SECTION 3
METHODS OF THE STABILITY STUDY OF MODELS OF PATHOLOGICAL PROCESSES

Since models of systemic medical research are mainly described by nonlinear differential equations that do not have analytical solutions, very often when studying the problems of evidence-based medicine, it is necessary to look for methods other than the analytical integration of differential equations. Along with the use of numerical methods for solving differential equations, it is often possible to identify important qualitative properties of solutions of nonlinear equations without solving them explicitly. Such qualitative properties include the stability of equation solutions, which will be discussed in the third section. In addition, the coordination of stability properties with the corresponding forms of the course of pathological processes will be shown. The obtained mathematical methods will be illustrated by a software implementation from the support environment for systemic medical research.

3.1. Studies of stability in medical biological systems with a delay

Our goal is to analyze systems of nonlinear differential equations with a delay of the third order, close to the model of immune defense of the human body, developed by a group of mathematicians and doctors headed by G.I. Marchuk [53]. The method of Lyapunov-Krasovsky functionals will be used in the analysis [143].

The main results of the theory of stability. A wide range of problems is associated with the study of the dynamics of objects described by differential equations with a delay

$$\frac{d}{dt}x(t) = F[x_t(s)], -\tau \le s \le 0, t \ge 0. \qquad (3.1.1)$$

Here $x(t) \in R^n$, is $F[x_t(s)]$ the functional defined for an arbitrary fixed $t \ge 0$ on a set of piecewise continuous functions

$$x_t(s) = \begin{vmatrix} x_1(t+s) \\ x_2(t+s) \\ \cdot \\ \cdot \\ \cdot \\ x_n(t+s) \end{vmatrix}, -\tau \le s \le 0$$

One of the most general methods for studying the stability of such problems is the direct Lyapunov method. The use of this technique for systems with aftereffects is associated with two directions. The first is based on Lyapunov's finite-dimensional functions and uses the theorems of B.S. Razumikhin. However, this approach has a drawback. Namely, the need for these stability conditions has not been proven. Differential-difference equations SLFD should be considered in infinite-dimensional spaces. The use of finite-dimensional Lyapunov functions leads to unnecessary sufficient conditions.

For this reason, M.M. Krasovsky [42] proposed to approach the study of stability from the point of view of studying processes in functional spaces. As a point of space, he proposed to consider not a vector $x(t)$, but a vector-segment of this trajectory $x_t(s) = \{x(t+s) : -\tau \le s \le 0\}$. Instead of a function $v(x(t))$, he proposed to use $V[x_t(s)]$ the functionality defined on the segment $x_t(s)$. The use of functionals is a natural generalization of the direct Lyapunov method for

ordinary differential equations to the delayed equations. The main result for autonomous systems is stated [102].

Theorem 3.1.1. Let there be $V : C \to R, V(0) = 0$- functionality and continuous functions $a, b : R^+ \to R^+$, such that $a(r) > 0$ at $r > 0$, $a(r) \to \infty$ at , at $r \to \infty$,

$$a(|x(t)|) \le V[x_t(s)], \dot{V}[x_t(s)] \le -b(|x(t)|).$$

Then the unperturbed solution of $x \equiv 0$ the system (3.1.1) is stable, and each solution is bounded. If, in addition, $b(r) > 0$ at $r > 0$, then each solution goes to zero at $t \to \infty$.

One common case of a third-order nonlinear system with a delay. Consider a system of differential equations with a delay

$$\begin{aligned} \dot{x}(t) &= ax(t) + X(x(t-\tau), y(t-\tau), z(t-\tau)), \\ \dot{y}(t) &= by(t) + Y(x(t-\tau), y(t-\tau), z(t-\tau)), \\ \dot{y}(t) &= cz(t) + Z(x(t-\tau), y(t-\tau), z(t-\tau)), \end{aligned} \tag{3.1.2}$$

which is a generalization of the models used to describe immunity. Here a, b and c are the negative constants, the functions X, Y, Z satisfy the following conditions

$$\begin{aligned}
&\frac{|X(x,y,z)|}{|x|} \to 0, npu\, |x|+|y|+|z| \to 0,\\
&\frac{|Y(x,y,z)|}{|x|} \le g_y |y|,\\
&\frac{|Z(x,y,z)|}{|x|} \le g_z |z|,
\end{aligned} \tag{3.1.3}$$

where g_y, g_z are positive constants.

Theorem 3.1.2. Let the conditions (3.1.3) be met.

Then the unperturbed solution $|x|=|y|=|z|\equiv 0$ (3.1.2) is stable and exponentially x stable.

The proof is given in [159, p. 78-79].

Resistance of the immune defense system. Equations have been proposed to describe the immune defense system [53]. Our further goal is to obtain sufficient resistance conditions explicitly for such a system:

$$\begin{aligned}
&\dot{x}(t) = \alpha x(t) - bx(t)y(t) - cx(t),\\
&\dot{y}(t) = -\beta y(t) + kx(t-\tau)y(t-\tau) + lz(t-\tau), \dot{z}(t) = mf(x(t-\tau)) - nz(t).
\end{aligned} \tag{3.1.4}$$

Here $f(x) = \frac{x}{q+x}$. For this purpose, we introduce the following notations. Let $h_1, h_2, h_3, g_1, g_2, g_3$ be arbitrary positive constants. Let

$$\Delta_1 = -2h_1 + g_1, \Delta_2 = -2h_2\beta + g_2, \Delta_3 = -2h_3 n + g_3,$$
$$\Delta_4 = -g_1\Delta_1\Delta_2\Delta_3 - \frac{h_3^2 m^2}{q^2}\Delta_1\Delta_2 - h_1^2\alpha^2\Delta_2\Delta_3,$$
$$\Delta_5 = -g_2\Delta_4, \Delta_6 = -g_3\Delta_5 + g_2h_2^2(-\Delta_1\Delta_3 g_1 - \Delta_1\frac{h_3^2 m^2}{q^2} - h_1^2\alpha^2\Delta_3).$$

Theorem 3.1.3. Let there be positive constants $h_1, h_2, h_3, g_1, g_2, g_3$ satisfying inequalities

$$\Delta_1 < 0, \Delta_2 < 0, \Delta_3 < 0, \Delta_4 > 0, \Delta_6 > 0.$$

Then the trivial solution (3.1.10) is asymptotically stable.

The proof is given in [159, pp. 80-81].

Exponential estimates. Next, we will consider only the case when the conditions of theorem 3.1.3 take place. Let us introduce some notation. Let $\lambda_{\max}(W)$ be the maximum eigenvalue of the matrix W. Let

$$\underline{h} = \min\{h_1, h_2, h_3\}, \underline{g} = \min\{g_1, g_2, g_3\},$$
$$\overline{h} = \max\{h_1, h_2, h_3\}, \overline{g} = \max\{g_1, g_2, g_3\},$$
$$a_1 = \frac{1}{\overline{h}}[\lambda_{\max}(W) - \overline{g}], b_1 = \frac{1}{\overline{h}}[\lambda_{\max}(W) + \overline{g}].$$

Theorem 3.1.4. Let the system (3.1.4) be such that the conditions of theorem 3.1.3 hold. In addition:

$$\lambda_{\max}(W) + \overline{g} \geq 0.$$

Then there is:

$$x(t)^2 + y(t)^2 + z(t)^2 \leq \frac{V(t_0)}{\underline{h}} e^{-\lambda(t-t_0)}, t \geq t_0.$$

Here λ is the positive solution of the equation:

$$\lambda + a_1 + b_1 e^{\lambda\tau} = 0$$

To prove this theorem, a lemma is required [40, p. 31], which is often used in qualitative analysis of systems with an aftereffect.

Lemma 3.1.1. Let the scalar function $p(t) \geq 0$ be continuous by $[t_0 - h, T]$. If $t \in [t_0, T]$, then the function $p(t)$ is continuously differentiable and satisfies the inequality

$$\dot{p}(t) \leq -\gamma p(t) + \beta \left\| p_t \right\|_\tau, t_0 \leq t \leq T, p_t = p(t+\theta), -\tau \leq \theta \leq 0.$$

Here γ and β are the constants and $\gamma > \beta \geq 0$. Then

$$p(t) \leq \left\| p_{t_0} \right\|_\tau e^{-\lambda(t-t_0)}, t_0 \leq t \leq T,$$

where λ is the only positive solution of the equation:

$$\lambda = \gamma - \beta e^{\lambda\tau}.$$

In proving theorem 3.1.4, L_2 the -norm in the space of squared functions on $[-\tau, 0]$:

$$\left\| x(s) \right\|_{\tau 2} = \left(\int_{-\tau}^{0} x^2(s) ds \right)^{1/2}.$$

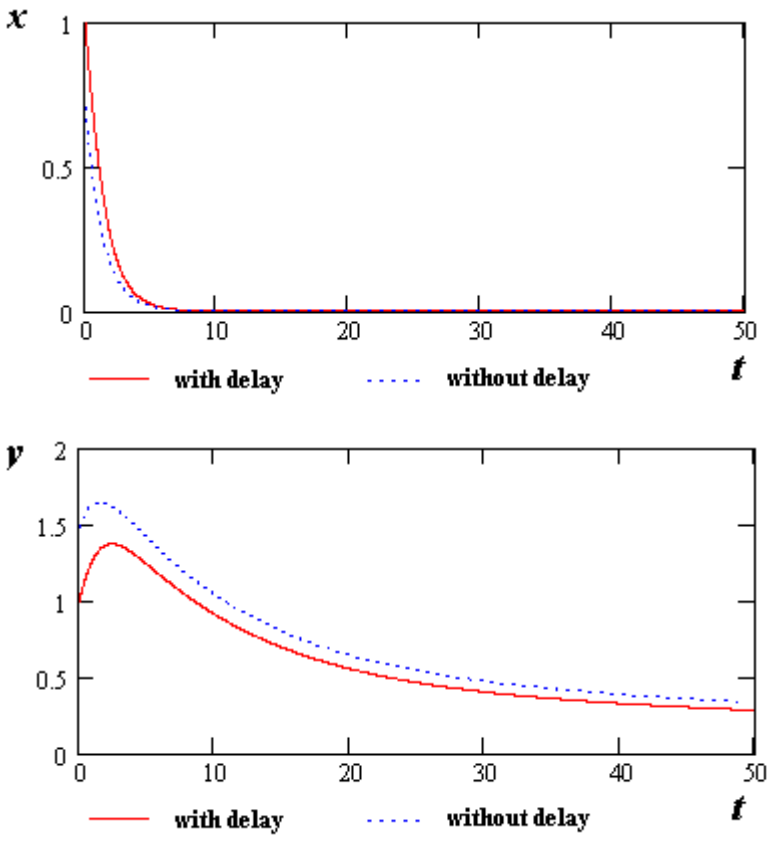
The proof of theorem 3.1.4 is given in [156, pp. 190-191].

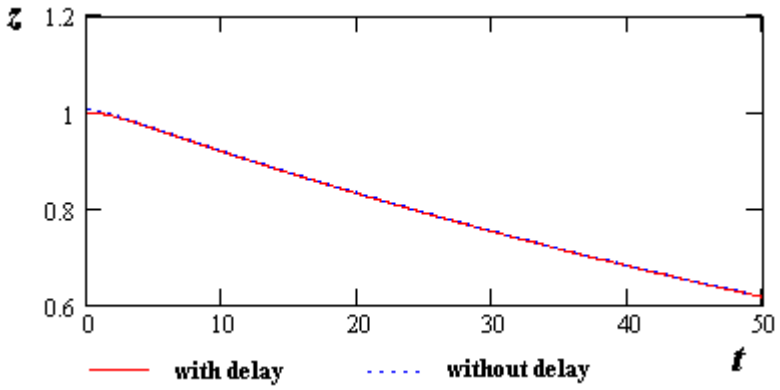
Examples. Consider an example illustrating the so-called subclinical form.

Let

$$\alpha = 1.04, b = 0.6, c = 1,$$
$$\beta = 0.1, k = 0.4, l = 0.04,$$
$$m = 1, q = 100, n = 0.01,$$
$$\tau = 0.1$$

Let's use the same Lyapunov-Krasovsky functionality at $h_1 = h_2 = h_3 = 3$, $g_1 = g_2 = g_3 = 1$. Applying theorem 3.1.4 to this system, we have: $\lambda = 0.98$. Fig. 3.1.1 shows changes x, y, z over time.





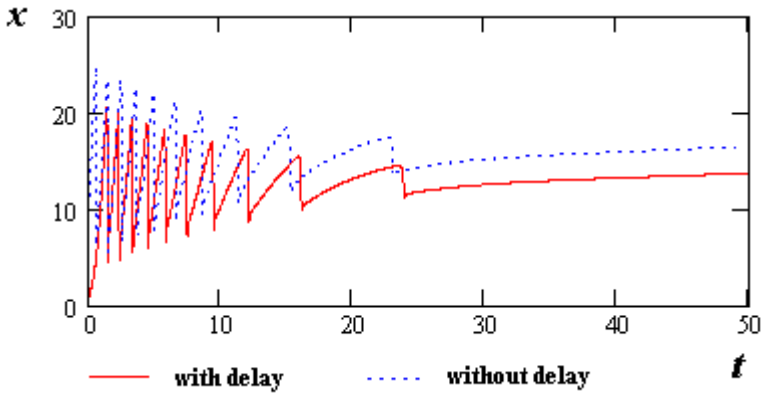
Rice. 3.1.1. Modeling of the subclinical form of the disease, using systems with and without delay.

