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Infectious disease model generalization based on diffuse perturbations under conditions of body's temperature reaction

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ABSTRACT

The infectious disease mathematical model is generalized based on the influence of diffuse perturbations on the development of the disease under conditions of the body's temperature reaction. The singularly perturbed model problem was reduced with delay to a sequence of problems without delay, for which the corresponding asymptotic expansions of solutions are obtained. The presented results of computer modeling in various situational states illustrate the expected decrease in the growth rate of the number of viral particles as a result of the action of the body's protective temperature reaction. The results of numerical experiments demonstrate the influence of the diffuse effect of "scattering" of forcing factors on the dynamics of a viral disease under conditions of the body's temperature reaction are presented too. It is noted that the decrease of the model amount of antigens in the epicenter of infection to a non-critical level caused by diffuse "scattering" over a relatively short time period makes them further destroyed by immune agents presented in the body, or requires the introduction of an injection solution with a smaller amount of donor antibodies.

1. Introduction

Modern concepts of the host's reaction to the identified pathogens indicate the existence of a complex system of dissimilar and interrelated immune defense mechanisms. Mathematical models of immune processes are the integral and important elements in the research of these mechanisms. The number of mathematical models of various levels of details were proposed in Ref. [1] to research and predict the process of interaction of the immune system with the pathogens found in the host. These models are based on the clonal selection theory of F. Burnet [1,2]. The most general patterns of the immune response are studied on the basis of the so-called infectious disease simplest model, which is represented by a system of four nonlinear differential equations with delay. In particular, the asymptotic stability of the stationary solution is substantiated, which describes the healthy body's state if the initial infection dose V^0 of some immunological barrier V^* is not exceeded. That is, when a healthy host is infected with small dose of viral particles, their neutralization according to the model is provided by available amount of antibodies. Moreover, the included certain variability in the simplest model makes it possible to explain some important features functioning of the immune system. Besides, this allows explaining the possibility of the formation of subclinical, acute and chronic processes of the disease and clarifying the mechanisms of biostimulation, etc. [1]. The improved mathematical models of antiviral and antibacterial immune response are proposed for taking into account the immunity of the T-cell type in Ref. [1]. These models include the mechanism of the humoral immune response with the production of antibodies and the mechanism of recognition and destruction by cytotoxic T-lymphocytes-effectors accumulated as a result of the immune response of the cells of their own body infected with the virus.

We also note that the results of the infectious disease modeling process given in Ref. [1], with corresponding identification of the model parameters, have good agreement with the medical observations data, confirming their adequacy.

Apart from the humoral and cellular type of immunity, the mechanism of temperature rise is a very important element in the host's defense system. The launch of this mechanism is also caused by the detection of pathogenic microorganisms in the body. In addition to humoral and cellular immunity, an important additional element in the body's self-defense system is the mechanism of temperature increase,

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the triggered of which is also caused by the detection in the body, in particular, pathogenic microorganisms. Almost all pathogens are susceptible to depressive effects of increased temperature. It is known [1] that the increase in body temperature leads to the decrease in the reproduction intensity of pathogenic microorganisms and reduce their ability to penetrate into cells, and to increase the activity of enzymes that stimulate immunological reactivity. The complexity of the influence of the body's temperature response on the dynamics of the infectious disease testifies the importance of this mechanism of self-defense and self-treatment and the importance of developing and investigating mathematical models that more accurately and systematically describe the various mechanisms of the immune response.

The aim of this research is the modification of the classical model of infectious disease to take into account the diffuse disturbances and the concentrated influences under conditions of the body's temperature reaction. The advantage of the proposed method is the effective procedure for "constructing" the solution of the original model problem, in which already known and initially acceptable "unperturbed" solutions are supplemented by various corrections. The developed mathematical model and the corresponding computational procedure are considered as the element of full complex system to support decision-making such as: Can we, according to the values of the corresponding input data, regarding the intensity of diffuse "redistribution" and the body's temperature reaction, etc., fully expect on the available body's immune protection or provide the external influence (treatment) otherwise?

Note that this kind of models are still not widely used today, and the corresponding problems in terms of the main factors dynamics perturbation by thermal phenomena have not been solved at all.

2. Literature reviews

The infectious disease simplest model which was built by G. Marchuk is presented in Ref. [1] by system of four nonlinear differential equations with delay:

$$\frac{\partial V}{\partial t} = \beta V - \gamma FV$$

$$\frac{\partial C}{\partial t} = \xi(m)\alpha V(t-\tau)F(t-\tau) - \mu_C(C - C^*)$$

$$\frac{\partial F}{\partial t} = \rho C - \eta\gamma VF - \mu_f F$$

$$\frac{\partial m}{\partial t} = \sigma V - \mu_m m$$

The acting factors of this model are the antigens concentration $V(t)$ (pathogenic viruses, bacteria, etc.); the specific immune agents' concentration $F(t)$ (antibodies, cell receptors, etc.) which are capable to neutralize this type of antigens; the immunological cells' concentration $C(t)$ which are antibodies' carriers and producers; the value of relative characteristic of target organ's damage $m(t)$. The antigens' dynamics described by first equation of the model is determined by growth of the antigens population as a result of their reproduction and neutralization by antibodies. According to M. Burnet's clonal-selection theory, antigens selectively connect to specific lymphocytes and activate them. Through time τ after activation, lymphocytes begin to reproduce and form clones population that will specifically respond to this type of antigen. In this model all immune agents which able to connecting with antigens refers to antibodies. Therefore, the number of lymphocytes activated in this way is considered to be proportional to the FV.

Such plasma cells cascade generation with the homeostasis mechanism determine the dynamics of immunological cells, which described by second equation in the model.

