Modelling the Biostimulation Effect on the Development of an Infectious Disease in View of Diffusion Perturbations and the Organism's Temperature Response

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Abstract

The general model of a bioinfection was modified to predict the effect of biostimulation on the dynamics of a viral infection taking into account small diffusion *scattering* in the conditions of the organism's temperature response. The solution of a singularly perturbed model problem with a time-delay is reduced to a sequence of problem solutions without a time-delay, for which numerical asymptotic approximations of the sought functions are defined as a perturbation of the solutions of the corresponding degenerate problems. The computer modelling results illustrate the ability of biostimulants to significantly influence the dynamics of a chronic viral infection in the conditions of their diffusion dispersion and the organism's temperature response. It is emphasized that an excessive dose of bio-stimulating agents can cause an increase in the antigen number to a level that significantly exceeds the *natural* maximum and can pose a threat to the normal functioning of the target organ.

Keywords 1

The general model of a bioinfection, dynamical systems with a time-delay, asymptotic methods, singularly perturbed problems.

1. Introduction

The formation of effective programs for infectious disease treatment requires the availability of a reliable toolkit for predicting the dynamics of the disease taking into account the influence of various types of therapeutic agents when they are used in various situational conditions. It is a common fact that within the framework of the simplest infectious disease model, depending on the efficiency of the immune system's response, four characteristic forms of the course of the disease are distinguished in [1]: subclinical, acute, chronic, and lethal. Therefore, the presence of various forms of the disease course, the establishment of which depends on the individual ability of the organism to produce an immune response of the required strength, necessitates various therapeutic treatment strategies use.

It should be considered that the general methodology for constructing mathematical models of both viral and bacterial infections presented in [1], along with the immune and other mechanisms of the organism's defence, is effectively used to predict the course of various diseases [2]. For instance, in [3], this approach was used to build a model of antitumour immunity, and in [4] a modification of the infectious disease model taking into account immunotherapy was proposed, which involves the introduction of donor antibodies into the organism. In the general model of local tissue inflammation presented in [5], Marchuk's approach was used to describe the systemic reaction. An interesting example of this methodology application is the mathematical model of the immune response to the COVID-19 infection dynamics presented in [6], taking into account the influence of immunotherapy.

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We should also note that within the framework of the basic model, the presence of a constant antigen concentration in a stationary state of the organism is a characteristic feature of the disease course in a chronic form. The establishment of this disease form is caused by a sluggish immune response. On the other hand, according to the model, a significant increase in the efficiency of the immune response can be achieved due to a significant increase in the dose of an infection. In [1] an assumption is made about the possibility of chronic infection treatment with an exacerbation, which can be achieved by introducing a suitable biostimulant.

It is worth pointing out that due to the uneven distribution of antigens, antibodies, and other active factors in the organism, the effect of their spatial dispersion can significantly affect the disease dynamics. In [7,8], the authors presented the approach to consider diffusion disturbances of the process in the conditions of concentrated administration of immunotherapy medicinal products into the organism. A model reduction in the concentration of antigens in the infection zone because of diffusion scattering is also demonstrated here. A similar effect occurs regarding medical drugs around the areas they were used for. It is essential to consider this statement when predicting the dynamics of a chronic disease in the conditions of using biostimulants.

A powerful tool to protect the organism from pathogens of infectious diseases is also a mechanism of raising organism temperature. This mechanism provides both a decrease in the rate of pathogenic microorganism reproduction and an increase in the activity of enzymes that stimulate immunological reactivity. In [9], the appropriate generalization of the basic model of viral infection, taking into account diffusion disturbances, concentrated effects, and the organism's temperature reaction, is proposed. The use of biostimulants for the treatment of chronic diseases can trigger the mechanism of temperature increase, which will ultimately affect the development of the disease. Therefore, considering this mechanism is also important when predicting the effect of biostimulants on the disease course.

Thus, the purpose of this work is to modify the basic model of viral infection to predict the impact of biostimulation on the disease dynamics taking into account diffusion disturbances and the organism's temperature response.

