Mathematical Biology and Bioinformatics
2023. V. 18. № 2. P. 543–567. doi: 10.17537/2023.18.543

==========**MATHEMATICAL MODELING** ==========

Stochastic Modeling in Immunology Based On a Stage-Dependent Framework with Non-Markov Constraints for Individual Cell and Pathogen Dynamics

Pertsev N.V.*, Loginov K.K.†

Sobolev Institute of Mathematics, Siberian Branch of the Russian Academy of Sciences, Novosibirsk, Russia
Marchuk Institute of Numerical Mathematics, Russian Academy of Sciences, Moscow, Russia

Abstract. We present a systematic approach to modelling the responses of the immune system to virus infections. Two continuous-discrete stochastic models arising in mathematical immunology are developed and computationally implemented. The variables of the models are integer random variables that denote the quantity of individuals (cells and viral particles), and sets of unique types of individuals that take into account the current state and history of stay of individuals in some stages of their development. The distribution laws of the durations of the mentioned stages are different from exponential or geometric. A probabilistic description of a one-stage stochastic model of population dynamics is presented. A stochastic model of the development of HIV-1 infection in the lymph node in the initial period after infection of a healthy person is formulated. A computational algorithm based on the Monte Carlo method is given. Each of the stochastic models is complemented by a deterministic analogue in the form of integral and delay differential equations. The results of numerical simulation are presented.

Key words: *stage-dependent model, non-Markov constraints for individuals, Monte Carlo method, computational experiment, immunology, HIV-1 infection.*

INTRODUCTION

One of the actively developing areas of mathematical modeling in immunology is associated with the use of deterministic and stochastic stage-dependent models. Deterministic stage-dependent models in immunology are usually based on delay differential equations (see, for example, [1]–[8] and references to articles by other authors given in the listed papers).

The penetration of a small number of viral particles into the human body can lead to infection of several target cells, the appearance of new viral particles due to reproduction in target cells and activation of cell production of a specific immune response. Modeling the dynamics of the infectious process in the initial period requires the use of integer variables reflecting the current numbers of viral particles and cells. In addition, within the framework of the stochastic stage-dependent model, it is necessary to use additional variables that take into account the prehistory of the formation of several populations – viral particles, infected, productively infected and immunocompetent cells. The distribution of the residence time of viral particles and cells in populations may differ from exponential or geometric. Therefore, a stochastic model must take into account non-Markov constraints for individuals to describe

*homlab@ya.ru
†kloginov85@mail.ru

the dynamics of the studied populations. One of the approaches to constructing stochastic stage-dependent models of population dynamics with non-Markov constraints for individuals, including models in immunology, is proposed in [9]–[11] (see also related articles [12]–[17]).

The paper presents two stochastic stage-dependent models that arise in the problems of immunology. Each of the models contains non-Markov restrictions reflecting the duration of stay of individuals at one or another stage of their development. Section 2 presents a probabilistic formalization of a one-stage stochastic model of population dynamics. The one-stage model illustrates the use of an integer variable to describe the current population size and the use of an additional variable in the form of a family of unique types of individuals. The family of unique types of individuals reflects the successive moments of time when individuals enter the population, contains the duration of stay of individuals in the population, set by a random variable distributed over a finite period of time, and indicators of the transition of individuals to other populations. The numerical simulation algorithm based on the Monte Carlo method is given. The model can describe the initial period of the cell production process of a heterogeneous population, regulated by feedback. Section 3 describes a stochastic stage-dependent model of the development of HIV-1 infection in the lymph node during the first few days after infection of an individual. Sections 2, 3 are accompanied by the results of numerical simulation of the dynamics of the studied populations at finite time intervals. To plan computational experiments with models, their deterministic analogues in the form of integral and delay differential equations are used.

2. ONE-STAGE STOCHASTIC MODEL

2.1. Notation and postulates of the model

We will study the dynamics of some population A. We assume that the population A can be replenished with new individuals from some source S. Denote by D and B the populations into which individuals enter after the end of their stay in the population A. Population D may reflect the dead individuals, population B – the next stage of development of individuals in population A. An explicit description of the «fate» of individuals of populations D and B is not considered in the model below. The scheme of the model is shown in Figure 1.

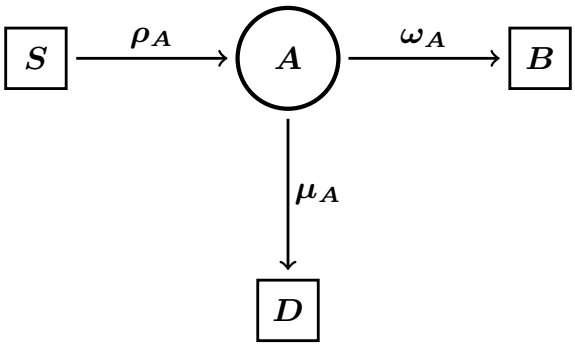

Fig. 1. Scheme of a one-stage model, symbols in the text.

Let t be a real variable denoting time, $[0; T_{mod}]$ is a simulation interval, $(t; t+h) \subset [0; T_{mod}]$ is an infinitesimal time interval, $h \to +0$. By $\rho_A(z)$ we will understand a function from an integer non-negative variable $z \in Z_+$ satisfying the condition: $0 < \rho_A(z) \leqslant \rho_A^*$ for all $z \in Z_+$, where $\rho_A^* > 0$ is some constant. Let the expressions $\xi_A \sim Exp(\mu_A)$, $\omega_A \sim F_{\omega_A}$ mean that the random variable ξ_A has an exponential distribution with the parameter $\mu_A > 0$, the random variable ω_A has a distribution function $F_{\omega_A}(u)$. We assume that ω_A is distributed over a finite interval $[0; \omega_A^*]$, $\omega_A^* > 0$, and $F_{\omega_A}(+0) = 0$.

Now we formulate the postulates of the model. Denote by $A(t)$ the population size of A at time t, $t \in [0; T_{mod}]$. For each fixed $t > 0$, $A(t)$ is a non-negative integer random variable. At the initial time $t = 0$, the population A either does not contain or contains a certain number of initially existing individuals, $A(0) = A_0 = const \geqslant 0$. Denote by $\mathcal{A}$ some or arbitrarily chosen individual of the population A. Let us fix t and assume that $A(t) = x$ is a non-negative integer constant. The postulates of the model are as follows.

H1. Regardless of the events preceding t, during the interval $(t; t + h)$ with probability $\rho_A(x)h + o(h)$ the population of A is replenished by one individual coming from S; the probability that more than one individual of A enters population from S is $o(h)$; the population A is not replenished from S for $(t; t + h)$ with probability $1 - \rho_A(x)h + o(h)$.

H2. Let the individual $\mathcal{A}$ appear in the population A at some point in time $t_{\mathcal{A}} \leqslant t$. Denote by $\xi_{\mathcal{A}} \sim Exp(\mu_A)$ the duration of time until the transition $\mathcal{A}$ to the population D. By $\omega_{\mathcal{A}} \sim F_{\omega_A}$ we denote the duration of time of stay $\mathcal{A}$ in the population A before the transition to the population B. Random variables $\xi_{\mathcal{A}}$, $\omega_{\mathcal{A}}$ are independent of each other, do not depend on $t_{\mathcal{A}}$ and do not depend on the behavior of other individuals in the population. The individual $\mathcal{A}$ leaves the population A at time $t_{\mathcal{A}} + \min\{\xi_{\mathcal{A}}, \omega_{\mathcal{A}}\}$.

2.2. The family of the unique types of individuals

To take into account for the population A the prehistory of its formation, in addition to the variable $A(t)$ we introduce for A a family of unique types $\Omega_A(t)$ of individuals, $t \in [0; T_{mod}]$. Let us assume that the variable $N_A(t)$ means a non-negative integer constant or a random variable that specifies the number of individuals who entered the population A over a period of time $(-\omega_A^*; t]$. If $t = 0$, then $N_A(0)$ takes into account initially existing individuals whose number is equal to A_0. If $t > 0$, then $N_A(t)$ reflects both the initially existing individuals of population A and the new individuals who entered this population during the time interval $(0; t]$.

Denote by $j = 1, 2, \ldots, N_A(t)$ the ordinal number of the next individual $\mathcal{A}$ entering the population A, and by $\mathcal{A}(j)$ – an individual $\mathcal{A}$ with the number j. Let us assume that the set

$$-\omega_A^* < t_{\mathcal{A}(1)}, t_{\mathcal{A}(2)}, \ldots, t_{\mathcal{A}(j)}, \ldots, t_{\mathcal{A}(N_A(t))} \leqslant t \tag{2.1}$$

means the moments when individuals enter the population A up to the moment of time t (inclusive), taking into account the initially existing individuals of this population. For $t = 0$, the elements of the set (2.1) are considered as initial data, reflecting the initially existing individuals of the population, and are constants satisfying the relations

$$-\omega_A^* < t_{\mathcal{A}(1)} < t_{\mathcal{A}(2)} < \cdots < t_{\mathcal{A}(j)} < \cdots < t_{\mathcal{A}(N_A(0))} \leqslant 0. \tag{2.2}$$

For $t = T_{mod}$, the elements of the set (2.1) take into account the initially existing individuals of the population A and the individuals who entered to the population A over the period $(0; T_{mod}]$.

Based on postulate **H1**, using the inequality $0 < \rho_A(z) \leqslant \rho_A^*$, $z \in Z_+$, and the results of [9] (Lemma 4.1, Theorem 5.1), we arrive at the following statements:

1) the unlimited growth of the population size $A(t)$ on the interval $[0; T_{mod}]$ is impossible, and for the time interval $[0; T_{mod}]$ the population A is replenished with a finite random number of individuals $N_A(T_{mod})$;

2) for each fixed $t > 0$, the upper estimate of the population size $A(t)$ is given as the sum of the number of initially existing individuals and the random variable $Y(t)$, which has a Poisson distribution with parameter

$$\lambda(t) = \rho_A^* \int_0^t (1 - F_{\omega_A}(u))\, e^{-\mu_A u} du.$$

It follows from the postulate **H1** that each moment $t_{\mathcal{A}(j)} > 0$ specified in (2.1) is due to a random variable with exponential distribution whose parameter depends on the current size of the population A. Taking into account that the exponential distribution refers to distributions of absolutely continuous type and using (2.2), we conclude that for each fixed $t \in (0; T_{mod}]$ the probability of matching any pair, triple, etc. from the set of elements, specified in (2.1) is equal to zero. As a consequence, for every fixed $t \in [0; T_{mod}]$

$$-\omega_A^* < t_{\mathcal{A}(1)} < t_{\mathcal{A}(2)} < \cdots < t_{\mathcal{A}(j)} < \cdots < t_{\mathcal{A}(N_A(t))}. \tag{2.3}$$

Relations (2.3) mean that the individuals of the population A are distinguishable from each other by the moments $t_{\mathcal{A}}$ of entering the population. In addition, it follows from postulate **H2** that the individuals of the population A are distinguishable from each other by $t_{\mathcal{A}} + \min\{\xi_{\mathcal{A}}, \omega_{\mathcal{A}}\}$ at which they leave the population.

Denote by

$$\varphi_{\mathcal{A}(j)} = \min\{\xi_{\mathcal{A}(j)}, \omega_{\mathcal{A}(j)}\} \tag{2.4}$$

the duration of the stay $\mathcal{A}(j)$ in the population A before the transition $\mathcal{A}(j)$ to the population D or B. Let $\eta_{\mathcal{A}(j)}$ denote the «fate» indicator of the individual $\mathcal{A}(j)$:

$$\eta_{\mathcal{A}(j)} = 0, \text{ if } \xi_{\mathcal{A}(j)} \leqslant \omega_{\mathcal{A}(j)}, \ \eta_{\mathcal{A}(j)} = 1, \text{ if } \xi_{\mathcal{A}(j)} > \omega_{\mathcal{A}(j)}. \tag{2.5}$$

In (2.5) it is assumed that $\eta_{\mathcal{A}(j)} = 0$ means the transition $\mathcal{A}(j)$ to the population D, while $\eta_{\mathcal{A}(j)} = 1$ – transition $\mathcal{A}(j)$ to the population B. Using (2.4), (2.5), we introduce the triple

$$\left(t_{\mathcal{A}(j)}, \varphi_{\mathcal{A}(j)}, \eta_{\mathcal{A}(j)}\right) \tag{2.6}$$

which we call the unique type of an individual $\mathcal{A}(j)$, $1 \leqslant j \leqslant N_A(T_{mod})$.

