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Numerical modelling of the transition of infected cells and virions between two lymph nodes in a stochastic model of HIV-1 infection

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Abstract — The paper is focused on stochastic modelling of the process of transition of infected cells and virions of HIV-1 infection between two lymph nodes. The model is based on the following assumptions: (1) the duration of transition of infected cells and virions between two lymph nodes is set using a time-dependent function, (2) infected cells produce virions in the process of transition between two lymph nodes, (3) infected cells and virions may die when moving between two lymph nodes. The methods of the theory of branching random processes are used to study analytically the model variables. An algorithm for statistical modelling of the number of infected cells and virions in the second lymph node is presented. The results of computational experiments studying the distribution law of the number of virions produced by one infected cell depending on the duration of movement between two lymph nodes are presented.

Keywords: Continuous-discrete stochastic model, branching random process, Monte Carlo method, computational experiment, HIV-1 infection, viral particles, lymphatic system.

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The present paper continues the study presented in [3, 4, 11, 12] and focused on modelling of population dynamics in application to the problem of studying the HIV-1 infection dynamics in the human body. An important aspect related to the study of the HIV-1 infection dynamics consists in taking into account the movement of cells of various types and viral particles through the human lymphatic system. The combination of mathematical models describing the flow of lymph in the human body [8, 9] and the dynamics of the HIV-1 infection development in individual lymph nodes [3, 11] is an urgent, but rather complex problem. To simplify the construction of a model of the HIV-1 infection dynamics without involving hydrodynamic models, an approach in which the transition of cells and viral particles between lymph nodes is set parametrically is proposed in [3, 4]. Functions reflecting the duration of transitions of cells and viral particles between lymph nodes and satisfying fairly simple assumptions are used here. In particular, functions containing

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constants and weighted sums of cosines with different oscillation periods were used in [3, 4].

The approach proposed in [3, 4, 12] can be used to construct a stochastic compartment model of the HIV-1 infection dynamics taking into account the production of viral particles by infected cells during their transition between lymph nodes. Infected cells are understood here as target cells for HIV-1 infection viruses (dendritic cells, macrophages, CD4+ T-lymphocytes). Viral particles produced by infected cells during the transition between lymph nodes represent an additional source of occurrence of viral particles in individual lymph nodes.

Such an additional source may significantly affect the dynamics of HIV-1 infection in the human body.

The aim of this paper is to construct and study a stochastic model describing the production of viral particles by infected cells during their transition between two lymph nodes. The goals of the work include: (1) description of the transition of infected cells and virus particles generated by them between two lymph nodes; (2) analytical study of probabilistic characteristics of the model variables using methods of the theory of branching random processes; (3) development of a computational algorithm based on the Monte Carlo method; (4) computational experiments to study the distribution law for the number of viral particles produced by one infected cell depending on the duration of transition between two lymph nodes.

1. Description of the model

Introduce the following notations:

- I is an infected cell beginning its transition from the lymph node N_1 to the lymph node N_2 through the lymphatic vessel N_{12};
- W is the viral particle produced by the cell I in the process of transition through the lymphatic vessel N_{12};
- D are the particles W and cells I dying in the process of transition through the lymphatic vessel N_{12};
- I_2 is the infected cell in the lymph node N_2;
- V_2 is the viral particle in the lymph node N_2.

Let the cell I begin its transition from the lymph node N_1 to the lymph node N_2 at the time moment $\tau \in R$. Assume that $\Delta(\tau) \in R_+$ specifies the duration of transition of the cell I through the lymphatic vessel N_{12}. In this case the expression $\tau + \Delta(\tau)$ means the moment when the transition of the cell I was completed if it did not die during the transition. Assume that $\Delta(\tau)$ satisfies the following two conditions:

C_1: if $\tau_1 < \tau_2$, then $\tau_1 + \Delta(\tau_1) < \tau_2 + \Delta(\tau_2)$, $\tau_1, \tau_2 \in R$;

C_2: $\Delta_* \leqslant \Delta(\tau) \leqslant \Delta^{**}$, $\tau \in R$, where Δ_*, Δ^{**} are positive constants.

Condition C_1 means that the cell I beginning its transition at the time moment $\tau_2 > \tau_1$ does not 'catch up' the cell I beginning its transition at the time moment τ_1. Condition C_2 means that neither instant, nor infinitely long transitions of the cell I from N_1 to N_2 are feasible.