2. Modification of the Viral Infection Model to Consider the Influence of Biostimulation and Diffusion Disturbances in the Conditions of the Organism's Temperature Response

The dynamics of a viral infection, taking into account the influence of biostimulation and diffusion disturbances in the conditions of the body's temperature response in the set $G=\{(x,t): -\infty\le x\le+\infty, t\le+\infty\}$, will be described by the following singularly perturbed system of nonlinear differential equations (with delays τ_1, τ_2):

$$
\begin{aligned}
&\frac{\partial V_1}{\partial t}=\omega_{V_1}+\beta_1(\theta)\cdot V_1-\gamma_1 F_1 V_1+\varepsilon D_{V_1}\frac{\partial^2 V_1}{\partial x^2},\\
&\frac{\partial C_1}{dt}=\xi(m)\frac{V_1F_1}{V_1F_1+V_2F_2}\alpha_1(\theta)\cdot V_1(t-\tau_1)F_1(t-\tau_1)-\mu_{C_1}(C_1-C_1^*)+\varepsilon^2 D_{C_1}\frac{\partial^2 C_1}{\partial x^2},\\
&\frac{\partial F_1}{dt}=u_{F_1}+\rho_1 C_1\left(1-\frac{C_1+C_2}{C^{**}}\right)-(\mu_{f1}+\eta_1\gamma_1 V_1)F_1+\varepsilon D_{F_1}\frac{\partial^2 F_1}{\partial x^2},\\
&\frac{\partial V_2}{\partial t}=u_{V_2}-\gamma_2 F_2 V_2+\varepsilon D_{V_2}\frac{\partial^2 V_2}{\partial x^2},\\
&\frac{\partial C_2}{dt}=\xi(m)\frac{V_2F_2}{V_1F_1+V_2F_2}\alpha_2(\theta)\cdot V_2(t-\tau_2)F_2(t-\tau_2)-\mu_{C_2}(C_2-C_2^*)+\varepsilon^2 D_{C_2}\frac{\partial^2 C_2}{\partial x^2},
\end{aligned}
\tag{1}
$$

$$\frac{\partial F_2}{dt}=\rho_2 C_2\left(1-\frac{C_1+C_2}{C^{**}}\right)-(\mu_{f\,2}+\eta_2\gamma_2 V_2)F_2+\varepsilon D_{F_2}\frac{\partial^2 F_2}{\partial x^2},$$
$$\frac{\partial m}{dt}=\sigma V_1-\mu_m(\theta)\cdot m+\varepsilon^2 D_m\frac{\partial^2 m}{\partial x^2},$$
$$\frac{\partial \theta}{\partial t}=\alpha_T V_1 F_1-\mu_T\cdot(\theta-\theta^*)-u_\theta+\varepsilon D_\theta\frac{\partial^2\theta}{\partial x^2}$$

for conditions

$$C_1(x,0)=C_1^0(x),\ C_2(x,0)=C_2^0(x),\ m(x,0)=m^0(x),\ \theta(x,0)=\theta^0(x),\ V_1(x,\tilde{t})=V_1^0(x,\tilde{t}),$$
$$F_1(x,\tilde{t})=F_1^0(x,\tilde{t}),V_2(x,\tilde{t})=V_2^0(x,\tilde{t}),\ F_2(x,\tilde{t})=F_2^0(x,\tilde{t}),\ -\overline{\tau}\le\tilde{t}\le 0,\ \overline{\tau}=max\{\tau_1,\tau_2\} \qquad (2)$$