The third equation takes into account the increase of antibodies caused by their production by immunological cells, the decrease of antibodies population caused by ageing and using of antibodies to neutralize antigens. To take into account the effect of weakening the body's vital functions during the disease, the model uses the additional factor m(t) connected with the damage stage of the immunological organ ($0 \le m \le 1$, where $m = 0$ when the immunological organ is completely healthy, $m = 1$ in case of its complete damage). According to the model, the dynamics of $m(t)$ is determined by the stage of damage, which is proportional to the number of antigens and the organ rehabilitation at the rate of μm. In this model, β is the rate of antigens reproduction, γ is the coefficient that takes into account the interaction effect of antigens from antibodies, μ_C is the reciprocal of the immunological cells lifespan, α is the coefficient of the immune system stimulation, C^* is the normal level of immunological cells concentration in a healthy body, ρ is the production rate of specific antibodies by one immunological cell, μ_f is the reciprocal of antibody lifetime, η is the use of antibodies to neutralize one antigen, σ is the rate of damage to target organ cells.

Function

$$\xi(m) = \begin{cases} 1, & 0 \le m \le m^*, \\ \xi^*(m), & m^* < m \le 1 \end{cases}$$

is used for taking into account the effect of reducing the efficiency of the immune system at significant damage, where m^* is the maximum value of the damage degree to the immune organ, at which normal functioning of the immune system is still possible, $\xi^*(m)$ – is monotonically decreasing continuously differentiated in the interval function $(m^*; 1)$, such as $\xi^*(m^*) = 1$, $\xi^*(1) = 0$ (for example $\xi(m) = (1 - m)/(1 - m^*)$). For this model, in particular, the asymptotic stability of the stationary solution is substantiated, which describes the healthy body's state if the initial infection dose V^0 of some immunological barrier $0 < V^0 < V^* = (\gamma\rho C^* - \beta\mu_f)/(\beta\eta\gamma)$ is not exceeded. So, when healthy body is infected by small dose of viral particles, their neutralization according to the model is provided by available amount of antibodies. Moreover, the included certain variability in the simplest model makes it possible to explain some important features functioning of the immune system. Besides, this allows explaining the possibility of the formation of subclinical, acute and chronic processes of the disease and clarifying the mechanisms of biostimulation, etc. [1].

The additional equation that describes the temperature change during the disease is proposed to take into account the influence of the body's temperature reaction on the disease dynamic by G. Marchuk [1]:

$$\frac{\partial \theta}{\partial t} = \alpha_T VF - \mu_T(\theta - \theta^*)$$

where $\alpha_T = \begin{cases} 0, & VF < (VF)^*, \\ \alpha_T^*, & VF \ge (VF)^*, \end{cases}$

$(VF)^*$ – the threshold value of VF-complexes, at which the temperature increase isn't stimulated yet (the hypothesis that body's temperature depends on the concentration of VF-complexes is accepted here), $\alpha_T^* = const > 0$, μ_T is the recovery rate of increased body's temperature to the temperature of a healthy host θ^*.

It should be noted that the mathematical models given in Ref. [1] have been studied in many works and have become the basis for various generalizations and modifications of them [3]. Particularly, such approach to infectious diseases modeling was developed and applied to the antitumor immunity models in Ref. [4]. The basic model for taking into account the immunotherapy effect on the immune response dynamics was modified in Ref. [5], and in Ref. [6] the approach to the construction of the distributed control to accelerate the output to a stationary solution was proposed. In Ref. [7], the model constructed by combining models describing the immune system various aspects was proposed to study the processes of local tissue inflammation. In particular, the Marchuk's approach was used to describe the systemic response. The mathematical model for studying the immune response

body's dynamics to coronavirus infection COVID-19 under immunotherapy conditions was built in Ref. [8] using the Marchuk's methodology for modeling infectious diseases.

It is indicated [3–5] that as the infectious disease simplest model and as the antiviral and antibacterial immune response models don't take into account the spatially distributed effects caused by uneven distribution of the forcing factors in the host. The uneven antigens distribution will take place naturally at the points of infected cells' destruction of the target organ and of release as a result of previously formed viral particles. The spatial effects of the infection spread and the immune response can be partially taken into account by using the compartment approach [9]. However, we should take into account the spatial diversity of the viral reproduction and immune response for more detailed description of the infectious disease dynamics. Immunology models containing spatially diffusive components are not widely used today [3]. Examples of such models described in Refs. [3,7,10–13].

The authors proposed in Refs. [3,4] the approach which takes into account influence of small spatially distributed diffuse "redistributions" on the dynamics of the infectious disease. The effect of concentration model decrease in the epicenter of infection caused by their diffuse "redistribution" of antigens is described here too. It also results the corresponding mitigation in the prognostic "severity" of the virus disease. This approach was extended [16] to generalize the antiviral mathematical model of Marchuk-Petrov immune response.

The simplest model including the diffuse perturbations of the infectious disease in conditions of pharmacotherapy was modified in Ref. [17]. The additional equation was added into the base model which describes the speed concentration change of the medicine solution injected into the host. The modified model provides the possibility of taking into account the medicine influence on the immune system functioning. The corresponding modification of the infectious disease basic model, which takes into consideration immunotherapy diffuse perturbation conditions were proposed in Refs. [18,19]. The effective methods of introducing of donor antibody solutions into the host are rapid injection through a syringe or slow introduction through a dropper. The generalization of the corresponding modification of the basic model is offered in Ref. [20] for taking into account various kinds of concentrated effects on the dynamics of infectious disease under conditions of diffusion perturbations. Theoretical researches of the existence and uniqueness of generalized solutions of similar mathematical models with concentrated influences are presented in Refs. [21,22]. The question of the controllability of such models was studied in Ref. [23].

It is clear that the temperature increase is one of the older evolutionarily host reactions on infections [24]. Many works have been devoted to the study of different aspects of rather complex and multifaceted mechanism of the temperature influence on the body's immune response [25–28]. In particular, it was noted [29] that fever is one of the most common symptoms for COVID-19 patients. To take into account the temperature influence on the coronavirus infection dynamics the additional equation was introduced into constructed mathematical model, which describes the change in body temperature during of the disease development [8].

The simplest model modification of infectious disease, which takes into consideration diffuse perturbation and concentrated influences under conditions of the body's temperature reaction is proposed in this paper.