The schematic representation of the 'destiny' of the cell I and virus particles W produced by it is as follows:

$$I \xrightarrow{\lambda} D, \quad I \xrightarrow{\nu} I + W, \quad W \xrightarrow{\mu} D \tag{1.1}$$

$$I|_\tau \longrightarrow I_2|_{\tau+\Delta(\tau)}, \quad W|_{\tau_W} \longrightarrow V_2|_{\tau+\Delta(\tau)} \tag{1.2}$$

where λ, ν, μ are positive constants, τ_W is the time of appearance of the viral particle W produced by the cell I during its transition. Relation (1.1) has the following probabilistic interpretation. Over a period of time $(\tau+t, \tau+t+h)$, $t \geqslant 0$, $h \to 0+$, the cell I dies with the probability $\lambda h + o(h)$, the cell I produces one viral particle W with the probability $\nu h + o(h)$. During the same time period, the viral particle W dies with the probability of $\mu h + o(h)$; the specified events do not occur with the probability $1 - (\nu + \lambda + \mu)h + o(h)$. Relations (1.2) are interpreted as a description of the cell I and viral particles W which complete their transitions at the time moment $\tau + \Delta(\tau)$. If the cell I did not die in the process of transition, then at the time moment $\tau + \Delta(\tau)$ it becomes the cell I_2. If the viral particle W appeared at the time moment $\tau < \tau_W < \tau + \Delta(\tau)$ and did not die in the process of transition, then at the time moment $\tau + \Delta(\tau)$ it becomes the viral particle V_2. Here we accept that each appearing viral particle W moves 'near' the cell I. We assume that the cell I and all viral particles W produced by it behave independently of each other and preceding events.

By $G_r(u) = 0$, $u < 0$, $G_r(u) = 1 - \mathrm{e}^{-ru}$, $u \geqslant 0$, we denote the exponential distribution with the parameter $r \geqslant 0$. Descriptions (1.1), (1.2) imply that the lifetime of the cell I has the distribution $G_\lambda(u)$, the lifetime of the viral particle W has the distribution $G_\mu(u)$. Moreover, the duration of time before production of the next viral particle W by the existing cell I has the distribution $G_\nu(u)$.

Assume $I(\tau + \Delta(\tau)) = 0$ if the cell I died before the time moment $\tau + \Delta(\tau)$ and $I(\tau + \Delta(\tau)) = 1$ otherwise; $W(\tau + \Delta(\tau))$ is the number of viral particles W at the time moment $\tau + \Delta(\tau)$. Using the above assumptions, we can write down the following expressions for the number $I_2(\tau + \Delta(\tau))$ of infected cells I_2 and number $V_2(\tau + \Delta(\tau))$ of viral particles V_2 in the lymph node N_2 at the time moment $\tau + \Delta(\tau)$:

$$I_2(\tau + \Delta(\tau)) = I_2(\tau + \Delta(\tau) - 0) + I(\tau + \Delta(\tau)) \tag{1.3}$$

$$V_2(\tau + \Delta(\tau)) = V_2(\tau + \Delta(\tau) - 0) + W(\tau + \Delta(\tau)) \tag{1.4}$$

where $I_2(\tau + \Delta(\tau) - 0)$ and $V_2(\tau + \Delta(\tau) - 0)$ are the numbers of infected cells I_2 and viral particles V_2 in the lymph node N_2 at the moment when survived viral particles W and the cell I complete their transition. The distribution law for the random variable $I(\tau + \Delta(\tau))$ has the following sufficiently simple form:

$$P\{I(\tau + \Delta(\tau)) = 0\} = 1 - \mathrm{e}^{-\lambda\Delta(\tau)}, \qquad P\{I(\tau + \Delta(\tau)) = 1\} = \mathrm{e}^{-\lambda\Delta(\tau)}.$$

To complete the construction in formulas (1.3), (1.4), we have to know the distribution law of the pair $I(\tau+\Delta(\tau))$, $W(\tau+\Delta(\tau))$, namely,

$$P_{nm} = P\{I(\tau+\Delta(\tau)) = n,\ \ W(\tau+\Delta(\tau)) = m\}, \quad n = 0,1, \quad m = 0,1,2,\dots\ . \tag{1.5}$$

The explicit form of distribution (1.5) is described in the next section.

2. Application of the theory of branching processes to study the model

We study distribution law (1.5) analytically in terms of a branching process with two types of particles [14]. We introduce the terminology typical for branching processes, replace the model from the first section to an equivalent one, and call this modification the 'BP-model', i.e., the model written in terms of a branching process. Assume that the original model has a single particle A_1 at the time moment $t = 0$. In the original model, the lifetime of the particle A_1 has the distribution $G_\lambda(t)$ with $\lambda > 0$. For the sake of convenience of studying a particular, but important case of the BP-model, we assume that the parameter λ may take zero value and hence $G_\lambda(t)$ is such that $\lambda \geqslant 0$. The particle A_1 may produce particles A_2 many times during its lifetime. The time before the first particle A_2 is produced by the particle A_1 and between births of next particles A_2 is random and has the distribution $G_\nu(t)$ with $\nu > 0$. The lifetime of the particle A_2 is described by the distribution $G_\mu(t)$ with $\mu > 0$. All random variables in this definition are independent.

