1 - \gamma_1{}^2\eta_1\mu_{c_1}C_1^*) / (\gamma_1\rho_1\xi_1\alpha_1 - \eta_1\mu_{c1}\gamma_1{}^2),\\
&\overline{F}1(t_0) = \beta_1 / \gamma_1,\\
&\overline{m}1(t_0) = \sigma_1\overline{V_1} / \mu_{m_1},
\end{aligned} \quad (36)$$

$$V_2(t_0) = 0, C_2(t_0) = C_2^*, F_2(t_0) = F_2^* = \rho_2 C_2^* / \mu_{f_2} m_2(t_0) = 0. \quad (37)$$

Applying statements of the Theorem 3.1 we obtain

Theorem 3.7. Suppose that there exists a positive number χ, $\chi > 0$, that satisfies the conditions

$$\beta_1 - \gamma_1\overline{F_1} < -\chi, (\overline{F_1} + 2\overline{V_1})\alpha_1\xi(\overline{m})p_S(V_1) - \mu_{c1} < -\chi,$$

$$\eta_1\gamma_1\overline{F_1} + q_1(C_1) - \mu_{f1} < -\chi, \sigma_1 - \mu_{m1} < -\chi$$

$$\beta_2 - \gamma_2\overline{F_2} < -\chi, (\overline{F_2} + 2\overline{V_2})\alpha_2\xi(\overline{m})p_S(V2) - \mu_{c2} < -\chi,$$

$$\eta_2\gamma_2\overline{F_2} + q_2(C_2) - \mu_{f2} < -\chi, \sigma_1 - \mu_{m2} < -\chi.$$

Then the stationary solution (36), (37) of the system (33) is stability.

The results presented here are used to obtain criteria for stability of a mathematical model of bacterial-viral infection.

Concluding remarks.

In this paper, it was offered method for investigation Lyapunov stability and asymptotical stability of solutions of ordinary differential equations without delay and with delay. By this method criteria of stability and asymptotical stability for some models with variable parameters was established. This method can be used for study other mathematical models in immunology and biology.

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МАТЕМАТИЧЕСКОЕ МОДЕЛИРОВАНИЕ В ЭКОНОМИЧЕСКОЙ СИНЕРГЕТИКЕ

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Экономическая синергетика рассматривает сложные вопросы математического образования студентов. С целью улучшения качества образования на кафедре «Высшей и прикладной математики» ПГУ были

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