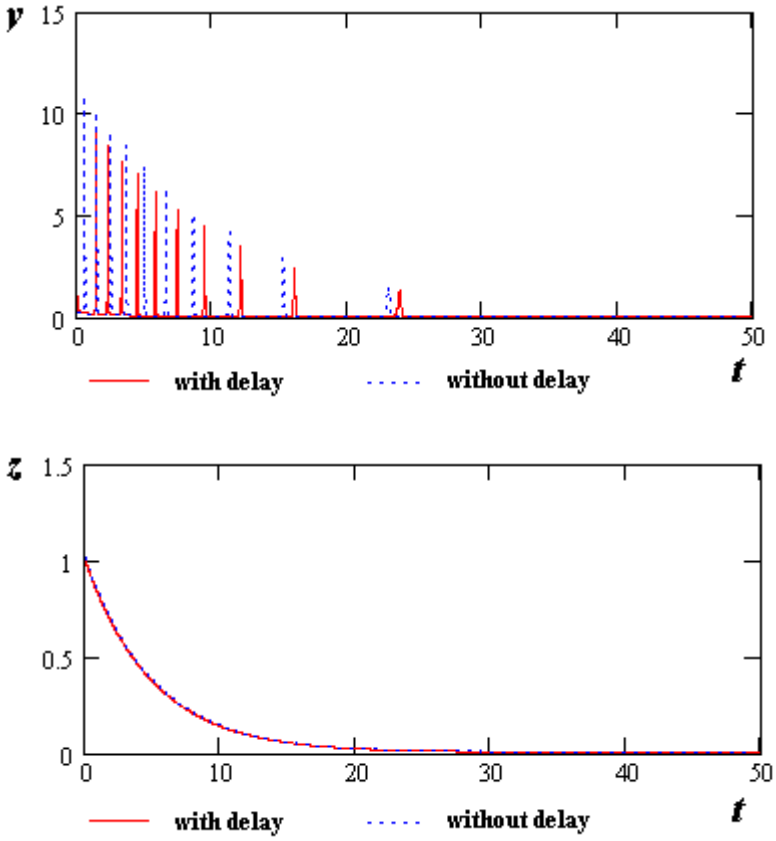
The following example illustrates the chronic form of the disease.

Let

$$\alpha = 1, b = 10, c = 1.01,$$
$$\beta = 100, k = -5, l = 34,$$
$$m = 1, q = 10000, n = 0.2,$$
$$\tau = 0.1$$

Fig. 3.1.2 shows changes x, y, z in time.





Rice. 3.1.2. Modeling of the chronic form of the disease using systems with a delay and without a delay.

Instability. In medicine, the case of instability corresponds to the acute and fatal forms of the disease. Our next goal is to show sufficient conditions of instability for a trivial solution of the system:

$$\begin{aligned} \dot{x}(t) &= \alpha x(t) - bx(t-\tau)y(t-\tau) - cx(t), \\ \dot{y}(t) &= -\beta y(t) + kx(t-\tau)y(t-\tau) + lz(t), \\ \dot{z}(t) &= mf(x(t-\tau)) - nz(t). \end{aligned} \tag{3.1.5}$$

The instability theorem for nonlinear systems of general appearance is stated [80].

Theorem 3.1.5. We consider the system (3.1.1). Let $x_t(\sigma,\varphi)$ be a solution starting from a point (σ,φ). Suppose that there exists $\gamma>0$, open in C the set U and continuous bounded scalar functionality $V:clU\to R$, such that:

(i) $V(\varphi)>0$ on U, $V(\varphi)=0$ on the border U;

(ii) 0 belongs to the closure U;

(iii) $V(\varphi)\le u(|\varphi(0)|)$ on $U\cap B(0,\gamma)$;

(iv) $\overset{\bullet}{V}{}^{*}\ge w(|\varphi(0)|)$ on $[\sigma,\infty)\times U\cap B(0,\gamma)$,

$$\overset{\bullet}{V}{}^{*}(t,\varphi)=\underline{\lim}_{h\to 0^{+}}\frac{1}{h}[V(x_{t+h}(t,\varphi)-V(\varphi)],$$

where $u(s),w(s)$ are continuous increasing and positive for $s>0$.

Then the trivial solution (3.1.1) is unstable. That is, every solution $x_t(\sigma,\varphi)$ with the initial function φ with $U\cap B(0,\gamma)$ must reach the limit $B(0,\gamma)$ for a finite time.

Theorem 3.1.6. Let positive constants α,β,b,c,k,l,m,n be such that there is a delay function $\tau=\tau_0(\alpha,\beta,b,c,k,l,m,n)$ and continuously differentiable positive functions $F(\theta),G(\theta),H(\theta),0\le\theta\le\tau$ in which the matrix

$$W=\begin{vmatrix}
\alpha-c & 0 & 0 & 0 & \frac{\alpha-c}{2}F(-\theta) & 0 & 0 & 0 & 0 & -\frac{b}{2} & 0\\
0 & -\beta & \frac{l}{2} & 0 & 0 & 0 & \frac{\beta}{2}G(-\theta) & 0 & 0 & \frac{k}{2} & 0\\
0 & \frac{l}{2} & -n & 0 & 0 & 0 & 0 & 0 & -\frac{n}{2} & 0 & \frac{m}{2}\\
0 & 0 & 0 & \frac{1}{2}F(\tau) & 0 & 0 & 0 & 0 & 0 & 0 & 0\\
\frac{\alpha-c}{2}F(-\theta) & 0 & 0 & 0 & -\frac{1}{2}\dot{F}(-\theta) & 0 & 0 & 0 & 0 & -\frac{b}{2}F(-\theta) & 0\\
0 & 0 & 0 & 0 & 0 & \frac{1}{2}G(\tau) & 0 & 0 & 0 & 0 & 0\\
0 & \frac{\beta}{2}G(-\theta) & 0 & 0 & 0 & 0 & -\frac{1}{2}\dot{G}(-\theta) & 0 & 0 & -\frac{k}{2}G(-\theta) & 0\\
0 & 0 & 0 & 0 & 0 & 0 & 0 & -\frac{1}{2}H(\tau) & 0 & 0 & 0\\
0 & 0 & -\frac{n}{2} & 0 & 0 & 0 & 0 & 0 & -\frac{1}{2}\dot{H}(-\theta) & 0 & -\frac{m}{2}H(-\theta)\\
-\frac{b}{2} & \frac{k}{2} & 0 & 0 & -\frac{b}{2}F(-\theta) & 0 & -\frac{k}{2}G(-\theta) & 0 & 0 & 0 & 0\\
0 & 0 & \frac{m}{2} & 0 & 0 & 0 & 0 & 0 & -\frac{m}{2}H(-\theta) & 0 & 0
\end{vmatrix}$$

is positive-defined.

Then the trivial solution (3.1.5) is unstable.

The proof is given in [156, pp. 494-495].

3.2. Conditions for the stability of the bone reconstruction system

In subsection 2.6, equations were given that describe the system of bone tissue reconstruction. Let us investigate the stability conditions of such a logistic-type equation.

Equation (2.6.2) has two steady-state $P_1=0$ states and $P_2=\beta$. Let us study the stability of the state P_2.

Lemma 3.2.1. The state P_2 of equation (2.6.2) is asymptotically stable at $\alpha\geq 0$.

The proof is given in [158, p. 295].

Suppose that the model (2.7.1) estimates the mineral density of bone tissue and the height of the vertebrae with a sufficient degree of accuracy. Let us study the structure of the equilibrium points of the system (2.7.1). The equilibrium points of our system are obtained for the following values $\rho(t)$ and $H^{-1}(t)$: $P_1(0,0)$ and $P_2(\underline{\rho},\underline{H^{-1}})$. Here

$$\underline{\rho}=\frac{\alpha\delta}{\nu\mu}-\frac{\gamma}{\nu}\ ,\qquad \underline{H^{-1}}=-\frac{\mu}{\delta}(\frac{\alpha\delta}{\nu\mu}-\frac{\gamma}{\nu})\ ,$$

The study of the stability of the solution P_2 will be reduced to the non-positive certainty of the matrix

$$C=\begin{pmatrix} 0 & 0 & 0 & 0 & -\frac{a\gamma}{2} \\ 0 & -b\mu & 0 & -\frac{1}{2}(a\alpha+b\delta) & \frac{1}{2}\left(\frac{a\gamma}{\underline{\rho}}-a\nu+\frac{b\delta}{\underline{H^{-1}}}\right) \\ 0 & 0 & 0 & \frac{1}{2}\left(\frac{a\alpha}{\underline{\rho}}+\frac{b\mu}{\underline{H^{-1}}}\right) & \frac{a\nu}{2\underline{\rho}} \\ 0 & -\frac{1}{2}(a\alpha+b\delta) & \frac{1}{2}\left(\frac{a\alpha}{\underline{\rho}}+\frac{b\mu}{\underline{H^{-1}}}\right) & 0 & 0 \\ -\frac{a\gamma}{2} & \frac{1}{2}\left(\frac{a\gamma}{\underline{\rho}}-a\nu+\frac{b\delta}{\underline{H^{-1}}}\right) & \frac{a\nu}{2\underline{\rho}} & 0 & 0 \end{pmatrix}$$

The following statement is true.

Theorem 3.2.1. Let the coefficients of the $\alpha,\nu,\gamma,\delta,\mu$ system of equations (2.7.1) be such that there are positive constants a and b, at which the

matrix is non-positively defined. Then the steady state of the P_2 system (2.7.1) is stable.

The proof is given in [158, p. 296-297].

3.3. Problems of stability of equilibrium states of the toxic colitis system

Consider a simplified example of the model (2.8.1)-(2.8.10), where immune defense is reduced to the action of IgA antibodies, the influence of circulating immune complexes and phagocytes is also not taken into account, $\xi(m) \equiv 1$. We assume that the increase in the concentration of lead acetate occurs continuously and it is proportional to its current concentration:

$$\begin{gathered}
\frac{dx_1(t)}{dt} = v_1 x_1(t) - k_{1,2} x_1(t) x_2(t), \\
\frac{dx_2(t)}{dt} = k_{2,6} x_6(t) - k_2(t) x_2(t) - k_{2,1} k_{1,2} x_1(t) x_2(t), \\
\frac{dx_6(t)}{dt} = k_{6,1,2} x_1(t-\tau_6) x_2(t-\tau_6) - k_6\left(x_6(t) - x_6^0\right), \\
\frac{dx_{10}(t)}{dt} = k_{10,1} x_1(t) - k_{10} x_{10}(t).
\end{gathered} \tag{3.3.1}$$

Initial conditions at $t \in [t_0 - \tau_6, t_0]$:

$$x_1(t) = x_1^0,\ x_2(t) = x_2^0,\ x_6(t) = x_6^0,\ x_{10}(t) = x_{10}^0. \tag{3.3.2}$$

System (3.3.1)-(3.3.2) has two stationary states. One of them is P_1:

$$x_1(t) = 0,$$

$$x_2(t) = \frac{k_{2,6}x_6^0}{k_2},$$

$$x_6(t) = x_6^0,$$

$$x_1(t) = 0$$

interpreted as a state of a healthy organism, the other is P_2:

$$x_1(t) = -k_6 \frac{-k_{2,6}x_6^0 k_{1,2} + k_2 v_1}{v_1\left(-k_{6,1,2}k_{2,6} + k_{2,1}k_{1,2}k_6\right)} = x_1^*,$$

$$x_2(t) = \frac{v_1}{k_{1,2}} = x_2^*,$$

$$x_6(t) = \frac{-k_{6,1,2}k_2 v_1 + x_6^0 k_{1,2}^2 k_{1,2}k_6}{\left(-k_{6,1,2}k_{2,6} + k_{2,1}k_{1,2}k_6\right)k_{1,2}} = x_6^*,$$

$$x_{10}(t) = -k_{10,1}k_6 \frac{-k_{2,6}x_6^0 k_{1,2} + k_2 v_1}{v_1\left(-k_{6,1,2}k_{2,6} + k_{2,1}k_{1,2}k_6\right)k_{10}} = x_{10}^*,$$

interpreted as a chronic course of the disease.

Study of the stability of the system (3.3.1)-(3.3.2) in the vicinity of points P_1 and P_2 is carried out by the method of linearization.

Statement 3.3.1. Let the coefficients and initial conditions of the system (3.3.1)-(3.3.2) be such that the inequality is satisfied:

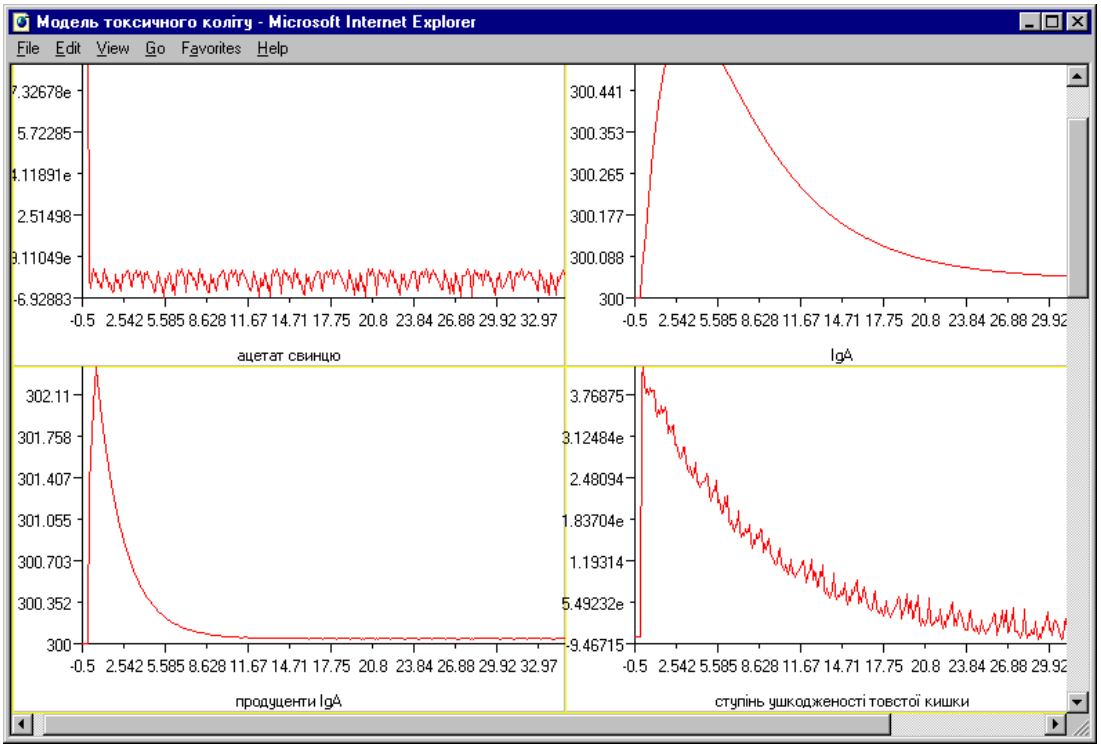
$$k_2 v_1 \le x_6^0 k_{1,2}k_{2,6}. \qquad (3.3.3)$$