Proceed to definition of the BP-model. Denote the studied particles in this new model by $\mathscr{A}_1$ and $\mathscr{A}_2$, respectively, and call them particles of the first and second types. The formal distinction from the original model is that at the moment of birth of the particle $\mathscr{A}_2$ we assume that $\mathscr{A}_1$ also dies and simultaneously generates new $\mathscr{A}_1$. The death of the original particle A_1 corresponds to the death of $\mathscr{A}_1$. In the theory of probability, this approach is called the method of probabilistic space. In this case, the distributions of lifetime of particles in the new process are changed, but the numbers of particles of all types coincide in both processes at each time moment.

Following [14], we describe the evolution of particles in terms of generating functions and lifetime distributions. By $s_1, s_2, s \in [0,1]$ we denote the arguments of the generating function used below. The lifetime of particles of the first type has the distribution $G_{\lambda+\nu}(t)$. If a particle of the first type dies, it does not generate descendants with the probability $p_{0,0} = \lambda/(\lambda+\nu)$, it generates a one descendant of the first type and one descendant of the second type with the probability $p_{1,1} = \nu/(\lambda+\nu)$. This implies that the generating function of the number of descendants of particles of the first type has the form

$$h_1(s_1,s_2) = p_{0,0}(s_1)^0(s_2)^0 + p_{1,1}(s_1)^1(s_2)^1 = \frac{\lambda}{\lambda+\nu} + \frac{\nu}{\lambda+\nu}s_1s_2.$$

The lifetime of each particle of the second type has the distribution $G_\mu(t)$ and they do not generate descendants in the case of their death, i.e., the generating function of the number of descendants of a particle of the second type is $h_2(s_1,s_2) = 1$.

By $x(t)$ and $y(t)$ we denote the numbers of particles of the first and second types, respectively, at the time moment $t \geqslant 0$. Assume that $x(0) = 1$, $y(0) = 0$. Introduce the following conditional generating functions of the process $(x(t), y(t))$:

$$F_i(t, s_1, s_2) = E\left(s_1^{x(t)} s_2^{y(t)} \big| (x(0), y(0)) = (\delta_{1i}, 1 - \delta_{1i})\right), \quad t > 0 \tag{2.1}$$

where the symbol $E(\cdot)$ denotes the mathematical expectation, for each fixed $t \geqslant 0$ the product $s_1^{x(t)} s_2^{y(t)}$ is an auxiliary random variable, the expression δ_{ij} is the Kronecker symbol ($\delta_{ij} = 1$ for $i = j$ and $\delta_{ij} = 0$ for $i \neq j$). Applying the traditional total probability formula for generations functions (2.1), we get the following system of equations for $F_1(t, s_1, s_2)$ and $F_2(t, s_1, s_2)$:

$$\begin{aligned} F_1(t, s_1, s_2) &= s_1\big(1 - G_{\lambda+\nu}(t)\big) + \lambda(\lambda+\nu)^{-1} G_{\lambda+\nu}(t) \\ &\quad + \nu(\lambda+\nu)^{-1} \int_0^t F_1(t-u, s_1, s_2) F_2(t-u, s_1, s_2) \mathrm{d}G_{\lambda+\nu}(u) \end{aligned} \tag{2.2}$$

$$F_2(t, s_1, s_2) = s_2\big(1 - G_{\mu}(t)\big) + G_{\mu}(t). \tag{2.3}$$

Using the explicit form of all $G_r(t)$ and the fact that $F_2(t, s_1, s_2) \equiv F_2(t, s_2)$, rewrite system (2.2), (2.3) in the form

$$\begin{aligned} F_1(t, s_1, s_2) &= s_1 \mathrm{e}^{-(\lambda+\nu)t} + \lambda(\lambda+\nu)^{-1}\big(1 - \mathrm{e}^{-(\lambda+\nu)t}\big) \\ &\quad + \nu(\lambda+\nu)^{-1} \int_0^t F_1(t-u, s_1, s_2) F_2(t-u, s_2) \mathrm{d}G_{\lambda+\nu}(u) \end{aligned} \tag{2.4}$$

$$F_2(t, s_2) = 1 + (s_2 - 1)\mathrm{e}^{-\mu t}. \tag{2.5}$$

Note that the component $x(t)$ of the studied process can take only two values, namely, $x(t) = 1$ or $x(t) = 0$. In addition, expression (2.4) contains an exponential under the sign of differential. This allows us to study solutions to system (2.4), (2.5) applying not the canonical method using the recovery function, but transforming (2.4), (2.5) to first order differential equations with separating variables.

Using the expression for the generating function $h_1(s_1, s_2)$, we obtain that for $\lambda = 0$ and $\nu > 0$ a particle of the first type always generates after its death one descendant in the form of particles of the first and second type, thus we have $P\{x(t) = 1\} = 1$. Therefore,

$$F_1(t, s_1, s_2) = F_1(t, 1, s_2) = E\left(s_2^{y(t)} \big| x(0) = 1\right)$$

and it is sufficient to describe $F_0(t, s) = E\big(s^{y(t)} \big| x(0) = 1\big)$.