where $V_1(x,t)$, $C_1(x,t)$, $F_1(x,t)$ are the number of viral infection antigens and their specific plasma cells and antibodies, respectively; $V_2(x,t)$, $C_2(x,t)$, $F_2(x,t)$ are the numbers of elements of non-pathogenic biostimulants, plasma cells and antibodies specific to them, respectively; $m=m(x,t)$ is relative characteristics of the lesion of the target organ; $\theta=\theta(x,t)$ is the temperature at the point x at the time t, $\beta_1(\theta)=\beta_1^0/(1+\beta_1^1(\theta-\theta^*))$ is the temperature-dependent rate of viral antigen reproduction, $\beta_1^1=const>0$; γ_1,γ_2 are coefficients related to the neutralization of viral antigens probability and biostimulants, respectively, by their specific antibodies during their interaction; $\alpha_k(\theta)=\alpha_k^0(1+\alpha_k^1(\theta-\theta^*))$, $k=1,2$ are the temperature-dependent stimulation coefficients of immunocompetent B-lymphocytes, $\alpha_k^1=const>0$; μ_{C_1}, μ_{C_2} are inverse values of the lifetime of plasma cells specific for antigens and biostimulants, respectively; C_1^*, C_2^* are the number of plasma cells specific for antigens and biostimulants, respectively, in a healthy organism; ρ_1, ρ_2 are rates of one plasma cell specific to antigens and biostimulants antibody production, respectively; μ_{f_1}, μ_{f_2} are inverse values of the duration of the existence of antibodies specific to antigens and biostimulants, respectively; η_1, η_2 are the numbers of antibodies needed to neutralize one antigen and one biostimulant element, respectively; σ is rate of damage to target the organ cells; εD_{V_1}, εD_{V_2}, $\varepsilon^2 D_{C_1}$, $\varepsilon^2 D_{C_2}$, εD_{F_1}, εD_{F_2}, $\varepsilon^2 D_m$, εD_θ are the diffusion coefficients, respectively, of viral antigens and biostimulants, plasma cells and antibodies specific to them, affected cells and thermal conductivity, ε is a small parameter that characterizes the small influence of these components on the development of the process; $V_1^0(x,\tilde{t})$, $V_2^0(x,\tilde{t})$, $C_1^0(x)$, $C_2^0(x)$, $F_1^0(x,\tilde{t})$, $F_2^0(x,\tilde{t})$, $m^0(x)$, $\theta^0(x)$ are the bounded sufficiently smooth functions. A monotonically decreasing smooth function provides consideration in the model of the effect of reducing the productivity of plasma cell generation after reaching a certain threshold value $m^*>0$ of the level of damage to the target organ, $\xi(m^*)=1$, $\xi(1)=0$.

It is natural to believe that an exacerbation of viral infection as the result of biostimulation use will cause an increase in body temperature, which will affect further dynamics of the disease. To take this effect into account in the system (1), unlike the well-known general model of bioinfection, we introduced an equation that describes the temperature dynamics. As in [1] here:

$$\alpha_T=\begin{cases}0, & VF<(VF)^*,\\ \alpha_T^*, & VF\ge(VF)^*\end{cases}\approx\frac{\alpha_T^*\cdot e^{\delta(VF-(VF)^*)}}{1+e^{\delta(VF-(VF)^*)}},$$

$(VF)^*$ is a certain threshold value of VF-complexes, exceeding which stimulates an increase in the temperature, $\alpha_T^*=const>0$; $\theta^*(x)$ is the temperature distribution in an organism in a healthy state. We should also note that the rise in organism temperature is ambiguous. On the one hand, a higher temperature has a depressing effect on the reproduction and penetration of viral elements into a cell and, to some extent, stimulates immunological reactivity [1]. In addition to that, excessively high

temperatures cause a destructive effect on the cell functioning of the target organ. We propose to consider such a diverse influence by introducing a temperature-dependent recovery rate of the affected organ: $\mu_m(\theta)=\mu_m^0/(1+\mu_m^1(\theta-\theta^*))$. At the same time, we will assume that the destructive effect of high temperature on the functioning of the target organ cells begins after exceeding a certain threshold value θ^{**}:

$$\mu_m^1=\begin{cases}0, & \theta<\theta^{**},\\ \mu_m^*, & \theta\geq\theta^{**}\end{cases}\approx\frac{\mu_m^*\cdot e^{\delta(\theta-\theta^{**})}}{1+e^{\delta(\theta-\theta^{**})}}.$$