For a fixed $t \in [0; T_{mod}]$ by $\Omega_A(t)$ we mean the family of unique types of individuals population A containing $N_A(t) \geqslant 1$ triples (2.6):

$$\Omega_A(t) = \left\{ \left(t_{\mathcal{A}(j)}, \varphi_{\mathcal{A}(j)}, \eta_{\mathcal{A}(j)}\right) : t_{\mathcal{A}(j)} \leqslant t, \ 1 \leqslant j \leqslant N_A(t) \right\}. \tag{2.7}$$

If for some $t \in [0; T_{mod}]$ is true $N_A(t) = 0$, then we assume that

$$\Omega_A(t) = \emptyset. \tag{2.8}$$

We write $A(t)$ in terms of $N_A(t)$ and $\Omega_A(t)$ for fixed $t \in [0; T_{mod}]$. If $N_A(t) = 0$, then (2.8) is true, and $A(t) = 0$. If $N_A(t) \geqslant 1$, then (2.7) is true, and $A(t) = |\widehat{\Omega}_A(t)|$ is the cardinality of the family

$$\widehat{\Omega}_A(t) = \left\{ \left(t_{\mathcal{A}(j)}, \varphi_{\mathcal{A}(j)}, \eta_{\mathcal{A}(j)}\right) \in \Omega_A(t) : t_{\mathcal{A}(j)} + \varphi_{\mathcal{A}(j)} > t, \ 1 \leqslant j \leqslant N_A(t) \right\}. \tag{2.9}$$

In accordance with postulate **H2**, the family $\widehat{\Omega}_A(t)$ given in (2.9) takes into account all individuals of the population A that exist at time t, namely: individuals appearing in the population up to the moment t (inclusive), and left the population at the time moments following t.

2.3. Recurrent relations for model variables

Let us introduce auxiliary variables $D(t)$, $B(t)$, meaning by them the number of individuals of the population A, who arrived respectively in the populations D and B during the time interval $[0; t]$, $0 < t \leqslant T_{mod}$, and assuming that $D(0) = 0$, $B(0) = 0$. We will describe the dynamics of

the population A using a random process

$$H(t) = \big(A(t), N_A(t), D(t), B(t), \Omega_A(t)\big),\ t \in [0; T_{mod}]. \tag{2.10}$$

Following [18], we construct sample functions of the process $H(t)$ on the time interval $[0; T_{mod}]$ using a sequence of pairs

$$(t_m, H(t_m)),\ m = 0, 1, 2, \ldots,\ t_0 = 0,\ t_m \leqslant T_{mod}. \tag{2.11}$$

Based on (2.1)–(2.10), we assume that the components of $H(t_0)$ are such that

$$A(t_0) = A_0,\ N_A(t_0) = A_0,\ D(t_0) = 0,\ B(t_0) = 0, \tag{2.12}$$

$$\Omega_A(t_0) = \Omega_A^{(0)},\ \text{if}\ N_A(t_0) \geqslant 1,\ \Omega_A(t_0) = \emptyset,\ \text{if}\ N_A(t_0) = 0. \tag{2.13}$$

The family $\Omega_A^{(0)}$ has the form

$$\Omega_A^{(0)} = \Big\{ \big(t_{\mathcal{A}(j)}, \varphi_{\mathcal{A}(j)}, \eta_{\mathcal{A}(j)}\big) : t_{\mathcal{A}(j)} \leqslant t_0 < t_{\mathcal{A}(j)} + \varphi_{\mathcal{A}(j)},\ 1 \leqslant j \leqslant N_A(t_0) \Big\}, \tag{2.14}$$

and contains given (nonrandom) triples (2.6) whose elements satisfy relations (2.2).

Let us construct recurrent relations for the sequence (2.11).

Put $m = 0$. Using (2.12)–(2.14), we introduce the quantities τ_0 and ψ_0. Let us assume that the quantity τ_0 has an exponential distribution with the parameter $\rho_A(A_0)$. The value of ψ_0 is given by the relations

$$\psi_0 = \min_{1 \leqslant j \leqslant N_A(t_0)} \{t_{\mathcal{A}(j)} + \varphi_{\mathcal{A}(j)}\},\ \text{if}\ A(t_0) \geqslant 1, \tag{2.15}$$

$$\psi_0 = +\infty,\ \text{if}\ A(t_0) = 0. \tag{2.16}$$

Based on (2.15), denote by $\big(t_{\mathcal{A}(*)}, \varphi_{\mathcal{A}(*)}, \eta_{\mathcal{A}(*)}\big)$ a unique triple of elements from (2.14) such that $\psi_0 = t_{\mathcal{A}(*)} + \varphi_{\mathcal{A}(*)}$. Let us define

$$t_1 = \min\big\{T_{mod}, \psi_0, t_0 + \tau_0\big\}, \tag{2.17}$$

and write that

$$H(t) = H(t_0),\ t \in [t_0, t_1). \tag{2.18}$$

If in (2.17) $t_1 = T_{mod}$, then

$$H(t_1) = H(t_0). \tag{2.19}$$

Relations (2.18), (2.19) complete the description of the process $H(t)$.

Let in (2.17) $t_1 = \psi_0$. Then

$$\begin{gathered} A(t_1) = A(t_0) - 1, \\ D(t_1) = D(t_0) + 1 = 1,\ B(t_1) = B(t_0) = 0,\ \text{if}\ \eta_{\mathcal{A}(*)} = 0, \\ D(t_1) = D(t_0) = 0,\ B(t_1) = B(t_0) + 1 = 1,\ \text{if}\ \eta_{\mathcal{A}(*)} = 1, \\ N_A(t_1) = N_A(t_0),\ \Omega_A(t_1) = \Omega_A(t_0). \end{gathered} \tag{2.20}$$

Let in (2.17) $t_1 = t_0 + \tau_0$. Then

$$A(t_1) = A(t_0) + 1,\ N_A(t_1) = N_A(t_0) + 1,$$

$$D(t_1) = D(t_0) = 0,\ B(t_1) = B(t_0) = 0,$$

$$j = N_A(t_1),\ \Omega_A(t_1) = \Omega_A(t_0) \cup \big(t_{\mathcal{A}(j)}, \varphi_{\mathcal{A}(j)}, \eta_{\mathcal{A}(j)}\big), \tag{2.21}$$
$$t_{\mathcal{A}(j)} = t_1,\ \varphi_{\mathcal{A}(j)} = \min\{\xi_{\mathcal{A}(j)}, \omega_{\mathcal{A}(j)}\},\ \xi_{\mathcal{A}(j)} \sim Exp(\mu_A),\ \omega_{\mathcal{A}(j)} \sim F_{\omega_A},$$
$$\eta_{\mathcal{A}(j)} = 0,\ \text{if}\ \xi_{\mathcal{A}(j)} \leqslant \omega_{\mathcal{A}(j)},\ \eta_{\mathcal{A}(j)} = 1,\ \text{if}\ \xi_{\mathcal{A}(j)} > \omega_{\mathcal{A}(j)}.$$

We fix $m = 1, 2, 3, \ldots$, and the components of the process $H(t_m)$:

$$H(t_m) = \big(A(t_m), N_A(t_m), D(t_m), B(t_m), \Omega_A(t_m)\big), \tag{2.22}$$

$$\Omega_A(t_m) = \emptyset,\ \text{if}\ N_A(t_m) = 0, \tag{2.23}$$

$$\Omega_A(t_m) = \Big\{\big(t_{\mathcal{A}(j)}, \varphi_{\mathcal{A}(j)}, \eta_{\mathcal{A}(j)}\big) : t_{\mathcal{A}(j)} \leqslant t_m,\ 1 \leqslant j \leqslant N_A(t_m)\Big\},\ \text{if}\ N_A(t_m) \geqslant 1. \tag{2.24}$$

Formula (2.22) includes non-negative integer constants $A(t_m)$, $N_A(t_m)$, $D(t_m)$, $B(t_m)$. If $N_A(t_m) \geqslant 1$, then (2.22) includes the family $\Omega_A(t_m)$ given by (2.24). Each triple $\big(t_{\mathcal{A}(j)}, \varphi_{\mathcal{A}(j)}, \eta_{\mathcal{A}(j)}\big)$ in (2.24) contains two real and one integer non-negative constant.

Using (2.22)–(2.24), we introduce the quantities τ_m and ψ_m. Let us assume that the quantity τ_m has an exponential distribution with the parameter $\rho_A(A(t_m))$. The value of ψ_m is given by the relations

$$\psi_m = \min_{1 \leqslant j \leqslant N_A(t_m)} \{t_{\mathcal{A}(j)} + \varphi_{\mathcal{A}(j)} : t_{\mathcal{A}(j)} + \varphi_{\mathcal{A}(j)} > t_m\},\ \text{if}\ A(t_m) \geqslant 1, \tag{2.25}$$

$$\psi_m = +\infty,\ \text{if}\ A(t_m) = 0. \tag{2.26}$$

Based on (2.25), denote by $\big(t_{\mathcal{A}(*)}, \varphi_{\mathcal{A}(*)}, \eta_{\mathcal{A}(*)}\big)$ a unique triple of elements from (2.24) such that $\psi_m = t_{\mathcal{A}(*)} + \varphi_{\mathcal{A}(*)}$. Let us define

$$t_{m+1} = \min\big\{T_{mod}, \psi_m, t_m + \tau_m\big\}, \tag{2.27}$$

and write that

$$H(t) = H(t_m),\ t \in [t_m, t_{m+1}). \tag{2.28}$$

If in (2.27) $t_{m+1} = T_{mod}$, then

$$H(t_{m+1}) = H(t_m). \tag{2.29}$$

Relations (2.28), (2.29) complete the description of the process $H(t)$.

Let in (2.27) $t_{m+1} = \psi_m$. Then

$$A(t_{m+1}) = A(t_m) - 1,$$
$$D(t_{m+1}) = D(t_m) + 1,\ B(t_{m+1}) = B(t_m),\ \text{if}\ \eta_{\mathcal{A}(*)} = 0, \tag{2.30}$$
$$D(t_{m+1}) = D(t_m),\ B(t_{m+1}) = B(t_m) + 1,\ \text{if}\ \eta_{\mathcal{A}(*)} = 1,$$
$$N_A(t_{m+1}) = N_A(t_m),\ \Omega_A(t_{m+1}) = \Omega_A(t_m).$$

Let in (2.27) $t_{m+1} = t_m + \tau_m$. Then

$$A(t_{m+1}) = A(t_m) + 1,\ N_A(t_{m+1}) = N_A(t_m) + 1,$$
$$D(t_{m+1}) = D(t_m),\ B(t_{m+1}) = B(t_m),$$
$$j = N_A(t_{m+1}),\ \Omega_A(t_{m+1}) = \Omega_A(t_m) \cup \big(t_{\mathcal{A}(j)}, \varphi_{\mathcal{A}(j)}, \eta_{\mathcal{A}(j)}\big), \tag{2.31}$$
$$t_{\mathcal{A}(j)} = t_{m+1},\ \varphi_{\mathcal{A}(j)} = \min\{\xi_{\mathcal{A}(j)}, \omega_{\mathcal{A}(j)}\},\ \xi_{\mathcal{A}(j)} \sim Exp(\mu_A),\ \omega_{\mathcal{A}(j)} \sim F_{\omega_A},$$

$$\eta_{\mathcal{A}(j)} = 0, \text{ if } \xi_{\mathcal{A}(j)} \leqslant \omega_{\mathcal{A}(j)}, \ \eta_{\mathcal{A}(j)} = 1, \text{ if } \xi_{\mathcal{A}(j)} > \omega_{\mathcal{A}(j)}.$$

We replace m with $m+1$ and return to relations (2.22)–(2.31).

2.4. Algorithm for numerical simulation

The Monte Carlo method is used to calculate the realizations of the random process $H(t)$. At the beginning of the calculations, the model parameters, initial data and the modeling interval $[0; T_{mod}]$ are specified. In addition, the constant $\psi_\infty > T_{mod}$ is specified, which is used for the quantities ψ_0, ψ_m in formulas (2.16), (2.26) instead of the symbol «$+\infty$».

Next, the sequence (2.11) is modeled based on relations (2.15)–(2.31). Simulation of a particular realization stops when $t_{m+1} \geqslant T_{mod}$. The simulation of the $H(t)$ process is completed when the specified number of realizations is received. To generate random variables, we use the formulas and generators of pseudo-random numbers described in [19]–[21].

The simulation algorithm is implemented as a console simulation program written in the C++ programming language in the Visual Studio 2008 integrated development environment. The input parameters are read from a special configuration file. Simulation results (realizations of model variables) are stored in a separate text file.

2.5. An example of numerical simulation

Let $[0; T_{mod}] = [0; 30]$ days, $A(0) = A_0 = 0$, $r_1 > 0$, $r_2 > 0$, $\beta > 0$ and

$$\rho_A(z) = r_1 \exp\{-\beta z\} + r_2, \ z \in Z_+.$$

The dimension of the parameters r_1, r_2 day^{-1}, β is a dimensionless parameter. The function $\rho_A(z)$ specifies a negative feedback that reflects the rate of influx of new individuals of population A depending on its current size $A(t)$. The function $F_{\omega_A}(u)$ sets the uniform distribution of the random variable ω_A over the interval $[0; \omega_A^*]$ of the day, the parameter μ_A of the exponential distribution $\xi_A \sim Exp(\mu_A)$ has the dimension day^{-1}.