Then the steady-state of P_1 the system (3.3.1)-(3.3.2) is stable. If the coefficients and initial conditions of the system (3.3.1)-(3.3.2) are such that the

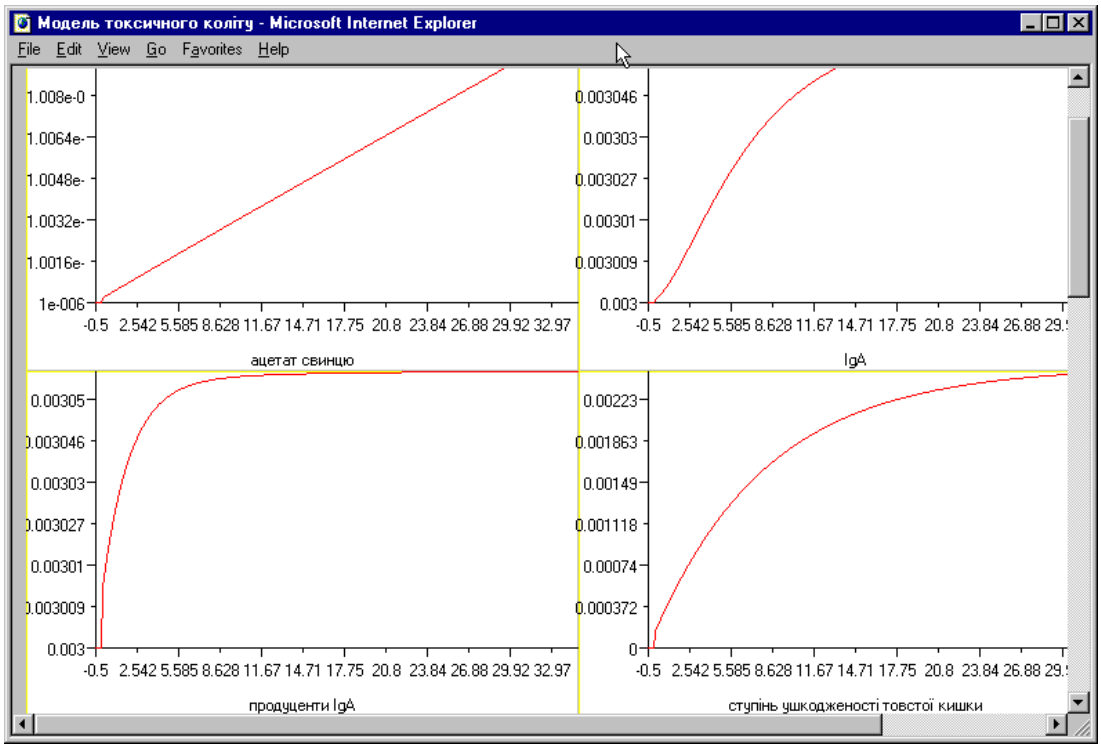
condition (3.3.3) is not met, then the steady-state of P_1 the system (3.3.1)-(3.3.2) is unstable.

The proof is given in [185, pp. 97-98]**.**

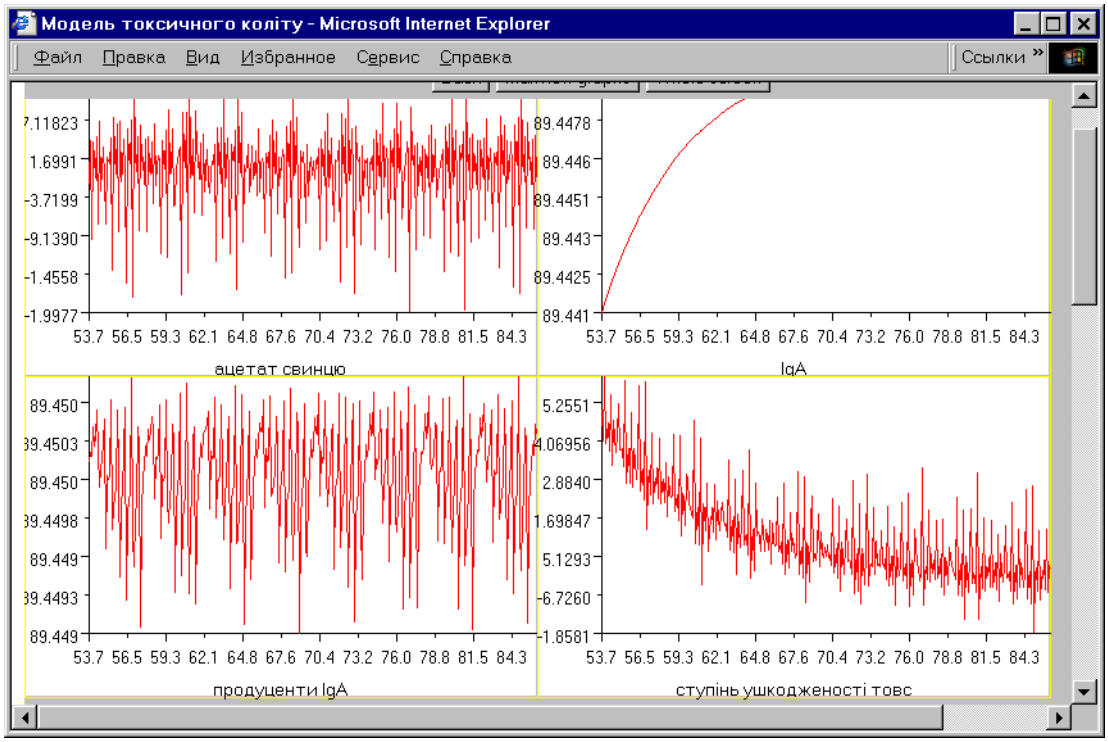
Example. Fig. 3.3.1 shows the results of numerical integration of the system (3.3.1)-(3.3.2) for parameter values and delay (2.8.12).



(a)



(b)



(c)

Rice. 3.3.1. System integration (3.3.1)-(3.3.2).

Fig. 3.3.1a Values close to the equilibrium state are taken as initial conditions:

$$P_1 = \begin{bmatrix} 0 \\ 297.3 \\ 297.3 \\ 0 \end{bmatrix}$$

Namely:

$x_1^0 = 10^{-6}$, , $x_2^0 = 300$ $x_3^0 = 300$, . $x_4^0 = 0$ In this case, the condition (3.3.3) is fulfilled – the solutions are approaching the steady state.

Fig. 3.3.1b Values close to the equilibrium state are taken as initial conditions:

$$P_1 = \begin{bmatrix} 0 \\ 0.0037 \\ 0.0037 \\ 0 \end{bmatrix}$$

Namely:

$x_1^0 = 10^{-6}$, $x_2^0 = 0.003$, $x_3^0 = 0.003$, . $x_4^0 = 0$ Note that in this case, the inequality (3.3.3) is violated - we observe an unstable solution.

Statement 3.3.2. Let the parameters and initial conditions of the system (3.3.1)-(3.3.2) be such that there are roots of the equation

$$\begin{aligned} &\left(-k_2 v_1 k_{10} + k_{1,2} x_2^* k_2 k_{10} + k_{10,1} k_{1,2} x_1^* k_{2,6} - v_1 k_{2,1} k_{1,2} x_1^* k_{10}\right)\gamma + \\ &+\left(k_{10} k_2 + k_{2,1} k_{1,2} x_1^* k_{10} - v_1 k_{10} + k_{1,2} x_2^* k_{10} - v_1 k_{2,1} k_{1,2} x_1^* - k_2 v_1 + k_{1,2} x_2^* k_2\right)\gamma^2 + \\ &+\left(k_{2,1} k_{1,2} x_1^* + k_{10} + k_2 + k_{1,2} x_2^* - v_1\right)\gamma^3 + \gamma^4 = 0 \end{aligned} \tag{3.3.4}$$

with a positive real part. Then the equilibrium state of P_2 the system (3.3.1)-(3.3.2) is unstable.

The proof is given in [185, pp. 101-102]**.**

Unfortunately, it is impossible to obtain the roots of equation (3.3.5) in analytical form in terms of coefficients even using the modern MAPLE symbol calculation package. Therefore, we will illustrate statement 3.3.2 using the

example of a system (3.3.1)-(3.3.2) with parameter values and delay (2.8.12). $x_6^0 = 89.45$ In this case, equation (3.3.5) has roots:

$$r = \begin{pmatrix} -0.601 - 1.822i \\ -0.601 + 1.822i \\ 0 \\ 3.28 \end{pmatrix},$$

one of which has a positive real part - solution P2 - unstable (Fig. 3.3.1c).

3.4. Qualitative study of piecemeal continuous systems in radiotherapy

Radiotherapy is an effective treatment in oncology. In the early (T1 and T2) stages of cancer, the results of radiotherapy are comparable to those achieved by surgery. And even more, radiotherapy is preferred in some cases when attention is paid to the protection of the affected organ. In more complex cases, radiotherapy is often used after surgery as paired therapy together with chemotherapy (chemoradiotherapy) .

Radiotherapy can be guided by external light flux or other techniques. The choice of one or another method depends on the location of the tumor and the purpose of therapy.

Today, using radiotherapy, they face numerous problems. The most important among them is how to control the number of cells in the tumor (level of damage). The goal is to achieve the desired tumor management. Even until now, this problem is being solved experimentally. But, as it has been established, the degree of damage to cells by radiation as a whole is an exponential function of the radiation dose [120]. Next, a method for constructing such exhibitors will be presented. Such exponential estimates are important in answering the following questions.

I. What radiation time (or radiation dose) do we need to reach the desired

tumor size;

II. When will we be able to achieve the desired tumor size by knowing the radiation dose?

III. What will be the minimum and maximum size of the tumor after radiotherapy?

IV. How long can a tumor (such as a prostate) be histologically noticeable after radiation.

Problem statement. For the first time, delayed differential equations for studying the cell's response to X-rays were proposed in [64] and were of the form

$$\begin{aligned} &\dot{x}(t) = ax(t) + b[x(t-\tau) - x_0],\ 0 \le t \le T, \\ &\dot{x}(t) = b[x(t-\tau) - x_0],\ t \ge T \end{aligned} \tag{3.4.1}$$

Here t is the time variable, the scalar function $x(t)$ denotes the concentration of a substance in the irradiated cell x_0 - the normal equilibrium concentration of this substance, when there is no irradiation, T is the irradiation time. It is assumed that cells have the ability to make up for the lack or eliminate the excess of this substance, but their reaction has a delay time equal to τ. Therefore:

$$x(t) \equiv x_0, t \le 0 \tag{3.4.2}$$

In equation (3.4.1), the constant a depends on the degree of irradiation, the constant b shows the reaction of the cell to deviations from the equilibrium concentration x_0.

Equations (3.4.1) and (3.4.2) were proposed in [64] and are widely used today in medical radiology to assess the effects of radiotherapy used in the treatment of cancer [128].

Let us denote through $L_2([-\tau,0],R^n)$ the space Lebesgue functions defined on $[-\tau,0]$ with values in R^n. For a fixed, $\tau \geq 0$ a Hilbert space $H = R^n \times L_2([-\tau,0],R^n)$ with a scalar product $\langle u_1,u_2 \rangle = v_1^T v_2 + \int_{-\tau}^{0} \phi_1^T(s)\phi_2(s)ds$ is considered, where $u_i = (v_i,\phi_i) \in H$ and the norm

$$\|(v,\phi)\ \| = v^T v + \int_{-\tau}^{0} \phi^T(s)\phi(s)ds$$

In the future, the trajectory interval $x(t)$ of length τ is denoted by x_t, i.e. $x_t = x(t+s)$ for any $-\tau \leq s \leq 0$.

We will use the following norms

$$\|x_t\ \|_2 = \left\{ \int_{-\tau}^{0} |x(t+s)\ |^2 ds \right\}^{1/2}, \|x_t\ \|_\tau = \max_{-\tau \leq s \leq 0} |x(t+s)|,$$

where $|x(t+s)\ |$ is the Euclidean norm.

Equations (3.4.1), (3.4.2) are representatives of the class of systems with a delay:

$$\begin{aligned} &\dot{x}(t) = A(t,x_t)x(t) + B(t,x_t)[x(t-\tau] - x_0], 0 \leq t \leq T, \\ &\dot{x}(t) = B(t,x_t)[x(t-\tau) - x_0], t \geq T, \\ &x(t) \equiv x_o, t \leq 0. \end{aligned} \qquad (3.4.3)$$

Here x_0 is a constant vector, $A,B: R \times L_2([-\tau,0],R^n) \to R^{n \times n}$ - matrix-significant operators. Equations (3.4.3) are not considered in this work, but it is believed that they will play an important role in applications similar to radiotherapy in the future.

The solution to the initial problem (3.4.3) for each $t > 0$ is the function It is known that there is a single solution (3.4.3), $x \in L_2([-\tau,t],R^n)$.

determined for $[-\tau,\infty]$ which continuously depends on the initial data in the norm H.

System (3) can be rewritten in the usual "linear" form

$$\frac{d}{dt}\begin{pmatrix} x_t(0) \\ x_t \end{pmatrix} = A\begin{pmatrix} x_t(0) \\ x_t \end{pmatrix}, \tag{3.4.4}$$

$$(x_0(0), x_0) = (x_0, x_0) \in H, \tag{3.4.5}$$

where

$$A\begin{pmatrix} x_t(0) \\ x_t \end{pmatrix} = \begin{pmatrix} \begin{cases} \dot{x}(t) = A(t, x_t)x(t) + B(t, x_t)[x(t-\tau) - x_0], 0 \le t < T, \\ \dot{x}(t) = B(t, x_t)[x(t-\tau) - x_0], t \ge T \end{cases} \\ \dfrac{dx_t(s)}{ds}, -\tau \le s \le 0 \end{pmatrix} \tag{3.4.6}$$

-- infinitesimal operator.

Linear transformations of dependent quantities. Corresponding transformations make it possible to simplify the system (3.4.3). This is very important in cases where it is necessary to find estimates of solutions in an explicit form.