The establishment of excessively high temperatures for a long period of time is quite dangerous for the ability of the organism to ensure the vital activity of the target organ. In this case, it is important to reduce the temperature to acceptable limits, which, as a rule, is carried out by various therapeutic means. To consider such a controlling influence, a source function was introduced into the temperature dynamics equation $u_\theta(x,t)$. Other functions of the source $\omega_{V_1}(x,t)$, $u_{F_1}(x,t)$, $u_{V_2}(x,t)$, similarly to [8,9], provide concentrated change consideration in the quantities of antigens and different specificity antibodies.

3. Numerical Asymptotic Approximation of the Model Problem Solution

Let us note that $\tau_1=\tau_2=\tau$. Then, similarly to [8,9], we find the solution of the model problem (1)-(2) with a time-delay τ, by the step method as a sequence of solutions on the intervals $r\tau\leq t\leq(r+1)\tau$, $r=0,1,...$. Note that because of such a step-by-step procedure for each separate interval, with the already found solution at the previous stage, we will get the problem without a time-delay. We will ensure the required level of smoothness of the solutions at time points τ, 2τ, ... by imposing additional conditions for their coordination. We find the approximation of the solution of each singularly perturbed problem from the obtained sequence by the numerical asymptotic method, which is similar to the way it was done in [8,9]. For example, in this case $\xi(m)=1$ we get the following problems for finding unknown functions (the members of asymptotic) $V_{1(r,i)}$, $C_{1(r,i)}$, $F_{1(r,i)}$, $V_{2(r,i)}$, $C_{2(r,i)}$, $F_{2(r,i)}$, $m_{(r,i)}$, $\theta_{(r,i)}$ ($i=0,1,...,n$):

$$\begin{aligned}
&\frac{\partial V_{1(r,0)}}{\partial t}=\omega_{V_1(r)}+\frac{\beta_1^0 V_{1(r,0)}}{1+\beta_1^1(\theta_{(r,0)}-\theta^*)}-\gamma_1 V_{1(r,0)}F_{1(r,0)},\\
&\frac{\partial C_{1(r,0)}}{\partial t}=p_{1(r,0)}\alpha_1^0(1+\alpha_1^1(\theta_{(r,0)}-\theta^*))\cdot\Psi_{1(r)}-\mu_{C_1}(C_{1(r,0)}-C_1^*),\\
&\frac{\partial F_{1(r,0)}}{\partial t}=u_{F_1(r)}+\rho_1 C_{1(r,0)}\cdot\left(1-\frac{C_{1(r,0)}+C_{2(r,0)}}{C_1^{**}}\right)-(\mu_{f1}+\eta_1\gamma_1 V_{1(r,0)})F_{1(r,0)},\\
&\frac{\partial V_{2(r,0)}}{\partial t}=u_{V_2(r)}-\gamma_2 V_{2(r,0)}F_{2(r,0)},\\
&\frac{\partial C_{2(r,0)}}{\partial t}=p_{2(r,0)}\alpha_2^0(1+\alpha_2^1(\theta_{(r,0)}-\theta^*))\cdot\Psi_{2(r)}-\mu_{C_2}(C_{2(r,0)}-C_2^*),\\
&\frac{\partial F_{2(r,0)}}{\partial t}=\rho_2 C_{2(r,0)}\cdot\left(1-\frac{C_{1(r,0)}+C_{2(r,0)}}{C_2^{**}}\right)-(\mu_{f2}+\eta_2\gamma_2 V_{2(r,0)})F_{2(r,0)},\\
&\frac{\partial m_{(r,0)}}{\partial t}=\sigma V_{1(r,0)}-\frac{\mu_m^0\cdot m_{(r,0)}}{1+\mu_m^1(\theta_{(r,0)}-\theta^*)},\\
&\frac{\partial \theta_{(r,0)}}{\partial t}=\alpha_T V_{1(r,0)}F_{1(r,0)}-\mu_T\cdot(\theta_{(r,0)}-\theta^*)-u_{\theta(r)},
\end{aligned}\qquad(3)$$