For a preliminary analysis of the possible behavior of $A(t)$, consider a deterministic analogue of the constructed model in the form of the integral equation

$$x_A(t) = \int_0^t \big(1 - F_{\omega_A}(u)\big)\, e^{-\mu_A u}\, \rho_A(x_A(t-u))du, \ t \geqslant 0. \tag{2.32}$$

Equation (2.32) was proposed and studied in [22]. The solution $x_A(t)$ of equation (2.32) is understood as a continuous non-negative real function describing the size of the population A at the time $t \in [0; \infty)$. Denote

$$\theta_A = \int_0^\infty \big(1 - F_{\omega_A}(u)\big)\, e^{-\mu_A u} du = \frac{1}{\mu_A}\Big(1 - \frac{1}{\mu_A \omega_A^*}\big(1 - e^{-\mu_A \omega_A^*}\big)\Big). \tag{2.33}$$

The constant $\theta_A > 0$ given by (2.33) is interpreted as the average time spent by individuals in the population A. Let x_A^* be the unique root of the equation

$$x = \theta_A \rho_A(x), \ x \in [0; \infty). \tag{2.34}$$

It follows from (2.32)–(2.34) that if the solution $x_A(t)$ has a finite

$$\lim_{t \to +\infty} x_A(t) = x_A(+\infty), \tag{2.35}$$

then $x_A(+\infty) = x_A^*$. One of the conditions necessary for the existence of the limit (2.35) is satisfied, since at the point $x = x_A^*$ the inequality $d\rho_A(x)/dx < 0$ is true. Sufficient conditions

for the existence of the limit (2.35) are given in [22].

Let us turn to the stochastic model. Consider the dynamics of $A(t)$ for two sets of model parameters (the dimension of the parameters is indicated above):

$$r_1 = 150,\ r_2 = 25,\ \beta = 0.01,\ \mu_A = 0.1,\ \omega_A^* = 5, \tag{2.36}$$

$$r_1 = 250,\ r_2 = 5,\ \beta = 0.05,\ \mu_A = 0.05,\ \omega_A^* = 10. \tag{2.37}$$

For the parameter sets (2.36), (2.37), the roots of equation (2.34) with an accuracy of two decimal places are as follows: $x_A^* = 136.62$ and $x_A^* = 64.24$.

Figures 2, 3 show ten typical realizations of the population size $A(t)$ for the parameter sets (2.36), (2.37), respectively.

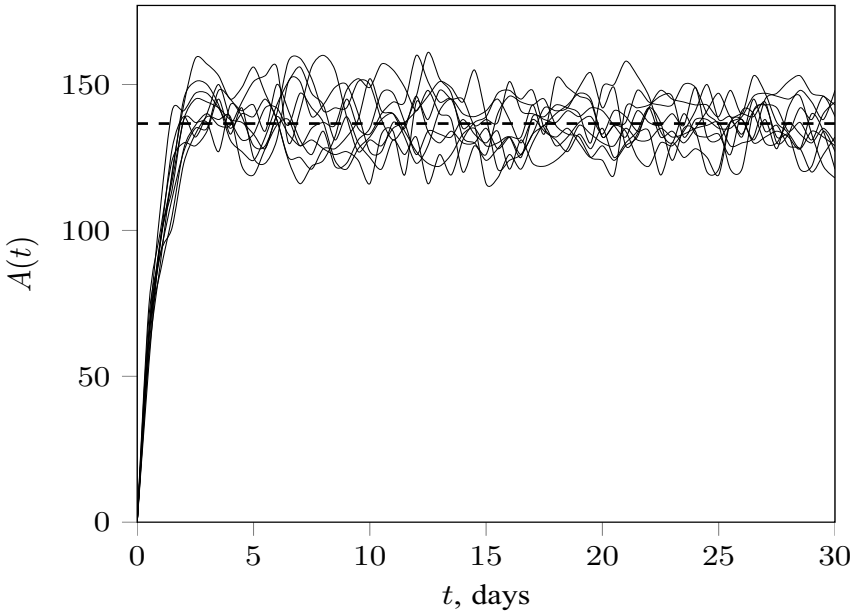

Fig. 2. Typical realizations of the population size $A(t)$ for a set of parameters (2.36); the dotted line denotes the value $x_A^* = 136.62$.

Table 1 presents interval estimates of the expectation $\mathbf{E}A(t)$ for fixed $t \in [0; T_{mod}]$ at the confidence level $P = 0.99$ [23]. Interval estimates are calculated on a sample of $N = 1000$ realizations of the random process $H(t)$.

From Figures 2, 3 and Table 1 it can be seen that the results of stochastic simulation are in good agreement with the analytical study of the deterministic model (2.32). First, the realizations of $A(t)$ after the completion of the transitional process on the time interval $t \in [0; 5]$ days reach a level close to x_A^*, and then oscillate in a limited range relative to x_A^*. Secondly, the expectation $A(t)$ takes values close enough to x_A^*, despite the nonlinearity of the model. The differences in the behavior of $A(t)$ for the set of parameters (2.36), (2.37) are mainly due to the values of the parameters of the function $\rho_A(z)$. Additionally, we note that the deviations of $A(t)$ and $\mathbf{E}A(t)$ from x_A^* are more pronounced for the set of parameters (2.36) due to the fact that $x_A^* = 136.62 > x_A^* = 64.24$.

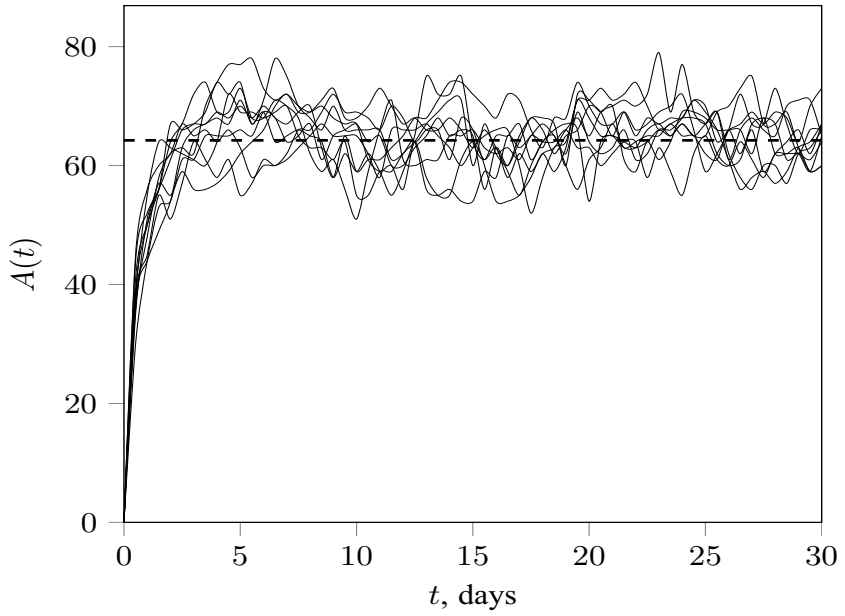

Fig. 3. Typical realizations of the population size $A(t)$ for a set of parameters (2.37); the dotted line denotes the value $x_A^* = 64.24$.

Table 1. Interval estimates of the expectation $\boldsymbol{E}A(t)$ at the confidence level $P = 0.99$ for parameter sets (2.36), (2.37)

***t*, day**	**Parameter set 2.36**	**Parameter set 2.37**
0	0	0
5	137.040 ± 0.699	68.277 ± 0.378
10	135.952 ± 0.714	62.860 ± 0.379
15	136.249 ± 0.689	64.993 ± 0.365
20	135.766 ± 0.699	64.495 ± 0.371
25	135.871 ± 0.682	64.427 ± 0.369
30	135.990 ± 0.685	64.589 ± 0.376

3. STOCHASTIC STAGE-DEPENDENT MODEL OF THE DEVELOPMENT OF HIV-1 INFECTION IN THE LYMPH NODE

3.1. Notation and postulates of the model

We will study the initial stage of the development of HIV-1 infection in the lymph node, which has penetrated a small number of viral particles V after infection of the individual at time $t = 0$. To build the model, we used publications listed in the references of [11] (articles No. 7, 8, 11, 12, 26, 28, 29, 30), monograph [24] and articles [25], [26].

Denote the simulation interval by $[0; T_{mod}]$ and assume that the duration of the interval is $[0; T_{mod}]$ is several days. Let us assume that the abbreviation LN means a lymph node. When building the model, we will take into account only a few factors and events that reflect the development of HIV-1 infection in the LN. We assume that the target cells for viral particles are T_0 cells – CD4+ T-lymphocytes at rest. T_0 cells can come into contact with virus particles V and become infected I_0 cells. Cell I_0 is susceptible to contact with antigen-presenting cells A. Cell I_0 after contact with cell A enters the phase G_1 of the cell cycle and turns into cell I_1.

After completion of the G_1 phase, the cell I_1 enters the $S - G_2 - M$ phases of the cell cycle and turns into one of the cells I_2, I_3, I_+. The I_2 cell is capable of a single division, after which its descendants turn into two productively infected cells I_4 (cells that produce viral particles V). Cell I_3 stops at the G_2 phase of the cell cycle and after a certain period of time turns into cell I_4. Cell I_+ is capable of further reproduction, but it and its descendants are not capable of producing virus particles V. The dynamics of the population of cells I_+ and their descendants is not considered in the model. Additionally, we note that cells I_0 can arise from cells T_0 due to contacts of cells I_4 with cells T_0.

Let us assume that the number of cell populations T_0 and antigen-presenting cells A in the LN are constant and equal, respectively $T_0^* > 0$, $A^* > 0$. Based on the short duration of the simulation interval $[0; T_{mod}]$, we will not take into account the decrease in the number of cell populations I_0, I_1, I_2, I_3 due to natural aging and death due to virus infection. The decrease in the population of I_0 cells is due to their migration outflow from the LN and contacts with A cells, leading to the transformation of I_0 cells into I_1 cells. Decrease in cell population I_4 is caused by the influence of the V virus particle production process that is destructive for these cells. The decrease in the population of viral particles V is due to their natural mortality, migratory outflow from the LN and absorption as a result of contacts with T_0 cells.

The scheme of the model is shown in Figure 4, where the following notation is used:

- D – cells I_0 and virus particles V that left the LN due to migration outflow, as well as virus particles that died due to natural mortality;
- K – I_4 cells that died under the influence of the viral particle production process;
- W – viral particles absorbed by infected T_0 cells.

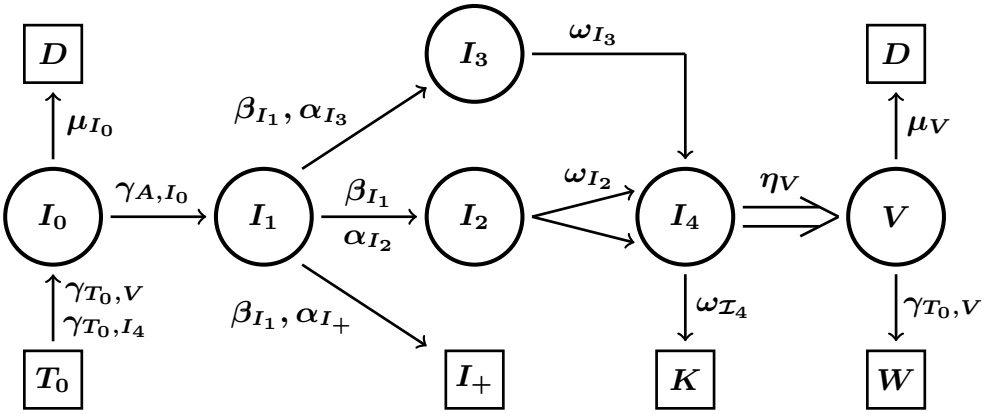

Fig. 4. Scheme of a stochastic model for the development of HIV-1 infection in a lymph node, symbols in the text.

The number of populations indicated above at time $t \in [0; T_{mod}]$ denoted by

$$X(t) = \big(I_0(t), I_1(t), I_2(t), I_3(t), I_4(t), V(t)\big). \tag{3.1}$$

For each fixed $t > 0$, the components $I_0(t)$, $I_1(t)$, $I_2(t)$, $I_3(t)$, $I_4(t)$, $V(t)$ in (3.1) are non-negative integer random variables. Let us assume that at the initial time ($t = 0$) there are virus particles in the LN and no cells of the I_k populations: $V(0) = V_0 = const > 0$, $I_k(0) = 0$, $0 \leqslant k \leqslant 4$.