3. Methods

3.1. Infection disease model modification

The spatio-temporal dynamics of the infectious disease process, based on diffuse perturbations under conditions of the body's temperature reaction in the domain $G_Z = \{(x,t):\ -\infty < x < +\infty,\ \ 0 < t < +\infty\}$ is described with such a singularity-perturbed system of nonlinear differential equations (with a delay):

$$\begin{aligned}
&\frac{\partial V}{\partial t} = \omega_V + (\beta(\theta) - \gamma F)V + \varepsilon D_V \frac{\partial^2 V}{\partial x^2},\\
&\frac{\partial C}{\partial t} = \xi(m)\cdot\alpha(\theta)\cdot F(t-\tau)\cdot V(t-\tau) - \mu_C(C - C^*) + \varepsilon^2 D_C \frac{\partial^2 C}{\partial x^2},\\
&\frac{\partial F}{\partial t} = \omega_F + \rho C - \left(\mu_f + \eta\gamma V\right)\cdot F + \varepsilon D_F \frac{\partial^2 F}{\partial x^2},\\
&\frac{\partial m}{\partial t} = \sigma\cdot V - \mu_m m + \varepsilon^2 D_m \frac{\partial^2 m}{\partial x^2},\\
&\frac{\partial \theta}{\partial t} = \alpha_T V F - \mu_T(\theta - \theta^*) + \varepsilon D_T \frac{\partial^2 \theta}{\partial x^2}
\end{aligned} \tag{1}$$

in terms

$$\begin{aligned}
&C(x,0) = C^0(x),\ \ m(x,0) = m^0(x),\ \ \theta(x,0) = \theta^0(x),\\
&V(x,\widetilde{t}) = V^0(x,\widetilde{t}),\ \ F(x,\widetilde{t}) = F^0(x,\widetilde{t}),\ \ -\tau \le \widetilde{t} \le 0,
\end{aligned} \tag{2}$$

where $V(x,t)$, $C(x,t)$, $F(x,t)$, $m(x,t)$, $\theta(x,t)$– respectively the concentrations of antigens (pathogenic viruses, bacteria, etc.), specific immune agents (antibodies, cell receptors, etc.) that are able to neutralize this type antigens, immunological cells that can produce appropriate specific immune agents, the relative characteristic value of the target organ damage and the temperature at the point x at the time t, $\beta(\theta) = \beta_0/(1+\beta_1(\theta-\theta^*))$ is the rate of antigens' multiplication, which decreases with a body temperature increase, $\beta_1 = const > 0$; $\alpha(\theta) = \alpha_0(1+\alpha_1(\theta-\theta^*))$ is the coefficient of stimulation of the immune system, which linearly depends on body temperature, $\alpha_1 = const > 0$; $\theta^*(x)$ is the temperature distribution in a healthy body; εD_V, εD_F, $\varepsilon^2 D_C$, $\varepsilon^2 D_m$, εD_T – coefficients of spatial diffusion redistribution, respectively, of antigens, antibodies, plasma and affected cells, thermal conductivity, ε – a small parameter that characterizes the small impact of the respective components compared to other components of the process; $C^0(x)$, $m^0(x)$, $V^0(x,\widetilde{t})$, $F^0(x,\widetilde{t})$ – the limited sufficiently smooth functions. Functions $\omega_V(x,t)$, $\omega_F(x,t)$ are intended to describe concentrated abrupt changes, antigens concentrations and antibodies in particular [19,20]. Such changes may occur as a result of introducing a concentrated dose of active viral particles into the host, or their release in the destruction points of a previously infected cell, the introduction of syringe injection of donor antibodies etc. Such values can be presented as a point-pulse functions of the source with maximum values in the points x_{Vs}, x_{Fs}, and in the time moments t_{Vs}, t_{Fs}, respectively:

$$\begin{aligned}
\omega_V(x,t) &= \sum_{s=1}^{n_V} A_{Vs} e^{-\alpha_{Vs}(x-x_{Vs})^2} e^{-\beta_{Vs}(t-t_{Vs})^2}, \quad \omega_F(x,t)\\
&= \sum_{s=1}^{n_F} A_{Fs} e^{-\alpha_{Fs}(x-x_{Fs})^2} e^{-\beta_{Fs}(t-t_{Fs})^2}.
\end{aligned} \tag{3}$$

When predicting the dynamics of infectious disease in cases of injection solutions through drip over time intervals $(\bar{t}_{Fs}, \bar{\bar{t}}_{Fs})$ at points x_{Fs}, the corresponding source function will be represented as:

$$\omega_F(x,t) = \sum_{s=1}^{n_F} A_{Fs} e^{-\alpha_{Fs}(x-x_{Fs})^2} \left[\frac{e^{-\beta_{Fs}(t-\bar{t}_{Fs})^2}}{1+e^{-\beta_{Fs}(t-\bar{t}_{Fs})^2}} - \frac{e^{-\beta_{Fs}(t-\bar{\bar{t}}_{Fs})^2}}{1+e^{-\beta_{Fs}(t-\bar{\bar{t}}_{Fs})^2}} \right] \tag{4}$$

It is known [1] that the increase in body temperature in a viral disease, as a rule, does not exceed a limit of 40–40.5 °C. In such cases, instead of equation in (1), which describes the change in temperature during the disease, it is possible to use a more complex equation

$$\frac{\partial \theta}{\partial t} = \alpha_T V F(1 - \alpha_2 V F) - \mu_T(\theta - \theta^*) + \varepsilon D_T \frac{\partial^2 \theta}{\partial x^2} \tag{5}$$

3.2. Asymptotics of the solution

We will further assume that system (1) is dimensionless [19,20].