$$V_{1(r,0)}(x,r\tau)=V_{1(r-1)}(x,r\tau), V_{2(r,0)}(x,r\tau)=V_{2(r-1)}(x,r\tau), C_{1(r,0)}(x,r\tau)=C_{1(r-1)}(x,r\tau),$$
$$C_{2(r,0)}(x,r\tau)=C_{2(r-1)}(x,r\tau), F_{1(r,0)}(x,r\tau)=F_{1(r-1)}(x,r\tau), F_{2(r,0)}(x,r\tau)=F_{2(r-1)}(x,r\tau),$$
$$m_{(r,0)}(x,r\tau)=m_{(r-1)}(x,r\tau), \theta_{(r,0)}(x,r\tau)=\theta_{(r-1)}(x,r\tau), r\tau\le t\le(r+1)\tau;$$
$$\cdots\cdots\cdots\cdots\cdots\cdots\cdots\cdots\cdots\cdots\cdots\cdots\cdots\cdots\cdots\cdots\cdots\cdots\cdots\cdots$$

$$\frac{\partial V_{1(r,i)}}{\partial t}=d_{1(r,0)}\theta_{(r,i)}+c_{1(r,0)}V_{1(r,i)}-\gamma_1\left(a_{1(r,0)}F_{1(r,i)}+b_{1(r,0)}V_{1(r,i)}\right)+\Phi_{V1(r,i)},$$
$$\frac{\partial C_{1(r,i)}}{\partial t}=p_{1(r,i)}\alpha_1^0\alpha_1^1\theta_{(r,i)}\cdot\Psi_{1(r)}-\mu_{C_1}C_{1(r,i)}+\Phi_{C_1(r,i)},$$
$$\frac{\partial F_{1(r,i)}}{\partial t}=\rho_1\left(C_{1(r,i)}\cdot\left(1-\frac{C_{1(r,0)}+C_{2(r,0)}}{C^{**}}\right)-\frac{C_{1(r,0)}(C_{1(r,i)}+C_{2(r,i)}}{C^{**}}\right)C_{1(r,i)}-\mu_{f_1}F_{1(r,i)}-$$
$$-\eta_1\gamma_1\left(a_{1(r,0)}F_{1(r,i)}+b_{1(r,0)}V_{1(r,i)}\right)+\Phi_{F_1(r,i)},$$
$$\frac{\partial V_{2(r,i)}}{\partial t}=-\gamma_2\left(a_{2(r,0)}F_{2(r,i)}+b_{2(r,0)}V_{2(r,i)}\right)+\Phi_{V_2(r,i)},$$
$$\frac{\partial C_{2(r,i)}}{\partial t}=p_{2(r,i)}\alpha_2^0\alpha_2^1\theta_{(r,i)}\cdot\Psi_{2(r)}-\mu_{C_2}C_{2(r,i)}+\Phi_{C_2(r,i)},\qquad(4)$$
$$\frac{\partial F_{2(r,i)}}{\partial t}=\rho_2\left(C_{2(r,i)}\cdot\left(1-\frac{C_{1(r,0)}+C_{2(r,0)}}{C^{**}}\right)-\frac{C_{2(r,0)}\left(C_{1(r,i)}+C_{2(r,i)}\right)}{C^{**}}\right)C_{2(r,i)}-\mu_{f_2}F_{2(r,i)}-$$
$$-\eta_2\gamma_2\left(a_{2(r,0)}F_{2(r,i)}+b_{2(r,0)}V_{2(r,i)}\right)+\Phi_{F_2(r,i)},$$
$$\frac{\partial m_{(r,i)}}{\partial t}=\sigma V_{1(r,i)}-d_{m(r,0)}\theta_{(r,i)}-c_{m(r,0)}m_{(r,i)}+\Phi_{m(r,i)},$$
$$\frac{\partial \theta_{(r,i)}}{\partial t}=\alpha_T\left(a_{1(r,0)}F_{1(r,i)}+b_{1(r,0)}V_{1(r,i)}\right)-\mu_T\theta_{(r,i)}+\Phi_{\theta(r,i)},$$
$$V_{1(r,i)}(x,r\tau)=0, V_{2(r,i)}(x,r\tau)=0, C_{1(r,i)}(x,r\tau)=0, C_{2(r,i)}(x,r\tau)=0, F_{1(r,i)}(x,r\tau)=0,$$
$$F_{2(r,i)}(x,r\tau)=0, m_{(r,i)}(x,r\tau)=0, \theta_{(r,i)}(x,r\tau)=0, r\tau\le t\le(r+1)\tau, i=1,2,...,n,$$