Lemma 3.4.1. The study of the behavior of the solution of the system (3) is $t \ge T$ reduced to the study of the equation

$$\frac{d\tilde{x}(t)}{dt} = B(t, \tilde{x}_t + x_0)\tilde{x}(t-\tau) \tag{3.4.7}$$

The proof is given in [211, pp. 263-264]**.**

Lemma 3.4.2. Let $A(t, x_t) \equiv A, B(t, x_t) \equiv B$ be the constants of the matrices that switch with each other. Then, when $0 \le t < T$ studying the stability of solutions, equations (3.4.3) can be reduced to the study of the stability of the system described by the equations

$$\frac{d\tilde{x}(t)}{dt} = B\tilde{x}(t-\tau) \tag{3.4.8}$$

The proof is given in [211, p. 264]**.**

In the future, we will consider only the system (3.4.3), assuming that the conditions of lemma 3.4.2 take place. This allows us to replace the initial problem (3.4.3) with the

$$\begin{aligned} &\frac{d\tilde{x}(t)}{dt} = B\tilde{x}(t-\tau), t \geq 0 \\ &\tilde{x}(t) = e^{At}(A+B)^{-1}Ax_0, -\tau \leq t \leq 0 \end{aligned} \tag{3.4.9}$$

where

$$\tilde{x}(t) = \begin{cases} e^{-At}(x(t) - (A+B)^{-1}Bx_0), 0 \leq t \leq T, \\ x(t) - x_0, t \geq T \end{cases}$$

The system (3.4.3) in the form (3.4.9) will be used to obtain exponential estimates of the solution. There are two main methods for finding estimates for systems with an explicit delay, based on the method of Lyapunov functionals. In this subsection, they are applied to the system (3.4.3).

Evaluation of the solution as a result of difference inequality. Consider the behavior of the solution (3.4.3) at $t > 0$. Let us use the technique proposed in [108] for functional-differential equations

$$\tilde{x}(t) = A(t, x_t)x(t) + B(t, x_t)x(t-\tau).$$

The main idea of this approach is the use of functionalities

$$v(t,\phi) = \phi^T(0)\phi(0) + \int_{-\tau}^{0} \phi^T(s)V(t+s)\phi(s)ds \qquad (3.4.10)$$

Note that for a specific solution, we can consider the functionality (3.4.10) as a function of t.

$$v(t) = v(t, x_t)$$

We also note that if $A(t,x_t) \equiv A, B(t,x_t) \equiv B$ are the constant matrices, then we can replace them in the functionality (3.4.10) $V(t+s) \equiv V$

In the paper [108], exponential estimates for $v(t)$. These estimates are based on inequality

$$v(t) \le v(t-2\tau)d, \qquad (3.4.11)$$

where $d < 1$ there is a constant that can be defined.

Theorem 3.4.1. [108]. Suppose that

(And) there is a number μ_1, such that

$$\dot{v}(t) \le \mu_1 |x(t)|^2, t \ge 0,$$

(ii) there are positive numbers a, b and c such that

$$|A| = |A(t,\phi| \le a, |B| = |B(t,\phi| \le b, \phi \in C, |V| = |V(t)| \le c, t \ge -\tau.$$

Then there are steels $\nu > 0$ and $N > 0$ those that

$$v(t) \le v(0)Ne^{-\nu t}, t \ge 2\tau. \qquad (3.4.12)$$

Remark 3.4.1. The above values $\nu > 0$ and $N > 0$ have an obvious form, namely let

$$\rho = \frac{1}{(1+\tau c)^{1/2}} \frac{1}{a+b}, \quad f = -\frac{\mu_1}{8(1+\tau c0}\rho, \quad d = \begin{cases} \dfrac{1}{1+\dfrac{f}{\rho}\tau}, \tau \le \tau_0 \\ c_0, \tau_0 < \tau \end{cases}$$

where c0 is the positive solution of the equation $fc_0^{3/2} + c_0 - 1 = 0$ and $\tau_0 = \rho\sqrt{c_0}$.

Then

$$v = -\frac{\ln d}{2\tau}, \quad N = \frac{1}{d}.$$

Let's apply the assumption (3.4.12) to the system(3.4.3) at $t > 0$.

Lemma 3.4.3. Let the system (3.4.3) be such that the conditions of theorem 3.4.1 are met. Then, if $2\tau \le t < T$, then

$$\left|x(t)\right| \le \frac{\left|B\right|}{\left|A+B\right|}\left|x_0\right| + (1+\tau c)^{1/2}\left\|\tilde{x}_0\right\|_\tau N^{1/2} e^{(|A|-\frac{p}{2})t}. \qquad (3.4.13)$$

The proof is given in [185, p. 109].

Lemma 3.4.4. Let the system (3.4.3) be such that the conditions of theorem 3.4.1 are met. Then, if $t \ge T \ge 2\tau$, then

$$\left|x(t)\right| \le \left|x_0\right| + (1+\tau c)^{1/2} N_1 N^{-1/2} e^{-\frac{vt}{2}} \qquad (3.4.14)$$

Here

$$N_1 = (1+\tau c)^{1/2}\left\|\tilde{x}_0\right\|_\tau N^{-1/2} e^{-v(T-\tau)}.$$

Proof. The same ideas are used as in lemma 3.4.3. N_1 is an estimate $\tilde{x}_T$.

Evaluation of the solution as a result of differential-difference inequalities. Irregularities (3.4.14) can be used to solve the following problems that arise in radiotherapy:

(i) Reaching tumor size L. The exposure time T is fixed. How to find the time t when the level of tumor size will be less than the specified L.

(II) Finding the exposure time T. It is necessary to obtain the desired tumor size that is smaller than the specified L for a fixed time t^* due to the change in the exposure time T.

Namely, the solutions of these problems lead to the solution of the corresponding exponential equations arising from (3.4.16).

Problems arise that require not only upper but also lower grades of the system (3.4.3). Namely:

(III) Reaching a tumor size larger than L.

(IV) Finding the exposure time T such as to exceed the size of the tumor L in a fixed time t^*.

To solve problems (I) – (IV), we will use the Lyapunov functionality (3.4.10) with a constant matrix V. This approach is based on obtaining difference-differential inequalities.

The complete derivative of the functionality $v(t)$ along the interchanges $\tilde{x}(t)$ has the form

$$\dot{v}(t) = -\xi^T C\xi,$$
$$\xi = \begin{pmatrix} \tilde{x}(t) \\ \tilde{x}(t-\tau) \end{pmatrix}, C = \begin{bmatrix} -V & -B \\ -B^T & V \end{bmatrix}.$$

Comments. We believe that the system (3.4.3) and functionality (3.4.10) are such that the matrix C is positively defined.

Let us present a method of two-way evaluation of the functionality v(t).

Lemma 3.4.5. The functionality $v(t)$ at the solutions $\tilde{x}(t)$, i.e. $v(t)=v(\tilde{x}_t)$ satisfies the difference-differential inequality:

$$\dot{v}(t)+a_1v(t)+b_1v(t-\tau)\le 0, t\ge\tau,$$
$$a_1=\lambda_{\min}(C)\left[1+\frac{\lambda_{\max}(V)}{\lambda_{\min n}(C)}\right], b_1=\lambda_{\min}(C)\left[1-\frac{\lambda_{\max}(V)}{\lambda_{\min}(C)}\right]$$

The proof is given in [185, pp. 111-112]**.**

Lemma 3.4.6. The functionality $v(t)$ along $\tilde{x}(t)$ the solutions satisfies the difference-differential inequality

$$0\le\dot{v}(t)+a_2v(t)+b_2v(t-\tau), t\ge\tau,$$
$$a_2=\lambda_{\max}(C)\left[1+\frac{\lambda_{\min}(V)}{\lambda_{\max}(C)}\right], b_2=\lambda_{\max}(C)\left[1-\frac{\lambda_{\min}(V)}{\lambda_{\max}(C)}\right].$$

Proof. The same reasoning is used as in lemma 3.4.5.

Lemma 3.4.7. Differential equation

$$\dot{z}+az(t)+bz(t-\tau)=0, t>0, z(t)=\phi(t), -\tau\le t\le 0 \qquad (3.4.15)$$

with coefficients $a=a_1$ and $b=b_1$ ($a=a_2$, $b=b_2$)) is asymptotically stable for any $\tau>0$.

The proof is given in [185, p. 112]**.**

Lemma 3.4.8. If $a-|b|>0$ then the solution $z(t)$ of equation (3.4.15) satisfies

$$|z(t)|\le\|z_0\|_\tau e^{-\frac{\nu_1 t}{2}}, t\ge 0,$$
$$\nu_1=\frac{2\tau(a-|b|)}{\tau(a-|b|)+\ln a-\ln|b|} \qquad (3.4.16)$$

and

$$\begin{aligned} &\left\|z_0\right\|_\tau^* e^{-\frac{v_2 t}{2}} \le \left|z(t)\right|, t \ge 0, \\ &v_2 = 2(a + \left|b\right| e^{\frac{v_1 \tau}{2}}). \end{aligned} \tag{3.4.17}$$

The designation used here is (it is not the norm)

$$\left\|z_t\right\|_\tau^* = \min_{-\tau \le s \le 0} \left|z(t+s)\right|$$

Let us use the Lyapunov function $e^{v_1 t} z^2$ and the Razumikhin inequality $\left|z(t-\tau)\right| < e^{v_1 t} \left|z(t)\right|$ to estimate its complete derivative. From here we get (3.4.16). The inequality (3.4.17) can be obtained in the same way.

Let's enter the notation

$$\gamma_1 = \frac{4\tau\lambda_{\min}(c)}{2\tau\lambda_{\min}(c) + \ln\left[\dfrac{\lambda_{\max}(V) + \lambda_{\min}(C)}{\lambda_{\max}(V) - \lambda_{\min}(C)}\right]},$$

$$\gamma_2 = 2\left[\lambda_{\max}(C)(1 + e^{\frac{\gamma_1 \tau}{2}}) + \lambda_{\min}(V)(1 - e^{\frac{\gamma_1 \tau}{2}}\right],$$

$$\phi(V) = 1 + \tau\lambda_{\max}(V).$$

Theorem 3.4.2. Suppose that there is such a positively defined matrix V that the C matrix is positively defined as well. Then the solution $x(t)$ of the initial problem (3.4.3) satisfies with $\tau < t \le T$ the following two inequalities:

$$\left|x(t)\right| < \frac{\left|B\right|}{\left|A+B\right|}\left|x_0\right| + \sqrt{\phi(V)}\left\|\tilde{x}_\tau\right\|_{2\tau} e^{(|A| - \frac{\gamma_1}{4})t}, \tau < t \le T$$

$$\left\|e^{-At}(x(t) - (A+B)^{-1}Bx_0\right\|_\tau \ge \frac{1}{\sqrt{\phi(V)}}\left\|\tilde{x}_\tau\right\|_{2\tau}^* e^{-\frac{\gamma_2 t}{4}}, \tau < t \le T$$

Here $\|\tilde{x}_\tau\|_{2\tau}^*$ and $\|\tilde{x}_\tau\|_{2\tau}$ are the minimum and maximum values $|\tilde{x}(t)|$ at $-\tau \le t \le \tau$.

The proof is given in [185, p. 114]**.**

At we $t > T > \tau$ can obtain a similar result presented in the following theorem.

Theorem 3.4.3. Suppose that there is a positively definite matrix V such that the C matrix is positively defined as well. Then the solution $x(t)$ of the initial problem (3.4.3) satisfies the $t > T > \tau$ two-sided inequalities

$$|x(t)| < |x_0| + \sqrt{\phi(V)}\,\|\tilde{x}_\tau\|_{2\tau}\, e^{-\frac{\gamma_1 t}{4}}, t > T > \tau$$

$$\|x(t) - x_0\|_\tau \ge \frac{1}{\sqrt{\phi(V)}}\|\tilde{x}_\tau\|_{2\tau}^*\, e^{-\frac{\gamma_2 t}{4}}, t > T > \tau$$

Example. To illustrate the results obtained, consider a two-dimensional stationary system for $\tau = 0.25$

$$x(t) = \begin{cases} Ax(t) + B[x(t-\tau) - x_0], 0 \le t < 5 \\ B[x(t-\tau) - x_0], t \ge 5 \end{cases} \qquad (3.4.18)$$

$$x(t) = x_0 = \begin{pmatrix} 1 \\ 1 \end{pmatrix}, \quad t \le 0,$$

where

$$x(t) = \begin{pmatrix} x_1(t) \\ x_2(t) \end{pmatrix} \in R^2,$$

here

$$A = \begin{bmatrix} -0.1 & 0 \\ 0 & -0.2 \end{bmatrix} \quad B = \begin{bmatrix} -5 & -1 \\ -3 & -2 \end{bmatrix}.$$

We use the functionality of Lyapunov

$$v(\phi) = \phi^T(0)\phi(0) + \int_{-\tau}^{0} \phi^T(s)V\phi(s)ds,$$

where

$$V = \begin{bmatrix} 0 & 0 \\ 0 & 1 \end{bmatrix}$$

We get the following values

$$\lambda_{\min}(C) = 1.82 \;\; \lambda_{\max}(C) = 14.48,$$
$$\gamma_1 = 1.3046, \;\; \gamma_2 = 63.05, \;\; \phi(V) = 1.25$$

According to Theorem 3.4.2, we have the following estimates:

$$|x(t)| < 1.01 + 1.12 \cdot e^{-0.33t}, \tau < t \le 5 \quad \|\tilde{x}(t)\|_\tau \ge 0.85 \cdot e^{-15.76t}, \tau < t \le 5$$

According to Theorem 3.4.3, there is:

$$|x(t)| < 1.01 + 1.12 \cdot e^{-0.33t}, t > 5 \quad \|\tilde{x}(t)\|_\tau \ge 0.85 \cdot e^{-15.76t}, t > 5.$$

Now let's try to solve the problem of finding time t when the tumor size becomes smaller than the given $L = 1.01$. Inequalities need to be resolved

$$1 + 1.12 \cdot e^{-0.33t} < 1.01, t > 5$$

We get $t > 7.3$.