Now we formulate the postulates of the model. Fix t and assume that $x_k = I_k(t)$, $0 \leqslant k \leqslant 4$, $x_5 = V(t)$ are non-negative integer constants. We accept that the events listed in the postulates

H1–**H7** occur independently of each other and independently of the events preceding the time t. Moreover, without loss of generality let us assume that $x_0 > 0$, $x_1 > 0$, $x_4 > 0$, $x_5 > 0$. The postulates **H1**–**H7** are as follows.

H1. During the interval $(t; t + h)$ some T_0 cell contacts with some virus particle V with probability $\gamma_{T_0,V} T_0^* x_5 h + o(h)$; the probability of contacts between two or more T_0 cells and viral particles V during $(t; t+h)$ is equal to $o(h)$; contact of T_0 cells and viral particles V during $(t; t + h)$ does not occur with probability $1 - \gamma_{T_0,V} T_0^* x_5 h + o(h)$; $\gamma_{T_0,V} = const > 0$. Contact of T_0 cell with virus particle V results in to the appearance of the I_0 cell and the absorption of the viral particle V.

H2. During the interval $(t; t + h)$ some T_0 cell contacts with some I_4 cell with probability $\gamma_{T_0,I_4} T_0^* x_4 h + o(h)$; the probability of contacts of two or more cells T_0 and I_4 during $(t; t+h)$ is equal to $o(h)$; cells T_0 and I_4 do not contact during $(t; t+h)$ with probability $1 - \gamma_{T_0,I_4} T_0^* x_4 h + o(h)$; $\gamma_{T_0,I_4} = const > 0$. Contact of T_0 cell with I_4 cell results in to the appearance of I_0 cell.

H3. During the interval $(t; t + h)$ some I_0 cell leaves the LN (migration outflow) with probability $\mu_{I_0} x_0 h + o(h)$; the probability that the LN will leave more than one I_0 cell for $(t; t + h)$ is equal to $o(h)$; with probability $1 - \mu_{I_0} x_0 h + o(h)$ no I_0 cell leaves the LN for $(t; t + h)$; $\mu_{I_0} = const > 0$.

H4. During the interval $(t; t + h)$ some A cell contacts with some I_0 cell with probability $\gamma_{A,I_0} A^* x_0 h + o(h)$; the probability of contacts of two or more cells A and I_0 during $(t; t + h)$ is equal to $o(h)$; cells A and I_0 do not contact during $(t; t + h)$ with probability $1 - \gamma_{A,I_0} A^* x_0 h + o(h)$; $\gamma_{A,I_0} = const > 0$. Contact of A cell with I_0 cell leads to the transition of I_0 cell from the G_0 phase to the G_1 phase of the cell cycle and transformation of I_0 cell into I_1 cell.

H5. During the interval $(t; t + h)$ some I_1 cell leaves the phase G_1 of the cell cycle with probability $\beta_{I_1} x_1 h + o(h)$; the probability that more than one I_1 cell leaves the phase G_1 of the cell cycle in $(t; t + h)$ is equal to $o(h)$; with probability $1 - \beta_{I_1} x_1 h + o(h)$ no I_1 cell leaves the phase G_1 of the cell cycle in $(t; t + h)$; $\beta_{I_1} = const > 0$. A cell I_1 that has completed its stay in the G_1 phase of the cell cycle, turns into one of the cells I_2, I_3, I_+ respectively with fixed probabilities

$$\alpha_{I_2} \geqslant 0,\ \alpha_{I_3} \geqslant 0,\ \alpha_{I_+} \geqslant 0,\ \alpha_{I_2} + \alpha_{I_3} + \alpha_{I_+} = 1.$$

H6. During the interval $(t; t+h)$ some I_4 cell produces one virus particle V with probability $\eta_V x_4 h + o(h)$; the probability of producing more than one virus particle V for $(t; t + h)$ is equal to $o(h)$; with probability $1 - \eta_V x_4 h + o(h)$ for $(t; t + h)$ no virus particles are produced; $\eta_V = const > 0$.

H7. During the interval $(t; t + h)$ some virus particle V leaves the LN with probability $\mu_V x_5 h + o(h)$ (migration outflow with probability p_V or natural mortality with probability $1 - p_V$); the probability that more than one viral particle V leaves the LN in $(t; t + h)$ is equal to $o(h)$; with probability $1 - \mu_V x_5 h + o(h)$ no virus particle V leaves the LN for $(t; t + h)$; $\mu_V = const > 0$, $0 < p_V = const < 1$.

For further description of the model we assume that the symbols $\mathcal{I}_2$, $\mathcal{I}_3$, $\mathcal{I}_4$ mean some or arbitrarily chosen cell respectively of the population I_2, I_3, I_4. The postulates **H8**–**H10** are as follows.

H8. Let the cell $\mathcal{I}_2$ appear in the population I_2 at some point in time $t_{\mathcal{I}_2} \leqslant t$. We assume that the cell $\mathcal{I}_2$ leaves the population I_2 at time $t_{\mathcal{I}_2} + \omega_{I_2}$ and, as a result of division, forms two cells of the population I_4. The parameter $\omega_{I_2} = const > 0$ means the duration of the phases $S - G_2 - M$ of the cell cycle for the cells of the population I_2.

H9. Let the cell $\mathcal{I}_3$ appear in the population I_3 at some point in time $t_{\mathcal{I}_3} \leqslant t$. We assume that the cell $\mathcal{I}_3$ leaves the population I_3 at time $t_{\mathcal{I}_3} + \omega_{I_3}$ and becomes a cell of the population I_4. The parameter $\omega_{I_3} = const > 0$ means the duration of stay of the cells of the population I_3 in the stopped phase G_2 of the cell cycle.

H10. Let the cell $\mathcal{I}_4$ appear in the population I_4 at some point in time $t_{\mathcal{I}_4} \leqslant t$. We assume that the cell $\mathcal{I}_4$ dies at the moment of time $t_{\mathcal{I}_4} + \omega_{\mathcal{I}_4}$ due to the process of producing viral particles that is destructive for the cells of the I_4 population. The random variable $\omega_{\mathcal{I}_4}$ is distributed over a finite time interval $[a; b]$, $0 < a < b$, with an absolutely continuous distribution function $F_{\omega_{I_4}}(s)$, $F_{\omega_{I_4}}(a) = 0$, $F_{\omega_{I_4}}(b) = 1$, and $\omega_{\mathcal{I}_4}$ does not depend on $t_{\mathcal{I}_4}$ and on the behavior of other individuals of the studied populations.

3.2. Families of unique cell types

Let us introduce families $\Omega_{I_2}(t)$, $\Omega_{I_3}(t)$, $\Omega_{I_4}(t)$ of unique cell types of populations I_2, I_3, I_4, $t \in [0; T_{mod}]$. In the following expressions, by A we mean a fixed population of cells from the set I_2, I_3, I_4. Taking into account the zero numbers of cell populations I_2, I_3, I_4 at $t = 0$, we assume that the variable $N_A(t)$ means a random variable that specifies the number of cells that entered the population A during the time interval $[0; t] \subset [0; T_{mod}]$, and $N_A(0) = 0$.

Relying on the postulates **H8**–**H10** and using the constructions from section 2, we introduce the family $\Omega_A(t)$ of unique types of cells in the population A:

$$\Omega_A(t) = \Big\{ \big(t_{\mathcal{A}(j)}, \varphi_{\mathcal{A}(j)}\big) : 0 < t_{\mathcal{A}(j)} \leqslant t,\ 1 \leqslant j \leqslant N_A(t) \Big\},\ \text{if } N_A(t) \geqslant 1, \tag{3.2}$$

$$\Omega_A(t) = \emptyset,\ \text{if } N_A(t) = 0. \tag{3.3}$$

In formula (3.2), the unique types of cells in the population A are represented by pairs

$$\big(t_{\mathcal{A}(j)}, \varphi_{\mathcal{A}(j)}\big), \tag{3.4}$$

where $j = 1, 2, \ldots, N_A(t)$ means the serial number of the next cell $\mathcal{A}$ entering the population A, $\mathcal{A}(j)$ – cell $\mathcal{A}$ with sequence number of j. Set

$$0 < t_{\mathcal{A}(1)}, t_{\mathcal{A}(2)}, \ldots, t_{\mathcal{A}(j)}, \ldots, t_{\mathcal{A}(N_A(t))} \leqslant t \tag{3.5}$$

specifies the moments of arrival of cells in the population A up to the time t (inclusive). The $\varphi_{\mathcal{A}(j)}$ component used in (3.4) is as follows. If $A = I_2$ then $\varphi_{\mathcal{A}(j)} = \omega_{I_2}$, if $A = I_3$ then $\varphi_{\mathcal{A}(j)} = \omega_{I_3}$ (the constants indicated in postulates **H8**, **H9**). For $A = I_4$ we assume that $\varphi_{\mathcal{A}(j)} = \omega_{\mathcal{I}_4}$ is a random variable introduced in postulate **H10**.

Note that, in accordance with postulates **H1**, **H2**, **H4**, **H5**, **H8**–**H10**, the moments (3.5) of the appearance of cells in the populations I_2, I_3, I_4 are due to random variables with an exponential distribution containing various parameters. The residence times of cells in the populations I_2, I_3 are given by constants, and the residence time of cells in the population I_4 is given by the distribution $F_{\omega_{I_4}}$. These distributions refer to distributions of absolutely continuous type. Based on the structure of family elements (3.2), we have that all cells located in the populations I_2, I_3, I_4 at the current moment of time are distinguishable from each other in time $t_{\mathcal{A}(j)} + \varphi_{\mathcal{A}(j)}$.

By analogy with (2.9), we note that the family

$$\widehat{\Omega}_A(t) = \Big\{ \big(t_{\mathcal{A}(j)}, \varphi_{\mathcal{A}(j)}\big) \in \Omega_A(t) : t_{\mathcal{A}(j)} + \varphi_{\mathcal{A}(j)} > t,\ 1 \leqslant j \leqslant N_A(t) \Big\} \tag{3.6}$$

takes into account all cells of the population A existing at time t, and its size $A(t) = |\widehat{\Omega}_A(t)|$ is the cardinality of family (3.6).

3.3. Recurrent relations for model variables

The dynamics of the populations $I_0, I_1, I_2, I_3, I_4, V$ will be described using a random process

$$H(t) = \big(X(t), Y(t), \Omega(t)\big),\ t \in [0; T_{mod}], \tag{3.7}$$

where

$$Y(t) = \big(N_{I_2}(t), N_{I_3}(t), N_{I_4}(t), I_+(t), I_{out}(t), V_{out}(t)\big),$$
$$\Omega(t) = \big(\Omega_{I_2}(t), \Omega_{I_3}(t), \Omega_{I_4}(t)\big). \tag{3.8}$$

The components $X(t)$, $Y(t)$, $\Omega(t)$ used in (3.7), (3.8) are indicated in (3.1), (3.2), (3.3). In addition, $I_+(t)$ is understood as an auxiliary variable reflecting the number of cells that entered the population I_+ during the time interval $[0; t]$, $0 < t \leqslant T_{mod}$, and $I_+(0) = 0$. Auxiliary variables $I_{out}(t)$, V_{out} reflect, respectively, the number of cells I_0 and virus particles V that left the LN during the time interval $[0; t]$, $0 < t \leqslant T_{mod}$, and $I_{out}(0) = V_{out}(0) = 0$.

We construct sample functions of the process $H(t)$ on the time interval $[0; T_{mod}]$ using a sequence of pairs

$$(t_m, H(t_m)),\ m = 0, 1, 2, \ldots,\ t_0 = 0,\ t_m \leqslant T_{mod}. \tag{3.9}$$

Based on the description of the model (sections 3.1, 3.2), we assume that the components of $H(t_0)$ are as follows:

$$I_0(t_0) = I_1(t_0) = I_2(t_0) = I_3(t_0) = I_4(t_0) = 0,\ V(t_0) = V_0, \tag{3.10}$$

$$N_{I_2}(t_0) = N_{I_3}(t_0) = N_{I_4}(t_0) = 0,\ I_+(t_0) = 0, \tag{3.11}$$

$$\Omega_{I_2}(t_0) = \emptyset,\ \Omega_{I_3}(t_0) = \emptyset,\ \Omega_{I_4}(t_0) = \emptyset. \tag{3.12}$$

Let us construct recurrent relations for the sequence (3.9).