Theorem 2.1. *Let $\lambda = 0$ in the BP-model. In this case the generating function of the number of particles of second type is*

$$F_0(t, s) = \exp\{(s-1)\nu\mu^{-1}(1 - \mathrm{e}^{-\mu t})\} \tag{2.6}$$

i.e., the random variable $y(t)$ has the Poisson distribution with the parameter $\nu\mu^{-1}(1 - \mathrm{e}^{-\mu t})$.

Proof. For $\lambda = 0$ equations (2.4), (2.5) imply

$$F_0(t,s) = \mathrm{e}^{-\nu t} + \nu \mathrm{e}^{-\nu t} \int_0^t F_0(u,s)\big(1 + (s-1)\mathrm{e}^{-\mu u}\big)\mathrm{e}^{\nu u}\mathrm{d}u. \tag{2.7}$$

Denote

$$\widetilde{F}(t,s) = F_0(t,s)\big(1 + (s-1)\mathrm{e}^{-\mu t}\big)\mathrm{e}^{\nu t}, \quad z = z(t) = \int_0^t \widetilde{F}(u,s)\mathrm{d}u$$

considering s as a parameter. Transform (2.7) to the differential equation

$$z' = \big(1 + (s-1)\mathrm{e}^{-\mu t}\big)(1 + \nu z)$$

and derive from this equation

$$1 + \nu z = \exp\{\nu t + (s-1)\nu\mu^{-1}(1 - \mathrm{e}^{-\mu t})\}. \tag{2.8}$$

Returning to the original notations and differentiating both sides of equation (2.8), we easily obtain the representation

$$\begin{aligned} z' = \widetilde{F}(t,s) &= F_0(t,s)\big(1 + (s-1)\mathrm{e}^{-\mu t}\big)\mathrm{e}^{\nu t} \\ &= \exp\{\nu t + (s-1)\nu\mu^{-1}(1 - \mathrm{e}^{-\mu t})\}(1 + (s-1)\mathrm{e}^{-\mu t}) \end{aligned}$$

which implies relation (2.6). It is well known that the Poisson distribution with the parameter $\gamma > 0$ has the generating function $\exp\{(s-1)\gamma\}$. This completes the proof of the theorem.

Substitute $s_1 = 0$, $s_2 = 1$ into system (2.4), (2.5). We get the equation for $P\{x(t) = 0\} = F_1(t,0,1)$ having the unique solution $1 - \mathrm{e}^{-\lambda t}$. Therefore, $P\{x(t) = 1\} = \mathrm{e}^{-\lambda t}$. This proves the equivalence of the original model and BP-model.

By $\chi(t)$ we denote the indicator of the event $\{x(t) = 1\}$ at the time moment $t \geqslant 0$. In this case,

$$P\{\chi(t) = 1\} = \mathrm{e}^{-\lambda t}, \;\; P\{\chi(t) = 0\} = 1 - \mathrm{e}^{-\lambda t}.$$

Corollary 2.1. Let $\lambda > 0$ in the BP-model. Then the conditional distribution of the random variable $(y(t)|x(t) = 1)$ is Poisson with the parameter $\nu\mu^{-1}\big(1 - \mathrm{e}^{-\mu t}\big)$ and, in addition,

$$E\big(s^{y(t)}\chi(t)\big) = \exp\big\{(s-1)\nu\mu^{-1}\big(1 - \mathrm{e}^{-\mu t}\big)\big\}\mathrm{e}^{-\lambda t} \tag{2.9}$$

$$E(y(t)\chi(t)) = \nu\mu^{-1}\big(1 - \mathrm{e}^{-\mu t}\big)\mathrm{e}^{-\lambda t}. \tag{2.10}$$

Proof. For $\lambda > 0$ denote the generating function of the conditional distribution of the variable $(y(t)|x(t) = 1)$ by

$$Q_1(t,s) = E\big(s^{y(t)}\big|x(t) = 1\big).$$

Associate $Q_1(t,s)$ with the original generating functions, i.e.,

$$\frac{\partial}{\partial s_1}F_1(t,s_1,s) = E\left(s^{y(t)}\chi(t)\right) = Q_1(t,s)P\{\chi(t)=1\} = Q_1(t,s)\mathrm{e}^{-\lambda t}.$$

Differentiating the left- and right-hand sides of (2.4) with respect to s_1 and taking into account (2.5), after obvious transformation we get the equation for $Q_1(t,s)$ coinciding with (2.7) after the change of $F_0(t,s)$ by $Q_1(t,s)$. Therefore, $Q_1(t,s) = F_0(t,s)$. Relation (2.9) follows from (2.7) according to the total probability formula and (2.10) follows from (2.9) as its derivative with respect to s at $s=1$. This completes the proof of the corollary.