3.5. Stability of solutions of the mathematical model of immune defense by G.I. Marchuk

A model of the inflammatory process of an infectious nature is considered. In general, the mathematical model of immunity is described in the work [53]. It is universal and valid not only for the inflammatory process, but also for infectious infection of the body. The model takes into account the following factors determining the course of the process:

I. Antigen population V multiplying in the body;

II. Population of antibody cells (plasma cells) C;

III. Number of antibodies (immunoglobulins) F in the body;

IV. Degree of organ damage m.

The equations that determine the dynamics of the process are of the form

$$\frac{dV}{dt} = (\beta - \gamma\ F)V\,,$$

$$\frac{dC}{dt} = \xi(m)\alpha\ \ V(t-\tau)F(t-\tau) - \mu_c(C - C_0)\,, \qquad (3.5.1)$$

$$\frac{dF}{dt} = \rho\ C - (\mu_f + \eta\ \gamma\ V)F\,,$$

$$\frac{dm}{dt} = \sigma\ V - \mu_m m$$

with initial conditions at $t \in [-\tau, 0]$:

$$V(t) = V_0, F(t) = F_0, C(t) = C_0, m(t) = 0\,.$$

Here β is the antigen multiplication coefficient; γ - a coefficient that determines the probability of neutralization of an antigen by an antibody; α -

the coefficient that determines the probability of antigen-antibody meeting; μ_c - the coefficient inverse of the life time of plasma cells; ρ - the rate of production of antibodies by one plasma cell; μ_f - a coefficient inversely proportional to the time of decay of antibodies; η - the number of antibodies required to neutralize one antigen; σ - a coefficient that determines the rate of cell death due to the damaging effect of the antigen; μ_m - a coefficient that takes into account the speed of recovery of the damaged organ; τ - delay phase (the time during which the formation of a cascade of plasma cells is carried out); $\xi(m)$ - continuous non-increasing function $(0 \le \xi(m) \le 1)$, which characterizes a violation of the normal functioning of the immune system due to significant damage to the target organ.

The listed parameters are positive and are specific both for the type of antigen, and for the organ, and for a specific organism.

The system of differential equations presented above has two states of equilibrium [53]. One of them is trivial, the other is denoted (V^*, F^*, C^*, m^*). Having carried out the linearization of the system of ordinary differential equations (ZDR) in the vicinity of a point (V^*, F^*, C^*, m^*), we get a linear system of ordinary differential equations with constant coefficients:

$$\frac{dx_1}{dt} = \beta x_1 - \gamma F^* x_1 - \gamma V^* x_3$$

$$\frac{dx_2}{dt} = \xi(m^*)\alpha F^* x_1(t-\tau) + \xi(m^*)\alpha V^* x_3(t-\tau) - \mu_C x_2 + \alpha V^* F^* \frac{d\xi(m^*)}{dm} x_4$$

$$\frac{dx_3}{dt} = \rho x_2 - \mu_f x_3 - \eta\gamma V^* x_3 - \eta\gamma F^* x_1$$

$$\frac{dx_4}{dt} = \sigma x_1 - \mu_m x_4$$

The characteristic polynomial of the resulting linear system ZDR is a quasipolynomial (exponential polynomial) of the fourth degree:

$$\lambda^4 + a_1\lambda^3 + a_2\lambda^2 + a_3\lambda + a_4 + b_1\lambda^2 e^{-\lambda\tau} + b_2\lambda e^{-\lambda\tau} + b_3 e^{-\lambda\tau} = 0, \tag{3.5.2}$$

where

$$a_1 = \gamma F^* + \eta V^* + \mu_f - \beta + \mu_m + \mu_C$$

$$a_2 = -\beta\mu_f + \mu_C\mu_m + \mu_C\mu_f - \beta\mu_m - \beta\mu_C + \gamma F^*\mu_m + \eta\gamma V^*\mu_m + \mu_C\eta\gamma V^* + \\ + \mu_f\mu_m - \beta\eta\gamma V^* + \gamma F^*\mu_f + \gamma F^*\mu_C$$

$$a_3 = \mu_C\mu_f\mu_m - \beta\mu_C\mu_f - \beta\mu_C\eta\gamma V^* - \beta\mu_f\mu_m - \beta\eta\gamma V^*\mu_m - \beta\mu_C\mu_m + \\ + \mu_C\eta\gamma V^*\mu_m + \gamma F^*\mu_C\mu_m + \gamma F^*\mu_C\mu_f + \gamma F^*\mu_f\mu_m$$

$$a_4 = \sigma\rho\gamma\left(V^*\right)^2\frac{d\xi(m^*)}{dm}\alpha F^* - \beta\mu_C\mu_f\mu_m - \beta\mu_C\eta\gamma V^*\mu_m + \gamma F^*\mu_C\mu_f\mu_m$$

$$b_1 = -\rho\xi(m^*)\alpha V^*$$

$$b_2 = \beta\rho\xi(m^*)\alpha V^* - \rho\mu_m\xi(m^*)\alpha V^*$$

$$b_3 = \beta\rho\mu_m\xi(m^*)\alpha V^*.$$

Study of the stability of the solutions of the immune defense model. When studying the placement of the roots of the equation based on an exponential polynomial (3.5.2), the following result will be used, proven in the paper [128] using the Rouche theorem [95].

Lemma 3.5.1. For an exponential polynomial

$$P(\lambda, e^{-\lambda\tau_1},...,e^{-\lambda\tau_m}) = \lambda^n + p_1^{(0)}\lambda^{n-1} + ... + p_{n-1}^{(0)}\lambda + p_n^{(0)}$$
$$+[p_1^{(1)}\lambda^{n-1} + ... + p_{n-1}^{(1)}\lambda + p_n^{(1)}]e^{-\lambda\tau_1}$$
$$+...+[p_1^{(m-1)}\lambda^{n-1} + ... + p_{n-1}^{(m-1)}\lambda + p_n^{(1m-1)}]e^{-\lambda\tau_m},$$

where $\tau_i \geq 0 (i = 1,2,...,m)$ and $p_j^{(i)} (i = 0,1,...m-1; j = 1,2,...,n)$ are constants, when changing, the $(\tau_1, \tau_2,..., \tau_m)$ sum of the orders of zeros $P(\lambda, e^{-\lambda\tau_1},...,e^{-\lambda\tau_m})$ in the open right half-plane can change when zero appears on the imaginary axis, or intersects it.

It is clear that $iw (w > 0)$ the root of equation (3.5.2) will be if and only if:

$$w^4 - ia_1w^3 - a_2w^2 + ia_3w + a_4 - b_1w^2(\cos w\tau - i\sin w\tau) +$$
$$+ib_2w(cow\tau - i\sin w\tau) + b_3(\cos w\tau - i\sin w\tau) = 0 \quad .$$

Separating the real and imaginary parts, we have:

$$\begin{aligned} w^4 - a_2w^2 + a_4 &= b_1w^2\cos w\tau - b_2w\sin w\tau - b_3\cos w\tau, \\ a_1w^3 + a_3w &= -b_1w^2\sin w\tau - b_2w\cos w\tau + b_3\sin w\tau \quad . \end{aligned} \tag{3.5.3}$$

Adding the squares of both equations (3.5.3), we have:

$$w^8 + (a^2_1 - 2a_2)w^6 + (a_2^2 + 2a_4 + 2a_1a_3)w^4 + (a^2_3 - 2a_2a_4)w^2 + a^2_4 =$$
$$= b^2_1 w^4 + b^2_2 w^2 + b^2_3 - 2b_1b_3w^2, \text{ тобто}$$
$$w^8 + (a^2_1 - 2a_2)w^6 + (a_2^2 + 2a_4 + 2a_1a_3 - b^2_1)w^4 +$$
$$+(a^2_3 - 2a_2a_4 - b^2_2 + 2b_1b_3)w^2 + (a^2_4 - b^2_3) = 0 \quad . \tag{3.5.4}$$

Let's put $z = w^2$ and enter the notation

$$p = a_1^2 - 2a_2,\ q = a^2_2 + 2a_4 + 2a_1a_3 - b_1^2,$$
$$r = a_3^2 - 2a_2a_4 - b_2^2 + 2b_1b_3,\ s = a_4^2 - b_3^2.$$

Then equation (3.5.4) takes the form:

$$h(z) := z^4 + pz^3 + qz^2 + rz + s = 0. \tag{3.5.5}$$

Statement 3.5.1. If $s < 0$, then equation (3.5.5) has at least one positive solution.

The proof is given in [195, pp. 108-109]**.**

Statement 3.5.2. If $s \geq 0$ equation (3.5.5) has positive real roots, then

$$\Delta = \xi^2/4 + \eta^3/27 \geq 0 \tag{3.5.6}$$

where $\xi = 18p^3/432 - pq/8 + r/4, \quad \eta = -3p^2/16 + q/2$

The proof is given in [195, p. 109].

In the case when $\Delta \geq 0$, among the roots of z1, z2, z3 equations

$$\frac{dh(z)}{dz} = 4z^3 + 3pz^2 + 2qz + r = 0,$$

calculated according to Cardano's formulas, there is at least one, which is the local minimum $h(z)$.

Let's denote:

$$z^* = \arg\min_{i=\overline{1,3}} h(z_i)$$

Statement 3.5.3. If $s \geq 0$, then equation (3.5.5) has positive roots if and only if $z^* > 0$ i $h(z^*) \leq 0$.

The proof is given in [195, p. 109]**.**

So, in the general case, we have:

Lemma 3.5.2. If $s < 0$, then equation (3.5.5) has at least one positive root.

If $s \geq 0$, then equation (3.5.5) has positive roots if and only if $z^* > 0$ i $h(z^*) \leq 0$. If $s \geq 0$ i $\Delta < 0$, then equation (3.5.5) has no positive roots.

Suppose that equation (3.5.5) has positive roots. Without limiting generality, let's assume that it has four positive roots, which we denote respectively z1, z2, z3, z4. Then equation (3.5.4) has four positive roots:

$$w_1 = \sqrt{z_1}, w_2 = \sqrt{z_2}, w_3 = \sqrt{z_3}, w_4 = \sqrt{z_4}$$

Let's mark

$$\tau_k^{(j)} = \frac{1}{w_k}\left[\arcsin\frac{a_1 w_k^3 + a_3 w_k}{\sqrt{b_2^2 w_k^2 + (b_3 - b_1 w_k^2)^2}} - \varphi + 2(j-1)\pi\right],$$

$k = 1,2,3,4,\ j = 0,1,...$

Here φ is the solution:

$$\sin\varphi = \frac{-b_2 w_k}{\sqrt{b_2^2 w_k^2 + (b_3 - b_1 w_k^2)^2}}, \quad \cos\varphi = \frac{b_3 - b_1 w_k^{\,2}}{\sqrt{b_2^2 w_k^2 + (b_3 - b_1 w_k^2)^2}}$$

Then, as follows from the second equation (3.5.3), $\pm i w_k$ are pairs of purely imaginary roots of equation (3.5.2) at $\tau = \tau_k^{(j)}$, $k = 1,2,3,4$, $j = 0,1,...$ It is clear that

$$\lim_{j \to \infty} \tau_k^{(j)} = \infty, \; k = 1,2,3,4,$$

So, let's denote

$$\tau_0 = \tau_{k_0}^{(j_0)} = \min_{1 \le k \le 4,\, j \ge 1} \left\{ \tau_k^{(j)} \right\}, \quad w_0 = w_{k_0}$$

Theorem 3.5.1. Suppose that all the major minors of the Hurvician

$$\begin{vmatrix} a_1 & 1 & 0 & 0 \\ a_3 + b_2 & a_2 + b_1 & a_1 & 1 \\ 0 & a_4 + b_3 & a_3 + b_2 & a_2 + b_1 \\ 0 & 0 & 0 & a_4 + b_3 \end{vmatrix} \tag{3.5.7}$$

Positive.

If $s \ge 0 \; i \; \Delta < 0$, then all the roots of equation (3.5.2) have negative real parts at all $\tau \ge 0$. If $s < 0$ or $s \ge 0$, $z^* > 0 \; i \, h(z^*) \le 0$, then all the roots of equation (3.5.2) have negative real parts at $\tau \in [0, \tau_0)$.

The proof is given in [195, pp. 110-111]**.**

The result presented above can be reformulated in terms of the coefficients of the immune defense model, thus obtaining a sufficient condition of resistance.

Theorem 3.5.2. Suppose that the coefficients of the immune defense model (3.5.1) satisfy the conditions of theorem 3.5.1.

Then, if $s \geq 0$ i $\Delta < 0$, then the equilibrium state (V^*, F^*, C^*, m^*) of the ZDR system (3.5.1) is absolutely stable (asymptotically stable for all $\tau \geq 0$). If $s < 0$ or $s \geq 0$, $z^* > 0$ i $h(z^*) \leq 0$, then the equilibrium state (V^*, F^*, C^*, m^*) of the ZDR system (1) is asymptotically stable at $\tau \in [0, \tau_0)$.

The proof follows from theorem 3.5.1 and the stability theorem at the first approximation [28].

Examples. With the help of the developed computer program, a quantitative study of the inflammatory process was carried out in the case when:

$\beta = 2, \gamma = 0.8, \alpha = 10^4, \mu_c = 0.5, \rho = 0.17, \mu_f = 0.17, \eta = 10, \mu_m = 0.12$.

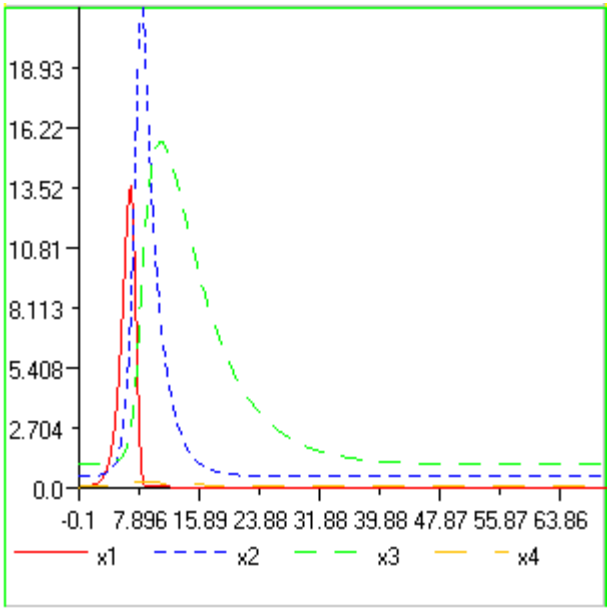
$$\xi(m) = \begin{cases} 1, m \leq 0.1 \\ (1-m)/(10/9), 0.1 \leq m \leq 1 \end{cases}$$

If $t \in [-\tau, 0]$ the following initial conditions are true

$V(t) = \max(0, x + 10^{-6}), C(t) = 1, F(t) = 1, m(t) = 0$.