Using the method of steps [30], we reduce the solution of problem (1)-(2) with a delay to the sequence of solutions of the corresponding problems without delay. So, at the intervals $r\tau < t \le (r+1)\tau$ ($r = 0, 1, 2, \ldots$) we have:

$$\begin{aligned}
&\frac{\partial V_0}{\partial t} = \omega_V + (\beta(\theta) - \gamma F_0)V_0 + \varepsilon D_V \frac{\partial^2 V_0}{\partial x^2},\\
&\frac{\partial C_0}{\partial t} = \xi(m)\cdot\alpha(\theta)\cdot F^0(x, t-\tau)\cdot V^0(x, t-\tau) - \mu_C(C_0 - C^*) + \varepsilon^2 D_C \frac{\partial^2 C_0}{\partial x^2},\\
&\frac{\partial F_0}{\partial t} = \omega_F + \rho C_0 - (\mu_f + \eta\gamma V_0)\cdot F_0 + \varepsilon D_F \frac{\partial^2 F_0}{\partial x^2},\\
&\frac{\partial m_0}{\partial t} = \sigma V_0 - \mu_m m_0 + \varepsilon^2 D_m \frac{\partial^2 m_0}{\partial x^2},\\
&\frac{\partial \theta_0}{\partial t} = \alpha_T V_0 F_0 - \mu_T(\theta_0 - \theta^*) + \varepsilon D_T \frac{\partial^2 \theta_0}{\partial x^2},\\
&C_0(x,0) = C^0(x),\ \ m_0(x,0) = m^0(x),\ \ \theta_0(x,0) = \theta^0(x),\\
&V_0(x,\widetilde{t}) = V^0(x,\widetilde{t}),\ \ F_0(x,\widetilde{t}) = F^0(x,\widetilde{t}),\ \ 0 < t \le \tau,
\end{aligned} \tag{6}$$

$$\begin{aligned}
&\frac{\partial V_r}{\partial t} = \omega_V + (\beta(\theta) - \gamma F_r)V_r + \varepsilon D_V \frac{\partial^2 V_r}{\partial x^2},\\
&\frac{\partial C_r}{\partial t} = \xi(m)\cdot\alpha(\theta)\cdot F_{r-1}(x, t-\tau)\cdot V_{r-1}(x, t-\tau) - \mu_C(C_r - C^*) + \varepsilon^2 D_C \frac{\partial^2 C_r}{\partial x^2},\\
&\frac{\partial F_r}{\partial t} = \omega_F + \rho C_r - (\mu_f + \eta\gamma V_r)\cdot F_r + \varepsilon D_F \frac{\partial^2 F_r}{\partial x^2},\\
&\frac{\partial m_r}{\partial t} = \sigma V_r - \mu_m m_r + \varepsilon^2 D_m \frac{\partial^2 m_r}{\partial x^2},\\
&\frac{\partial \theta_r}{\partial t} = \alpha_T V_r F_r - \mu_T(\theta_r - \theta^*) + \varepsilon D_T \frac{\partial^2 \theta_r}{\partial x^2},\\
&C_r(x, r\tau) = C_{r-1}(x, r\tau),\ \ m_r(x, r\tau) = m_{r-1}(x, r\tau),\ \ \theta_r(x,0) = \theta_{r-1}(x, r\tau),\\
&V_r(x, r\tau) = V_{r-1}(x, r\tau),\ \ F_r(x, r\tau) = F_{r-1}(x, r\tau),\ \ r\tau < t \le (r+1)\tau,
\end{aligned} \tag{7}$$

We provide the necessary smoothness order of the corresponding solutions for $t = 0$, $t = \tau$, …, $t = r\tau$, … by setting the usual smoothness conditions for the functions of the initial conditions of the model problem and additional conditions for their consistency for $t = -\tau$ and $t = 0$, … [20]. In particular, the condition must be met:

$$\begin{aligned}
\frac{\partial C_0(x,0)}{\partial t} &= \xi(m)\cdot\alpha_0\cdot F^0(x, -\tau)V^0(x, -\tau) - \mu_C(C_0(x,0) - C^*)\\
&+ \varepsilon^2 D_C \frac{\partial^2 C_0(x,0)}{\partial x^2}
\end{aligned} \tag{8}$$

Since we consider small diffusion redistributions of active process factors to find solutions of singularly perturbed problems (6)–(7), we apply the asymptotic method [3–9]. Note that in the case of such an approach, the transition from "unperturbed" to "perturbed" tasks can be done so that the classical forms of patterns that describe the development of the viral disease remain initially acceptable. And without starting "first", the obtained classical "unperturbed" solutions will be supplemented with different kinds of corrections in the future. Thus, we present the solutions of problems (6)–(7) formally in the form of asymptotic series

$$\begin{aligned}
&V_r(x,t) = \sum_{i=0}^{n} \varepsilon^i V_{ir}(x,t) + R^V_{nr}(x,t,\varepsilon),\ \ C_r(x,t) = \sum_{i=0}^{n} \varepsilon^i C_{ir}(x,t) + R^C_{nr}(x,t,\varepsilon),\\
&F_r(x,t) = \sum_{i=0}^{n} \varepsilon^i F_{ir}(x,t) + R^F_{nr}(x,t,\varepsilon),\ \ m_r(x,t) = \sum_{i=0}^{n} \varepsilon^i m_{ir}(x,t) + R^m_{nr}(x,t,\varepsilon),\\
&\theta_r(x,t) = \sum_{i=0}^{n} \varepsilon^i \theta_{ir}(x,t) + R^\theta_{nr}(x,t,\varepsilon)
\end{aligned} \tag{9}$$