Put $m = 0$. Using (3.10)–(3.12), we introduce a random variable $\tau^{(0)}$ with exponential distribution, whose parameter

$$\rho(t_0) = \gamma_{T_0,V} T_0^* V(t_0) + \mu_V V(t_0) > 0. \tag{3.13}$$

Let us define

$$t_1 = \min\big\{T_{mod}, t_0 + \tau^{(0)}\big\}. \tag{3.14}$$

We will preliminarily assume that

$$H(t) = H(t_0),\ t \in [t_0, t_1]. \tag{3.15}$$

If in (3.14) $t_1 = T_{mod}$, then (3.15) completes the description of the process $H(t)$.

Let in (3.14) $t_1 = t_0 + \tau^{(0)}$. Then some of the components $H(t)$ are subject to change at the point $t = t_1$, namely:

$$\text{with probability } \frac{\gamma_{T_0,V} T_0^* V(t_0)}{\rho(t_0)}:$$
$$I_0(t_1) = I_0(t_0) + 1 = 1;\ V(t_1) = V(t_0) - 1 = V_0 - 1; \tag{3.16}$$

$$\text{with probability } \frac{\mu_V V(t_0)}{\rho(t_0)}:$$
$$V(t_1) = V(t_0) - 1 = V_0 - 1, \text{and additionally,}$$
$$V_{out}(t_1) = V_{out}(t_0) + 1 = 1 \text{ with probability } p_V. \tag{3.17}$$

We fix $m = 1, 2, 3, \ldots$ and the components of the process $H(t_m)$:

$$H(t_m) = \big(X(t_m), Y(t_m), \Omega(t_m)\big). \tag{3.18}$$

Formula (3.18) includes $X(t_m)$, $Y(t_m)$ whose components are non-negative integer constants. Components

$$\Omega(t_m) = \big(\Omega_{I_2}(t_m), \Omega_{I_3}(t_m), \Omega_{I_4}(t_m)\big),$$

used in (3.18) have the following structure. Let $A \in \{I_2, I_3, I_4\}$. If $N_A(t_m) \geqslant 1$, then (3.18) includes the family $\Omega_A(t_m)$ given by (3.2). Each pair $\big(t_{\mathcal{A}(j)}, \varphi_{\mathcal{A}(j)}\big)$ in $\Omega_A(t_m)$ contains two real positive constants. If $N_A(t_m) = 0$, then (3.18) includes family $\Omega_A(t_m) = \emptyset$.

Using (3.18), we introduce the quantities $\tau^{(m)}$, $\psi_{I_2}^{(m)}$, $\psi_{I_3}^{(m)}$, $\psi_{I_4}^{(m)}$. Denote:

$$\rho(t_m) = \gamma_{T_0,V} T_0^* V(t_m) + \gamma_{T_0,I_4} T_0^* I_4(t_m) + \mu_{I_0} I_0(t_m)$$

$$+ \gamma_{A,I_0} A^* I_0(t_m) + \beta_{I_1} I_1(t_m) + \eta_V I_4(t_m) + \mu_V V(t_m). \tag{3.19}$$

Let us assume that for $\rho(t_m) > 0$ the quantity $\tau^{(m)}$ has an exponential distribution with parameter $\rho(t_m)$. If $\rho(t_m) = 0$, then we assume that $\tau^{(m)} = +\infty$.

Let us define the quantities $\psi_{I_2}^{(m)}$, $\psi_{I_3}^{(m)}$, $\psi_{I_4}^{(m)}$ using the following relations:

$$\psi_{I_2}^{(m)} = \min_{1 \leqslant j \leqslant N_{I_2}(t_m)} \{t_{\mathcal{I}_2(j)} + \varphi_{\mathcal{I}_2(j)} : t_{\mathcal{I}_2(j)} + \varphi_{\mathcal{I}_2(j)} > t_m\}, \text{ if } I_2(t_m) \geqslant 1, \tag{3.20}$$

$$\psi_{I_2}^{(m)} = +\infty, \text{ if } I_2(t_m) = 0, \tag{3.21}$$

$$\psi_{I_3}^{(m)} = \min_{1 \leqslant j \leqslant N_{I_3}(t_m)} \{t_{\mathcal{I}_3(j)} + \varphi_{\mathcal{I}_3(j)} : t_{\mathcal{I}_3(j)} + \varphi_{\mathcal{I}_3(j)} > t_m\}, \text{ if } I_3(t_m) \geqslant 1, \tag{3.22}$$

$$\psi_{I_3}^{(m)} = +\infty, \text{ if } I_3(t_m) = 0, \tag{3.23}$$

$$\psi_{I_4}^{(m)} = \min_{1 \leqslant j \leqslant N_{I_4}(t_m)} \{t_{\mathcal{I}_4(j)} + \varphi_{\mathcal{I}_4(j)} : t_{\mathcal{I}_4(j)} + \varphi_{\mathcal{I}_4(j)} > t_m\}, \text{ if } I_4(t_m) \geqslant 1, \tag{3.24}$$

$$\psi_{I_4}^{(m)} = +\infty, \text{ if } I_4(t_m) = 0. \tag{3.25}$$

Let us define

$$t_{m+1} = \min\big\{T_{mod}, \psi_{I_2}^{(m)}, \psi_{I_3}^{(m)}, \psi_{I_4}^{(m)}, t_m + \tau^{(m)}\big\}. \tag{3.26}$$

We will preliminarily assume that

$$H(t) = H(t_m), \ t \in [t_m, t_{m+1}]. \tag{3.27}$$

Suppose that in (3.26) $t_{m+1} = T_{mod}$. Then (3.27) completes the description of the process $H(t)$. If, on the contrary, $t_{m+1} < T_{mod}$ in (3.26), then some of the $H(t)$ components change at the point $t = t_{m+1}$. Changes in the components of $H(t)$ are reflected in the relations below.

Let in (3.26) $t_{m+1} = \psi_{I_2}^{(m)}$. Then

$$I_2(t_{m+1}) = I_2(t_m) - 1, \ I_4(t_{m+1}) = I_4(t_m) + 2, \ N_{I_4}(t_{m+1}) = N_{I_4}(t_m) + 2,$$

$$j = N_{I_4}(t_{m+1}) - 1, \ k = N_{I_4}(t_{m+1}), \ t_{\mathcal{I}_4(j)} = t_{\mathcal{I}_4(k)} = t_{m+1}, \tag{3.28}$$

$$\Omega_{I_4}(t_{m+1}) = \Omega_{I_4}(t_m) \cup \big(t_{\mathcal{I}_4(j)}, \varphi_{\mathcal{I}_4(j)}\big) \cup \big(t_{\mathcal{I}_4(k)}, \varphi_{\mathcal{I}_4(k)}\big),$$

where $\varphi_{\mathcal{I}_4(j)}$, $\varphi_{\mathcal{I}_4(k)}$ are independent random variables distributed over a finite interval $[a; b]$ with distribution function $F_{\omega_{I_4}}$.

Let in (3.26) $t_{m+1} = \psi_{I_3}^{(m)}$. Then

$$I_3(t_{m+1}) = I_3(t_m) - 1,\ I_4(t_{m+1}) = I_4(t_m) + 1,\ N_{I_4}(t_{m+1}) = N_{I_4}(t_m) + 1,$$

$$j = N_{I_4}(t_{m+1}),\ t_{\mathcal{I}_4(j)} = t_{m+1},\ \Omega_{I_4}(t_{m+1}) = \Omega_{I_4}(t_m) \cup \left(t_{\mathcal{I}_4(j)}, \varphi_{\mathcal{I}_4(j)}\right), \tag{3.29}$$

where $\varphi_{\mathcal{I}_4(j)}$ is a random variable distributed over a finite interval $[a; b]$ with distribution function $F_{\omega_{I_4}}$.

Let in (3.26) $t_{m+1} = \psi_{I_4}^{(m)}$. Then

$$I_4(t_{m+1}) = I_4(t_m) - 1. \tag{3.30}$$

Let, finally, in (3.26) $t_{m+1} = t_m + \tau^{(m)}$. Changes in the $H(t)$ components at the point $t = t_{m+1}$ are caused by the occurrence of one of the events whose intensities are presented in formula (3.19). The changes are:

$$\text{with probability } \frac{\gamma_{T_0,V} T_0^* V(t_m)}{\rho(t_m)}:$$

$$I_0(t_{m+1}) = I_0(t_m) + 1;\ V(t_{m+1}) = V(t_m) - 1; \tag{3.31}$$

$$\text{with probability } \frac{\gamma_{T_0,I_4} T_0^* I_4(t_m)}{\rho(t_m)}:$$

$$I_0(t_{m+1}) = I_0(t_m) + 1; \tag{3.32}$$

$$\text{with probability } \frac{\mu_{I_0} I_0(t_m)}{\rho(t_m)}:$$

$$I_0(t_{m+1}) = I_0(t_m) - 1,\ I_{out}(t_{m+1}) = I_{out}(t_m) + 1; \tag{3.33}$$

$$\text{with probability } \frac{\gamma_{A,I_0} A^* I_0(t_m)}{\rho(t_m)}:$$

$$I_0(t_{m+1}) = I_0(t_m) - 1,\ I_1(t_{m+1}) = I_1(t_m) + 1; \tag{3.34}$$

$$\text{with probability } \alpha_{I_2} \frac{\beta_{I_1} I_1(t_m)}{\rho(t_m)}:$$

$$I_1(t_{m+1}) = I_1(t_m) - 1,\ I_2(t_{m+1}) = I_2(t_m) + 1,\ N_{I_2}(t_{m+1}) = N_{I_2}(t_m) + 1,\ j = N_{I_2}(t_{m+1}),$$
$$t_{\mathcal{I}_2(j)} = t_{m+1},\ \varphi_{\mathcal{I}_2(j)} = \omega_{I_2},\ \Omega_{I_2}(t_{m+1}) = \Omega_{I_2}(t_m) \cup \left(t_{\mathcal{I}_2(j)}, \varphi_{\mathcal{I}_2(j)}\right); \tag{3.35}$$

$$\text{with probability } \alpha_{I_3} \frac{\beta_{I_1} I_1(t_m)}{\rho(t_m)}:$$

$$I_1(t_{m+1}) = I_1(t_m) - 1,\ I_3(t_{m+1}) = I_3(t_m) + 1,\ N_{I_3}(t_{m+1}) = N_{I_3}(t_m) + 1,\ j = N_{I_3}(t_{m+1}),$$
$$t_{\mathcal{I}_3(j)} = t_{m+1},\ \varphi_{\mathcal{I}_3(j)} = \omega_{3_2},\ \Omega_{I_3}(t_{m+1}) = \Omega_{I_3}(t_m) \cup \left(t_{\mathcal{I}_3(j)}, \varphi_{\mathcal{I}_3(j)}\right); \tag{3.36}$$

$$\text{with probability } \alpha_{I_+} \frac{\beta_{I_1} I_1(t_m)}{\rho(t_m)}:$$

$$I_1(t_{m+1}) = I_1(t_m) - 1,\ I_+(t_{m+1}) = I_+(t_m) + 1; \tag{3.37}$$

$$\text{with probability } \frac{\eta_V I_4(t_m)}{\rho(t_m)}:$$

$$V(t_{m+1}) = V(t_m) + 1; \tag{3.38}$$

$$\text{with probability } \frac{\mu_V V(t_m)}{\rho(t_m)}:$$

$$V(t_{m+1}) = V(t_m) - 1, \text{ and additionally,}$$

$$V_{out}(t_{m+1}) = V_{out}(t_m) + 1 \text{ with probability } p_V. \tag{3.39}$$

We replace m with $m+1$ and return to relations (3.18)–(3.39).

3.4. Algorithm for numerical simulation

The modeling algorithm is similar to the algorithm given in Section 2.4. However, there are also some differences. In particular, we use the constants $\psi_{I_2}^{(\infty)}$, $\psi_{I_3}^{(\infty)}$, $\psi_{I_4}^{(\infty)}$ in relations (3.21), (3.23), (3.25) instead of the symbol «$+\infty$», accepting that

$$T_{mod} < \psi_{I_2}^{(\infty)} < \psi_{I_3}^{(\infty)} < \psi_{I_4}^{(\infty)}.$$

Similarly, if in formula (3.19) it turns out that $\rho(t_m) = 0$, then we assume that

$$\tau^{(m)} = \tau^{(\infty)} = const > \psi_{I_4}^{(\infty)}.$$

Note that for a fixed t_m the elements of each family $\Omega_{I_2}(t_m) \neq \emptyset$, $\Omega_{I_3}(t_m) \neq \emptyset$ sorted in ascending order $t_{\mathcal{I}_2(j)} + \varphi_{\mathcal{I}_2(j)}$, $t_{\mathcal{I}_3(j)} + \varphi_{\mathcal{I}_3(j)}$, indicated in relations (3.20), (3.22). This property significantly reduces the computational costs associated with finding the quantities $\psi_{I_2}^{(m)}$, $\psi_{I_3}^{(m)}$ introduced in (3.20), (3.22).

