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========== REVIEW ARTICLES ==========

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Application of M-Matrices in Studies of Mathematical Models of Living Systems

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Abstract. We present some results of the application of M-matrices to the study the stability problem of the equilibriums of differential equations used in models of living systems. The models of living systems are described by differential equations with several delays, including distributed delay, and by high-dimensional systems of differential equations. To study the stability of the equilibriums the linearization method is used. Emerging systems of linear differential equations have a specific structure of the right-hand parts, which allows to effectively use the properties of M-matrices. As examples, the results of studies of models arising in immunology, epidemiology and ecology are presented.

Key words: *mathematical models for living systems, mathematical models in immunology, epidemiology and ecology, basic reproductive number, delay differential equations, high-dimensional differential systems, stability, M-matrix.*

INTRODUCTION

Differential equations-based models of living systems can be nominally distributed into two families.

The first family includes low-dimensional models with small numbers of parameters. The models of this type are applied, usually, in simple analytical or numerical studies and in estimations of their parameters according to real data.

The second family includes high-dimensional models and those containing many parameters, delays or essential non-linearity. Any of these parameters is a challenge for analytical and numerical studies. In some cases differential equations of the second family have specific structures giving them a possibility to account for positive and negative feedbacks at descriptions of inflows, reproduction and death of a living system elements. Besides, a number of models have a distinctive feature: living systems described by the models include specific development stages. Duration of a stage is a fixed constant or a value described in terms of some distribution functions. This feature of a model, the same as big numbers of its variables, call for rather complex mathematical tools to examine behavior of its solutions. One of the possible tools is application of a monotone operators theory and properties of special matrices,

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for example, M-matrices.

The article concentrates on researches applying M-matrices to study stability of equilibria of living models systems belonging to the second family. It contains two main parts. The first one provides necessary backgrounds from theories of matrix and of stability for linear systems of delay differential equations, and estimates of the Cauchy problem solutions for linear heterogeneous systems of differential equations. The second part presents the analyses of several models that can be applied to solve some problems arising in immunology, epidemiology and ecology with the use of M-matrices. Some results contained in the second part, namely in sections 4, 7, 8 were already published in previous papers of the authors and their coauthors, while sections 5, 6 contain only fresh materials.

Any model considered in sections 4–8 has one of distinctive features: it can either contain several delays, including a distributed delay, or have high dimensions. Study of stability of the mentioned models equilibria by the linearization method meets with challenges at the analysis of a characteristic equation roots and at application of Lyapunov functions or Lyapunov-Krasovskii functional. At the same time, the system of linear approximation of these models allow a researcher to apply effectively the M-matrices theory and to obtain necessary and sufficient conditions of the asymptotical stability.

The Conclusion contains a list of some routine tasks arising at examination of the living system models and requiring application of various mathematical methods.

NECESSARY BACKGROUNDS FROM MATRIX AND STABILITY THEORIES

1. Backgrounds from the matrix theory

Let $v \in \mathbb{R}^m$ be a certain vector and $S = (s_{ij})$ be a certain real $m \times m$ matrix. Then, according to the [1, 2, 3, 4, 5, 6], we assume that

- v^T is a transposed vector;
- expressions $v > 0$, $v \geq 0$, $v < 0$, $v \leq 0$ have meanings of inequalities realized for all components of the vector v;
- $||v||_1 = \sum_{i=1}^{m} |v_i|$ is the L_1 norm of the vector v in the space $\mathbb{R}^m$;
- S^T is a transposed matrix;
- $||S||_1 = \max\limits_j \sum\limits_i |s_{ij}|$ is the matrix norm agreed with the vector $|| \cdot ||_1$ norm;
- $S^+ = (|s_{ij}|)$;
- S is *a nonnegative* matrix, if $s_{ij} \geq 0$ for all i, j;
- S is *a quasinonnegative (Metzler)* matrix, if $s_{ij} \geq 0$ for all $i \neq j$;
- S is *a stable (Hurwitz)* matrix, if any of its eigenvalues has a negative real part;
- S is *a nonsingular M-matrix*, if $s_{ij} \leq 0$ for all $i \neq j$, S is nonsingular and matrix S^{-1} is nonnegative.

The article will use the following statements [1, 6].

T h e o r e m 1 (Sevast'anov-Kotelyanski'i criterion). *Let matrix S be quasinonnegative. Then in order to S be stable it is necessary and sufficient that for each angular minor M_k with $k \times k$ dimensions of the matrix S an inequality $(-1)^k M_k > 0$ is realized.*

Theorem 2. *Let a real quadratic matrix S be such that $s_{ij} \le 0$ for all $i \ne j$. Then the following statements are equivalent:*

- *S is a nonsingular M-matrix;*
- *all angular minors S are positive;*
- *the matrix $(-S)$ satisfies Sevast'anov-Kotelyanski'i criterion;*
- *there exists a vector $\xi \in \mathbb{R}^m$ such that $\xi > 0$ and $S\xi > 0$;*
- *there exists a vector $\psi \in \mathbb{R}^m$ such that $\psi > 0$ and $S^T\psi > 0$.*

Let us consider the following example

$$S = \begin{pmatrix} 1.5 & -1 & 0 \\ -0.8 & 1.2 & -0.1 \\ 0 & -0.2 & 2 \end{pmatrix}.$$

The matrix S is a nonsingular M-matrix, because all its angular minors are positive: $M_1 = 1.5$, $M_2 = 1$, $M_3 = 1.97$. A vector $\xi = (\xi_1, \xi_2, \xi_3)^T$, satisfying the condition $\xi > 0$, $S\xi > 0$, is sought as a solution of the inequality system

$$\xi_1 > 0, \quad \xi_2 > 0, \quad \xi_3 > 0,$$

$$1.5\,\xi_1 - \xi_2 > 0, \quad -0.8\,\xi_1 + 1.2\,\xi_2 - 0.1\,\xi_3 > 0, \quad -0.2\,\xi_2 + 2\,\xi_3 > 0.$$

One can see that a vector $\xi = (1, 1, 1)^T$ satisfies this system. In turn, the vector $\psi = (2, 2, 1)^T$ is one of the solutions of the inequality system $\psi > 0$, $S^T\psi > 0$.

2. M-matrices in the system of delay differential equations

Let $x(t) : \mathbb{R} \mapsto \mathbb{R}^m$ be a vector-function of a real argument t. We shall consider a system of delay differential equations

$$\frac{dx(t)}{dt} = \sum_{k=0}^{n} A_k x(t - \omega_k) + \int_{-\tau}^{0} A_{n+1}(\theta) x(t + \theta) d\theta - Bx(t), \quad t \in [0; \infty), \tag{1}$$

supplemented with an initial condition

$$x(t) = \varphi(t), \quad t \in [-\omega; 0], \quad \omega = \max\{\omega_1, \ldots, \omega_n, \tau\}, \tag{2}$$

where $A_k = (a_{ij}^{(k)})$ are real $m \times m$ matrices; $A_{n+1}(\theta) = (a_{ij}^{(n+1)}(\theta)) - m \times m$ is a matrix with Riemann integrable elements; $\omega_0 = 0$, $\omega_k \in (0; \infty)$, $k \ge 1$, are durations of point delays; $\tau \in [0; \infty)$ is duration of a distributed delay; ω is a total duration of a delay; $B = \mathrm{diag}(b_{11}, \ldots, b_{mm})$ is a diagonal matrix with elements $b_{ii} > 0$; $\varphi(t) \in \mathbb{R}^m$ is a defined continuous on the $[-\omega; 0]$ function. At $t = 0$ $\frac{dx(t)}{dt}$ means the right-hand derivative:

$$\frac{dx(0)}{dt} = \sum_{k=0}^{n} A_k \varphi(-\omega_k) + \int_{-\tau}^{0} A_{n+1}(\theta) \varphi(\theta) d\theta - B\varphi(0).$$

Following [7, 8], refer as a solution of the Cauchy problem (1), (2) on the interval $[0; \infty)$ to a continuous function $x(t)$, on the interval $[-\omega; \infty)$, which is continuously differentiable on

the interval $[0;\infty)$, and satisfies the initial conditions (2) and equations (1) for all $t \in [0;\infty)$. At $\varphi \equiv 0$ system (1) has the trivial solution $x(t) \equiv 0$.

Definition 1. *A trivial solution of system* (1) *is called stable (according to Lyapunov), if for any* $\epsilon > 0$ *we can find a number* $\delta > 0$*, such that from the inequality*

$$\max_{t\in[-\omega;0]} ||\varphi(t)||_1 < \delta$$

it follows the inequality $||x(t)||_1 < \epsilon$ *for all* $t \in [0;\infty)$.

Definition 2. *A stable trivial solution of system* (1) *is called asymptotically stable (according to Lyapunov), if for any* φ *it exists the*

$$\lim_{t\to+\infty} x(t) = 0.$$

We shall give two theorems setting necessary and sufficient conditions of the asymptotical stability for the trivial solution of system (1) [9, 10, 11].

Theorem 3. *Let matrices* $A_0, A_1, \ldots, A_n$, $A_{n+1}(\theta)$*, contained in* (1)*, be nonnegative. We define:*

$$A_\Sigma = \sum_{k=0}^{n} A_k + \int_{-\tau}^{0} A_{n+1}(\theta)d\theta.$$

A trivial solution of the system (1) *is asymptotically stable Iff the matrix* $A_\Sigma - B$ *satisfies Sevast'yanov – Kotelyanski'i criterion or, equally,* $B - A_\Sigma$ *is a nonsingular M-matrix.*

Theorem 4. *Let one or more from the matrices* $A_0, A_1, \ldots, A_n$, $A_{n+1}(\theta)$*, contained in* (1)*, be not nonnegative. Assume that*

$$A_\Sigma^+ = \sum_{k=0}^{n} A_k^+ + \int_{-\tau}^{0} A_{n+1}^+(\theta)d\theta.$$

For the asymptotical stability of a trivial solution of the system (1) *it is sufficient that the matrix* $A_\Sigma^+ - B$ *satisfies Sevast'yanov – Kotelyanski'i criterion or, equally,* $B - A_\Sigma^+$ *is a nonsingular M-matrix.*

We can consider an example: the system (1) of the following form

$$\frac{dx_1(t)}{dt} = \int_{-2}^{0} x_2(t+\theta)d\theta - 1.5x_1(t), \tag{3}$$

$$\frac{dx_2(t)}{dt} = 0.5x_1(t) + 0.3x_1(t-1) - 1.2x_2(t). \tag{4}$$

The matrices B, A_Σ and $B - A_\Sigma$ are:

$$B = \begin{pmatrix} 1.5 & 0 \\ 0 & 1.2 \end{pmatrix}, \quad A_\Sigma = \begin{pmatrix} 0 & 2 \\ 0.8 & 0 \end{pmatrix}, \quad B - A_\Sigma = \begin{pmatrix} 1.5 & -2 \\ -0.8 & 1.2 \end{pmatrix}.$$

All angular minors of the matrix $B - A_\Sigma$ are positive, so it is a nonsingular M-matrix. Therefore, the trivial solution of the system (3), (4) is asymptotically stable.