as a perturbation solutions of the corresponding degenerate problems [14–20], where $r = 0, 1, 2, \ldots$, $V_{ir}(x,t)$, $C_{ir}(x,t)$, $F_{ir}(x,t)$, $m_{ir}(x,t)$, $\theta_{ir}(x,t)$ – sought terms of the asymptotics; $R^V_{nr}(x,t,\varepsilon)$ $R^C_{nr}(x,t,\varepsilon)$ $R^F_{nr}(x,t,\varepsilon)$ $R^m_{nr}(x,t,\varepsilon)$, $R^\theta_{nr}(x,t,\varepsilon)$ – corresponding residual terms. The problems of finding unknown functions $V_{ir}(x,t)$ $C_{ir}(x,t)$ $F_{ir}(x,t)$ $m_{ir}(x,t)$, $\theta_{ir}(x,t)$ are obtained by applying the standard "equalization procedure" [31]. At $\xi(m) = 1$ (i.e. at $0 \le m \le m^*$, when the damage level of the immunological organ hasn't coused the reduced productivity of antibodies production) we have the following tasks for finding functions V_{i0}, C_{i0}, F_{i0}, m_{i0}, θ_{i0} ($i = 0, 1, \ldots, n$) on the interval $0 < t \le \tau$ as in Refs. [19,20]:

$$\begin{aligned}
&\frac{\partial V_{0,0}}{\partial t} = \omega_V + (B_{0,0} - \gamma F_{0,0})V_{0,0},\\
&\frac{\partial C_{0,0}}{\partial t} = \alpha_0(1 + \alpha_1(\theta_{0,0} - \theta^*))\Psi_{C,0} - \mu_C(C_{0,0} - C^*),\\
&\frac{\partial F_{0,0}}{\partial t} = \omega_F + \rho C_{0,0} - (\mu_f + \eta\gamma V_{0,0})F_{0,0},\\
&\frac{\partial m_{0,0}}{\partial t} = \sigma V_{0,0} - \mu_m m_{0,0},\\
&\frac{\partial \theta_{0,0}}{\partial t} = \alpha_T V_{0,0} F_{0,0} - \mu_T(\theta_{0,0} - \theta^*),\\
&C_{0,0}(x,0) = C^0(x),\ \ m_{0,0}(x,0) = m^0(x),\ \ \theta_{0,0}(x,0) = \theta^0(x),\\
&V_{0,0}(x,\widetilde{t}) = V^0(x,\widetilde{t}),\ \ F_{0,0}(x,\widetilde{t}) = F^0(x,\widetilde{t}),\ \ 0 < t \le \tau,
\end{aligned} \tag{10}$$

$$\begin{aligned}
&\frac{\partial V_{1,0}}{\partial t} = a_{0,0}B_{1,0} + c_{0,0}V_{1,0} - \gamma(a_{0,0}F_{1,0} + b_{0,0}V_{i,0}) + \Phi_{V\,1,0},\\
&\frac{\partial C_{1,0}}{\partial t} = \alpha_0\alpha_1\theta_{1,0}\cdot\Psi_{C,0} - \mu_C C_{1,0},
\end{aligned} \tag{11}$$

$$\begin{aligned}
&\frac{\partial F_{1,0}}{\partial t} = \rho C_{1,0} - \mu_F F_{1,0} - \eta\gamma(a_{0,0}F_{1,0} + b_{0,r}V_{1,0}) + \Phi_{F\,1,0},\\
&\frac{\partial m_{1,0}}{\partial t} = \sigma V_{1,0} - \mu_m m_{1,0},\\
&\frac{\partial \theta_{1,0}}{\partial t} = \alpha_T(a_{0,0}F_{1,0} + b_{0,0}V_{1,0}) - \mu_T\theta_{1,0} + \Phi_{\theta\,1,0},\\
&C_{1,0}(x,0) = 0,\ \ m_{1,0}(x,0) = 0,\ \ \theta_{1,0}(x,0) = 0,\\
&V_{1,0}(x,\widetilde{t}) = 0,\ \ F_{1,0}(x,\widetilde{t}) = 0,\ \ 0 < t \le \tau,
\end{aligned}$$

$$\begin{aligned}
&\frac{\partial V_{i,0}}{\partial t} = a_{0,0}B_{i,0} + c_{0,0}V_{i,0} - \gamma(a_{0,0}F_{i,0} + b_{0,0}V_{i,0}) + \Phi_{V\,i,0},\\
&\frac{\partial C_{i,0}}{\partial t} = \alpha_0\alpha_1\theta_{i,0}\cdot\Psi_{C,0} - \mu_C C_{i,0} + \Phi_{C\,i,0},\\
&\frac{\partial F_{i,0}}{\partial t} = \rho C_{i,0} - \mu_F F_{i,0} - \eta\gamma(a_{0,0}F_{i,0} + b_{0,r}V_{i,0}) + \Phi_{F\,i,0},\\
&\frac{\partial m_{i,0}}{\partial t} = \sigma V_{i,0} - \mu_m m_{i,0} + \Phi_{m\,i,0},\\
&\frac{\partial \theta_{i,0}}{\partial t} = \alpha_T(a_{0,0}F_{i,0} + b_{0,0}V_{i,0}) - \mu_T\theta_{i,0} + \Phi_{\theta\,i,0},\\
&C_{i,0}(x,0) = 0,\ \ m_{i,0}(x,0) = 0,\ \ \theta_{i,0}(x,0) = 0,\\
&V_{i,0}(x,\widetilde{t}) = 0,\ \ F_{i,0}(x,\widetilde{t}) = 0,\ \ 0 < t \le \tau,\ \ i = 2, 3, \ldots, n
\end{aligned} \tag{12}$$

The problem (10) is the degeneration of the initial problem (6) received by setting $\varepsilon = 0$ in (6). Problems (11)–(12) are used to find the appropriate corrections for the solution of degenerated problem to take into account the diffusion at this point in time. Similarly, we get problems for finding the functions V_{ir}, C_{ir}, F_{ir}, m_{ir}, θ_{ir} ($i = 0, 1, \ldots, n$) at the next time steps $r\tau < t \le (r+1)\tau$ ($r = 1, 2, \ldots$)