3.5. An example of numerical simulation

The stochastic model contains a large number of parameters that affect the dynamics of the $X(t)$ components given by formula (3.1). For an analytical study of $X(t)$, some methods of the theory of branching random processes can be used [27], [28], but a detailed study is a very difficult task. By analogy with Section 2.5, to plan computational experiments with the model, we use a deterministic analogue of the stochastic stage-dependent model. To construct the equations of a deterministic model and study its solutions, we will rely on the results of [10], [11], [29].

In contrast to (3.1), we assume that continuous non-negative real functions

$$I_0(t),\ I_1(t),\ I_2(t),\ I_3(t),\ I_4(t),\ V(t) \tag{3.40}$$

describe the number of populations I_0, I_1, I_2, I_3, I_4, V at time $t \in [0;\infty)$. The equations of the deterministic model have the form:

$$\frac{dI_0(t)}{dt} = \gamma_{T_0,V} T_0^* V(t) + \gamma_{T_0,I_4} T_0^* I_4(t) - (\mu_{I_0} + \gamma_{A,I_0} A^*) I_0(t), \tag{3.41}$$

$$\frac{dI_1(t)}{dt} = \gamma_{A,I_0} A^* I_0(t) - \beta_{I_1} I_1(t), \tag{3.42}$$

$$\frac{dI_2(t)}{dt} = \alpha_{I_2}\beta_{I_1} I_1(t) - \alpha_{I_2}\beta_{I_1} I_1(t-\omega_{I_2}) \ \sim\ I_2(t) = \int_{t-\omega_{I_2}}^{t} \alpha_{I_2}\beta_{I_1} I_1(s)ds, \tag{3.43}$$

$$\frac{dI_3(t)}{dt} = \alpha_{I_3}\beta_{I_1} I_1(t) - \alpha_{I_3}\beta_{I_1} I_1(t-\omega_{I_3}) \ \sim\ I_3(t) = \int_{t-\omega_{I_3}}^{t} \alpha_{I_3}\beta_{I_1} I_1(s)ds, \tag{3.44}$$

$$I_4(t) = \int_0^t \big(1 - F_{\omega_{I_4}}(s)\big)\big(2\,\alpha_{I_2}\beta_{I_1} I_1(t-\omega_{I_2}-s) + \alpha_{I_3}\beta_{I_1} I_1(t-\omega_{I_3}-s)\big)ds, \tag{3.45}$$

$$\frac{dV(t)}{dt} = \eta_V I_4(t) - (\mu_V + \gamma_{T_0,V} T_0^*) V(t),\ t \geqslant 0, \tag{3.46}$$

$$I_0(0) = 0,\ I_1(t) = 0,\ t \in [-\max\{\omega_{I_2}, \omega_{I_3}\}; 0], \tag{3.47}$$

$$I_2(0) = 0,\ I_3(0) = 0,\ I_4(0) = 0,\ V(0) = V_0 > 0. \tag{3.48}$$

The symbol «$\sim$» in equations (3.43), (3.44) means the equivalence of differential and integral equations, taking into account the initial data (3.47), (3.48). In equations (3.41)–(3.46) the derivatives of variables at the point $t = 0$ are their right-hand derivatives. For the subsequent study, it is important that the stochastic model and system (3.41)–(3.48) have the same parameters and initial data.

Note that system (3.41)–(3.46) is linear, the variable $I_4(t)$ is expressed in terms of the variable $I_1(t)$, and the variables $I_2(t)$, $I_3(t)$ are not explicitly included in the equations for the rest of the model variables. We also take into account that $1 - F_{\omega_{I_4}}(s) = 0$ for $s \geqslant b > 0$. Therefore, to study the asymptotic behavior of the dynamics of variables (3.40), it suffices to consider the system of equations

$$\frac{dI_0(t)}{dt} = \gamma_{T_0,V} T_0^* V(t) + \gamma_{T_0,I_4} T_0^* \widetilde{I}_4(t) - (\mu_{I_0} + \gamma_{A,I_0} A^*) I_0(t), \tag{3.49}$$

$$\frac{dI_1(t)}{dt} = \gamma_{A,I_0} A^* I_0(t) - \beta_{I_1} I_1(t), \tag{3.50}$$

$$\frac{dV(t)}{dt} = \eta_V \widetilde{I}_4(t) - (\mu_V + \gamma_{T_0,V} T_0^*) V(t),\ t \geqslant b, \tag{3.51}$$

supplemented by initial data (3.47), (3.48) and recording the variable $\widetilde{I}_4(t)$ in integral form:

$$\widetilde{I}_4(t) = \int_0^b \big(1 - F_{\omega_{I_4}}(s)\big)\big(2\,\alpha_{I_2}\beta_{I_1} I_1(t - \omega_{I_2} - s) + \alpha_{I_3}\beta_{I_1} I_1(t - \omega_{I_3} - s)\big) ds. \tag{3.52}$$

System (3.49)–(3.51), taking into account (3.52), refers to systems of Wazhevsky equations (positive systems) with delay. To study the solutions of the system (3.49)–(3.51), the properties of matrices of a special kind can be used. Denote

$$\omega_{I_4}^* = \int_0^b \big(1 - F_{\omega_{I_4}}(s)\big) ds,\ \varphi_{I_4} = (2\,\alpha_{I_2} + \alpha_{I_3})\beta_{I_1}\omega_{I_4}^*,$$

and introduce the matrix

$$Q = \begin{pmatrix} \mu_{I_0} + \gamma_{A,I_0} A^* & -\gamma_{T_0,I_4} T_0^* \varphi_{I_4} & -\gamma_{T_0,V} T_0^* \\ -\gamma_{A,I_0} A^* & \beta_{I_1} & 0 \\ 0 & -\eta_V \varphi_{I_4} & \mu_V + \gamma_{T_0,V} T_0^* \end{pmatrix}.$$

System (3.49)–(3.51) has a trivial equilibrium

$$I_0(t) \equiv 0,\ I_1(t) \equiv 0,\ V(t) \equiv 0. \tag{3.53}$$

Using the results of [29], we establish that the equilibrium (3.53) is asymptotically Lyapunov stable if $\det Q > 0$, which is equivalent to the inequality $R_0 < 1$, where

$$R_0 = \frac{(2\,\alpha_{I_2} + \alpha_{I_3})\,\omega_{I_4}^* \gamma_{A,I_0} A^* \big(\eta_V \gamma_{T_0,V} T_0^* + \gamma_{T_0,I_4} T_0^* (\mu_V + \gamma_{T_0,V} T_0^*)\big)}{(\mu_{I_0} + \gamma_{A,I_0} A^*)(\mu_V + \gamma_{T_0,V} T_0^*)}. \tag{3.54}$$

The constant R_0 given by formula (3.54) is called the base reproduction number. Since the system (3.49)–(3.51) is autonomous, the asymptotic stability of the trivial equilibrium (3.53) means also the exponential stability (3.53) [30]. Consequently, for $R_0 < 1$, the components of solution (3.40) after a certain transitional period will decrease exponentially.

If $R_0 > 1$ ($\det Q < 0$), then the behavior of the solution (3.40) on the interval $[0; T_{mod}]$ will essentially depend on V_0. In addition, some model parameters are not included in the expression for R_0, for example, β_{I_1}, ω_{I_2}, ω_{I_3}. Following the Euler method [30], we will look for a solution to the system of equations (3.49)–(3.51) in the form

$$X(t) = (I_0(t), I_1(t), V(t)) = (c_1, c_2, c_3)e^{\lambda t},$$

where c_1, c_2, c_3 are some constants, λ is a complex number. It is easy to establish, that for $R_0 > 1$ among the roots λ of the characteristic equation there exists a real root $\lambda_0 > 0$ [29]. This implies that for some initial data (3.47), (3.48) the solution of system (3.49)–(3.51) admits asymptotically exponential growth.

Let us turn to the stochastic model. Next, in parentheses, the dimension of the model parameters is indicated. Based on the [7], [8], [10], [11], we assume that $T_0^* = 5{\cdot}10^8$, $A^* = 2{\cdot}10^6$, $\mu_{I_0} = 2.5$ (day^{-1}), $\beta_{I_1} = 0.8$ (day^{-1}), $\omega_{I_2} = 0.75$ (day), $\eta_V = 150$ (day^{-1}), $\mu_V = 3.5$ (day^{-1}), $\gamma_{T_0,V} = 1.2 \cdot 10^{-9}$ (day^{-1}), $\gamma_{T_0,I_4} = 2.5 \cdot 10^{-7}$ (day^{-1}). Additionally, we assume that $p_V = 0.7$, $\omega_{I_3} = 1.25$ (day), the random variable ω_{I_4} is given by the expression $\omega_{I_4} = 0.75 + 0.6\,\xi^{2.5}$, where ξ is uniformly distributed over the interval $[0; 1]$, $[a; b] = [0.75; 1.35]$ (day), $\omega^*_{I_4} = 0.921$ (day). We will say that the reduced values of the parameters constitute the reference set.

Consider the dynamics of (3.1) on the interval $[0; T_{mod}] = [0; 10]$ days for model parameters that include parameters from the reference set and three additional sets:

$$\alpha_{I_2} = 0.45,\ \alpha_{I_3} = 0.25,\ \gamma_{A,I_0} = 7.3 \cdot 10^{-9}\ (\text{day}^{-1}), \tag{3.55}$$

$$\alpha_{I_2} = 0.25,\ \alpha_{I_3} = 0.65,\ \gamma_{A,I_0} = 2.1 \cdot 10^{-8}\ (\text{day}^{-1}), \tag{3.56}$$

$$\alpha_{I_2} = 0.25,\ \alpha_{I_3} = 0.65,\ \gamma_{A,I_0} = 4.5 \cdot 10^{-8}\ (\text{day}^{-1}). \tag{3.57}$$

Using (3.54) we find that $R_0 = 0.9037$, $R_0 = 2.5716$, $R_0 = 5.4084$ for the reference set of parameters supplemented with sets (3.55), (3.56), (3.57), respectively.

The results of numerical simulation are presented in Figures 5, 6, 7 and in Tables 2, 3, 4. Figures 5, 6, 7 show ten typical realizations of the auxiliary variable $\log_{10}(X_S(t) + 1)$ for the parameter sets (3.55), (3.56), (3.57), respectively, and $V_0 = 10, 50, 100$, where $X_S(t)$ — total number of all $X(t)$ components:

$$X_S(t) = I_0(t) + I_1(t) + I_2(t) + I_3(t) + I_4(t) + V(t).$$

Tables 2, 3, 4 contain interval estimates for the probability of the event $\mathbf{P}\{X_S(t) = 0\}$ for fixed $t \in [0; T_{mod}]$ at the confidence level $P = 0.99$ [23]. These interval estimates were calculated using a sample of $N = 10000$ realizations of the random process $H(t)$.

It can be seen from Figure 5 that for $R_0 < 1$, most of the $n = 10$ realizations of the variable $\log_{10}(X_S(t)+1)$ go to zero in a fairly short period of time, while others, oscillating, are supported at some level. It follows from Table 2 that the probability $\mathbf{P}\{X_S(t) = 0\}$ increases as t increases.

Figure 6 shows that for $R_0 = 2.5716$ only a part of $n = 10$ realizations of the variable $\log_{10}(X_S(t) + 1)$ vanishes in a short period of time (which is similar to the behavior of realizations for parameter set (3.55)), however, the remaining realizations allow significant growth. It can be seen from Table 3 that, with the set of parameters (3.56), the probability of the event $\mathbf{P}\{X_S(10) = 0\}$ is less than with the set (3.55).