3. Estimates of the Cauchy problem solutions for linear inhomogeneous systems of differential equations

Let us consider the Cauchy problem

$$\frac{dx(t)}{dt} = Ax(t) + f(t), \quad t \in [0;\infty), \tag{5}$$

$$x(0) = x_0 \in \mathbb{R}^m, \tag{6}$$

where $x(t) : \mathbb{R} \mapsto \mathbb{R}^m$ is a sought vector-function; A is a set real $m \times m$ matrix; $f(t) : \mathbb{R} \mapsto \mathbb{R}^m$ is a set vector-function continuous on the interval $[0;\infty)$; at $t = 0$ $\frac{dx(t)}{dt}$ means a right-hand derivative:

$$\frac{dx(0)}{dt} = Ax_0 + f(0).$$

A solution of the Cauchy problem (5), (6) on the interval $[0,\infty)$ will have a form of function $x(t)$ continuously differentiable on $[0;\infty)$, satisfying equations of the system (5) and the initial condition (6).

The Cauchy problem (5), (6) has a unique solution $x(t)$, that can be written in form

$$x(t) = e^{At}x_0 + \int_0^t e^{A(t-s)}f(s)ds, \quad t \in [0;\infty). \tag{7}$$

The expressions of the form e^{At}, $e^{A(t-s)}$ contained in (7), mean the matrix exponents [3, 12].

If a matrix A is stable (Hurwitz), then at $t \geq 0$, $t - s \geq 0$, we have estimates

$$||e^{At}||_1 \leq b\, e^{-\alpha t}, \quad ||e^{A(t-s)}||_1 \leq b\, e^{-\alpha(t-s)}, \tag{8}$$

where $b > 0$, $\alpha > 0$ are some constants [12]. If, at that, $f(t) \to 0$ at $t \to +\infty$, then from (7), (8) it follows the estimate

$$||x(t)||_1 \leq b \max\left\{||x_0||_1, \ \frac{f^*}{\alpha}\right\}, \quad t \in [0;\infty), \quad f^* = \max_{[0;\infty)} ||f(t)||_1, \tag{9}$$

and exists

$$\lim_{t\to+\infty} x(t) = 0. \tag{10}$$

If a matrix A is quasinonnegative (Metzler), a matrix e^{At} is nonnegative at $t \geq 0$ [3]. In this case, from (7) it follows that the solution $x(t)$ is nonnegative, if $x_0 \geq 0$ and $f(t) \geq 0$ for all $t \in [0;\infty)$.

STUDY OF EQUILIBRIA STABILITY OF MATHEMATICAL MODELS FOR LIVING SYSTEMS

4. Model of an antiviral immune response

The monographs [13, 14] present one of the fundamental mathematical models in immunology, a model of an antiviral immune response. Analysis of this model, its instances and various modifications is of special interest for researchers: it helps to look for applied problems in immunology and their solutions.

4.1. Equations of the model

Basing the [13, 14], we shall define the following variables of an antiviral immune response model:

- $V_f(t)$ – number of viruses freely circulating in a body;
- $M_V(t)$ – number of stimulated (antigen-presenting) macrophages;
- $H_E(t)$ – number of T-lymphocytes, helpers of cellular immunity;
- $H_B(t)$ – number of T-lymphocytes, helpers of humoral immunity;
- $E(t)$ – number of T-cells effectors (killers);
- $B(t)$ – number of B-lymphocytes;
- $P(t)$ – number of plasmatic cells;
- $F(t)$ – number of antibodies;
- $C_V(t)$ – number of virus-affected cells of a target organ;
- $m(t)$ – a nonfunctioning (virus-affected) part of a target organ.

Let $M^* > 0$ be a marrow cell-maintained constant macrophage level in a body. Similarly, H_E^*, H_B^*, E^*, B^* and P^* are numbers of the appropriate cells in the conditions of a virus absence from a body. Assume $C^* > 0$ is a number of a target organ cells in a healthy (virus-free) body.

The equation system of the model is as follows:

$$\frac{dV_f(t)}{dt} = \nu C_V(t) + nb_{CE}C_V(t)E(t) - \gamma_{VF}F(t)V_f(t) - \\ - \gamma_{VM}M^*V_f(t) - \gamma_{VC}(C^* - C_V(t) - m(t))V_f(t), \tag{11}$$

$$\frac{dM_V(t)}{dt} = \gamma_{MV}M^*V_f(t) - \alpha_M M_V(t), \tag{12}$$

$$\frac{dH_E(t)}{dt} = b_H^{(E)}\Big(\xi(m(t))\rho_H^{(E)}M_V(t-\omega_H^{(E)})H_E(t-\omega_H^{(E)}) - M_V(t)H_E(t)\Big) - \\ - b_p^{(H_E)}M_V(t)H_E(t)E(t) + \alpha_H^{(E)}(H_E^* - H_E(t)), \tag{13}$$

$$\frac{dH_B(t)}{dt} = b_H^{(B)}\Big(\xi(m(t))\rho_H^{(B)}M_V(t-\omega_H^{(B)})H_B(t-\omega_H^{(B)}) - M_V(t)H_B(t)\Big) - \\ - b_p^{(H_B)}M_V(t)H_B(t)B(t) + \alpha_H^{(B)}(H_B^* - H_B(t)), \tag{14}$$

$$\frac{dE(t)}{dt} = b_p^{(E)}\Big(\xi(m(t))\rho_E M_V(t-\omega_E)H_E(t-\omega_E)E(t-\omega_E) - M_V(t)H_E(t)E(t)\Big) - \\ - b_{EC}C_V(t)E(t) + \alpha_E(E^* - E(t)), \tag{15}$$

$$\frac{dB(t)}{dt} = b_p^{(B)}\Big(\xi(m(t))\rho_B M_V(t-\omega_B)H_B(t-\omega_B)B(t-\omega_B) - M_V(t)H_B(t)B(t)\Big) + \\ + \alpha_B(B^* - B(t)), \tag{16}$$

$$\frac{dP(t)}{dt} = b_p^{(P)}\xi(m(t))\rho_P M_V(t-\omega_P)H_B(t-\omega_P)B(t-\omega_P) + \alpha_P(P^* - P(t)), \tag{17}$$

$$\frac{dF(t)}{dt} = \rho_F P(t) - \gamma_{FV}V_f(t)F(t) - \alpha_F F(t), \tag{18}$$

$$\frac{dC_V(t)}{dt} = \sigma V_f(t)(C^* - C_V(t) - m(t)) - b_{CE}C_V(t)E(t) - b_m C_V(t), \tag{19}$$

$$\frac{dm(t)}{dt} = b_{CE}C_V(t)E(t) + b_m C_V(t) - \alpha_m m(t), \quad t \in [0;\infty). \tag{20}$$

All parameters of the equations system (11)–(20) are defined as positive.

The function $\xi(m)$ accounts for decrease in effectiveness of immune system activity, when a target organ is affected by viruses. We assume that $\xi(0) = 1$, $\xi(m) = 0$ at $m \geq C^*$, $\xi(m)$ is a continuous nonincreasing function on the interval $[0; C^*]$ and it has a continuous derivative on this interval (in the point $m = C^*$ the derivative means the left-hand derivative). A typical example of such function has the form $\xi(m) = \max\{1 - m/C^*, 0\}$.

The system (11)–(20) is supplemented with the initial data

$$V_f(0) = V_f^0 \geq 0, \quad M_V(0) = M_V^0 \geq 0, \tag{21}$$

$$H_E(0) = H_E^0 \geq 0, \quad H_B(0) = H_B^0 \geq 0, \quad E(0) = E^0 \geq 0, \tag{22}$$

$$B(0) = B^0 \geq 0, \quad P(0) = P^0 \geq 0, \quad F(0) = F^0 \geq 0, \tag{23}$$

$$C_V(0) = C_V^0 \geq 0, \quad m(0) = m^0 \geq 0, \tag{24}$$

$$M_V(t)H_E(t) = \eta_1(t), \quad t \in [-\omega_H^{(E)}; 0], \tag{25}$$

$$M_V(t)H_B(t) = \eta_2(t), \quad t \in [-\omega_H^{(B)}; 0], \tag{26}$$

$$M_V(t)H_E(t)E(t) = \eta_3(t), \quad t \in [-\omega_E; 0], \tag{27}$$

$$M_V(t)H_B(t)B(t) = \eta_4(t), \quad t \in [-\max\{\omega_B, \omega_P\}; 0]. \tag{28}$$

The functions $\eta_i(t)$, contained in (25)–(28) are defined as nonnegative and continuous in their definition ranges $1 \leq i \leq 4$ and, besides,

$$\eta_1(0) = M_V^0 H_E^0, \quad \eta_2(0) = M_V^0 H_B^0, \quad \eta_3(0) = M_V^0 H_E^0 E^0, \quad \eta_4(0) = M_V^0 H_B^0 B^0.$$

The monograph [14] states that the Cauchy problem (11)–(28) has the unique solution

$$W(t) = (V_f(t), M_V(t), H_E(t), H_B(t), E(t), B(t), P(t), F(t), C_V(t), m(t))^T,$$

on the interval $t \in [0; \infty)$ and the components of this solution are nonnegative.

4.2. Equilibria of the model and their stability

Let us analyze stability of the system (11)–(20) equilibria. Search for all equilibria is a challenge due to essential nonlinearity and high dimensions of the system (11)–(20). One of the nonnegative equilibria can easily be found at $V_f = 0$ and has a form

$$U_0 = (0, 0, H_E^*, H_B^*, E^*, B^*, P^*, F^*, 0, 0)^T,$$

where $F^* = \rho_F P^* / \alpha_F$.

The system (11)–(20) can contain nonnegative equilibria

$$U = (V_f, M_V, H_E, H_B, E, B, P, F, C_V, m)^T \in \mathbb{R}_+^{10},$$

for which the following conditions are realized

$$V_f > 0, \quad C_V > 0, \quad m > 0, \quad C_V + m < C^*. \tag{29}$$

Existence of such equilibria was demonstrated in the numerical form by models of chronic viral hepatitis [13].

The equilibrium U_0 is interpreted as a healthy body (an organism is virus-free). The nonnegative equilibria satisfying (29) are interpreted as the chronic course of the disease, when counts of viruses and virus-affected cells of a target organ are maintained at a certain non-zero

level.