The function $1-\chi(t)$ is the indicator of the event $\{x(t)=0\}$ at the time moment $t \geqslant 0$, $1-\chi(0)=0$.

Theorem 2.2. *Let $\lambda > 0$ in the BP-model. Then the generating function of the random variable $y(t)(1-\chi(t))$ is a convolution of the functions from* (2.6) *with the function $G_\lambda(u)$ over the temporal parameter, and the mathematical expectation for $y(t)(1-\chi(t))$ has the form*

$$E(y(t)(1-\chi(t))) = \frac{\lambda\nu}{\mu(\mu-\lambda)}\mathrm{e}^{-\lambda t} - \frac{\lambda}{\mu-\lambda}\mathrm{e}^{-\mu t} + \frac{\lambda}{\mu}\mathrm{e}^{-(\mu+\lambda)t}, \quad \mu \neq \lambda$$
$$E(y(t)(1-\chi(t))) = \nu\mathrm{e}^{-\mu t}t - \nu\mu^{-1}\mathrm{e}^{-\mu t}(1-\mathrm{e}^{-\mu t}), \quad \mu = \lambda.$$

Proof. Fix $t,\ell \in R$, so that $t > \ell > 0$. Assume $(x(\ell),y(\ell)) = (0,n)$, where n is some natural number. According to the definition, the generating function of our process is

$$E\left(s^{y(t)}\middle|x(\ell)=0, y(\ell)=n\right) = \left(1-\mathrm{e}^{-\mu(t-\ell)}(1-s)\right)^n. \tag{2.11}$$

The generating function of (2.11) corresponds to a random variable having the binomial distribution with the parameters n and $p = \mathrm{e}^{-\mu(t-\ell)}$. If n is a random variable having the Poisson distribution with the parameter $\gamma > 0$, then instead of (2.11) we get the generating function

$$F_{\ell,\gamma}(t,s) = \sum_{i=0}^{\infty}\frac{\gamma^i}{i!}(1-\mathrm{e}^{-\mu(t-\ell)}(1-s))^i\mathrm{e}^{-\gamma} = \exp\{\gamma\mathrm{e}^{-\mu(t-\ell)}(s-1)\} \tag{2.12}$$

which corresponds to a random variable having the Poisson distribution with the parameter $\gamma\mathrm{e}^{-\mu(t-\ell)}$. Let $\ell > 0$ be the moment of death of a particle of the first type. In this case for $t=\ell$ the number of particles of the second type has the Poisson distribution with the parameter $\nu\mu^{-1}\left(1-\mathrm{e}^{-\mu\ell}\right)$, and for $t > \ell$ it has the Poisson distribution with the parameter

$$\nu\mu^{-1}\mathrm{e}^{-\mu(t-\ell)}\left(1-\mathrm{e}^{-\mu\ell}\right) = \nu\mu^{-1}\mathrm{e}^{-\mu t}\left(\mathrm{e}^{\mu\ell}-1\right)$$

which follows from (2.12). Therefore, according to the total probability formula, we get

$$E\big(s^{y(t)}(1-\chi(t))\big) = \lambda \int_0^t \mathrm{e}^{-\lambda u} \exp\{(s-1)\nu\mu^{-1}\mathrm{e}^{-\mu t}\big(\mathrm{e}^{\mu u}-1\big)\}\mathrm{d}u. \qquad (2.13)$$

Differentiating both sides of relation (2.13) with respect to s and assuming $s = 1$, for $\mu \neq \lambda$ we get

$$\begin{aligned} E(y(t)(1-\chi(t))) &= \lambda \mathrm{e}^{-\mu t} \int_0^t \mathrm{e}^{-\lambda u} \nu\mu^{-1}\big(\mathrm{e}^{\mu u}-1\big)\mathrm{d}u \\ &= \frac{\lambda\nu}{\mu(\mu-\lambda)}\mathrm{e}^{-\lambda t} - \frac{\lambda}{\mu-\lambda}\mathrm{e}^{-\mu t} + \frac{\lambda}{\mu}\mathrm{e}^{-(\mu+\lambda)t} \end{aligned}$$

and for $\mu = \lambda$ we have

$$E(y(t)(1-\chi(t))) = \nu\mathrm{e}^{-\mu t}t - \nu\mu^{-1}\mathrm{e}^{-\mu t}(1-\mathrm{e}^{-\mu t})$$

which completes the proof of the theorem.

Remark 2.1. The generating function for $y(t)(1-\chi(t))$ is determined by integral (2.13) which cannot be expressed in elementary functions. Substituting $s = 0$ into the indicated generating function, we get the probability $P\{y(t) = 0; x(t) = 0\}$ of degeneration of the process to the time moment t. For fixed $t > 0$ and the parameters λ, ν, μ, the probability $P\{y(t) = 0; x(t) = 0)$ can be calculated only approximately by using known numerical methods for calculation of definite integrals. Note that for $s = 0$ the right-hand side of (2.13) implies $P\{y(t) = 0; x(t) = 0) \to 1$ for $t \to +\infty$.