Table 2. Interval estimates of the probability of the event $\boldsymbol{P}\{X_S(t) = 0\}$ at the confidence level $P = 0.99$ and $R_0 = 0.9037$ for the set of parameters (3.55)

t, day	V_0=10	V_0=50	V_0=100
0	0	0	0
0.1	0	0	0
0.4	0.0489 ± 0.0056	0	0
0.7	0.3542 ± 0.0123	0.0046 ± 0.0017	0
1.0	0.6595 ± 0.0122	0.1237 ± 0.0085	0.0151 ± 0.0031
5.0	0.9942 ± 0.0019	0.9730 ± 0.0042	0.9465 ± 0.0058
10.0	0.9972 ± 0.0014	0.9863 ± 0.0031	0.9738 ± 0.0041

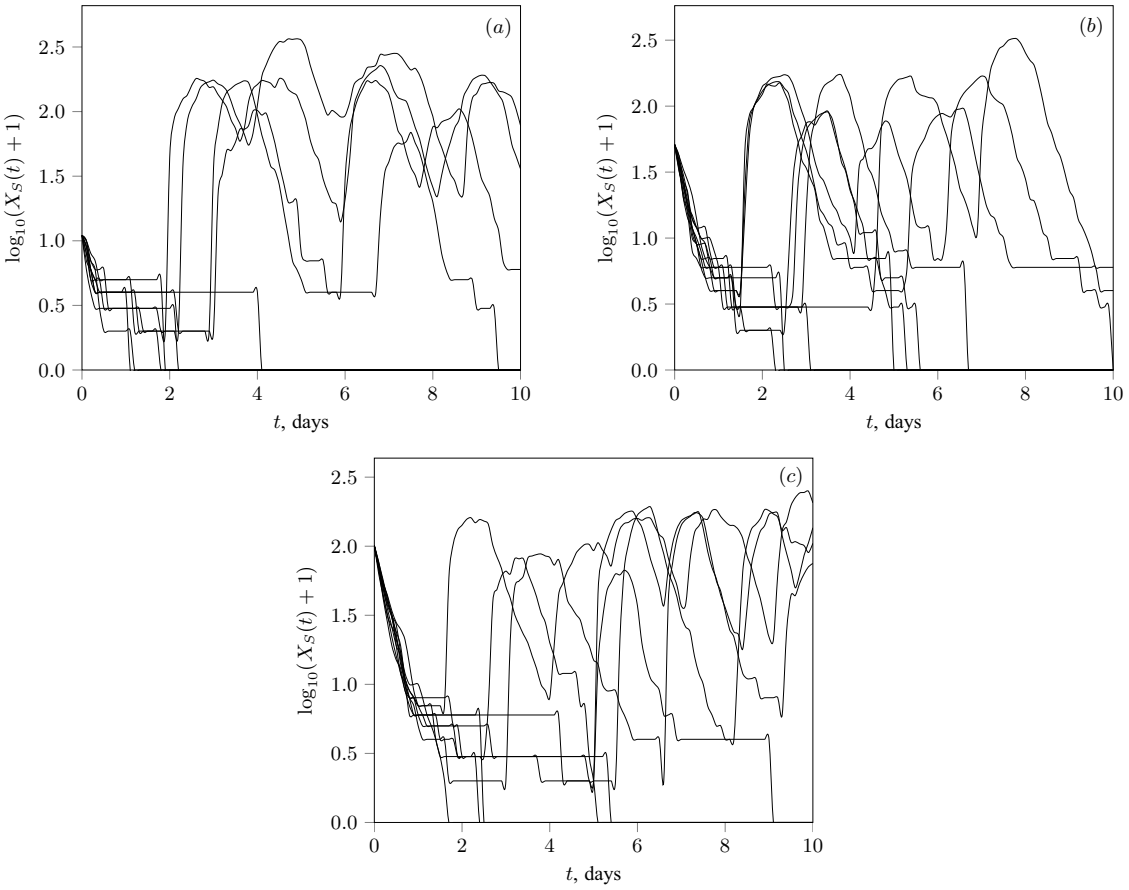

Fig. 5. Typical realizations of $\log_{10}(X_S(t) + 1)$ with $R_0 = 0.9037$ for a set of parameters (3.55) and (**a**) $V_0 = 10$; (**b**) $V_0 = 50$; (**c**) $V_0 = 100$.

Table 4 shows that with an increase in R_0 and V_0, the probability of eradicating the infection in the LN on the tenth day $\mathbf{P}\{X_S(10) = 0\}$ significantly decreases compared to the option (3.56). This is also confirmed by Figure 7, which demonstrates a significant increase in at least half of the $n = 10$ realizations of $\log_{10}(X_S(t) + 1)$.

Tables 5, 6 present interval estimates of expectations $\mathbf{E}I_{out}(t)$, $\mathbf{E}V_{out}(t)$ at the confidence level $P = 0.99$ [23] for $t = 10$ days in dependencies on V_0 and R_0. The interval estimates $\mathbf{E}I_{out}(t)$, $\mathbf{E}V_{out}(t)$ are calculated from a sample of $N = 10000$ realizations of the process $H(t)$.

Table 3. Interval estimates of the probability of the event $\boldsymbol{P}\{X_S(t) = 0\}$ at the confidence level $P = 0.99$ and $R_0 = 2.5716$ for the set of parameters (3.56)

t, day	V_0=10	V_0=50	V_0=100
0	0	0	0
0.1	0	0	0
0.4	0.0505 ± 0.0056	0	0
0.7	0.3486 ± 0.0123	0.0050 ± 0.0018	0
1.0	0.6483 ± 0.0123	0.1121 ± 0.0081	0.0133 ± 0.0029
5.0	0.9772 ± 0.0038	0.9015 ± 0.0077	0.8121 ± 0.0101
10.0	0.9792 ± 0.0037	0.9104 ± 0.0074	0.8290 ± 0.0099

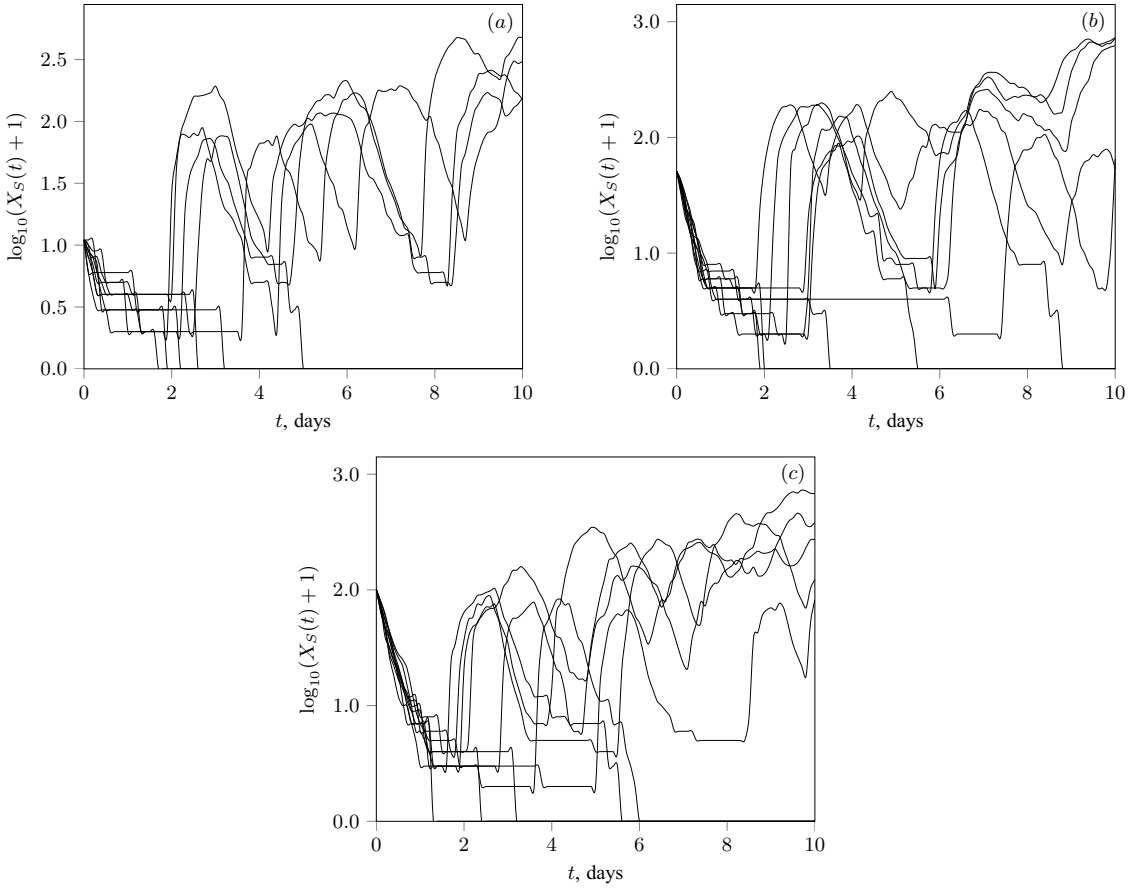

Fig. 6. Typical realizations of $\log_{10}(X_S(t) + 1)$ with $R_0 = 2.5716$ for a set of parameters (3.56) and (**a**) $V_0 = 10$; (**b**) $V_0 = 50$; (**c**) $V_0 = 100$.

The simulation results given in Tables 5, 6 have the following interpretation. An increase in R_0 and V_0 leads to a significant increase in the average number of I_0 cells and V virions that left the LN during the period $[0; 10]$ days. An increase in the average number of I_0 cells and V

Table 4. Interval estimates of the probability of the event $\boldsymbol{P}\{X_S(t) = 0\}$ at the confidence level $P = 0.99$ and $R_0 = 5.4084$ for the set of parameters (3.57)

t, day	V_0=10	V_0=50	V_0=100
0	0	0	0
0.1	0	0	0
0.4	0.0482 ± 0.0055	0	0
0.7	0.3420 ± 0.0122	0.0042 ± 0.0017	0
1.0	0.6406 ± 0.0124	0.1065 ± 0.0079	0.0112 ± 0.0027
5.0	0.9541 ± 0.0054	0.7964 ± 0.0104	0.6302 ± 0.0124
10.0	0.9548 ± 0.0054	0.7990 ± 0.0103	0.6340 ± 0.0124

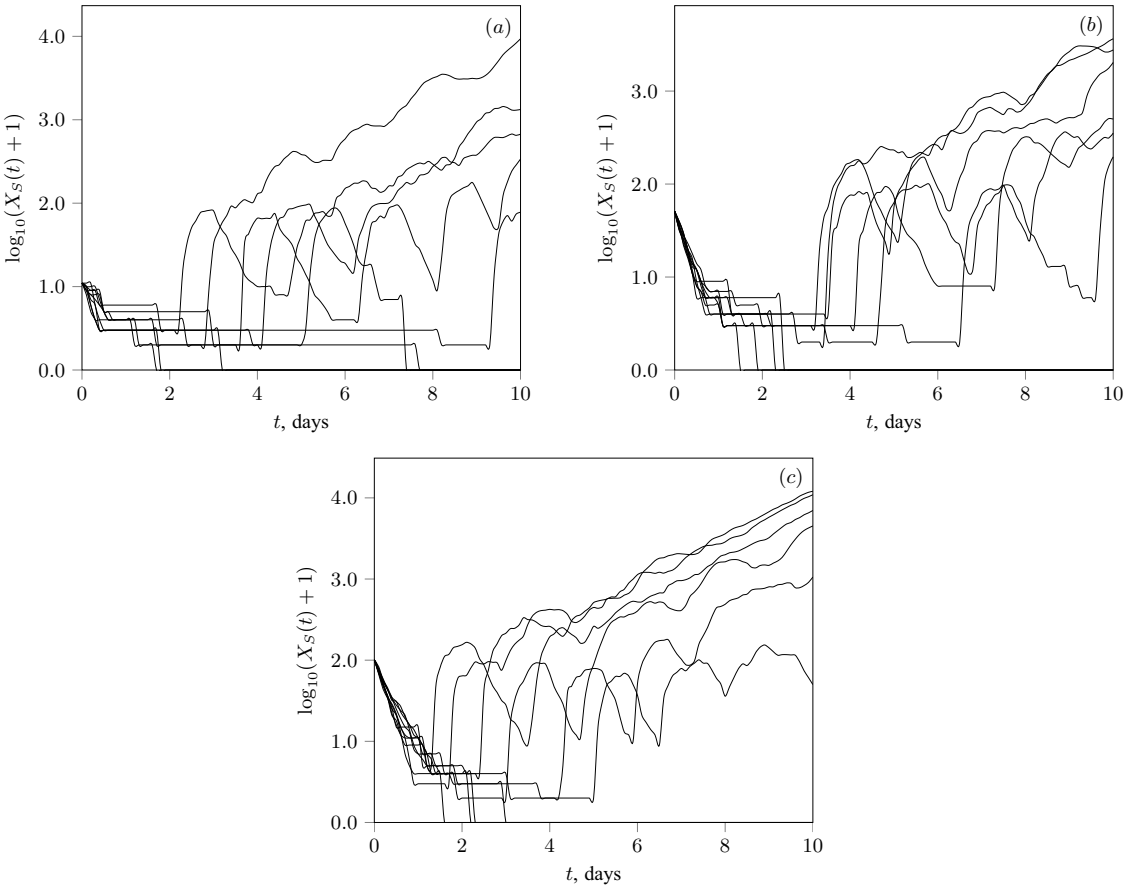

Fig. 7. Typical realizations of $\log_{10}(X_S(t) + 1)$ with $R_0 = 5.4084$ for a set of parameters (3.57) and (**a**) $V_0 = 10$; (**b**) $V_0 = 50$; (**c**) $V_0 = 100$.

virions that left the LN means an increase in the spread of HIV-1 infection in the body of an infected individual.