$$\begin{aligned}
&\frac{\partial V_{0,r}}{\partial t} = \omega_V + \left(B_{0,r} - \gamma F_{0,r}\right)V_{0,r},\\
&\frac{\partial C_{0,r}}{\partial t} = \alpha_0\left(1 + \alpha_1\left(\theta_{0,r} - \theta^*\right)\right)\Psi_{C,r} - \mu_C\left(C_{0,r} - C^*\right),\\
&\frac{\partial F_{0,r}}{\partial t} = \omega_F + \rho C_{0,r} - \left(\mu_f + \eta\gamma V_{0,r}\right)F_{0,r},\\
&\frac{\partial m_{0,r}}{\partial t} = \sigma V_{0,r} - \mu_m m_{0,r},\\
&\frac{\partial \theta_{0,r}}{\partial t} = \alpha_T V_{0,r}F_{0,r} - \mu_T\left(\theta_{0,r} - \theta^*\right),\\
&C_{0,r}(x,0) = C_{0,r-1}(x),\ \ m_{0,r}(x,0) = m_{0,r-1}(x),\ \ \theta_{0,r}(x,0) = \theta_{0,r-1}(x),\\
&V_{0,r}(x,\widetilde{t}) = V_{0,r-1}(x,\widetilde{t}),\ \ F_{0,r}(x,\widetilde{t}) = F_{0,r-1}(x,\widetilde{t}),\ \ r\tau < t \le (r+1)\tau,
\end{aligned} \tag{13}$$

$$\begin{aligned}
&\frac{\partial V_{1,r}}{\partial t} = a_{0,r}B_{1,r} + c_{0,r}V_{1,r} - \gamma\left(a_{0,r}F_{1,r} + b_{0,r}V_{1,r}\right) + \Phi_{V\ 1,r},\\
&\frac{\partial C_{1,r}}{\partial t} = \alpha_0\alpha_1\theta_{1,r}\cdot\Psi_{C,r} - \mu_C C_{1,r},\\
&\frac{\partial F_{1,r}}{\partial t} = \rho C_{1,r} - \mu_F F_{1,r} - \eta\gamma\left(a_{0,r}F_{1,r} + b_{0,r}V_{1,r}\right) + \Phi_{F\ 1,r},\\
&\frac{\partial m_{1,r}}{\partial t} = \sigma V_{1,r} - \mu_m m_{1,r},\\
&\frac{\partial \theta_{1,r}}{\partial t} = \alpha_T\left(a_{0,r}F_{1,r} + b_{0,r}V_{1,r}\right) - \mu_T\theta_{1,r} + \Phi_{\theta\ 1,r},\\
&C_{1,r}(x,0) = 0,\ \ m_{1,r}(x,0) = 0,\ \ \theta_{1,r}(x,0) = 0,\\
&V_{1,r}(x,\widetilde{t}) = 0,\ \ F_{1,r}(x,\widetilde{t}) = 0,\ \ r\tau < t \le (r+1)\tau,
\end{aligned} \tag{14}$$

$$\begin{aligned}
&\frac{\partial V_{i,r}}{\partial t} = a_{0,r}B_{i,r} + c_{0,r}V_{i,r} - \gamma\left(a_{0,r}F_{i,r} + b_{0,r}V_{i,r}\right) + \Phi_{V\ i,r},\\
&\frac{\partial C_{i,r}}{\partial t} = \alpha_0\alpha_1\theta_{i,r}\cdot\Psi_{C,r} - \mu_C C_{i,r} + \Phi_{C\ i,r},\\
&\frac{\partial F_{i,r}}{\partial t} = \rho C_{i,r} - \mu_F F_{i,r} - \eta\gamma\left(a_{0,r}F_{i,r} + b_{0,r}V_{i,r}\right) + \Phi_{F\ i,r},\\
&\frac{\partial m_{i,r}}{\partial t} = \sigma V_{i,r} - \mu_m m_{i,r} + \Phi_{m\ i,r},\\
&\frac{\partial \theta_{i,r}}{\partial t} = \alpha_T\left(a_{0,r}F_{i,r} + b_{0,r}V_{i,r}\right) - \mu_T\theta_{i,r} + \Phi_{\theta\ i,r},\\
&C_{i,r}(x,0) = 0,\ \ m_{i,r}(x,0) = 0,\ \ \theta_{i,r}(x,0) = 0,\\
&V_{i,r}(x,\widetilde{t}) = 0,\ \ F_{i,r}(x,\widetilde{t}) = 0,\ \ r\tau < t \le (r+1)\tau,\ \ i = 2,3,\ldots,n
\end{aligned} \tag{15}$$

Here

$$a_{0,r}(x,t) = V_{0,r}(x,t)b_{0,r}(x,t) = F_{0,r}(x,t)$$

$$\begin{aligned}
c_{0,r}(x,t) = B_{0,r}(x,t) &= \frac{\beta_0}{1 + \beta_1\left(\theta_{0,r} - \theta^*\right)}B_{i,r}\\
&= -\frac{\beta_1}{1 + \beta_1\left(\theta_{0,r} - \theta^*\right)}\cdot\sum_{k=0}^{i-1}\theta_{i-k,r}B_{k,r}
\end{aligned}$$

$$\Psi_{C,0}(x,t) = F^0(x,t-\tau)V^0(x,t-\tau)\Psi_{C,r}(x,t) = F_{r-1}(x,t-\tau)V_{r-1}(x,t-\tau)$$

$$\begin{aligned}
\Phi_{V1,r}(x,t) = D_V\frac{\partial^2 V_{0,r}(x,t)}{\partial x^2}&\Phi_{F1,r}(x,t) = D_F\frac{\partial^2 F_{0,r}(x,t)}{\partial x^2}\Phi_{\theta 1,r}(x,t)\\
&= D_T\frac{\partial^2\theta_{0,r}(x,t)}{\partial x^2}
\end{aligned}$$

$$\Phi_{V_{i,r}}\left(x,t\right) = \sum_{k=1}^{i-1}\left(B_{k,r}\left(x,t\right) - \gamma F_{i-k,r}\left(x,t\right)\right)V_{i-k,r}\left(x,t\right) + D_V\frac{\partial^2 V_{i-1,r}(x,t)}{\partial x^2}$$

$$\begin{aligned}
\Phi_{Ci,r}(x,t) = D_C\frac{\partial^2 C_{i-2,r}(x,t)}{\partial x^2}&\Phi_{Fi,r}(x,t) = -\eta\gamma\sum_{k=1}^{i-1}V_{k,r}(x,t)F_{i-k,r}(x,t)\\
&+ D_F\frac{\partial^2 F_{i-1,r}(x,t)}{\partial x^2}
\end{aligned}$$

$$\begin{aligned}
\Phi_{m\ \ i,r}(x,t) = D_m\frac{\partial^2 m_{i-2,r}(x,t)}{\partial x^2}&\Phi_{\theta i,r}(x,t) = \alpha_T\sum_{k=1}^{i-1}V_{k,r}(x,t)F_{i-k,r}(x,t)\\
&+ D_T\frac{\partial^2\theta_{i-1,r}(x,t)}{\partial x^2}
\end{aligned}$$