Using Theorems 2.1, 2.2, Corollary 2.1, and omitting obvious calculations, we obtain the following result.

Corollary 2.2. The mathematical expectations $Ex(t)$, $Ey(t)$ of the numbers of particles of the first and second types in the BP-model have the form

$$\begin{aligned} Ex(t) &= \mathrm{e}^{-\lambda t} \\ Ey(t) &= \nu t\,\mathrm{e}^{-\mu t}, \quad \mu = \lambda > 0 \\ Ey(t) &= \frac{\nu}{\mu-\lambda}\big(\mathrm{e}^{-\lambda t} - \mathrm{e}^{-\mu t}\big), \quad \mu \neq \lambda > 0 \\ Ey(t) &= \nu\mu^{-1}(1-\mathrm{e}^{-\mu t}), \quad \lambda = 0. \end{aligned}$$

For $\lambda > 0$ the mathematical expectation $Ey(t)$ attains its maximal value at the point $t = t_{\max}$, i.e.,

$$t_{\max} = \frac{1}{\mu}, \quad \mu = \lambda \qquad (2.14)$$

$$t_{\max} = \frac{1}{\lambda-\mu}\ln\frac{\lambda}{\mu}, \quad \mu \neq \lambda. \qquad (2.15)$$

3. Numerical simulation algorithm

In order to study the model described in the first section numerically, we apply the Monte Carlo method. Let the cell I begin its transition from the lymph node N_1 to the lymph node N_2 at some time moment τ. Assume that $T = \Delta(\tau)$ and construct the algorithm to simulate values of the pair $x(t)$, $y(t)$, i.e., the numbers of particles of the first and second type considered in the second section for $t = T$. Here we use the results of Theorems 2.1, 2.2 and Corollary 2.1. Taking into account the notations introduced earlier, we assume that

$$I(\tau+\Delta(\tau)) = x(T), \quad W(\tau+\Delta(\tau)) = y(T).$$

To generate the random variables $x(T)$ and $y(T)$, we use the generators of pseudorandom numbers and formulas described in [6, 5, 7]. Let $[\xi]$ denote the integer value of the variable ξ. The simulation algorithm consists of several successive steps.

Step 0. Specify the parameters $\lambda > 0$, $\nu > 0$, $\mu > 0$ of the model, time moments τ and $T = \Delta(\tau)$.

Step 1. Simulate the lifetime L_{A_1} of a particle of the first type by the formula

$$L_{A_1} = -\frac{1}{\lambda}\ln\alpha_1$$

where α_1 is a random variable distributed uniformly in the interval $(0,1)$. If $L_{A_1} \geqslant T$, then assume $x(T) = 1$ and calculate the parameter

$$\gamma = \nu\mu^{-1}(1-\mathrm{e}^{-\mu T}).$$

If $L_{A_1} < T$, then assume $x(T) = 0$ and calculate the parameter

$$\gamma = \nu\mu^{-1}\mathrm{e}^{-\mu T}(\mathrm{e}^{\mu L_{A_1}} - 1).$$

Step 2. Simulate the number of particles of the second type as a random variable $y(T)$ having the Poisson distribution with the parameter γ. Following Section 1.3.8 of [7], for $\gamma < 9$ we use recurrent formulas linking the probabilities P_{k+1} and P_k, $k = 0,1,2,\ldots$, in the Poisson distribution. If $\gamma \geqslant 9$, then assume $y(T) = [\sqrt{\gamma}\eta_{0,1} + \gamma]$, where $\eta_{0,1}$ is a random variable having the standard normal distribution. Here we use formulas from Section 1.10.2 of [7] allowing us to obtain pairs of independent random variables $\eta_{0,1}$ simultaneously.

Step 3. Assume $I(\tau+\Delta(\tau)) = x(T)$, $W(\tau+\Delta(\tau)) = y(T)$ and complete the calculations.

This algorithm is implemented in the form of a console modelling application written in the C++ programming language in the Visual Studio 2008 integrated development environment. Input parameters are read from a special configuration inifile. The simulation results, i.e., implementations of the variables $x(T)$, $y(T)$ are stored in a separate text file.