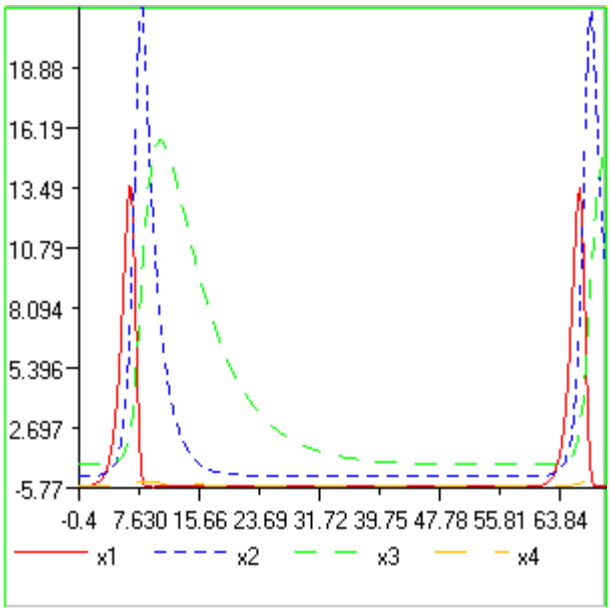
The simulation shows that the time of reappearance of the inflammatory process and the degree of its activity depend on the coefficient σ, which is consistent with experimental data.

Let's put $\tau = 0.1, \sigma = 10$. We have a case when $\tau < \tau_0$ (Fig. 3.5.1), which corresponds to a stable solution (V^*, F^*, C^*, m^*).

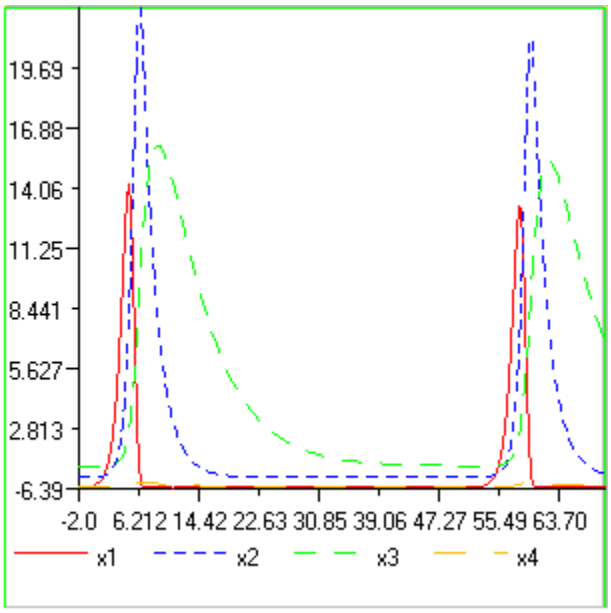


Rice. 3.5.1

The following examples illustrate cases where $\tau \geq \tau_0$. So, for example, let's put $\tau = 0.4, \sigma = 10$ (Fig. 3.5.2), $\tau = 2, \sigma = 10$ (Fig. 3.5.3). There is a periodic solution (chronic form of the pathological process), which turns into an unstable one (acute form of the pathological process with a fatal outcome).



Rice. 3.5.2



Rice. 3.5.3

3.6. On stability in the model of immune defense, taking into account the dysfunction of the target organ. Lyapunov's method of degenerate functionals

This subsection will study the issues of stability of the simplified immune response system by G.I. Marchuk [53]:

$$\begin{aligned}
\frac{dV}{dt} &= (\beta - \gamma F)V, \\
\frac{dC}{dt} &= \xi(m)\alpha V(t-\tau)F(t-\tau) - \mu_c(C-\overline{C}), \\
\frac{dF}{dt} &= \rho C - (\mu_f + \eta\gamma V)F, \\
\frac{dm}{dt} &= \sigma - \mu_m m
\end{aligned} \tag{3.6.1}$$

The biological content of the coordinates and coefficients of the system is discussed in subsection 3.5. In the paper [53], sufficient conditions for the asymptotic stability of the system are established (3.6.1) in the absence of the influence of the damaging effect of the organ on the immune response, i.e. when $\xi(m) \equiv 1$. In this case, the system (3.6.1) takes the form:

$$\begin{aligned} \frac{dV}{dt} &= (\beta - \gamma F)V, \\ \frac{dC}{dt} &= \alpha V(t-\tau)F(t-\tau) - \mu_c(C - \overline{C}), \\ \frac{dF}{dt} &= \rho C - (\mu_f + \eta\gamma V)F, \\ \frac{dm}{dt} &= \sigma V - \mu_m m \end{aligned} \tag{3.6.2}$$

Here $\overline{C}$ is a constant level of plasma cells in a healthy body.

It is established in [53] that the system (3.6.2) has two states of equilibrium:

$$\text{And. } V_1 = 0, \quad C_1 = \overline{C}, \quad F_1 = \frac{\rho C^*}{\mu_f}, \quad m_1 = 0 \tag{3.6.3}$$

$$\text{II. } V_2 = \frac{\mu_C\left(\mu_f\beta - \gamma\rho\overline{C}\right)}{\beta\left(\alpha\rho - \mu_C\eta\gamma\right)}, \quad C_2 = \frac{\alpha\mu_f\beta - \eta\mu_C\gamma^2\overline{C}}{\gamma\left(\alpha\rho - \mu_C\eta\gamma\right)}, \quad F_2 = \frac{\beta}{\gamma}, \quad m_1 = \frac{\sigma}{\mu_m}V_2 \tag{3.6.4}$$

The study was carried out on the basis of linearization and the study of the placement of zeros of a characteristic quasipolynomial [53, 169, 185]. Below are the main results.

Theorem 3.6.1. [53] A sufficient condition for the asymptotic stability of the steady state (3.6.3) is the fulfillment of the inequality

$$\beta < \gamma F_1. \tag{3.6.5}$$

Theorem 3.6.2. [53] A sufficient condition for steady-state stability (3.6.4) is the $\mu_C \tau \le 1$ fulfillment of inequality

$$0 < \frac{f-d}{a-g\tau} < b-g-f\tau \tag{3.6.6}$$

Here a, b, d, g, f are the coefficients of the corresponding characteristic quasi-polynomial.

This subsection is a continuation of subsection 3.5 and is devoted to the application of the method of degenerate functionalities of Lyapunov [102] to the study of system stability (3.6.2). It should be noted that it is distinctive that this method will establish the conditions for the global stability of the system (3.6.1) in the general case, taking into account the effect of the damaging effect of the organ $\xi(m)$ on the immune response.

It should be noted that for the initial nonlinear system (3.6.1) it is theoretically possible to exist a state of equilibrium other than (3.6.3), (3.6.4) – it depends on the type of function $\xi(m)$. The subsection will establish the conditions for the global stability of equilibrium states, which we will conditionally designate as $\left(V^*, C^*, F^*, m^*\right)$.

Degenerate functionalities of Lyapunov. We will follow the definition of the Lyapunov functionality introduced in [80] for the system with a delay

$$\frac{dx(t)}{dt} = f(t, x_t), \quad x_{t_0} = \phi(s) \tag{3.6.7}$$

where $f : R \times C \to R^n$ is the continuous functionality and $f(t,0) = 0$.

Definition 3.6.1. The functionality is $V : R \times C \to R$ called the functionality of the Lyapunov system (3.6.7) if:

(i) $u(|\phi(0)|) \le V(t,\phi) \le v(\|\phi\|)$;

(ii), $\dot{V}(t,\phi) \le -w(|\phi(0)|)$

where $u(s), v(s), w(s) : R_+ \to R_+$ are continuous and non-decreasing, $u(s) > 0, v(s) > 0$ at $s > 0$ and $u(0) = v(0) = w(0) = 0$.

For the first time, the concept of degenerate Lyapunov functionals was introduced in the work [99] when studying the asymptotic stability of the trivial solution of the next non-autonomous linear system with a delay

$$\dot{x}(t) + \sum_{j=1}^{2} a_{ij}(t) x_j(t - \tau_{ij}) = 0, \quad i = 1,2. \tag{3.6.8}$$

As noted in [99], it is usually difficult to find or construct Lyapunov functionals with negatively defined complete derivatives on the solutions of the system. The approach of combining the principle of invariance with conditions of the Razumikhin type also seems to be difficult to apply to equations of the Lott-Voltaire type. To overcome such problems, K. Gopalsamy [99] uses the functionality $V(x_1, x_2) = (V_1 + V_2)(x_1, x_2)$, where

$$V_1(x_1, x_2) = \sum_{i=1}^{2} \left[x_i(t) + \sum_{j=1}^{2} \int_{t-\tau_{ij}}^{t} a_{ij}(s+\tau_{ij}) x_j(s) ds \right]^2 \qquad (3.6.9)$$

and some $V_2(x_1, x_2) \geq 0$.

With the help of the functionality V and lemma 1.3.2 (Barbalat's lemma), K. Gopalsami was able to obtain the conditions of asymptotic stability (3.6.8). As an example, he obtained some sufficient conditions for the global asymptotic stability of the positive equilibrium state of the next system of competition with a delay

$$\dot{N}_i(t) = N_i(t) \left[r_i - \sum_{j=1}^{2} b_{ij} N_j(t-\tau_{ij}) \right], \quad i = 1,2. \qquad (3.6.10)$$

The results were also extended to a generalized form (3.6.10), including continuously distributed delays.

It can be noted that the functionality (3.6.9) does not satisfy condition (i) in the definition of the Lyapunov functionality. This type of functionals is called "degenerate" Lyapunov functionals [99].

A more complete overview of the application of Lyapunov's method of degenerate functionals is given in [196]. Here we will only give the definition of degenerate Lyapunov functionals, introduced in [99].

Definition 3.6.2. A functional is $V: R \times C \to R$ called a weakly degenerate functional for (3.6.7) if for all large t (say at $t \geq T$ for some $T > 0$)

(i) there is a continuous and non-decreasing function $v(s): R_+ \to R_+$, $v(0) = 0$ and $v(s) > 0$ at $s > 0$ such that $0 \leq V(t, \phi) \leq v(\|\phi\|)$;

(ii) there is a continuous and non-decreasing function $w(s): R_+ \to R_+$, $w(0) = 0$ and $w(s) > 0$ at $s > 0$ such that $V'(t,\phi) \le -w(|\phi(0)|)$.

If instead of (ii) is

(iii) there is a continuous and non-decreasing function $w(s): R_+^m \to R_+$, $m < n$, $w(0) = 0$ and $w(s_1,\ldots,s_m) > 0$ at $(s_1,\ldots,s_m) \ne 0$ such that $V'(t,\phi) \le -w(\phi_1(0),\ldots\phi_m(0))$,

then such a functional V is called strictly degenerate Lyapunov functionality for (3.6.7).

Degenerate Lyapunov functionals without taking into account the influence of the action of the damaged organ. Let's rewrite the system (3.6.2) in the form of:

$$\frac{d}{dt}\left\{\log\left[V(t)/V^*\right]\right\} = \frac{d}{dt}\left\{\log V(t) - \log V^*\right\} = \frac{\dot{V}(t)}{V(t)} - (\beta - \gamma F^*) = -\gamma(F(t) - F^*);$$

$$\frac{d}{dt}\left\{C(t) - C^*\right\} = \alpha V(t-\tau)F(t-\tau) - \mu_c(C - \overline{C}) - \alpha V^* F^* + \mu_c(C^* - \overline{C})$$

$$= \alpha\left[V(t-\tau)F(t-\tau) - V^*F^*\right] - \mu_c\left[C(t) - C^*\right];$$

$$\frac{d}{dt}\left\{F(t) - F^*\right\} = \rho\left[C(t) - C^*\right] - \mu_f\left[F(t) - F^*\right] - \eta\gamma\left[V(t)F(t) - V^*F^*\right];$$

$$\frac{d}{dt}\left\{m(t) - m^*\right\} = \sigma\left[V(t) - V^*\right] - \mu_m\left[m(t) - m^*\right] \qquad (3.6.11)$$

The next stability condition will be established using a quadratic functional. On the basis of functionals of this type, stability conditions are obtained, which are called "medium-diagonal dominance".

Theorem 3.6.3. Suppose that:

(i) $\beta = \gamma F^*$

(ii) the parameters of the system (3.6.2) are such that there are positive constants a, b, c, d at which the matrix

$$U = -\begin{bmatrix} 0 & 0 & -\gamma/2 & c\sigma & 0 & 0 \\ 0 & -2a\mu_c & b\rho & 0 & 0 & a\alpha \\ -\lambda/2 & b\rho & -2b\mu_f & 0 & -b\eta\gamma & 0 \\ c\sigma & 0 & 0 & -2c\mu_m & 0 & 0 \\ 0 & 0 & -b\eta\gamma & 0 & d & 0 \\ 0 & a\alpha & 0 & 0 & 0 & -d \end{bmatrix}$$

positively defined. Then all solutions (3.6.2) corresponding to the integral initial conditions satisfy

$$\lim_{t\to\infty} V(t) = V^*, \qquad \lim_{t\to\infty} C(t) = C^* \qquad \lim_{t\to\infty} F(t) = F^* \qquad \lim_{t\to\infty} m(t) = m^* \tag{3.6.12}$$

The proof is given in [196, p. 157-158]**.**

The effect of the action of the damaged organ on the immune response. Next, consider a system (3.6.1) with $\xi : [0,1] \to [0,1]$ the function , which is a non-increasing function of the performance of immunological organs. Let's introduce the replacement of variables:

$$x_1 = \log\left(\frac{V}{V^*}\right), \; x_2 = C - C^*, \; x_3 = F - F^*, \; x_4 = m - m^*.$$

Hence: $V(t) = V^* e^{x_1}$, $C(t) = x_2 + C^*$, $F(t) = x_3 + F^*$, . $m(t) = x_4 + m^*$

Let's mark

$$Z\left(x_4(t)\right)=\xi\left(m^*\right)-\xi\left(x_4(t)+m^*\right).$$

Through $V_{\max},F_{\max},V_{\min},F_{\min}$ let's designate the maximum and minimum values of antigen and antibody concentrations, respectively. These values can be established experimentally.