A condition of the asymptotical stability U_0 can easily be found by examination of the characteristic polynomial roots of the linear approximation equations system. This condition is an inequality [14]:

$$(\gamma_{VM}M^* + \gamma_{VF}F^* + \gamma_{VC}C^*)(b_{CE}E^* + b_m) > \sigma C^*(\nu + nb_{CE}E^*).$$

Let us consider a nonnegative equilibrium U, for which the conditions (29) are realized. Following the study [11] and applying the method of linearization, we obtain the sufficient conditions of the asymptotic stability U. Assume

$$x(t) = W(t) - U, \quad t \in [0; \infty).$$

The system of linear approximation equations in the neighborhood of the equilibrium U can be written as (1):

$$\frac{dx(t)}{dt} = A_0x(t) + A_1x(t - \omega_H^{(E)}) + A_2x(t - \omega_H^{(B)}) + \\ + A_3x(t - \omega_E) + A_4x(t - \omega_B) + A_5x(t - \omega_P) - Bx(t). \quad (30)$$

The matrices B, A_k have dimension 10×10. Their elements can be found by the standard linearization procedure for the right hands of the system (11)–(20). The explicit form of these matrices is not given because the resulting expressions are too awkward. The vector of the terms rejected at linearization satisfies the necessary smallness condition [15]. Therefore, the system (30) can be used for the analysis of the equilibrium U asymptotical stability.

We assume $A_\Sigma^+ = \sum_{k=0}^5 A_k^+$, $G = B - A_\Sigma^+$ and apply theorem 4. After calculating the diagonal minors of the matrix G we come to the inequality system

$$\frac{(\gamma_{VM}M^* + \gamma_{VF}F)\,m + 2\gamma_{VC}(C^* - m)\,m}{\gamma_{VM}M^* + \gamma_{VF}F + 2\gamma_{VC}\,m} < C_V, \quad (31)$$

$$(\rho_E\xi(m) + 1)(b_p^{(E)}M_VH_EE)^2 < \alpha_H^{(E)}\alpha_EH_E^*E^*, \quad (32)$$

$$(\rho_B\xi(m) + 1)(b_p^{(B)}M_VH_BB)^2 < \alpha_H^{(B)}\alpha_BH_B^*B^*, \quad (33)$$

$$\det(G_6) > 0, \quad \det(G) > 0, \quad (34)$$

where $\det(G_6)$, $\det(G)$ is the sixth order diagonal minor and determinant of the matrix G.

The inequalities (31)–(34) are separated out all possible equilibria by the asymptotically equilibria with the following property: numbers of cells H_E, H_B, E, B and P slightly exceed their numbers in U_0, while the number of C_V virus infected cells is close to C^*. Analysis of the equations (11)–(20) with specific numerical values of the parameters tells on the existence of nonnegative equilibria satisfying the inequalities (29), (31)–(34).

Therefore, the model under consideration allows for such a body state, at which a considerable portion of a target organ cells are virus-infected, while the parameters of their immune systems are almost «normal», in other words, the immune system «ignores» these cells the same as viruses circulating in blood. The appropriate solutions of the model can be interpreted as alternates of immune deficient states of the organism.

5. Two models of HIV-1-infection

One of the rapidly developing branches of mathematical modeling in immunology is establishment of models for HIV-1 infection dynamics in a human body. One of the key moments

in creation of HIV-1 infection models is accounting for the development stages of viral particles and infected cells, and for separate stages in immune response formation. Durations of the mentioned stages and steps can take from several hours to several days, therefore, we include delay variables into the differential equations. The current approaches to modeling of HIV-1 infection dynamics and typical models are presented, for example, in the [16, 17, 18, 19, 20].

5.1. First model

We assume that dynamics of HIV-1 infection is described in terms of the following components:

- T – T-lymphocytes (virion target cells);
- C – infected cells (cells at the stage of preparing for viral particles production);
- I – product-infected cells (cells producing viral particles);
- U – immature viral particles;
- V – mature viral particles (virions);
- E – cytotoxic T-lymphocytes (effectors);
- K – cells – precursors of the lymphocytes-effectors.

We shall call counts of the mentioned components at a moment t as $T(t)$, $C(t)$, $I(t)$, $U(t)$, $V(t)$, $E(t)$ and $K(t)$, respectively. Using the description of the main regularities of the HIV-1 infection dynamics [17], we shall consider the system of differential and integral equations as follows:

$$\frac{dT(t)}{dt} = r_T - \mu_T T(t) - (\gamma_{T,V} V(t) + \gamma_{T,I} I(t))T(t), \tag{35}$$

$$\begin{aligned}\frac{dI(t)}{dt} = & -(\mu_I + \sigma_U \nu_U) I(t) - \gamma_{I,E} I(t) E(t) \quad + \\ & + \quad e^{-\mu_C \omega_C} \big(\gamma_{T,V} V(t-\omega_C) + \gamma_{T,I} I(t-\omega_C)\big) T(t-\omega_C),\end{aligned} \tag{36}$$

$$\frac{dV(t)}{dt} = -\mu_V V(t) - \gamma_{T,V} T(t) V(t) + e^{-\mu_U \omega_U}\, \nu_U I(t-\omega_U), \tag{37}$$

$$\frac{dE(t)}{dt} = -\mu_E E(t) + n_E\, \nu_K I(t-\omega_K), \tag{38}$$

$$C(t) = \int_{t-\omega_C}^{t} e^{-\mu_C (t-s)} \big(\gamma_{T,V} V(s) + \gamma_{T,I} I(s)\big) T(s)\, ds, \tag{39}$$

$$U(t) = \int_{t-\omega_U}^{t} e^{-\mu_U (t-s)}\, \nu_U I(s)\, ds, \tag{40}$$

$$K(t) = \int_{t-\omega_K}^{t} \nu_K I(s)\, ds, \quad t \in [0;\infty), \tag{41}$$

$$T(t) = T_0(t), \quad I(t) = I_0(t), \quad V(t) = V_0(t), \quad E(0) = E_0, \quad t \in [-\omega; 0], \tag{42}$$

$$\omega = \max\{\omega_C, \omega_U, \omega_K\}.$$

All parameters of the equation system (35)–(41) are defined as positive. The parameter r_T sets a rate of a T-cells inflow from marrow cells. The parameters μ_T, μ_I, μ_C, μ_V, μ_U and μ_E are a component death intensities per a cell or a viral particle. The parameter ν_U defines intensity of particles U production per a cell I. The parameter $\sigma_U \nu_U$ means intensity of cells I death

(per a cell) due to the deleterious process of the particles U budding from the membranes of the mentioned cells. The parameter ν_K sets intensity of stimulation of K cells production by mediated effects of the cells I on immune competent cells (per a cell). The parameter n_E is a mean number of descendants of a reproduction-stimulated cell K. The parameters $\gamma_{T,V}$, $\gamma_{T,I}$ and $\gamma_{I,E}$ mean intensities of interactions between cells per a pair (T,V), (T,I) and (I,E), respectively. The delays ω_U and ω_C present aging durations for the particles U and cells C; the delay ω_K is duration of reproduction process of the stimulated cells K.

The functions contained in (42) are assumed as nonnegative and continuous, the constant E_0 is nonnegative. The addends in form of

$$\gamma_{T,V}V(t)T(t), \quad e^{-\mu_C\omega_C}\gamma_{T,I}I(t-\omega_C)T(t-\omega_C), \quad \sigma_U\nu_U I(t),$$

contained in equations (35), (36) and the integral relations (39)–(41) are new elements in the models of the HIV-1 infection dynamics as compared to the models from the [18, 19, 20]. Note that equations (39)–(41) can be considered as subsidiary and used to account for balance of cell and viral particle counts.

Applying the results of [21], we get that the system (35)–(38) supplemented with the initial conditions (42) has a unique solution on the interval $[0;\infty)$ and, besides, the solution components are nonnegative. As a consequence, the functions $C(t)$, $U(t)$ and $K(t)$, set by the formulas (39)–(41), are defined, continuous and nonnegative on the interval $[0;\infty)$.

The equations (35)–(38) of the model have a trivial equilibrium

$$S^* = (T^*, I^*, V^*, E^*),$$

where $T^* = r_T/\mu_T$, $I^* = V^* = E^* = 0$. Let us examine stability of this equilibrium. For this purpose, we shall construct a system of the linear approximation differential equations in the neighborhood of S^*. The variables of the system are designated the same as the initial ones. The rejected nonlinear terms are productions of the variables, including the delay variables. The vector of terms rejected at linearization satisfies the necessary condition of smallness [15]. We shall write the resulting equation system in the block form, putting a block containing only two variables to the first place:

$$\frac{dI(t)}{dt} = -(\mu_I + \sigma_U\nu_U)I(t) + e^{-\mu_C\omega_C}\big(\gamma_{T,V}V(t-\omega_C) + \gamma_{T,I}I(t-\omega_C)\big)T^*, \tag{43}$$

$$\frac{dV(t)}{dt} = -(\mu_V + \gamma_{T,V}T^*)V(t) + e^{-\mu_U\omega_U}\,\nu_U I(t-\omega_U), \tag{44}$$

$$\frac{dT(t)}{dt} = -\mu_T T(t) - (\gamma_{T,V}V(t) + \gamma_{T,I}I(t))T^*, \tag{45}$$

$$\frac{dE(t)}{dt} = -\mu_E E(t) + n_E\,\nu_K I(t-\omega_K). \tag{46}$$

A block structure of the system (43)–(46) and inequalities $\mu_T > 0$ and $\mu_E > 0$ make it possible to explore a problem of stability of the system (43)–(46) trivial equilibrium by examination of the equation system of its first block. Indeed, if the trivial equilibrium of the system (43), (44) is asymptotically stable, relations (9) and (10) are true for the variables $T(t)$ and $E(t)$, satisfying (45) and (46) (refer to 3). Therefore, the asymptotic stability of the (43) and (44) trivial equilibrium provides asymptotic stability of the (43)–(46) trivial equilibrium. It is clear that the instability of the system (43) and (44) trivial equilibrium leads to instability of the system (43)–(46) trivial equilibrium.

The equations (43) and (44) are an example of the differential system (1) with the

nonnegative matrices A_k. Let us introduce the matrices

$$B = \begin{pmatrix} \mu_I + \sigma_U \nu_U & 0 \\ 0 & \mu_V + \gamma_{T,V} T^* \end{pmatrix}, \quad A_\Sigma = \begin{pmatrix} e^{-\mu_C \omega_C} \gamma_{T,I} T^* & e^{-\mu_C \omega_C} \gamma_{T,V} T^* \\ e^{-\mu_U \omega_U}\, \nu_U & 0 \end{pmatrix},$$

$$G = B - A_\Sigma = \begin{pmatrix} \mu_I + \sigma_U \nu_U - e^{-\mu_C \omega_C} \gamma_{T,I} T^* & -e^{-\mu_C \omega_C} \gamma_{T,V} T^* \\ -e^{-\mu_U \omega_U}\, \nu_U & \mu_V + \gamma_{T,V} T^* \end{pmatrix}.$$

and apply theorem 3. We shall test realization of the inequalities $M_1 > 0$ and $M_2 > 0$, where M_1 and M_2 are the angular minors G. Then $M_1 = \mu_I + \sigma_U \nu_U - e^{-\mu_C \omega_C} \gamma_{T,I} T^*$, $M_2 = \det(G)$. Conditions for the realization of the inequalities $M_1 > 0$ and $M_2 > 0$ can be expressed in terms of the index

$$R_{0,1} = \frac{\gamma_{T,I} T^* e^{-\mu_C \omega_C}}{\mu_I + \sigma_U \nu_U} + \frac{\nu_U \gamma_{T,V} T^* e^{-(\mu_C \omega_C + \mu_U \omega_U)}}{(\mu_I + \sigma_U \nu_U)(\mu_V + \gamma_{T,V} T^*)}, \tag{47}$$

called a basic reproductive number. As a result, we come to the conclusion: 1) if $R_{0,1} < 1$, the equilibrium S^* is asymptotically stable; 2) at $R_{0,1} > 1$ the equilibrium S^* is unstable. A case $R_{0,1} = 1$ calls for a separate study.