4. Results of numerical experiments

The goal of computational experiments was to study the distribution of the number of viral particles W coming to the lymph node N_2 depending on changes in the duration of the transition $\Delta(\tau)$ relative to the time $t_{\max}$ given by formulas (2.14), (2.15). The simulation of the pair of random variables $x(T)$, $y(T)$ was performed for four values of $T = \Delta(\tau)$. The results of simulation are presented in the form of histograms of the random variables

$$W_i = W_i(\tau + \Delta(\tau)) = y(T_i), \quad i = 1,2,3,4.$$

Each histogram is constructed based on a sample of $N = 500$ implementations of the pair of random variables $x(T_i)$, $y(T_i)$ for given T_i, $i = 1,2,3,4$. The values of parameters of the model (in dimensional form) are taken according to [1, 3, 11] (including the estimates of the parameters from the papers cited there), namely, $\lambda = 0.81$ day^{-1}, $\nu = 250$ day^{-1}, $\mu = 3.2$ day^{-1}. This gives that the average lifetimes of cells I and viral particles W are 29.63 and 7.5 hours, respectively, and the average time to the reproduction of the next viral particle W by a cell I is 5.76 minutes. For these values of the parameters we get that $t_{\max} = 0.5748$ days. For our calculations we used $T_1 = 0.05$, $T_2 = 0.5748$, $T_3 = 0.75$, and $T_4 = 1.25$ days. In each experiment, the dimensional time and dimensional parameters were transformed to dimensionless form so that the transition of cells I and viral particle W between two lymph nodes occurs within the time interval $[0,1]$.

Figure 1 presents the results of the first experiment. The duration of the transition T_1 is such that the probability of death of a particle of the first type (cell I) within the period $[0,T_1]$ is sufficiently small, i.e., $1 - \mathrm{e}^{-\lambda T_1} \approx 0.0397$. It is seen that the number of viral particles W_1 varies from 0 to 23 and the most probable values of W_1 are located in the interval from 7 to 16.

Processing the sample of values of the variable W_1 with the use of Neyman–Pearson χ^2 criterion [2], we can show that the H_0 hypothesis on Poisson distribution law for W_1 should be rejected. Here we have the calculated value $\chi^2 = 51.67$ for 7 degrees of freedom. The table value $\chi^2_\alpha(7) = 24.322$ is at the significance level $\alpha = 0.001$. Therefore, the deviation of the hypothesis H_0 on the Poisson nature of the distribution law of W_1 is highly statistically significant [2]. At the same time, if we consider the distribution of W_1 under the assumption that the cell I lives to the end of the period $[0,T_1]$, then the situation changes. The results of processing the sample values of W_1 obtained under this assumption (475 observations out of 500) are the following: $\chi^2 = 7.54$ for 6 degrees of freedom. The table value $\chi^2_\alpha(6) = 10.647$ is at the significance level $\alpha = 0.1$. Therefore, we can confidently accept the hypothesis that the specified conditional distribution of W_1 is Poisson. Note that the sample size $N = 500$ provides the condition of applicability of the χ^2 criterion recommended in [2], taking into account unlikely values of the function W_1, namely, $Np_i \geqslant 10$, where p_i is the theoretical probability that the variable W_1 fits the given interval of data group with the number $j = 1,2,\ldots,r$, $r \geqslant 3$.

Figures 2 and 3 show the results of the second and third experiments. In the second experiment, the duration of transition is $T_2 = t_{\max}$, i.e., the maximal value

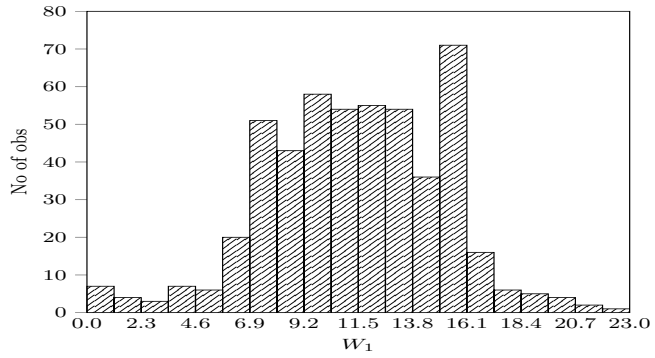

Figure 1. Histogram of the distribution of W_1.

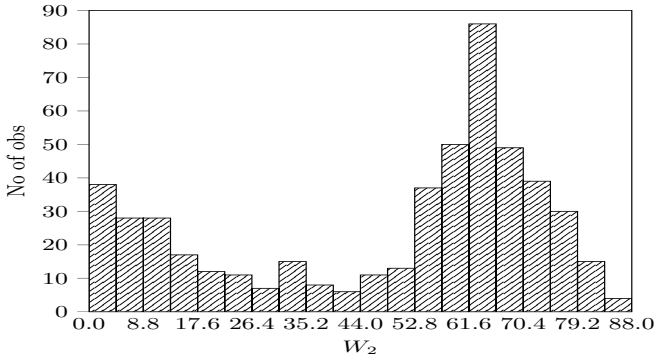

Figure 2. Histogram of the distribution of W_2.