where $C_{1(-1)}(x,0)=C_1^0(x)$, $C_{2(-1)}(x,0)=C_2^0(x)$, $m_{(-1)}(x,0)=m^0(x)$, $\theta_{(-1)}(x,0)=\theta^0(x)$, $V_{1(-1)}(x,t-\tau)=V_1^0(x,t-\tau)$, $V_{2(-1)}(x,t-\tau)=V_2^0(x,t-\tau)$, $F_{1(-1)}(x,t-\tau)=F_1^0(x,t-\tau)$, $F_{2(-1)}(x,t-\tau)=F_2^0(x,t-\tau)$, $\Psi_{1(r)}=V_{1(r-1)}(x,t-\tau)$, $\Psi_{2(r)}=\quad=V_{2(r-1)}(x,t-\tau)F_{2(r-1)}(x,t-\tau)$, $a_{1(r,0)}=V_{1(r,0)}$, $b_{1(r,0)}=F_{1(r,0)}$, $c_{1(r,0)}=\frac{\beta_1^0}{1+\beta_1^1(\theta_{0,r}-\theta^*)}$,

$d_{1(r,0)}=-\frac{\beta_1^0\beta_1^1\cdot V_{1(r,0)}}{(1+\beta_1^1(\theta_{0,r}-\theta^*))^2}$, $c_{m(r,0)}=\frac{\mu_m^0}{1+\mu_m^1(\theta_{0,r}-\theta^*)}$, $d_{m(r,0)}=-\frac{\mu_m^0\mu_m^1\cdot m_{(r,0)}}{(1+\mu_m^1(\theta_{0,r}-\theta^*))^2}$,

$p_{1(r,0)}=\frac{F_{1(r,0)}V_{1(r,0)}}{\sum_{l=1}^{2}F_{l(r,0)}V_{l(r,0)}}$, $p_{1(r,i)}=\frac{\sum_{j=0}^{i}F_{1(r,i-j)}V_{1(r,j)}-\sum_{j=1}^{i}p_{1(r,i-j)}\cdot\sum_{l=0}^{j}\left(F_{1(r,j-l)}V_{1(r,l)}+F_{2(r,j-l)}V_{2(r,l)}\right)}{\sum_{l=1}^{2}F_{l(r,0)}V_{l(r,0)}}$,

$p_{2(r,0)}=\frac{F_{2(r,0)}V_{2(r,0)}}{\sum_{l=1}^{2}F_{l(r,0)}V_{l(r,0)}}$, $p_{2(r,i)}=\frac{\sum_{j=0}^{i}F_{2(r,i-j)}V_{2(r,j)}-\sum_{j=1}^{i}p_{2(r,i-j)}\cdot\sum_{l=0}^{j}\left(F_{1(r,j-l)}V_{1(r,l)}+F_{2(r,j-l)}V_{2(r,l)}\right)}{\sum_{l=1}^{2}F_{l(r,0)}V_{l(r,0)}}$.

Functions $\Phi_{V_2(r,i)}$, $\Phi_{C_2(r,i)}$, $\Phi_{F_2(r,i)}$, $\Phi_{m(r,i)}$, $\Phi_{\theta(r,i)}$, similarly to [8,9], are expressed in equation terms of asymptotic already found in the previous steps.