Within the frames of the model under examination, we have the following result: 1) if $R_{0,1} < 1$, the infection does not develop, when an individual is infected with a small amount of HIV-1 virions; 2) if $R_{0,1} > 1$, the HIV-1 infection cannot be eliminated from an infected individual.

5.2. Second model

Let us consider a modification of the model (35)–(42) related to the more detailed description of death process caused by production of immature viral particles in the product-infected cells. We assume that the cells I form a heterogeneous population consisting of the cells I_0, I_1, …, I_m. A cell I_0 originates directly from a cell C, a cell I_1 – from a cell I_0, …, a cell I_m – from a cell I_{m-1}. The cells I_0, I_1, …, I_m produce the immature viral particles U with the intensity $\nu_U > 0$ per a cell. After production of viral particles U, a part $p_{j,j+1}$ of the cells I_j transforms into the cells I_{j+1}, while a part $1 - p_{j,j+1}$ $0 < p_{j,j+1} < 1$, $0 \le j \le m-1$ dies. All I_m cells produce viral particles U and die.

We assume that the precursors K of the cytotoxic T-lymphocytes E originate from the specific marrow cells due to mediate impacts of the cells I_0, I_1, …, I_m with the intensity $\nu_K > 0$ per a cell I_j, $0 \le j \le m$. The cells I_0, I_1, …, I_m die at contacts with the cytotoxic T-lymphocytes E with the intensity $\gamma_{I,E} > 0$ per a pair (I_j, E), $0 \le j \le m$. The cells C appear due to interactions between the target cells T with virions V, and/or with the product-infected cells I_0, I_1, …, I_m with intensities $\gamma_{T,V} > 0, \gamma_{T,I} > 0$ per a pair (T, V), (T, I_j), $0 \le j \le m$, respectively.

Let $T(t)$, $C(t)$, $I_0(t)$, $I_1(t), \ldots, I_m(t)$, $U(t)$, $V(t)$, $E(t)$ and $K(t)$ be the amounts of components at a moment t. We consider the following system instead of (35)–(42)

$$\frac{dT(t)}{dt} = r_T - \mu_T T(t) - \big(\gamma_{T,V} V(t) + \sum_{j=0}^{m} \gamma_{T,I} I_j(t)\big) T(t), \tag{48}$$

$$\frac{dI_0(t)}{dt} = -(\mu_I + \nu_U) I_0(t) - \gamma_{I,E} I_0(t) E(t) \quad + \tag{49}$$

$$+ \quad e^{-\mu_C \omega_C} \big(\gamma_{T,V} V(t - \omega_C) + \sum_{j=0}^{m} \gamma_{T,I} I_j(t - \omega_C)\big) T(t - \omega_C), \tag{50}$$

$$\frac{dI_j(t)}{dt} = -(\mu_I + \nu_U) I_j(t) - \gamma_{I,E} I_j(t) E(t) + \nu_U p_{j-1,j} I_{j-1}(t), \quad 1 \le j \le m, \tag{51}$$

$$\frac{dV(t)}{dt} = -\mu_V V(t) - \gamma_{T,V} T(t) V(t) + e^{-\mu_U \omega_U} \sum_{j=0}^{m} \nu_U I_j(t-\omega_U), \tag{52}$$

$$\frac{dE(t)}{dt} = -\mu_E E(t) + n_E \sum_{j=0}^{m} \nu_K I_j(t-\omega_K), \tag{53}$$

$$C(t) = \int_{t-\omega_C}^{t} e^{-\mu_C(t-s)} \big(\gamma_{T,V} V(s) + \sum_{j=0}^{m} \gamma_{T,I} I_j(s)\big) T(s)\, ds, \tag{54}$$

$$U(t) = \int_{t-\omega_U}^{t} e^{-\mu_U(t-s)} \sum_{j=0}^{m} \nu_U I_j(s)\, ds, \tag{55}$$

$$K(t) = \int_{t-\omega_K}^{t} \sum_{j=0}^{m} \nu_K I_j(s)\, ds, \quad t \in [0;\infty), \tag{56}$$

$$T(t) = T^0(t), \quad I_j(t) = I_j^0(t), \quad V(t) = V^0(t), \quad E(0) = E^0, \quad t \in [-\omega; 0], \tag{57}$$

$$\omega = \max\{\omega_C, \omega_U, \omega_K\}.$$

All functions contained in the (57) are defined as nonnegative and continuous, the constant $E^0 \geq 0$.

It is easy to show that the system (35)–(56) supplemented with the initial conditions (57) has the unique solution on the interval $[0;\infty)$ and, besides, the solution components are nonnegative.

The differential system (48)–(53) of the model has a trivial equilibrium

$$X^* = (T^*, I_0^*, I_1^*, \ldots, I_m^*, V^*, E^*)$$

with the components $T^* = r_T/\mu_T$, $I_0^* = I_1^* = \cdots = I_m^* = V^* = E^* = 0$. Let us explore the equilibrium X^*, relying upon the linear approximation differential system in the neighborhood of X^*. The variables of the linearized system are designated the same as the initial ones. The rejected nonlinear terms are products of the variables, including the delay variables. The vector of the terms rejected at linearization satisfies the necessary condition of smallness [15].

Let us write the system of linear approximation equations:

$$\frac{dT(t)}{dt} = -\mu_T T(t) - \gamma_{T,V} T^* V(t) - \gamma_{T,I} T^* \sum_{j=0}^{m} I_j(t), \tag{58}$$

$$\frac{dI_0(t)}{dt} = -(\mu_I + \nu_U) I_0(t) + e^{-\mu_C \omega_C} T^* \big(\gamma_{T,V} V(t-\omega_C) + \gamma_{T,I} \sum_{j=0}^{m} I_j(t-\omega_C)\big), \tag{59}$$

$$\frac{dI_j(t)}{dt} = -(\mu_I + \nu_U) I_j(t) + \nu_U p_{j-1,j} I_{j-1}(t), \quad 1 \leq j \leq m, \tag{60}$$

$$\frac{dV(t)}{dt} = -(\mu_V + \gamma_{T,V} T^*) V(t) + e^{-\mu_U \omega_U} \nu_U \sum_{j=0}^{m} I_j(t-\omega_U), \tag{61}$$

$$\frac{dE(t)}{dt} = -\mu_E E(t) + n_E \nu_K \sum_{j=0}^{m} I_j(t-\omega_K). \tag{62}$$

One can see that the variables $T(t)$ and $E(t)$ are not the members of equations (59), (60) and (61). Moreover, the parameters $\mu_T > 0$, $\mu_E > 0$. By analogy with the first model analysis (refer to the analysis of the system structure (43)–(46)), it is sufficient to consider a problem of stability of the system (59), (60), (61) trivial equilibrium, rejecting the equalities (58) and (62).

To simplify a record, we shall introduce the designations:

$$a = \mu_I + \nu_U, \quad b_j = \nu_U p_{j,j+1}, \quad 0 \le j \le m-1, \quad c = e^{-\mu_C \omega_C} \gamma_{T,V} T^*,$$

$$d = e^{-\mu_C \omega_C} \gamma_{T,I} T^*, \quad e = \mu_V + \gamma_{T,V} T^*, \quad f = e^{-\mu_U \omega_U}\, \nu_U,$$

$$g_0 = 1, \quad g_1 = p_{0,1}, \quad g_2 = p_{0,1}\, p_{1,2}, \ldots, g_m = p_{0,1}\, p_{1,2} \cdots p_{m-1,m}.$$

Let us analyse stability of the system (59), (60), (61) trivial equilibrium, presented in the explicit form:

$$\frac{dI_1(t)}{dt} = -aI_1(t) + b_0 I_0(t), \tag{63}$$

$$\frac{dI_2(t)}{dt} = -aI_2(t) + b_1 I_1(t), \tag{64}$$

$$\frac{dI_3(t)}{dt} = -aI_3(t) + b_2 I_2(t), \tag{65}$$

$$\cdots\cdots\cdots\cdots,$$

$$\frac{dI_m(t)}{dt} = -aI_m(t) + b_{m-1} I_{m-1}(t), \tag{66}$$

$$\frac{dI_0(t)}{dt} = -aI_0(t) + d \sum_{j=0}^{m} I_j(t - \omega_C) + cV(t - \omega_C), \tag{67}$$

$$\frac{dV(t)}{dt} = -eV(t) + f \sum_{j=0}^{m} I_j(t - \omega_U). \tag{68}$$

The equation system (63)–(68) has a dimension $m+2$ and its form corresponds to the differential system (1) with nonnegative matrices A_k and matrix $B = \mathrm{diag}(a, a, a, \ldots, a, a, e)$. Using presentation of the variables of the system (63)–(68) in form

$$x(t) = (I_1(t), I_2(t), I_3(t), \ldots, I_{m-1}(t), I_m(t), I_0(t), V(t))^T,$$

it is not hard to write out the matrix A_Σ and pass to the $(m+2) \times (m+2)$ matrix

$$G = B - A_\Sigma = \begin{pmatrix} a & 0 & 0 & \ldots & 0 & 0 & -b_0 & 0 \\ -b_1 & a & 0 & \ldots & 0 & 0 & 0 & 0 \\ 0 & -b_2 & a & \ldots & 0 & 0 & 0 & 0 \\ \ldots & \ldots & \ldots & \ldots & \ldots & \ldots & \ldots & \ldots \\ 0 & 0 & 0 & \ldots & -b_{m-1} & a & 0 & 0 \\ -d & -d & -d & \ldots & -d & -d & a-d & -c \\ -f & -f & -f & \ldots & -f & -f & -f & e \end{pmatrix}.$$