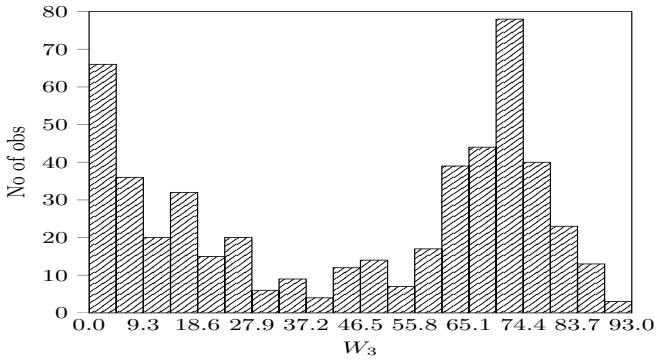

Figure 3. Histogram of the distribution of W_3.

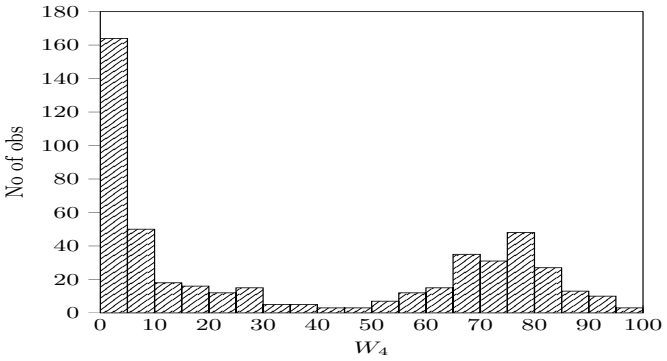

Figure 4. Historgam of the distribution of W_4.

of the mathematical expectation of the variable W_2 is attained at such duration of transition. In the third experiment, the duration T_3 of transition exceeds T_2 approximately 1.3 times. Note that the distribution histograms of the variables W_2 and W_3 differ essentially from the distribution histogram of W_1. Each of distribution histograms of W_2 and W_3 has a typical form similar to the other one, which is explained by the fact that a cell I lives to the end of the period $[0, T_2]$, $[0, T_3]$ or by its death within these intervals. The left parts of these histograms mainly correspond to viral particles W produced by the cell I not surviving to the end of the intervals $[0, T_2]$, $[0, T_3]$, respectively, the right parts of the histograms correspond to a cell I surviving to the end of these intervals. Figures 2 and 3 show that, in comparison with experiment 1, the range of the number of viral particles W_2, W_3 increases significantly and takes values from 0 to 88 and from 0 to 93, respectively, in experiments 2 and 3. This result is explained by an increase in the duration of the transition between two lymph nodes and the appearance of both small and sufficiently large number of viral particles W produced by the cell I during its transition.

Figure 4 presents the results of the fourth experiment where the duration of transition T_4 correspond to a sufficiently long duration of transition of a cell I and viral particles W between two lymph nodes in comparison with experiments 1, 2, 3. The histogram presented in Fig. 4 shows that the range of the number of viral particles W_4 is from 0 to 100. In addition, the most probable values of W_4 are from 0 to 10 and other values of W_4 with a relatively high probability lie in the range from 65 to 85. Therefore, a prolonged transition of a cell I from the first lymph node to the second one may result in formation of both a small and a large number of virus particles W.

5. Conclusion

The present paper proposes an approach to stochastic modelling of the number of infected cells and viral particles produced by them during the transition through a lymphatic vessel connecting two lymph nodes. The main analytical result of the pa-

per is the distribution law of the number of viral particles entering the second lymph node. The distribution law obtained here is quite complex and is not expressed explicitly. At the same time, depending on the lifetime of an infected cell moving from the first lymph node to the second one, this law is described by a Poisson distribution. The Poisson distribution parameter takes into account the duration of the transition of an infected cell between lymph nodes and its lifetime. The obtained formulas are used to construct a compact algorithm for modelling model variables based on the Monte Carlo method.

The results of computational experiments show that different durations of transitions of infected cells between the first and second lymph nodes have a significant impact on the number of viral particles produced by them and entering the second lymph node. During a long transition, a large number of viral particles can be formed, which can be interpreted as creation of a temporary 'depot' or 'storage' of viral particles in the lymphatic vessel. The simultaneous appearance of a large number of viral particles in the second lymph node can lead to activation of the process of infection of target cells and to development of HIV-1 infection in this and, as a result, in other lymph nodes. At the same time, if the transition of infected cells is short enough, the number of viral particles produced by them may vary from zero to several particles. In this case the main external source of replenishment of the population of viral particles of the second lymph node will be viral particles coming from the first or from other lymph nodes.

The approach described in the present paper can be applied to a stochastic compartment model of the HIV-1 infection dynamics taking into account the movement of cells of various types and viral particles through the human lymphatic system. To set the parameters of the compartment model, one should use estimates of actual duration of transitions of infected cells and viral particles between lymph nodes, which can be obtained from hydrodynamic models and models describing the structure of the human lymphatic system presented, for example, in [8, 9, 10, 13].

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