The solution to problems (3)-(4) at each stage will be found by numerical methods (for example, Runge-Kutta methods), using the values of the functions $V_{1(r-1)}$, $F_{1(r-1)}$, $V_{2(r-1)}$, $F_{2(r-1)}$ already found at the previous stages. Establishing space-time intervals of convergence when predicting real diseases course is carried out similarly to [7-9].

4. Numerical Experiments Results

As mentioned above, the introduction of biostimulants into the organism will cause an exacerbation of a chronic viral infection course, which is often accompanied by an increase in temperature. Thus, an important problem in the formation of an effective treatment program is the qualitative prediction of the exacerbation level and the disease course when introducing a certain dose of biostimulants. Computer experiments were focused on the study of these aspects.

Fig. 1 illustrates a chronic viral infection model dynamics in the conditions of the organism's temperature reaction with the concentrated introduction of various doses of biostimulants into the locus of the infection. Here, the effect of introducing biostimulants was modelled by the source function $u_{V_2} = A_{V_2} e^{-(\alpha_{V_2}(t-t_{V_2})^2+\beta_{V_2}(x-x_{V_2})^2)}$ ($t_{V_2} = 100$). The presented results of computer modelling prove the ability of biostimulants introduced into the organism to significantly influence the chronic infection dynamics. As should be expected, increasing the dose of biostimulants leads to a significant exacerbation of the disease, which can exceed the *natural* level of its course and become quite dangerous if the dosage of biostimulants is incorrect.

The effect of the protective mechanism of temperature increase on the model course of viral infection with the concentrated use of biostimulants is shown in fig. 2, a), b). Here, the introduction of biostimulants was modelled in the same way as in the previous case. Computer experiments were conducted at different values α_T of the rate of temperature increase. As expected, at higher rates of organism temperature increase, the severity of viral infection decreases. At the same time, taking into account such a temperature protection mechanism ensures the predictable stabilization of a chronic disease at lower values of the number of viral elements. We should also note that according to the assumptions of the model (1)-(2) biostimulants are not capable of multiplying independently in the organism, and the increase in their number is determined by the procedure of introducing the appropriate injection solution. Therefore, the mechanism of temperature increase practically does not affect the dynamics of biostimulants.

5. Conclusions

The paper presents a general bioinfection model modification to predict the impact of biostimulation on the dynamics of a viral infection, considering small diffusion *scattering* in the conditions of the organism's temperature reaction. It is proposed to apply an effective step-by-step procedure to find out the solution of the model singular of the perturbed problem. According to the procedure, firstly, we reduce the original problem with a time-delay to a sequence of problems without a time-delay. And further on, step by step, considering the conditions of the required level of smoothness, we find the numerical asymptotic approximation of the obtained problem solutions at each time interval as a perturbation of the solutions corresponding degenerate problems.

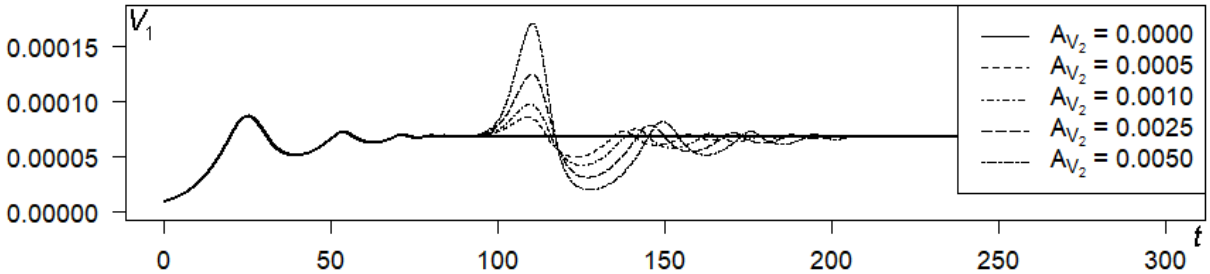

Fig. 1. Dynamics of Chronic Infection Antigens in the Locus of Infection with the Introduction of Different Doses of Biostimulants