Let us apply theorem 3 and test realization of the inequalities $M_k > 0$ relatively angular minors of the matrix G, $1 \le k \le m+2$. It is clear that $M_k = a^k > 0$ for all $1 \le k \le m$. To find M_{m+1} and $M_{m+2} = \det(G)$ we shall use elementary manipulations (expansion of the last column in elements, step-by-step summation of the first, second etc. columns, multiplied by combinations of several parameters, with the last column of the minor under consideration). Performing all intermediate calculations, we get

$$M_{m+1} = a^m \left(a - d \sum_{j=0}^{m} \left(\nu_U / a\right)^j g_j\right),$$

$$M_{m+2} = a^m \left(e\,a - \left(e\,d + c\,f \right) \sum_{j=0}^{m} \left(\nu_U / a \right)^j g_j \right).$$

Define

$$S_U = \sum_{j=0}^{m} \left(\frac{\nu_U}{\mu_I + \nu_U} \right)^{j+1} g_j. \tag{69}$$

Conditions of realization for the inequalities $M_{m+1} > 0$, $M_{m+2} > 0$ can be expressed in terms of the index

$$R_{0,2} = \frac{\gamma_{T,I} T^* e^{-\mu_C \omega_C}\, S_U}{\nu_U} + \frac{\gamma_{T,V} T^* e^{-(\mu_C \omega_C + \mu_U \omega_U)}\, S_U}{\mu_V + \gamma_{T,V} T^*}, \tag{70}$$

which, the same as earlier, we shall call a basic reproductive number. The constant $S_U \in [0; m+1]$, set by formula (69) and included into (70), can be interpreted as a mean number of viral particles U, produced by a cell I_0 and its descendants I_1, …, I_m. As a result, we come to a conclusion: 1) if $R_{0,2} < 1$, equilibrium X^* is asymptotically stable; 2) at $R_{0,2} > 1$ equilibrium X^* is unstable. A case $R_{0,2} = 1$ calls for a separate investigation.

Within the frames of the high-dimensional model under examination, we have the following result: 1) if $R_{0,2} < 1$, the infection does not develop, when an individual is infected with a small amount of HIV-1 virions, 2) if $R_{0,2} > 1$, infection cannot be eliminated from an individual infected with the HIV-1.

6. Two models of tuberculosis spread in an isolated region

The section presents two models for dynamics of tuberculosis spread in an isolated region. A region's isolation means lack of people inflows from other regions. The region's population size is maintained due to the birth of new individuals. We assume that rate of birth for new individuals and their surviving to a fixed age are defined by some functions taken, for simplification of the models study, in form of fixed constants. Below mentioned versions of the models differ between each other by structure of population groups considering specifics of an epidemic process under examination. The models are based on [22, 23].

6.1. First model

Let all adult population of a region be distributed in three groups: S is susceptible to infecting, I is latent infected without clinical manifestations of the disease, and C is patients with sputum smear-positive tuberculosis. Let $S(t)$, $I(t)$ and $C(t)$ denote sizes of the mentioned groups at the moment t. An equation system for the model is:

$$\frac{dS(t)}{dt} = -\beta S(t)C(t) - \lambda S(t) + \rho \exp\left(-\int_0^\tau g(a)C(t-\tau+a)da \right), \tag{71}$$

$$\frac{dI(t)}{dt} = (1-p)\beta S(t)C(t) - \lambda I(t) - (\gamma + \alpha C(t))I(t) + \eta\, C(t) + \\ + \rho \left(1 - \exp\left(-\int_0^\tau g(a)C(t-\tau+a)da \right) \right), \tag{72}$$

$$\frac{dC(t)}{dt} = p\beta S(t)C(t) - (\eta + \mu)C(t) + (\gamma + \alpha C(t))I(t), \quad t \in [0; \infty), \tag{73}$$

$$S(0) = S_0, \quad I(0) = I_0, \quad C(t) = C_0(t), \quad t \in [-\tau; 0]. \tag{74}$$

Let us describe parameters of the model. The parameter $\tau > 0$ sets age, when a young individual gets mature. The constant $\rho > 0$ is a fixed rate of the groups S and I recruitment due to aging

of young individuals survived to age τ. The function $g(a)$, nonnegative and continuous on the interval $[0;\tau]$, describes intensity of young individuals infecting by sick individuals, when a young individual reaches the age $a \in [0;\tau]$. The parameters $\beta > 0$, $\alpha > 0$ define intensities of contacts between individuals from S and I groups and individuals from C group. The parameters $\lambda > 0$ and $\mu > 0$ present natural mortality intensities in members of the S, I and C groups with account for emigration of individuals from these groups to regions beyond the model under consideration. Besides, the parameter μ includes intensities of death caused by tuberculosis in the group C individuals. The constant $p \in (0;1)$ accounts for a share of the group S members, in whom disease develops immediately after infecting. The parameter $\gamma > 0$ means intensities of spontaneous disease development in the group I members. The parameter $\eta > 0$ sets intensities of self-recoveries and recoveries due to treatment in medical institutions for the individuals from the group C.

In (74) it is assumed that the constants $S_0 \geq 0$, $I_0 \geq 0$, the initial function $C_0(t)$ is nonnegative and continuous on the interval $t \in [-\tau;0]$.

6.2. Second model

We supplement the groups S, I and C, used in the first version of the model with a fourth group of adult individuals: T – containing self-cured patients or patients recovered form active tuberculosis. Let $S(t)$, $I(t)$, $C(t)$ and $T(t)$ denote sizes of the mentioned groups at a moment t. An equations system of the model is:

$$\frac{dS(t)}{dt} = -\beta S(t)C(t) - \lambda S(t) + \rho \exp\left(-\int_0^\tau g(a)C(t-\tau+a)da\right), \tag{75}$$

$$\frac{dI(t)}{dt} = (1-p)\beta S(t)C(t) - \lambda I(t) - (\gamma + \alpha C(t))I(t) + \\ + \rho\left(1 - \exp\left(-\int_0^\tau g(a)C(t-\tau+a)da\right)\right), \tag{76}$$

$$\frac{dC(t)}{dt} = p\beta S(t)C(t) - (\eta+\mu)C(t) + (\gamma+\alpha C(t))I(t) + \\ + \int_0^\omega e^{-\lambda a}\,\eta\, C(t-a)dF(a), \tag{77}$$

$$T(t) = \int_0^\omega e^{-\lambda a}\,(1-F(a))\,\eta\, C(t-a)da, \quad t \in [0;\infty), \tag{78}$$

$$S(0) = S_0, \quad I(0) = I_0, \quad C(t) = C_0(t), \quad t \in [-\max(\tau,\omega);0]. \tag{79}$$

The system (75)–(79) contains functions and constants described for the first model. The initial function $C_0(t)$ is defined, nonnegative and continuous on the interval $t \in [-\max(\tau,\omega);0]$. The function F, used in the (77) and (78), sets distribution of durations of an individual presence in the group T until he/she passes to the group C, due to the disease exacerbation (before its transition into the active form). We assume that duration of an individual presence in the group T before he/she passes to the group C does not exceed some constant $\omega > 0$, and density of distribution F is f:

$$F(a) = \int_0^a f(s)\,ds, \quad a \in [0;\infty).$$

Frequency curve $f(s)$ is assumed as nonnegative, continuous on $[0,\infty)$ function, such that $f(s) = 0$ at $s \geq \omega$ and $\int_0^\infty f(s)\,ds = 1$. Note that in (77) and in the following formulas (80), (89) $dF(a)$ means $f(a)da$.

In the formula (78) an expression $\eta\, C(t-a)$ sets rates, at which individuals pass from the

group C to the group T at $t-a$, and an expression $e^{-\lambda a}\,(1-F(a))$ is a share of individuals that passed to the group T at the moment $t-a$ and did not leave it for the interval $(t-a;t)$. In the formula (77) the integral term describes rate, at which individuals from the group T pass to the group C because of the disease exacerbation. In the presented version of the model, the group T and equation (78) are subsidiary.

Note that the structure of the model (75)–(79), equations, for example, the term

$$\int_0^{\omega} e^{-\lambda a}\,\eta\,C(t-a)dF(a),$$

contained in (77), and integral relation (78), are the new elements of the tuberculosis spread model developing the approach described in [22, 23].

6.3. Results of the first and second models analysis

We shall consider each of two models as a Cauchy problem for a system of delay differential equations. Applying the results of [21], we can prove the existence, uniquiness and nonnegativity of the solution on $[0;\infty)$.

Each of the equation systems (71)–(73) and (75)–(77) has a trivial equilibrium

$$X^* = (S^*, I^*, C^*) = \big(\rho/\lambda, 0, 0\big).$$

We shall denote

$$J_g = \int_0^{\tau} g(a)da, \quad J_{\lambda,F} = \int_0^{\omega} e^{-\lambda a}dF(a), \tag{80}$$

$$R_{0,1} = \frac{(\lambda p+\gamma)\beta S^* + \gamma\eta + \gamma\rho J_g}{(\lambda+\gamma)(\eta+\mu)}, \tag{81}$$

$$R_{0,2} = \frac{(\lambda p+\gamma)\beta S^* + (\lambda+\gamma)\eta J_{\lambda,F} + \gamma\rho J_g}{(\lambda+\gamma)(\eta+\mu)}. \tag{82}$$

We shall examine stability conditions for a trivial equilibrium X^* with the linearization method. Let us use a known relation $1-\exp(-y)\sim y$, $y\to 0$, making it possible to transform expressions

$$\exp\Big(-\int_0^{\tau} g(a)C(t-\tau+a)da\Big), \quad 1-\exp\Big(-\int_0^{\tau} g(a)C(t-\tau+a)da\Big),$$

contained in the equations of the models under examination.

The variables of each linearized system are designated the same as the initial ones. Totality of terms rejected at linearization satisfies the necessary condition of smallness [7, 8].

For the first model, we get the following equation system of linear approximation:

$$\frac{dS(t)}{dt} = -\lambda S(t) - \beta S^* C(t) - \rho\int_0^{\tau} g(a)C(t-\tau+a)da, \tag{83}$$

$$\frac{dI(t)}{dt} = -(\lambda+\gamma)I(t) + ((1-p)\beta S^* + \eta)C(t) + \rho\int_0^{\tau} g(a)C(t-\tau+a)da, \tag{84}$$

$$\frac{dC(t)}{dt} = -(\eta+\mu)C(t) + \gamma I(t) + p\beta S^* C(t). \tag{85}$$

From (83)–(85) it is clear that the variable $S(t)$ is not a member of the equations for the variables $I(t)$ and $C(t)$. Besides, the constant $\lambda > 0$. Therefore ((refer to section 5.1 and system (43)–(46)), is sufficient to consider the problem of a trivial equilibrium stability for the equation

system (84), (85). According to its form, the system (84), (85) corresponds to the differential system (1) with nonnegative matrices A_k and matrix $B = \mathrm{diag}(\lambda + \gamma, \eta + \mu)$. Let us introduce the matrix

$$G = B - A_\Sigma = \begin{pmatrix} \lambda + \gamma & -((1-p)\beta S^* + \eta) - \rho J_g \\ -\gamma & \eta + \mu - p\beta S^* \end{pmatrix}, \tag{86}$$

where the constant J_g is set by the formula (80). Applying theorem 3, we get the following result: 1) if $R_{0,1} < 1$, the equilibrium X^* of the system (71)–(73) is asymptotically stable; 2) if $R_{0,1} > 1$, the equilibrium X^* of the system (71)–(73) is instable. A case $R_{0,1} = 1$ calls for a separate examination.