Concluding the section, we note that for any $V_0 > 0$, the deterministic model (3.41)–(3.48) does not allow eradication of HIV-1 infection in the LN on finite time intervals both for $R_0 < 1$ and for $R_0 \geqslant 1$. The calculations show that, within the framework of the stochastic model, it is possible to eradicate HIV-1 infection in LN at finite time intervals. For given sets of model parameters, the probability of eradication of HIV-1 infection in the LN on the time interval

Table 5. Interval estimates of the expectation $\boldsymbol{E}I_{out}(10)$ at the confidence level $P = 0.99$ depending on from V_0 and R_0

R_0	V_0=10	V_0=50	V_0=100
0.9037	5.347 ± 1.648	23.617 ± 3.229	50.015 ± 5.140
2.5716	40.014 ± 8.767	162.799 ± 17.713	320.057 ± 24.773
5.4084	297.835 ± 53.062	1437.796 ± 113.064	2924.625 ± 161.858

Table 6. Interval estimates of the expectation $\boldsymbol{E}V_{out}(10)$ at the confidence level $P = 0.99$ depending on from V_0 and R_0

R_0	V_0=10	V_0=50	V_0=100
0.9037	8.418 ± 1.040	40.140 ± 2.037	81.951 ± 3.234
2.5716	31.465 ± 5.788	132.323 ± 11.682	261.038 ± 16.332
5.4084	211.903 ± 36.877	1022.588 ± 78.512	2077.983 ± 112.318

$[0; 10]$ days is positive and takes values greater than 0.6 (see Tables 2, 3, 4). Therefore, the stochastic model provides more meaningful information than the deterministic model regarding the dynamics of the development of HIV-1 infection in the LN at the initial stage after infection of the individual.

Let us additionally note one of the computational problems that arise in the stochastic model. An increase in the size of the population I_4 to the values $I_4(t) \sim 10^6$ leads to a significant increase in the computational cost of finding the value $\psi_{I_4}^{(m)}$ specified in (3.24). It requires the involvement of methods for working with large data sets and parallel computing algorithms. Another possible way to reduce the cost of calculating $\psi_{I_4}^{(m)}$ is related to the modification of postulate **H10**. Let us assume that postulate **H10** uses the discrete distribution function $F_{\omega_{I_4}}(s)$ with a finite set of admissible values of the random variable ω_{I_4}. In this case it is possible to introduce several auxiliary families of unique types of cells in the population I_4. Each auxiliary family will be ordered by the time points at which the cells leave the I_4 population. Setting a unique type for the cell $\mathcal{I}_4$ and including it in one of the auxiliary families is simulated immediately after the appearance of $\mathcal{I}_4$ in the population I_4. The current value of $\psi_{I_4}^{(m)}$ is either kept unchanged, or the new value $\psi_{I_4}^{(m)}$ is found after several comparison operations.

4. CONCLUSIONS

The article presents deterministic and stochastic approaches to the construction of stage-dependent models that arise in immunological problems. An important aspect of stochastic stage-dependent models is the inclusion of non-Markovian constraints on individuals. Non-Markovian constraints on individuals are due to the use of rather arbitrary distribution functions that describe the duration of stay of individuals in populations.

The examples given in the article show that the deterministic and stochastic approaches complement each other and allow one to study the dynamics of variables in a continuous-discrete formulation. The results of the analytical study of deterministic models make it possible to plan

computational experiments with stochastic models based on the Monte Carlo method.

It should be noted that stochastic stage-dependent models are important for studying the dynamics of small populations. Within the framework of stochastic stage-dependent models, it is possible to estimate the probabilities of degeneration of populations and study the distribution laws of the number of populations over finite time intervals depending on the variation of model parameters. Fluctuations of variables can lead to the appearance of various variants of population dynamics, which are impossible within the framework of deterministic models.

The approach proposed in the article can be generalized to the construction and study of stage-dependent models that describe the dynamics of populations in problems of epidemiology, ecology, and demography.

The article was prepared with the financial support of the Russian Science Foundation, project 23-11-00116.

REFERENCES

1. Marchuk G.I. *Mathematical Models in Immunology. Numerical Methods and Experiments.* Moscow: Nauka, 1991. 300 p.
2. Banks H.T., Bortz D.M. A parameter sensitivity methodology in the context of HIV delay equation models. *J. Math. Biol.* 2005. V. 50. P. 607–625. doi: 10.1007/s00285-004-0299-x
3. Pawelek K.A., Liu S., Pahlevani F., Rong L. A model of HIV-1 infection with two time delays: mathematical analysis and comparison with patient data. *Math. Biosci.* 2012. V. 235. № 1. P. 98–109. doi: 10.1016/j.mbs.2011.11.002
4. Luzyanina T., Cupovic J., Ludewig B., Bocharov G. Mathematical models for CFSE labelled lymphocyte dynamics: asymmetry and time-lag in division. *J. Math. Biol.* 2014. V. 69. P. 1547–1583. doi: 10.1007/s00285-013-0741-z
5. Pitchaimani M., Monica C. Global stability analysis of HIV-1 infection model with three time delays. *J. Appl. Math. Comput.* 2015. V. 48. P. 293–319. doi: 10.1007/s12190-014-0803-4
6. Nechepurenko Yu., Khristichenko M., Grebennikov D., Bocharov G. Bistability analysis of virus infection models with time delays. *Disc. Cont. Dyn. Syst. - Series S.* 2020. V. 13. № 9. P. 2385–2401. doi: 10.3934/dcdss.2020166
7. Pertsev N., Loginov K., Bocharov G. Nonlinear effects in the dynamics of HIV-1 infection predicted by mathematical model with multiple delays. *Disc. Cont. Dyn. Syst. - Series S.* 2020. V. 13. № 9. P. 2365–2384. doi: 10.3934/dcdss.2020141
8. Pertsev N.V., Bocharov G.A., Loginov K.K. Numerical Simulation of T-Lymphocyte Population Dynamics in a Lymph Node. *J. Appl. Ind. Math.* 2022. V. 16. № 4. P. 737–750. doi: 10.1134/s1990478922040147
9. Pichugin B.J., Pertsev N.V., Topchii V.A., Loginov K.K. Stochastic modeling of age-structured population with time and size dependence of immigration rate. *Russ. J. Numer. Anal. Math. Model.* 2018. V. 33. № 5. P. 289–299. doi: 10.1515/rnam-2018-0024
10. Pertsev N.V., Pichugin B.Y., Loginov K.K. Stochastic Analog of the Dynamic Model of HIV-1 Infection Described by Delay Differential Equations. *J. Appl. Ind. Math.* 2019. V. 13. № 1. P. 103–117. doi: 10.1134/S1990478919010125
11. Bocharov G.A., Loginov K.K., Pertsev N.V., Topchii V.A. Direct statistical modeling of HIV-1 infection based on a non-Markovian stochastic model. *Comp. Math. and Math. Phys.* 2021. V. 61. № 8. P. 1229–1251. doi: 10.1134/S0965542521060026
12. Barbour A.D., Luczak M.J. Individual and patch behaviour in structured metapopulation models. *J. Math. Biol.* 2015. V. 71. No. 3. P. 713–733. doi: 10.1007/s00285-014-0834-3
13. Hyrien O., Peslak S.A., Yanev N.M., Palis J. Stochastic modeling of stress erythropoiesis

using a two-type age-dependent branching process with immigration. *J. Math. Biol.* 2015. V. 70. No. 7. P. 1485–1521. doi: 10.1007/s00285-014-0803-x
14. Chou T., Greenman C.D. A Hierarchical Kinetic Theory of Birth, Death and Fission in Age-Structured Interacting Populations. *J. Stat. Phys.* 2016. V. 164. No. 1. P. 49–76. doi: 10.1007/s10955-016-1524-x
15. Konstantin K. Loginov, Nikolay V. Pertsev, Valentin A. Topchii. Stochastic Modeling of Compartmental Systems with Pipes. *Math. Biol. Bioinf.* 2019. V. 14. No. 1. P. 188–203. doi: 10.17537/2019.14.188
16. Pertsev N., Loginov K., Lukashev A., Vakulenko Yu. Stochastic Modeling of Dynamics of the Spread of COVID-19 Infection Taking Into Account the Heterogeneity of Population According To Immunological, Clinical and Epidemiological Criteria. *Math. Biol. Bioinf.* 2022. V. 17. No. 1. P. 43–81. doi: 10.17537/2022.17.43
17. Pertsev N., Topchii V., Loginov K. Stochastic Modeling of the Epidemic Process Based On a Stage-Dependent Model with Non-Markov Constraints for Individuals. *Math. Biol. Bioinf.* 2023. V. 18. No. 1. P. 145–176. doi: 10.17537/2023.18.145
18. Geehman I.I., Skorohod A.V. *Introduction to the Theory of Random Processes.* Moscow: Nauka, 1977. 568 p.
19. Marchenko M.A., Mikhailov G.A. Parallel realization of statistical simulation and random number generators. *Russ. J. Numer. Anal. Math. Model.* 2002. V. 17. № 1. P. 113–124. doi: 10.1515/rnam-2002-0107
20. Marchenko M. *PARMONC – A Software Library for Massively Parallel Stochastic Simulation. Parallel Computing Technologies.* Berlin, Heidelberg: Springer-Verl. 2011. V. 6873. P. 302–316. (Lecture Notes in Computer Science). doi: 10.1007/978-3-642-23178-0_27
21. Mikhailov G.A., Voitishek A.V. *Numerical Statistical Simulation. Monte-Carlo Methods.* Moscow: Akademia, 2006. 367 p.
22. Pertsev N.V., Pichugin B.J., Pichugina A.N. Investigation of solutions to one family of mathematical models of living systems. *Russian Math.* 2017. V. 61. № 9. P. 48–60. doi: 10.3103/S1066369X17090067
23. Kramer G. *Mathematical Methods of Statistics.* Princeton: Princeton Univ. Press, 1999. 575 p.
24. Abbas A.K., Likhtman A.H., Pillai S. *Basic Immunology. Functions and Disorders of the Immune System.* Moscow: Geotar Media, 2022. 404 p.
25. Sattentau Q.J., Stevenson M. Macrophages and HIV-1: An Unhealthy Constellation. *Cell Host & Microbe.* 2016. V. 19. No. 3. P. 304–310. doi: 10.1016/j.chom.2016.02.013
26. Dimopoulos Y., Moysi E., Petrovas C. The Lymph Node in HIV Pathogenesis. *Curr. HIV/AIDS Rep.* 2017. V. 14. P. 133–140. doi: 10.1007/s11904-017-0359-7
27. Sevastijanov B.A. *Branching Processes.* Moscow: Nauka, 1971. 436 p.
28. Jagers P. *Branching Processes with Biological Applications.* New York: Wiley, 1975. 268 p.
29. Pertsev N.V. Stability of Linear Delay Differential Equations Arising in Models of Living Systems. *Sib. Adv. Math.* 2020. V. 30. № 1. P. 43–54. doi: 10.3103/s1055134420010046
30. Kolmanovskii V.B., Nosov V.R. *Stability and Periodic Modes of Regulated Systems with Delay.* Moscow: Nauka, 1981. 448 p.

Accepted 21.11.2023
Revised 29.11.2023
Published 13.12.2023

Математическая биология и биоинформатика
doi: 10.17537/2023.18.543

==========**МАТЕМАТИЧЕСКОЕ МОДЕЛИРОВАНИЕ** ==========

Стохастическое моделирование в иммунологии на основе стадия-зависимой структуры с немарковскими ограничениями для динамики отдельных клеток и патогенов

Перцев Н.В., Логинов К.К.

Институт математики им. С.Л. Соболева Сибирского отделения Российской академии наук, Новосибирск, Россия
Институт вычислительной математики им. Г.И. Марчука Российской академии наук, Москва, Россия

Аннотация. В работе приведен системный подход к моделированию реакции иммунной системы на вирусные инфекции. Разработаны и численно реализованы две непрерывно-дискретные стохастические модели, возникающие в математической иммунологии. Переменными моделей являются целочисленные случайные величины, отражающие количество индивидуумов (клеток и вирусных частиц), и наборы уникальных типов индивидуумов, учитывающие текущее состояние и историю пребывания индивидуумов в некоторых стадиях их развития. Законы распределения длительности указанных стадий отличны от экспоненциального или геометрического. Представлено вероятностное описание одно-стадийной стохастической модели динамики численности некоторой популяции. Сформулирована стохастическая модель развития ВИЧ-1 инфекции в лимфатическом узле в начальный период после заражения здорового человека. Приведен вычислительный алгоритм, основанный на методе Монте-Карло. Каждая из стохастических моделей дополняется детерминированным аналогом в форме интегральных и дифференциальных уравнений с запаздыванием. Представлены результаты численного моделирования.

Ключевые слова: *стадия-зависимая модель, немарковские ограничения для индивидуумов, метод Монте-Карло, вычислительный эксперимент, иммунология, ВИЧ-1 инфекция.*