In contrast to the work [53], where the model parameters β,γ were assumed (3.6.5), we will consider a wider area

$$\beta<\gamma F_{\max} \tag{3.6.13}$$

Lemma 3.6.1. The function $Z\left(x_4(t)\right)$ has the following properties:

(and)$\left|Z\left(x_4(t)\right)\right|\le 1$ and $0\le Z\left(x_4(t)\right)\le 1$ at $x_4(t)\ge 0$, $-1\le Z\left(x_4(t)\right)<0$ at $x_4(t)<0$;

(ii). $Z\left(x_4(t)\right)x_4(t)\ge 0$

Using the above designations, the system (3.6.1) can be rewritten in the form of:

$$\begin{aligned}
&\dot{x}_1(t)=-\gamma x_3(t),\\
&\dot{x}_2(t)=\alpha\begin{bmatrix}-Z\left(x_4(t)\right)V^*e^{x_1(t-\tau)}(x_3(t-\tau)+F^*)+\xi\left(m^*\right)V^*e^{x_1(t-\tau)}(x_3(t-\tau)+F^*)\\-\xi(m^*)V^*F^*\end{bmatrix}-\\
&-\mu_C x_2(t);\\
&\dot{x}_3(t)=\rho x_2(t)-\mu_f x_3(t)-\eta\gamma\left[V^*e^{x_1(t)}(x_3(t)+F^*)-V^*F^*\right],\\
&\dot{x}_4(t)=\sigma V^*\left[e^{x_1(t)}-1\right]-\mu_m x_4(t)
\end{aligned} \tag{3.6.14}$$

Lemma 3.6.2. At the solutions of the system (3.6.14) there is an inequality:

$$x_3(t-\tau) \geq Z^2\left(x_4(t)\right)\frac{F^*}{\xi^2\left(m^*\right)} + Ae^{-x_1(t-\tau)} + Z\left(x_4(t)\right)Be^{-x_1(t-\tau)} - F^* \qquad (3.6.15)$$

where

$$A = F^* + \frac{\mu_C\left(\bar{C} - C^*\right)}{\alpha\xi\left(m^*\right)V^*}, \quad B = \frac{F^*}{\xi\left(m^*\right)} + \frac{\mu_C\left(\bar{C} - C^*\right)}{\alpha\xi^2\left(m^*\right)V^*}.$$

The proof is given in [196, p. 159]**.**

Lemma 3.6.3. At the solutions of the system (3.6.14) there is an inequality

$$Z\left(x_4(t)\right) \geq \xi\left(m^*\right) - \frac{\xi\left(m^*\right)F^*V^* + V_{\max}F_{\max} + \frac{\mu_C}{\alpha}\left(\bar{C} - C^*\right)}{V_{\min}F_{\min}} =: Z_{\min} \qquad (3.6.16)$$

The proof is given in [196, p. 160]**.**

Lemma 3.6.4. Suppose that the inequality (3.6.13) takes place. Then, at the solutions of the system (3.6.1), an estimate is performed:

$$\int_{t-\tau}^{t} V(s)ds \leq \frac{V(t)}{\gamma F_{\max} - \beta}\left[e^{(\gamma F_{\max} - \beta)\tau} - 1\right] \qquad (3.6.17)$$

The proof is given in [196, p. 160]**.**

Lemma 3.6.5. For solutions (3.6.1) there is an assessment:

$$V\left(t-\tau\right)\geq V\left(t\right)e^{-\beta\tau}$$

The proof is given in [196, p.160]**.**

Let's enter the functionality:

$$W_1(x_4\left(t\right))=\int_0^{x_4(t)}Z(u)du\,.$$

Then we have $W_1(x_4)\geq 0$ at the junctions (3.6.11):

$$\frac{dW_2(x(t))}{dt}=Z(x_4(t))\dot{x}_4(t)=\sigma Z(x_4(t))V^*\left[e^{x_1(t)}-1\right]-\mu_m Z(x_4(t))x_4(t)\,.$$

Because

$$e^{x_1(t)}-1=\left[e^{x_1(t)}-e^{x_1(t-\tau)}\right]+\left[e^{x_1(t-\tau)}-1\right]=\int_{t-\tau}^{t}e^{x_1(s)}\dot{x}_1(s)ds+\left[e^{x_1(t-\tau)}-1\right],$$

then

$$\frac{dW_2(x(t))}{dt}=\sigma Z(x_4(t))V^*\left\{\int_{t-\tau}^{t}e^{x_1(s)}(-\gamma x_3(s))ds+\left[e^{x_1(t-\tau)}-1\right]\right\}-\mu_m Z(x_4(t))x_4(t)=$$

$$=-\gamma\sigma V^*\int_{t-\tau}^{t}e^{x_1(s)}Z(x_4(t))x_3(s)ds+\sigma Z(x_4(t))V^*\left[e^{x_1(t-\tau)}-1\right]-\mu_m Z(x_4(t))x_4(t)$$

Using the inequality $ab\leq\frac{1}{2}\left(a^2+b^2\right)$, we come to the next

$$\frac{dW_2(x(t))}{dt} \le \frac{1}{2}\gamma\sigma V^* \left\{ \left(\int_{t-\tau}^{t} e^{x_1(s)} ds \right) Z^2(x_4(t)) + \int_{t-\tau}^{t} e^{x_1(s)} x_3^2(s) ds \right\} +$$
$$+\sigma Z(x_4(t)) V^* \left[e^{x_1(t-\tau)} - 1 \right]$$
$$-\mu_m Z(x_4(t)) x_4(t)$$

Let's define the functionality:

$$W_2(x(t)) = \frac{1}{2}\gamma\sigma V^* \int_{t-\tau}^{t} \int_{v}^{t} e^{x_1(s)} x_3^2(s) ds dv$$

Have:

$$\frac{dW_2(x(t))}{dt} = \frac{1}{2}\gamma\sigma V^* \left\{ -\int_{t-\tau}^{t} e^{x_1(s)} x_3^2(s) ds + \int_{t-\tau}^{t} e^{x_1(t)} x_3^2(t) dv \right\} =$$
$$= \frac{1}{2}\gamma\sigma V^* \left\{ -\int_{t-\tau}^{t} e^{x_1(s)} x_3^2(s) ds + \tau e^{x_1(t)} x_3^2(t) \right\}$$

Away:

$$\frac{d}{dt}(W_1 + W_2)(x(t)) \le \frac{1}{2}\gamma\sigma V^* \left\{ \left(\int_{t-\tau}^{t} e^{x_1(s)} ds \right) Z^2(x_4(t)) + \tau e^{x_1(t)} x_3^2(t) \right\} +$$
$$+\sigma Z(x_4(t)) V^* \left[e^{x_1(t-\tau)} - 1 \right] - \mu_m Z(x_4(t)) x_4(t)$$

Next, we will evaluate $V^* \int_{t-\tau}^{t} e^{x_1(s)} ds = \int_{t-\tau}^{t} V(s) ds$ by virtue of lemma 3.6.4. We have:

$$\frac{d}{dt}(W_1+W_2)(x(t)) \le \frac{1}{2}\gamma\sigma V(t)\left\{\left[\frac{1}{\gamma F_{\max}-\beta}(e^{(\gamma F_{\max}-\beta)\tau}-1)\right]Z^2\left(x_4(t)\right)+\tau x_3^2(t)\right\}+$$
$$+\sigma Z(x_4(t))V^*\left[e^{x_1(t-\tau)}-1\right]-$$
$$-\mu_m Z(x_4(t))x_4(t)$$

Let's introduce functionality

$$W_3(x_1(t)) = \int_0^{x_1(t-\tau)}\left[e^s-1\right]ds\,.$$

Then:

$$\frac{d}{dt}W_3(x_1(t)) = -\gamma x_3(t-\tau)\left[e^{x_1(t-\tau)}-1\right].$$

Let's define the functionality of Lyapunov as follows:

$$W(x(t)) = W_1(x_4(t)) + W_2(x_1(t), x_3(t)) + \delta W_3(x_1(t)).$$

Here $\delta > 0$ it is unknown so far.

Then, by virtue of the previous calculations:

$$\frac{d}{dt}W(x(t)) \le \frac{1}{2}\gamma\sigma V(t)\left\{\left[\frac{1}{\gamma F_{\max}-\beta}(e^{(\gamma F_{\max}-\beta)\tau}-1)\right]Z^2\left(x_4(t)\right)+\tau x_3^2(t)\right\}$$
$$+\sigma Z(x_4(t))V^*\left[e^{x_1(t-\tau)}-1\right]-\delta\gamma x_3\left(t-\tau\right)\left[e^{x_1(t-\tau)}-1\right] \qquad (3.6.18)$$
$$-\mu_m Z(x_4(t))x_4(t)$$

Using in (3.6.18) the inequality of the lemma 3.6.2, we have:

$$\frac{d}{dt}W(x(t)) \le \frac{1}{2}\gamma\sigma V(t)\left\{\left[\frac{1}{\gamma F_{\max}-\beta}(e^{(\gamma F_{\max}-\beta)\tau}-1)\right]Z^2\left(x_4(t)\right)+\tau x_3^2(t)\right\}$$
$$+\sigma Z(x_4(t))V^*\left[e^{x_1(t-\tau)}-1\right]$$
$$-\delta\gamma\left(Z^2\left(x_4(t)\right)\frac{F^*}{\xi^2\left(m^*\right)}+Ae^{-x_1(t-\tau)}+Z\left(x_4(t)\right)Be^{-x_1(t-\tau)}-F^*\right)\left[e^{x_1(t-\tau)}-1\right]$$
$$-\mu_m Z(x_4(t))x_4(t)$$

Using the inequality of the lemma 3.6.5, we have:

$$\frac{d}{dt}W(x(t)) \le \frac{1}{2}\gamma\sigma V(t)\left\{\left[\frac{1}{\gamma F_{\max}-\beta}(e^{(\gamma F_{\max}-\beta)\tau}-1)-\delta\gamma\frac{F^*}{\xi^2\left(m^*\right)V^*}e^{-\beta\tau}\right]Z^2\left(x_4(t)\right)+\tau x_3^2(t)\right\}$$
$$+\sigma Z(x_4(t))V^*\left[e^{x_1(t-\tau)}-1\right]$$
$$-\delta\gamma\left(Ae^{-x_1(t-\tau)}+Z\left(x_4(t)\right)Be^{-x_1(t-\tau)}-F^*\right)\left[e^{x_1(t-\tau)}-1\right]+\delta\gamma Z^2\left(x_4(t)\right)\frac{F^*}{\xi^2\left(m^*\right)}$$
$$-\mu_m Z(x_4(t))x_4(t) \le$$
$$\le \frac{1}{2}\gamma\sigma V(t)\left\{\left[\frac{1}{\gamma F_{\max}-\beta}(e^{(\gamma F_{\max}-\beta)\tau}-1)-\delta\gamma\frac{F^*}{\xi^2\left(m^*\right)V^*}e^{-\beta\tau}\right]Z^2\left(x_4(t)\right)+\tau x_3^2(t)\right\}$$
$$+\sigma V^*\left[\frac{V_{\max}}{V^*}-1\right]-\delta\gamma\left(A\frac{V^*}{V_{\max}}-B\frac{V^*}{V_{\max}}-F^*\right)\left[\frac{V_{\min}}{V^*}-1\right]+\delta\gamma\frac{F^*}{\xi^2\left(m^*\right)}$$
$$-\mu_m Z(x_4(t))x_4(t) \qquad (3.6.19)$$

Let's choose $\delta > 0$ one that:

$$\delta \ge \frac{\sigma V^*\left[\frac{V_{\max}}{V^*}-1\right]}{\gamma\left\{\left(A\frac{V^*}{V_{\max}}-B\frac{V^*}{V_{\max}}-F^*\right)\left[\frac{V_{\min}}{V^*}-1\right]-\frac{F^*}{\xi^2\left(m^*\right)}\right\}}$$

In this case, from (3.6.19) we get:

$$\frac{d}{dt}W(x(t)) \le \frac{1}{2}\gamma\sigma V(t)\left\{\left[\frac{1}{\gamma F_{\max}-\beta}(e^{(\gamma F_{\max}-\beta)\tau}-1)-\delta\gamma\frac{F^*}{\xi^2\left(m^*\right)V^*}e^{-\beta\tau}\right]Z^2\left(x_4(t)\right)+\tau x_3^2(t)\right\}$$
$$-\mu_m Z(x_4(t))x_4(t)$$

From the property (ii) for $Z\left(x_4(t)\right)$ we have:

$$\frac{d}{dt}W(x(t)) \le \frac{1}{2}\gamma\sigma V(t)\left\{\left[\frac{1}{\gamma F_{\max}-\beta}(e^{(\gamma F_{\max}-\beta)\tau}-1)-\delta\gamma\frac{F^*}{\xi^2\left(m^*\right)V^*}e^{-\beta\tau}\right]Z^2\left(x_4(t)\right)+\tau x_3^2(t)\right\} \tag{3.6.20}$$

Let's choose $\tau > 0$ such that

$$\frac{1}{\gamma F_{\max}-\beta}(e^{(\gamma F_{\max}-\beta)\tau}-1) < \delta\gamma\frac{F^*}{\xi^2\left(m^*\right)V^*}e^{-\beta\tau}. \tag{3.6.21}$$

and to

$$\frac{\tau}{\delta\gamma\frac{F^*}{\xi^2\left(m^*\right)V^*}e^{-\beta\tau}-\frac{1}{\gamma F_{\max}-\beta}(e^{(\gamma F_{\max}-\beta)\tau}-1)} \le \frac{Z_{\min}^2}{\left(F_{\max}-F^*\right)^2} \tag{3.6.22}$$

Then on the right side (3.6.20) there is a negatively defined quadratic form of the arguments $Z\left(x_4(t)\right), x_3(t)$. So, W - strictly degenerate Lyapunov functionality.