In the sizable damage case to the immunological organ ($m^* \le m < 1$), it is necessary to take into account the corresponding reducing the productivity of immunological cells, determined by the function $\xi^*(m)$. In this case, the equations describing the rate of change in the immunological cells concentration, in particular, in the tasks (13), (14), (15), will be written as:

$$\frac{\partial C_{0,r}}{\partial t} = \alpha_0[(1-m_0)/(1-m^*)]\cdot\left(1 + \alpha_1\left(\theta_{0,r} - \theta^*\right)\right)\Psi_{C,r} - \mu_C\left(C_{0,r} - C^*\right), \tag{16}$$

$$\frac{\partial C_{1,r}}{\partial t} = \alpha_0[1/(1-m^*)]\cdot\left[\alpha_1(1-m_0)\theta_{1,r} - \left(1 + \alpha_1\left(\theta_{0,r} - \theta^*\right)\right)m_1\right]\cdot\Psi_{C,r} - \mu_C C_{1,r}, \tag{17}$$

$$\frac{\partial C_{i,r}}{\partial t} = \alpha_0[1/(1-m^*)]\cdot\left[\alpha_1(1-m_0)\theta_{i,r} - \left(1 + \alpha_1\left(\theta_{0,r} - \theta^*\right)\right)m_{i,r}\right]\cdot\Psi_{C,r} + \overline{\Phi}_{C\ \ i,r}, \tag{18}$$

where $\overline{\Phi}_{Ci,r}(x,t) = -\alpha_0[1/(1-m^*)]\alpha_1\Psi_{C,r}\cdot\sum_{k=1}^{i-1}\theta_k m_{i-k} + D_C\frac{\partial^2 C_{i-2,r}(x,t)}{\partial x^2}$.

At each stage of the iterative process, we find the solutions of the corresponding problems at intervals $r\tau \le t \le (r+1)\tau$ ($r = 0,1,2,\ldots$) by numerical methods (for example, Runge-Kut methods), using the previously found solutions of the problems at the previous stage. In the insufficient smoothness case of the initial data or their discrete specification, it is possible to use the Chebyshov approximation of the function by the polynomial sum and an expression with some nonlinear parameter according to Refs. [32,33]. Therefore, the application of the asymptotic method reduced the rather complex initial problem to a series of simpler problems. The numerical solution technologies of such problems have already been well educated and reliable software packages have been developed [34]. We note the problems of the type (10), (13) for finding the first terms of the asymptotics regular parts coincide in form with the well-known and rather well-studied corresponding problem already approved basic model. Estimation of residual terms of $R_{nj}^V(x,t,\varepsilon)$, $R_{nj}^C(x,t,\varepsilon)$, $R_{nj}^F(x,t,\varepsilon)$, $R_{nj}^m(x,t,\varepsilon)$, $R_{nj}^\theta(x,t,\varepsilon)$ and the space-time intervals establishment convergence in predicting specific processes is based on the maximum principle, similarly to Ref. [31]. Note that the proposed approach can be easily transferred to cases where there is also convective transfer of antigens, immune agents and immunological cells in the body [31].

4. Numerical experiments

Numerical experiments were conducted to study the effect of body temperature response and diffusive "redistribution" of forcing factors on the development of infectious disease in a chronic form. In computer modeling, the values obtained in Refs. [1,2] were appropriately reformed after the dimensionlessization procedure and used for the parameters: $\beta_0 = 1$, $\beta_1 = 10$; $\gamma = 0.8$; $\mu_c = 0.5$; $\alpha_0 = 1000$, $\alpha_1 = 25$; $u_2^* = 1$; $\rho = 0.17$; $\mu_f = 0.17$; $\eta = 10$; $\sigma = 10$; $\mu_f = 0.12$. Computer modeling was implemented for the different values of parameter α_T^*, which determines the temperature rise rate, the different levels of the diffusion redistribution intensity (values of parameter ε), the different values of parameter α_1 in the coefficient of protein synthesis stimulation and for different values of parameter β_1 for the antigen multiplication coefficient. In this case, at the initial moment of time, the following values of the process acting factors were taken: $C^0(x) = 1$, $m^0(x) = 0$, $\theta^0(x) = 1$, $V^0(x,\widetilde{t}) = 10^{-4}e^{-x^2}e^{-\widetilde{t}}$, $F^0(x,\widetilde{t}) = 1$. In cases where there are