For the second model, we have an equation system of the linear approximation as follows:

$$\frac{dS(t)}{dt} = -\lambda S(t) - \beta S^* C(t) - \rho \int_0^\tau g(a) C(t - \tau + a) da, \tag{87}$$

$$\frac{dI(t)}{dt} = -(\lambda + \gamma) I(t) + (1-p)\beta S^* C(t) + \rho \int_0^\tau g(a) C(t - \tau + a) da, \tag{88}$$

$$\frac{dC(t)}{dt} = -(\eta + \mu) C(t) + \gamma I(t) + p\beta S^* C(t) + \int_0^\omega e^{-\lambda a}\, \eta\, C(t-a) dF(a). \tag{89}$$

Using the previous reasoning about the first model, we can ignore the equation (87). Basing (88), (89), we must substitute the matrix (86) with the matrix

$$G = B - A_\Sigma = \begin{pmatrix} \lambda + \gamma & -(1-p)\beta S^* - \rho J_g \\ -\gamma & \eta + \mu - p\beta S^* - \eta J_{\lambda,F} \end{pmatrix}, \tag{90}$$

where the constant $J_{\lambda,F}$ is set by the formula (80). Applying theorem 3 and using matrix (90), we come to the conclusion: 1) if $R_{0,2} < 1$, the equilibrium X^* of the system (75)–(77) is asymptotically stable; 2) if $R_{0,2} > 1$, the equilibrium X^* of the system (75)–(77) is instable. A case $R_{0,2} = 1$ calls for a separate examination.

Within the frames of the models under examination, the result can be interpreted as follows. Inequality $R_{0,1} < 1$ (respectively $R_{0,2} < 1$) defines the conditions, at which tuberculosis could be eliminated from an isolated region. But if $R_{0,1} > 1$ (respectively $R_{0,2} > 1$), the mentioned elimination is impossible.

7. High-dimensional model for dynamics of the HIV infection dissemination in the population of a certain region

The section explores a high-dimensional model for dynamics of the HIV infection spread in the population of a certain region. High dimensionality of the model is conditioned by the description of a population structure by means of various groups presenting socio-economic, demographic and other aspects of life of individuals. The model is based on the studies [24, 25] and their generalization in case of high dimensionality [26].

7.1. Equations of the model

Following [26], we shall consider some region, presenting its adult population in form of groups of individuals

$$S_1, \ldots, S_n, \quad I_1, \ldots, I_n.$$

The groups $S_1, \ldots, S_n$ include individuals susceptible to HIV infection, the groups $I_1, \ldots, I_n$ include HIV-infected individuals, the index $1 \le j \le n$ means level of social adaptation (desaptation) of the individuals from the groups S_j and I_j.

Let $x_i(t)$, $y_j(t)$ mean counts of individuals in the groups S_i and I_j at a moment t, $1 \le i, j \le$

n. We shall write the equation system of the model in the following form:

$$\frac{dx_i(t)}{dt} = \sum_{k=1,k\neq i}^{n} \gamma_{ki}x_k(t) - \sum_{k=1}^{n}\gamma_{ik}x_i(t) - \sum_{j=1}^{n}\beta_{ij}y_j(t)x_i(t) + f_{S_i}(t), \tag{91}$$

$$\frac{dy_i(t)}{dt} = \sum_{k=1,k\neq i}^{n} \alpha_{ki}y_k(t) - \sum_{k=1}^{n}\alpha_{ik}y_i(t) + \sum_{j=1}^{n}\beta_{ij}y_j(t)x_i(t) + f_{I_i}(t), \quad t \in [0;\infty), \tag{92}$$

$$x_i(0) = x_i^{(0)} \geq 0, \quad y_i(0) = y_i^{(0)} \geq 0, \quad 1 \leq i \leq n. \tag{93}$$

Here the functions $f_{S_j}(t)$ and $f_{I_j}(t)$ set rates of inflows of individuals into the groups S_j and I_j, respectively, due to demographic processes (oncoming generation of a region, migration of individuals from other regions) with accounts for society stratification into various social groups, including risk groups (heavy drinkers, drug addicts, etc.). Assume that the functions $f_{S_j}(t)$ and $f_{I_j}(t)$ are nonnegative, continuous and limited on $[0;\infty)$. The parameters $\gamma_{jk} \geq 0$, $k \neq j$ are intensities of transitions of the group S_j members to the group S_k, and parameters $\gamma_{jj} > 0$ set intensity of natural mortality and emigration for the group S_j members. The parameters $\alpha_{jk} \geq 0$ have the similar sense (for the individuals from the groups I_j, and I_k), at that, $\alpha_{jj} > 0$ includes intensities of deaths caused by the HIV infection for the group I_j members. The parameters $\beta_{ij} \geq 0$ mean contact intensities of the groups S_i and I_j members leading to appearance of new HIV-infected individuals. We assume that for each $1 \leq i \leq n$, $\beta_{i1} + \cdots + \beta_{in} > 0$ is true.

Let us introduce the following designations:

$$x(t) = (x_1(t), \ldots, x_n(t))^T, \quad y(t) = (y_1(t), \ldots, y_n(t))^T,$$

$$f_S(t) = (f_{S_1}(t), \ldots, f_{S_n}(t))^T, \quad f_I(t) = (f_{I_1}(t), \ldots, f_{I_n}(t))^T,$$

$$A = (a_{ij}), \quad a_{ii} = -\sum_{k=1}^{n}\gamma_{ik} < 0, \quad a_{ik} = \gamma_{ki} \geq 0, \quad 1 \leq i,\, k \leq n, \;\; k \neq i,$$

$$L = (\ell_{ij}), \quad \ell_{ii} = -\sum_{k=1}^{n}\alpha_{ik} < 0, \quad \ell_{ik} = \alpha_{ki} \geq 0, \quad 1 \leq i,\, k \leq n, \;\; k \neq i,$$

$$C = (\beta_{ij}), \quad D(x(t)) = \mathrm{diag}(x_1(t), \ldots, x_n(t)).$$

Then the model (91)–(93) can be written in the vector form

$$\frac{dx(t)}{dt} = Ax(t) - D(x(t))Cy(t) + f_S(t), \tag{94}$$

$$\frac{dy(t)}{dt} = Ly(t) + D(x(t))Cy(t) + f_I(t), \quad t \in [0;\infty), \tag{95}$$

$$x(0) = x^{(0)}, \quad y(0) = y^{(0)}. \tag{96}$$

The matrices A and L contained in (94), (95) are quasinonnegative. The inequalities

$$(-A)^T(1, \ldots, 1)^T > 0, \quad (-L)^T(1, \ldots, 1)^T > 0.$$

are realized; this can easily be noted. From here it follows that A and L have nonnegative real parts.

Using standard methods, we may show that the Cauchy problem (94)–(96) has a unique, nonnegative, limited from above solution defined on the interval $[0;\infty)$.

Let $f_{I_j}(t) \equiv 0$ and $y_j^{(0)} = 0$, $1 \leq j \leq n$. Then the problem (94)–(96) admits a solution, in

which $y(t) \equiv 0$, and $x(t)$ is sought as a solution of a subsidiary Cauchy problem

$$x(0) = x^{(0)}, \quad \frac{dx(t)}{dt} = Ax(t) + f_S(t), \quad t \in [0; \infty). \tag{97}$$

The problem (97) has a unique solution

$$x(t) = e^{At}x^{(0)} + \int_0^t e^{A(t-a)} f_S(a)da, \quad t \in [0; \infty). \tag{98}$$

From the results of section 3 it follows that the solution $x(t)$, set by the formula (98), is nonnegative for all $t \geq 0$.

Solution of the problem (94)–(96) of the form $x(t) \geq 0$, $y(t) \equiv 0$ can be interpreted as the absence of the HIV-infection in the region under consideration.

7.2. Special case of the model and its equilibrium

Let us pass to a special case, in which

$$f_S(t) \equiv f^* = (f_1^*, \ldots, f_n^*)^T = \text{const} \neq 0, \quad f_I(t) \equiv 0, \quad t \in [0; \infty).$$

Therefore, equations of the model are written in form

$$\frac{dx(t)}{dt} = Ax(t) - D(x(t))Cy(t) + f^*, \tag{99}$$

$$\frac{dy(t)}{dt} = Ly(t) + D(x(t))Cy(t), \quad t \in [0; \infty), \tag{100}$$

and supplemented with the initial data (96). Differential system (99), (100) can have solutions in form of

$$x(t) \equiv x = \text{const} \geq 0, \quad y(t) \equiv y = \text{const} \geq 0,$$

presenting nonnegative equilibria of the system. The mentioned equilibria can be found from the equations system

$$0 = Ax - D(x)Cy + f^*, \tag{101}$$

$$0 = Ly + D(x)Cy, \quad x \geq 0, \;\; y \geq 0. \tag{102}$$

The system (101)–(102) has a solution

$$x^* = (-A)^{-1} f^* \geq 0, \quad y^* = 0. \tag{103}$$

Note that $x^* \neq 0$. Really, according to the condition $f^* \geq 0$, $f^* \neq 0$, $(-A)$ is a nonsingular M-matrix. All elements of the matrix $(-A)^{-1}$ are nonnegative, each its line and each its column are non-zero.

We shall call equilibrium (103) the trivial equilibrium of the system (99), (100).

For the further analysis we shall introduce the matrices

$$Q^* = D(x^*)C, \quad H^* = -(L + Q^*). \tag{104}$$

It is easy to note that Q^* is a nonnegative matrix, while off-diagonal elements of the matrix H^* are nonpositive.

Appealing to the structure of the system (101), (102), we can prove the following important

result [26].