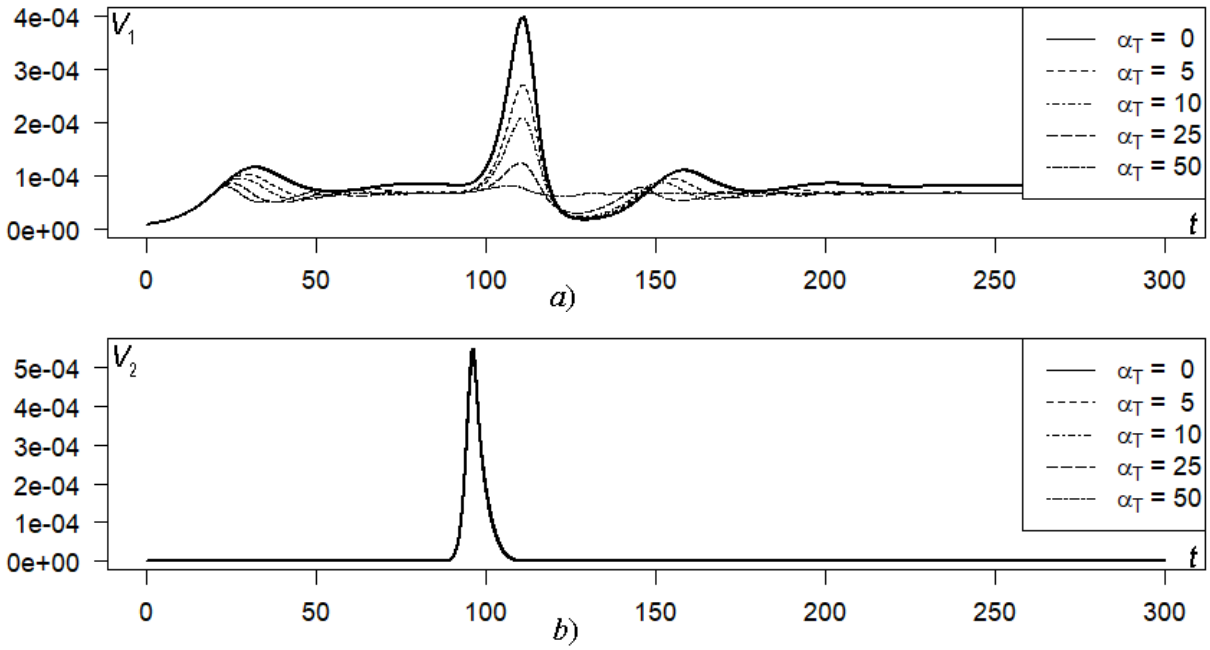

Fig. 2. Dynamics of a) Chronic Infection Antigens;
b) Biostimulants in the Locus of Infection at Different Rates of Organism Temperature Increase

The given results of computer modelling illustrate the ability of the introduced in the organism biostimulants to significantly affect the dynamics of the initial chronic viral infection even in the conditions of their diffusion *scattering* and temperature reaction of the organism. Increasing the dose of biostimulants leads to a significant exacerbation of the viral infection. It is emphasized that an excessive dose of biostimulating agents can cause an increase in the number of antigens to a level that significantly exceeds the *natural* maximum and may pose a threat to the normal functioning of the target organ. It has also been demonstrated that high temps of increasing the temperature within certain limits can effectively reduce the severity of the disease flow and provide predictable stabilization of chronic disease in smaller values of the viral element number.

Let us note that the results presented in the paper were obtained in the cases of one-dimensional homogeneous model environments, which is a certain limitation. In our opinion, it is promising to generalize the proposed approach for predicting the dynamics of mixed infections with a comprehensive account of diffusion perturbations in environments with essentially spatial effects, the temperature response of the organism, and various kinds of concentrated effects [10–12] in immunotherapy and pharmacotherapy, including those based on antiviral and antiviral immune response models.

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