Applying the asymptotic stability theorem, we get the following result.

Theorem 3.6.4. Suppose that:

(i) the inequality is fulfilled (3.6.13);

(ii) $$\frac{\sigma V^*\left[\frac{V_{\max}}{V^*}-1\right]}{\gamma\left\{\left(A\frac{V^*}{V_{\max}}-B\frac{V^*}{V_{\max}}-F^*\right)\left[\frac{V_{\min}}{V^*}-1\right]-\frac{F^*}{\xi^2\left(m^*\right)}\right\}}>0;$$

(iii) the delay $\tau>0$ is finite and satisfies the inequalities (3.6.21), (3.6.22).

Then the positive state of equilibrium of the system (3.6.1) is asymtotically stable for some approximate initial conditions.

3.7. Stability of the generalized model of Gompertz dynamics

The model described by equations (1.4.4)-(1.4.6) on the semi-axis $t\ge t_0$ with initial conditions (1.4.7)-(1.4.9) in the absence of treatment ($c(t)\equiv 0$) is considered:

$$\frac{dL_{P_i}(t)}{dt}=\left[\left\{1-\alpha_i-\sum_{s=1}^{M}\left(\mu_{P_i,P_s}+\mu_{P_i,C_s}\right)\right\}L_{P_i}(t)+\sum_{s=1}^{M}\mu_{P_s,P_i}L_{P_s}(t)\right]G_i+$$
$$+\beta_i L_{C_i}(t)-\delta_{P_i}L_{P_i}(t),\quad i=\overline{1,M}. \tag{3.7.1}$$

$$\frac{dL_{C_i}(t)}{dt}=\left[\alpha_i L_{P_i}(t)+\sum_{s=1}^{M}\mu_{P_s,C_i}L_{P_s}(t)\right]G_i-$$
$$-\beta_i L_{C_i}(t)-\delta_{C_i}L_{C_i}(t),\quad i=\overline{1,M}. \tag{3.7.2}$$

$$\frac{dN_i(t)}{dt}=\lambda_i N_i(t)\ln\frac{\theta_i}{N_i(t)}-\sum_{s=1}^{M}\sigma_{P_s,N_i}L_{P_s}(t)N_i(t)-\sum_{s=1}^{M}\sigma_{C_s,N_i}L_{C_s}(t)N_i(t), \tag{3.7.3}$$

Put:

$$G_i\left(L_{P_1}(t),...,L_{P_M}(t),L_{C_1}(t),...,L_{C_M}(t)\right)=$$

$$=G\left(L_{P_1}(t),...,L_{P_M}(t),L_{C_1}(t),...,L_{C_M}(t)\right)=\lambda\ln\left(\frac{\theta_L}{\sum_{i=1}^{M}\left[L_{P_i}(t)+L_{C_i}(t)\right]}\right). \quad (3.7.4)$$

Here $\lambda>0$ is the rate of development of the disease, $\theta_L>0$ is the upper limit of the total number of cancer cells.

Statement 3.7.1. Populations for which at some point in time $t>t_0$:

$$\sum_{s=1}^{M}\left[L_{P_s}(t)+L_{C_s}(t)\right]=\theta_L \quad (3.7.5)$$

(i.e $G=0$.) is not a state of equilibrium of the system (3.7.1)-(3.7.4).

The proof is given in Appendix A.3**.**

Let's enter the notation of matrices and vectors:

$\mu_{PP}=\left\{\mu_{P_i,P_j}\right\}_{i,j=\overline{1,M}}$, $\mu_{PC}=\left\{\mu_{P_i,C_j}\right\}_{i,j=\overline{1,M}}$, $\Xi=\begin{pmatrix}1 & \dots & 1\\ \vdots & \ddots & \vdots\\ 1 & \dots & 1\end{pmatrix}\in R^{M\times M}$ is a matrix, all elements of which are units, $e_M=(1...1)^T\in R^{2M}$ is a vector, all elements of which are units,

$\alpha=(\alpha_1,...,\alpha_M)^T$, $\beta=(\beta_1,...,\beta_M)^T$, $\delta_P=\left(\delta_{P_1},...,\delta_{P_M}\right)^T$, $\delta_C=\left(\delta_{C_1},...,\delta_{C_M}\right)^T$,
- unit matrix.

Consider a matrix of block form:

$$\mathbf{C}=\left(\begin{array}{c|c}\left(I-\alpha I-\left(\mu_{PP}+\mu_{PC}\right)\Xi\right)IG+\mu_{PP}^TG-\delta_PI & \beta I\\ \hline \left(\alpha I+\mu_{PC}^T\right)G & -\left(\beta+\delta_C\right)I\\ \hline e_M^T & \end{array}\right)\in R^{2M+1\times 2M} \quad (3.7.6)$$

and vector

$$b = \begin{pmatrix} 0 \\ \vdots \\ 0 \\ \theta_L e^{-\frac{G}{\lambda}} \end{pmatrix} \in R^{2M+1}$$

Statement 3.7.2. Let the coefficients of the system (3.7.1)-(3.7.4) be such that there is a constant $G > 0$ such that $rank\complement = 2M$. Then for a given there $G > 0$ is a single state of equilibrium $E^* = \left(L^*, N^*\right) \in R^{2M+n}$, where $L^* = \left(L^*_{P_1}, ..., L^*_{P_M}, L^*_{C_1}, ..., L^*_{C_M}\right) \in R^{2M}$, $N^* = \left(N^*_1 ... N^*_n\right) \in R^{2n}$, the components of which can be found from the equations:

$$\complement L^* = b \tag{3.7.7}$$

$$N^*_i = \theta_i \exp\left(-\frac{1}{\lambda_i} \sum_{s=1}^{M} \left[\sigma_{P_s, N_i} L^*_{P_s} + \sigma_{C_s, N_i} L^*_{C_s} \right] \right) \tag{3.7.8}$$

The proof is given in Appendix A.3**.**

The study of the stability of the state of equilibrium E^* (3.7.1)-(3.7.3) can be carried out using the Lyapunov vector function:

$$v\left(L_{P_i}(t), L_{C_i}(t), N_j(t)\right) = \begin{pmatrix} a\left[\ln \dfrac{\sum_{s=1}^{M}\left[L_{P_s}(t) + L_{C_s}(t)\right]}{\theta^*_L} - \dfrac{\sum_{s=1}^{M}\left[L_{P_s}(t) + L_{C_s}(t)\right]}{\theta^*_L} - 1 \right] \\ \sum_{j=1}^{n} b_j \left[\ln \dfrac{N_j(t)}{\theta^*_j} - \dfrac{N_j(t)}{\theta^*_j} - 1 \right] \end{pmatrix} = \begin{pmatrix} v_1(t) \\ v_2(t) \end{pmatrix}$$

3.8. Stability of solutions of a simplified model of antitumor immunity

The following partial case of the system (1.6.1)-(1.6.5) is considered:

$$\frac{dL(t)}{dt} = \alpha_L L(t) \ln \frac{\theta_L}{L(t)} - \gamma_L F(t) L(t), \tag{3.8.1}$$

$$\frac{dC(t)}{dt} = \xi(m) \alpha L(t-\tau) F(t-\tau) - \mu_C (C - C_0), \tag{3.8.2}$$

$$\frac{dF(t)}{dt} = b_f C - (\mu_f + \eta \gamma_L L(t)) F(t), \tag{3.8.3}$$

$$\frac{dm(t)}{dt} = \sigma L(t) - \mu_m m(t), \tag{3.8.4}$$

That is, the process of maturation of plasma cells in the bone marrow is not taken into account.

The system of differential equations presented above has equilibrium states. Having (L^*, F^*, C^*, m^*) carried out linearization of the system of ordinary differential equations (3.8.1-3.8.4) in the vicinity (L^*, F^*, C^*, m^*) of a point, we get a linear system with constant coefficients:

$$\frac{dx_1}{dt} = \alpha_L x_1 \left(\ln \frac{\theta_L}{L^*} - 1 \right) - \gamma_L F^* x_1 - \gamma_L L^* x_3$$

$$\frac{dx_2}{dt} = \xi(m^*) \alpha F^* x_1(t-\tau) + \xi(m^*) \alpha L^* x_3(t-\tau) - \mu_C x_2 + \alpha L^* F^* \frac{d\xi(m^*)}{dm} x_4$$

$$\frac{dx_3}{dt} = b_f x_2 - \mu_f x_3 - \eta \gamma_L L^* x_3 - \eta \gamma_L F^* x_1$$

$$\frac{dx_4}{dt} = \sigma x_1 - \mu_m x_4$$

In the case when $\xi(m) \equiv 1$, then the characteristic polynomial of the resulting linear system is a quasipolynomial (exponential polynomial) of the fourth degree:

$$\lambda^4 + a_1\lambda^3 + a_2\lambda^2 + a_3\lambda + a_4 + b_1\lambda^2 e^{-\lambda\tau} + b_2\lambda e^{-\lambda\tau} + b_3 e^{-\lambda\tau} = 0 \qquad (3.8.5)$$

where

$$a_1 = \eta\gamma_L L^* + \mu_f + \mu_C + \mu_m$$

$$a_2 = \mu_C\left(\eta\gamma_L L^* + \mu_f\right) - \alpha_L\left(\ln\frac{\theta_L}{L^*} - 1\right)\eta\gamma_L L^* + \mu_m\left(\eta\gamma_L L^* + \mu_f + \mu_C\right)$$

$$a_3 = -\alpha_L\left(\ln\frac{\theta_L}{L^*} - 1\right)\mu_C\eta\gamma_L L^* + \mu_m\left(\mu_C\left(\eta\gamma_L L^* + \mu_f\right) - \alpha_L\left(\ln\frac{\theta_L}{L^*} - 1\right)\eta\gamma_L L^*\right)$$

$$a_4 = -\alpha_L\left(\ln\frac{\theta_L}{L^*} - 1\right)\mu_C\eta\gamma_L L^*\mu_m$$

$$b_1 = -b_f\alpha L^*$$

$$b_2 = \alpha_L\left(\ln\frac{\theta_L}{L^*} - 1\right)b_f\alpha L^* - b_f\alpha L^*\mu_m$$

$$b_3 = \alpha_L\left(\ln\frac{\theta_L}{L^*} - 1\right)b_f\alpha L^*\mu_m$$

When studying the placement of the roots of the equation based on the exponential polynomial (3.8.5), the following results were obtained, proved in paragraph III.5 (theorems 3.5.1 and 3.5.2) for the simplified model of the immune system of G.I. Marchuk using Rochet's theorem [126].

For the purpose of formulation, we will enter the designation

$$p = a_1^2 - 2a_2,\ q = a^2{}_2 + 2a_4 + 2a_1a_3 - b_1^2,$$
$$r = a_3^2 - 2a_2a_4 - b_2^2 + 2b_1b_3,\ s = a_4^2 - b_3^2.$$

and consider the equation:

$$h(z) = z^4 + pz^3 + qz^2 + rz + s = 0. \qquad (3.8.6)$$

At the same time, we will also use the designations introduced in III.5.

The result proven in paragraph III.5 can be reformulated in terms of the coefficients of the antitumor immunity model, thus obtaining a sufficient condition of resistance.

Theorem 3.8.1. Suppose that the coefficients of the antitumor immunity model (3.8.1)-(3.8.4) satisfy the conditions of theorem 3.5.1.

Then, if $s \geq 0$ i $\Delta < 0$, then the equilibrium state (L^*, F^*, C^*, m^*) of system (12)-(15) is absolutely stable (asymptotically stable for all $\tau \geq 0$). If $s < 0$ or $s \geq 0$, $z^* > 0$ i $h(z^*) \leq 0$, then the equilibrium state (L^*, F^*, C^*, m^*) of system (12)-(15) is asymptotically stable at $\tau \in [0, \tau_0)$.

The proof follows from theorem 3.5.1 and the stability theorem at the first approximation.

Conclusions. 1. A qualitative analysis of one third-order nonlinear system with a time delay with the appearance of the right parts close to the general one has been carried out. The system can be considered as a generalization of the immunological model of the antigen-antibody-plasma cell. Sufficient conditions for the stability and instability of its trivial solution have been obtained. In the case of stability, an exponential estimate has been built in an explicit form. In the proofs and constructions, the method of Lyapunov-Krasovsky functionalities has been used.

2. The conditions for the stability of stationary states of the bone tissue reconstruction model based on the functions of the Lyapunov logistic type are indicated.

3. The conditions for the stability of the equilibrium states of the toxic colitis system are obtained, and they are illustrated on computer programs.

4. The application of equations with a delay with a piecewise continuous right part in the theory of cell response to radiation is substantiated. Exponential estimates of solutions have been found that allow solving problems of controlling the time of irradiation, as well as finding the time required to achieve the desired concentration of a substance in the cell.

5. A method for studying the stability of the model of immune protection of G.I. Marchuk by studying the zeros of a characteristic polynomial - a quasipolynomial of the fourth degree has been developed.

6. A method of constructing degenerate Lyapunov functionals in the study of the stability of the immune defense model of G.I. Marchuk is presented. The results are presented both without taking into account the influence of the action of the damaged organ on the immune system $\xi(m) \equiv 1$, and in the presence of such an influence. Comparing with the results of previous work, which was performed on the basis of excellent methods [53], the conditions of stability for a wider range of parameters $\beta < \gamma F_{\max}$ (as opposed to the area of $\beta < \gamma F^*$). In this case, additional conditions are imposed on the amount of delay. The prospect of the proposed method is the study of the immune defense system with a continuously distributed delay.

7. The ways of studying the stability of the generalized model of Gompertz dynamics are indicated.

8. Sufficient conditions for asymptotic stability of the equilibrium state of the antitumor immunity model in terms of the coefficients of the characteristic quasipolynomial have been obtained.

These results were reflected in monographs [170, 185], a number of journal articles [36, 139, 141, 143, 156, 159, 160, 169, 175, 195, 196, 210, 211] and conference proceedings [138, 140, 144, 152, 167, 207].