Statement A. *If H^*, set by the formula* (104)*, is a nonsingular M-matrix,* (103) *is the unique solution for the system* (101)*,* (102)*.*

7.3. Asymptotic stability of the trivial equilibrium.

Let us examine asymptotic stability of the equilibrium (103). We shall apply the linearization method and examine stability of linear differential system for variables in the deviations

$$\varphi(t) = x(t) - x^*, \quad \eta(t) = y(t) - y^*.$$

Let us substitute $x(t) = \varphi(t) + x^*$, $y(t) = \eta(t) + y^*$ into the system (99), (100) and reject its nonlinear terms $\pm \sum_{j=1}^{n} \beta_{ij}\varphi_i(t)\eta_j(t)$. We come to the system

$$\frac{d\varphi(t)}{dt} = A\varphi(t) - Q^*\eta(t), \tag{105}$$

$$\frac{d\eta(t)}{dt} = -H^*\eta(t), \tag{106}$$

where matrices Q^* and H^* are set with the formulas (104). Passing to the investigation of stability of the nontrivial solution of the system (105), (106), we can see that the system matrix has a block form, because $\varphi(t)$ is not a member of the equation group for $\eta(t)$. It is shown above that all eigenvalues λ_A of the matrix A satisfies the condition $\mathrm{Re}(\lambda_A) < 0$, that is, A is a stable (Hurwitz) matrix. For the matrix $(-H^*)$ the condition $\mathrm{Re}(\lambda_{(-H^*)}) < 0$ can be realized Iff H^* is a nonsingular M-matrix. Note that in the consequence of the section 3 results, asymptotical stability of the trivial solution of the differential system (106) will be followed by the asymptotical stability of the trivial solution of the differential system (105), (106). Besides, it is clear that instability of the trivial solution of the differential system (106) will be followed with instability of the trivial solution of the differential system (105), (106). Finally, we come to the following result.

Statement B. *If H^*, set by the formula* (104)*, is a nonsingular M matrix, the trivial equilibrium* (103) *of the system* (99)*,* (100) *is asymptotically stable. If H^* is not a nonsingular M-matrix and, in addition,* $\det H^* \neq 0$*, trivial equilibrium* (103) *of the system* (99)*,* (100) *is unstable.*

The results of the statements A and B can be interpreted as one of the sufficient conditions for HIV-infection elimination in a case when no HIV-infected individuals from other regions resupply the groups. The vector x^* can be considered as a regulated variable presenting sizes of the groups $S_1, \ldots, S_n$ of the HIV-susceptible individuals. Since $(-L)$ is a nonsingular M-matrix, a certain smallness of the matrix $Q^* = D(x^*)C$ can lead to the fact that H^* is a nonsingular M-matrix. Among other factors, there exists $\xi \in \mathbb{R}^n$, $\xi > 0$, such that $(-L)\xi > 0$. From here it follows that the inequality

$$H^*\xi = -(L + Q^*)\xi = (-L)\xi - Q^*\xi > 0$$

is true, if all elements of the matrix Q^* are close to zero. Therefore, any measures decreasing sizes of some groups from $S_1, \ldots, S_n$ (decrease in individual components of the vector x^*) can facilitate elimination of HIV-infection in a separate region. A list of these groups depends on ratio of matrices $(-L)$ and Q^*.

8. Dynamics model for a population developing in the conditions of harmful substances affecting reproduction of individuals

The section presents a mathematical model for dynamics of the population affected by harmful substances that an individual's body obtains from the environment with food. To describe a population dynamics, we use a model of the "resource-consumer" type accounting for the processes of reproduction, self-limiting, migration and natural mortality of individuals, along with effects of harmful substances consumption. It is supposed that the individuals can be affected by any consumables or products of the consumable interactions in various combinations.

8.1. Equations of the model

Following [27, 28], we shall consider a population of individuals, which dynamics is defined by the following factors:

- individuals die due to ageing and self-limiting,
- individuals are prone to migrations,
- no exogenous inflows of individuals,
- inflows of harmful substances $X_1, \ldots, X_k$, into individuals' environment, where the substances are metabolized, accumulated in food resources and consumed by individuals,
- no individuals competition for food resources containing substances $X_1, \ldots, X_k$,
- various combinations of consumed substances $X_1, \ldots, X_k$ can interact between each other,
- some of the substances $X_1, \ldots, X_k$ or products of their interaction adversely affect reproduction rate of the individuals.

Let us introduce the following designations: $x_i = x_i(t)$ is amount of harmful substances X_i, $y = y(t)$ is a population size at a moment t. The function $d(y(t))$ means intensity of individuals migration and death due to natural ageing and self-limiting. Intensity of individuals reproduction discounting impacts of harmful substances will be described with the function $b(y(t))$. The function $\beta(u(t))$ is assumed to present impacts of harmful substances on the reproductive potential of the individuals. Harmful substances level is set with the function $u(t) = \varphi(x_1(t), \ldots, x_k(t))$, accounting for some or all harmful substances and products of their interaction. We assume that in the conditions of the harmful substances impact, intensity of the population size growth is described with an expression $\beta(u(t))\, b(y(t))$. The constants $r_i > 0$ and $\delta_i > 0$ set rates of a harmful substance X_i inflow and degradation, respectively. The function $\theta_i(x_i)$ describes rate, at which an individual consumes the substance X_i with the food and accounts for the saturation effect.

The model equations have the following form:

$$\frac{dx_i(t)}{dt} = r_i - \theta_i(x_i(t))\, y(t) - \delta_i\, x_i(t), \quad 1 \le i \le k, \tag{107}$$

$$\frac{dy(t)}{dt} = \beta(\varphi(x_1(t), \ldots, x_k(t)))\, b(y(t))\, y(t) - d(y(t))\, y(t), \quad t \in [0; \infty), \tag{108}$$

$$x_i(0) = x_i^{(0)} \ge 0, \quad 1 \le i \le k, \quad y(0) = y^{(0)} \ge 0. \tag{109}$$

The functions $b(y)$, $d(y)$ are assumed to have the following properties: $b(y)$ and $d(y)$ are continuous on the interval $[-a;\infty)$, where $a > 0$ is some constant; $b(y) \in [0;\bar{b}]$ for all $y \in [0,\infty)$, where $\bar{b} > 0$ is some constant; $d(y)$ is positive on the interval $[0;\infty)$, and increasing, and $d(y) \to +\infty$ at $y \to +\infty$. The function $\beta(u)$ is continuous on the interval $[-p;\infty)$, where $p > 0$ is some constant, positive, decreases on the interval $[0;\infty)$, $\beta(0) = 1$, $\beta(u) \to 0$ at $u \to +\infty$. Each function $\theta_i(x_i)$, $1 \le i \le k$, is continuous on the interval $[-q;\infty)$, where $q > 0$ is some constant, increases on the interval $[0;\infty)$, $\theta_i(0) = 0$, and $\theta_i(x_i) \to \bar{\theta}_i \in (0;\infty)$ at $x_i \to +\infty$. The function $\varphi(x_1,\dots,x_k)$ is continuous on $[-q;\infty)^k$, does not decrease on $[0;\infty)^k$ with respect to each argument, $\varphi(0,\dots,0) = 0$, $\varphi(x_1,\dots,x_k) > 0$ at $(0;\infty)^k$.

Note that the constant $\bar{b} > 0$ corresponds to the physiological limit of reproduction, that is, to the maximal number of descendants per an individual. Hypotheses about the function $\beta(u)$ tell that a reproductive potential of an individual decreases under impacts of harmful substances. The properties of the function $\varphi(x_1,\dots,x_k)$ present impacts of one or another harmful substance, individually or combined with other substances, on individuals of the population. Besides, without a loss of generality we shall exclude from the consideration the simplest case, when $b(y) \le d(y)$ for all $y \in [0;\infty)$.

In addition to the above mentioned hypotheses, we shall assume that the functions $b(y)$, $d(y)$, $\beta(u)$, $\theta_1(x_1)$, ..., $\theta_k(x_k)$ have continuous derivatives, and the function $\varphi(x_1,\dots,x_k)$ has continuous partial derivatives with respect to all arguments in their definition domains.

In [28] it is shown that the problem (107)–(109) has a unique solution $(x_1(t),\dots,x_k(t),y(t))$, defined on the interval $[0;\infty)$, and each component of the solution is a nonnegative and limited from above function.

8.2. Existence of equilibria

Let us obtain the conditions for the existence of the system (107)–(108) nonnegative equilibria. Any equilibrium of the system (107)–(108) is a solution of the system

$$0 = r_i - \theta_i(x_i)\,y - \delta_i\,x_i, \quad 1 \le i \le k, \tag{110}$$

$$0 = \big(\beta(\varphi(x_1,\dots,x_k))\,b(y) - d(y)\big)y. \tag{111}$$

At $y = 0$ the system (110)–(111) has a unique solution $U_0 = (x_1^*,\dots,x_k^*,0)$, where $x_i^* = r_i/\delta_i > 0$, $1 \le i \le k$.

Suppose next that the system (110)–(111) has a solution

$$U_1 = (\bar{x}_1,\dots,\bar{x}_k,\bar{y})$$

such that $\bar{y} > 0$. We shall define the constant $K_y > 0$ as an equation root

$$\bar{b} - d(y) = 0, \quad y \in [0;\infty).$$

Then from the equation (111) and inequality $\beta(u) \le 1$ it follows that $0 < \bar{y} \le K_y$.

Let us fix $1 \le i \le k$ and rewrite (110) in the form:

$$r_i - \delta_i\,x_i = \theta_i(x_i)\,y. \tag{112}$$

One can see that for each set $y \in [0;\infty)$ the equation (112) has exactly one root $\bar{x}_i = \bar{x}_i(y)$, at that, $0 < \bar{x}_i(y) \le x_i^*$. It is easy to note that $\bar{x}_i(y)$ is a decreasing, continuous and differentiable function. Using (112), we find that

$$\bar{x}_i'(y) = \frac{-\theta_i(\bar{x}_i(y))}{\theta_i'(\bar{x}_i(y))\,y + \delta_i}.$$

Let us define the function

$$h(y) = \varphi(\bar{x}_1(y), \ldots, \bar{x}_k(y)), \quad y \in [0; \infty), \tag{113}$$

that is positive, non-increasing and continuous $[0; \infty)$. The function's derivative is:

$$h'(y) = -\sum_{i=1}^{k} \varphi'_{x_i}(\bar{x}_1(y), \ldots, \bar{x}_k(y)) \frac{\theta_i(\bar{x}_i(y))}{\theta'_i(\bar{x}_i(y))\, y + \delta_i}. \tag{114}$$

Substituting (113) into (111), we come to the equation for the component $\bar{y}$ of the solution U_1:

$$\beta(h(y))\, b(y) = d(y), \quad 0 < y \le K_y. \tag{115}$$

Note that $\beta(h(y))$ is a function non-decreasing on $[0; \infty)$ and, besides, $\beta(h(0)) > 0$. The positive roots of the equation (115) make it possible to find all solutions of the system (110), (111) of the form U_1, that together with the solution U_0 set all nonnegative equilibria of the system (107), (108).

8.3. Stability of equilibria

Let us investigate stability of the system (107), (108) nonnegative equilibria using a linearization method. Possibility for application of the method is conditioned by the existence of continuous partial derivatives of the differential system (107), (108)) right hands in the neighborhood of all equilibria.

We shall study stability of the trivial solution of the differential system of the order $m = k+1$

$$\frac{dz(t)}{dt} = Cz(t), \tag{116}$$

where $z : \mathbb{R} \mapsto \mathbb{R}^m$, $C - m \times m$ is a matrix of linear approximation in the neighborhood of the set equilibrium. A trivial solution $z = 0$ of the system (116) is asymptotically stable, if a matrix C is stable: $\mathrm{Re}(\lambda_C) < 0$ for all eigenvalues λ_C of the matrix C. If among the numbers λ_C we find one or more with $\mathrm{Re}(\lambda_C) > 0$, solution $z = 0$ is unstable.

Let us consider an equilibrium U_0. The matrix C has a form

$$C = C_0 = \begin{pmatrix} -\delta_1 & 0 & 0 & \ldots & 0 & -\theta_1(x_1^*) \\ 0 & -\delta_2 & 0 & \ldots & 0 & -\theta_2(x_2^*) \\ 0 & 0 & -\delta_3 & \ldots & 0 & -\theta_3(x_3^*) \\ \ldots & \ldots & \ldots & \ldots & \ldots & \ldots \\ 0 & 0 & 0 & \ldots & -\delta_k & -\theta_k(x_k^*) \\ 0 & 0 & 0 & \ldots & 0 & \delta_m \end{pmatrix},$$

where $\delta_m = \beta(h(0))\, b(0) - d(0)$. Eigenvalues C_0 are:

$$\lambda_i = -\delta_i < 0, \quad 1 \le i \le k, \quad \lambda_m = \delta_m.$$

From here it follows that U_0 is asymptotically stable, if

$$\beta(h(0))\, b(0) - d(0) < 0, \tag{117}$$

and unstable, if

$$\beta(h(0))\, b(0) - d(0) > 0. \tag{118}$$

A case $\beta(h(0))\, b(0) - d(0) = 0$ calls for more detailed examination.

Let us turn to the equilibrium U_1, for which $\bar{y} > 0$. In such a case

$$C = C_1 = \begin{pmatrix} c_{11} & 0 & 0 & \dots & 0 & c_{1m} \\ 0 & c_{22} & 0 & \dots & 0 & c_{2m} \\ 0 & 0 & c_{33} & \dots & 0 & c_{3m} \\ \dots & \dots & \dots & \dots & \dots & \dots \\ 0 & 0 & 0 & \dots & c_{kk} & c_{km} \\ c_{m1} & c_{m2} & c_{m3} & \dots & c_{mk} & c_{mm} \end{pmatrix},$$

$$c_{ii} = -\theta_i'(\bar{x}_i)\,\bar{y} - \delta_i < 0, \quad c_{im} = -\theta_i(\bar{x}_i) < 0, \quad \bar{x}_i = \bar{x}_i(\bar{y}), \quad 1 \le i \le k,$$

$$c_{mj} = \beta'(\varphi(\bar{x}_1, \dots, \bar{x}_k))\,\varphi'_{x_j}(\bar{x}_1, \dots, \bar{x}_k)\,b(\bar{y})\,\bar{y} \le 0, \quad 1 \le j \le k,$$

$$c_{mm} = \big(\beta(\varphi(\bar{x}_1, \dots, \bar{x}_k))\,b'(\bar{y}) - d'(\bar{y})\big)\,\bar{y}.$$

Eigenvalues of the matrix C_1 can be found from the characteristic equation

$$\det(C_1 - \lambda E) = (-1)^m \lambda^m + p_1\lambda^{m-1} + p_2\lambda^{m-2} + \dots + p_m = 0, \tag{119}$$

where E is an identity matrix. The coefficients $p_1, \dots, p_m$ of the equation (119) can be calculated by standard formulas, for example, $p_m = \det(C_1)$.

Assume

$$f(y) = \beta(h(y))\,b(y), \quad y \in [0; \infty). \tag{120}$$

Derivative $f(y)$ with the account of (114) is:

$$f'(y) = \beta'(h(y))\,h'(y)\,b(y) + \beta(h(y))\,b'(y) =$$
$$= -\beta'(h(y))\,b(y)\sum_{i=1}^{k}\varphi'_{x_i}(\bar{x}_1(y), \dots, \bar{x}_k(y))\frac{\theta_i(\bar{x}_i(y))}{\theta_i'(\bar{x}_i(y))\,y + \delta_i} + \beta(h(y))\,b'(y). \tag{121}$$

Applying (121),we rewrite the element c_{mm} of the matrix C_1 as follows:

$$c_{mm} = (\beta(h(\bar{y}))\,b'(\bar{y}) - d'(\bar{y}))\,\bar{y} = -(d'(\bar{y}) - f'(\bar{y}) + \beta'(h(\bar{y}))\,h'(\bar{y})\,b(\bar{y}))\,\bar{y}. \tag{122}$$

Now we show that for the system

$$\frac{dz(t)}{dt} = C_1 z(t) \tag{123}$$

asymptotic stability (unstability) of the solution $z = 0$ is related to the realization of an appropriate inequality

$$d'(\bar{y}) - f'(\bar{y}) > 0, \tag{124}$$

$$d'(\bar{y}) - f'(\bar{y}) < 0. \tag{125}$$

Let us use several criteria, application of which is conditioned by the structural properties of the matrix C_1 (signs and locations of its non-zero elements).

Stage 1. From the Routh-Hurwitz criterion [12] it follows that for the asymptotical stability of the system (123) zero solution it is necessary that all coefficients of the equation (119) have the same sign. After the elementary transformations (from the last line C_1 we subtract serially the first, second and other lines multiplied by the appropriate coefficients), we find that

$$\det(C_1) = \prod_{i=1}^{k} c_{ii}\big(c_{mm} - \sum_{j=1}^{k} c_{mj}\, c_{jm}/c_{jj}\big) =$$

$$= (-1)^{\,k}\, \bar{y} \prod_{i=1}^{k} \big(\theta_i'(\bar{x}_i)\, \bar{y} + \delta_i\big)\, \big(\beta(h(\bar{y}))\, b'(\bar{y}) - d'(\bar{y}) + b(\bar{y})\, \beta'(h(\bar{y}))\, h'(\bar{y})\big) =$$

$$= (-1)^m\, \bar{y} \prod_{i=1}^{k} \big(\theta_i'(\bar{x}_i)\, \bar{y} + \delta_i\big)\, \big(d'(\bar{y}) - f'(\bar{y})\big). \quad (126)$$

Therefore, if the inequality (125) is realized, the equilibrium U_1 is instable, while the inequality (124) provides, at least, a necessary sign for the coefficient p_m, a member of the equation (119).

Stage 2. Let inequation (124) be true. From (122) it follows that $c_{mm} < 0$, because $\beta'(h(\bar{y})) < 0$, $h'(\bar{y}) \le 0$. We shall write (123) in the form

$$\frac{dz(t)}{dt} = A_0 z(t) - Bz(t), \quad (127)$$

where $B = \mathrm{diag}(-c_{11}, \ldots, -c_{mm})$, $A_0 = C_1 + B$. The system (127) is the system (1) at $n = 0$ and $A_1(\theta) \equiv 0$. According to the theorem 4, if $B - A_0^+$ is a nonsingular M-matrix, a zero solution of the system (127) is asymptotically stable.

Let us calculate the main minors of the matrix $B - A_0^+$:

$$M_1 = (-c_{11}) > 0, \quad M_2 = (-c_{11})(-c_{22}) > 0, \quad \ldots, \quad M_k = (-c_{11}) \ldots (-c_{kk}) > 0,$$

$$M_m = \det(B - A_0^+) = (-1)^m \det(A_0^+ - B) = (-1)^m \det(C_1) =$$

$$= \bar{y} \prod_{i=1}^{k} \big(\theta_i'(\bar{x}_i)\, \bar{y} + \delta_i\big)\, \big(d'(\bar{y}) - f'(\bar{y})\big).$$

Equality of the determinants $\det(A_0^+ - B) = \det(C_1)$ follows from the formula (126) and equalities

$$c_{mj}\, c_{jm} = |c_{mj}|\, |c_{jm}|, \quad 1 \le j \le k.$$

If the (124) is realized, a minor M_m is positive. In this case, under theorem 2 the matrix $B - A_0^+$ is a nonsingular M-matrix. Therefore, the inequality (124) is not only necessary, but also sufficient condition of the asymptotical stability for a zero solution of the system (127).

Note, in addition, that a case $d'(\bar{y}) - f'(\bar{y}) = 0$ calls for a special consideration.

Study of the system (107), (108) equilibria stability shows that a qualitative analysis of the high-dimensional model (107)–(109) solutions can be traced to the solution of the models in form

$$\frac{dy(t)}{dt} = \big(f(y(t)) - d(y(t))\big) y(t), \quad t \in [0; \infty), \quad (128)$$

$$y(0) = y^{(0)} \ge 0, \quad (129)$$

where the function $f(y)$ is defined by the formula (120). The equation (128) with the account for the introduced designation, has the same form as the equation (108). They differ in a factor $\beta(h(y(t)))$ at $b(y(t))$. The factor accounts for impacts of harmfulous substances on the reproduction process of the individuals.

One can see that the nonnegative equilibria of the equation (128) and conditions of their asymptotical stability (instability) are equivalent to the nonnegative equilibria and the respective conditions of the system (107), (108).

For the equation (128) existence of equilibria and their asymptotical stability (instability) can easily be tested by the analysis of the equation

$$f(y) - d(y) = 0, \quad y \in [0; \infty),$$

roots and relative position of the functions $f(y)$, $d(y)$ graphs in the neighborhood of these roots.

Finally we get that behavior of the solution $y(t)$ for the model (128), (129) in a small neighborhood of the equilibrium y_s closely presents behavior of the component $y(t)$ of the model (107)–(109) solution, if only initial data in this model belong to the small neighborhood of the equilibrium $U = (\bar{x}_1(y_s), \ldots, \bar{x}_k(y_s), y_s)$.

Note that the mentioned behavior of the model (107)–(109) solution could be obtained under the familiar theorem on «fast» and «slow» variables [29]. However the model (107)–(109) structure is such that it can be investigated, using the model (128), (129), without separation of the variables $x_1(t), \ldots, x_k(t), y(t)$ into «fast» and «slow». Only deviations of the initial data from the equilibrium play a role here.

CONCLUSION

Results presented in the article show that M-matrices can be effectively applied in analyses of the solutions for the mathematical models of living systems with certain structural properties. At the same time, application of the M-matrices provides a possibility to study only some properties of solutions for this model family. Models of living systems are rather variable. So, we should apply familiar but rather complex mathematical methods to solve some routine problems. The problems include: 1) analysis of equilibria stability for differential equations with several or distributed delays; 2) search for conditions of existence for oscillation solutions of high-dimensional differential systems; 3) finding of lower and upper bounds for solutions of differential equations; 4) study of the functional sensitivities from model solutions to variations of their parameters; 5) numerical study of solutions for differential equations, including the delay equations. Examples of successful solutions of the listed problems are given in the articles [23, 30, 31, 32, 33, 34, 35].

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