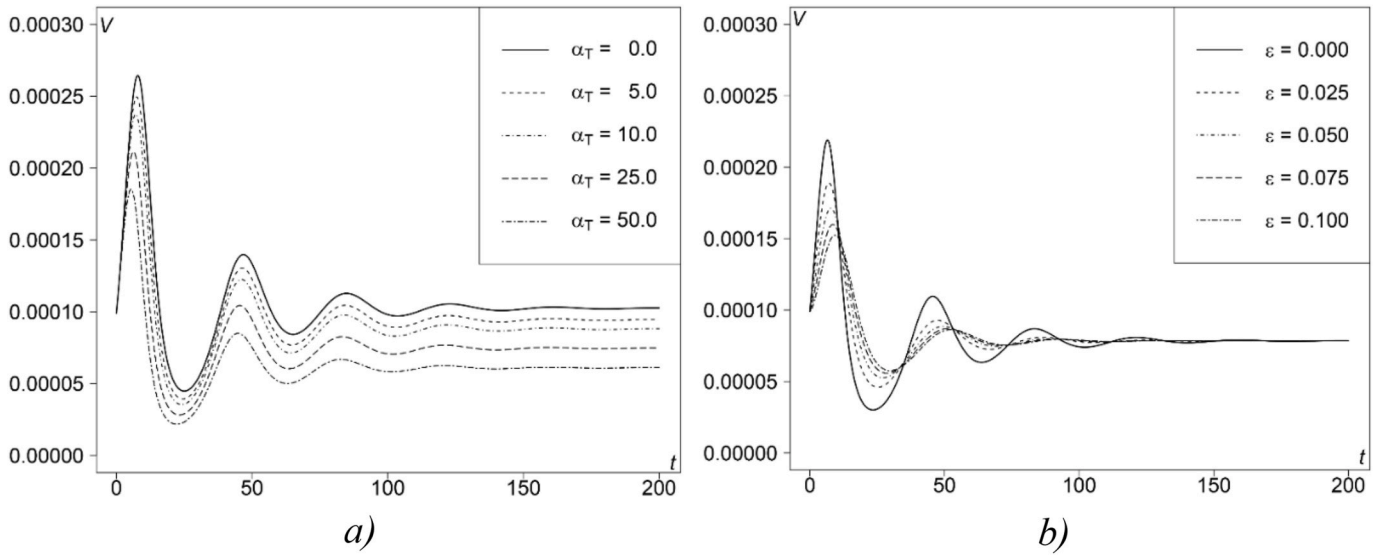

Fig. 1. Model dynamics of antigen concentration in the chronic form disease:
a) at different values α_T of the temperature increase rate; *b*) at different intensity levels of the diffuse influence.

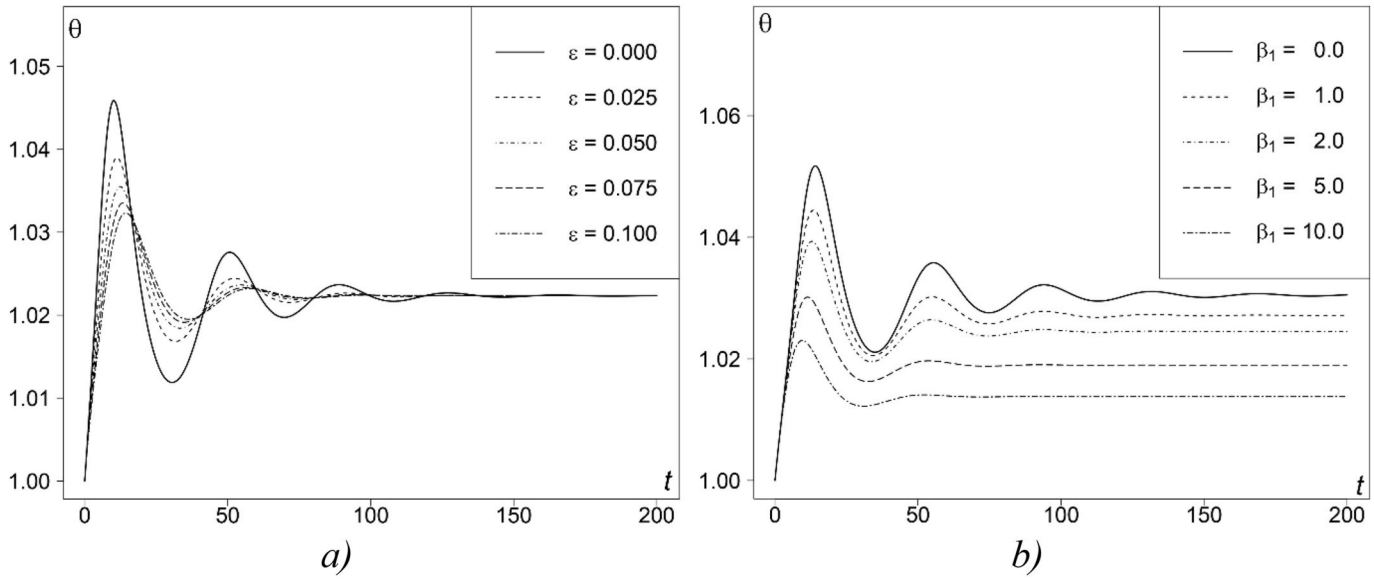

Fig. 2. Model dynamics of body temperature in the chronic form disease:
a) at different levels of diffuse impact intensity; *b*) at the different values β_1 in the reproduction rate of antigens.

several concentrated sources of antigens and donor antibodies the stationary solution values characterizing the healthy organism state were taken as the initial values of the process acting factors: $C^0(x) = 1$, $m^0(x) = 0$, $\theta^0(x) = 1$, $V^0(x,\widetilde{t}) = 0$, $F^0(x,\widetilde{t}) = 1$.

5. Results and discussion

Fig. 1, a) shows the modeling dynamics of the concentration of antigens at the infection epicenter in a chronic form of the disease at different values of the temperature rate increase α_T depending on the concentration of *VF*-complexes without taking into account diffusion perturbations. As expected, with increasing coefficient α_T of the model concentration of antigens in the epicenter of infection with the development of the disease process and in the steady state decrease. Thus, the predicted "severity" of the infectious disease course in a chronic form will decrease due to the temperature reaction influence on the immune response. In addition, the effect of diffusion "redistribution" of active factors with their uneven distribution in the body also reduces the "severity" of the disease. Fig. 1,b) illustrates the dynamics of the model concentration of antigens in the epicenter of infection in the chronic form of the disease, taking into account the influence of the body's temperature response at different levels of intensity of diffusion "redistribution".

The dynamics of the model body temperature in the epicenter of infection under conditions of infectious disease in the chronic form at different values of the parameter is illustrated in Fig. 2, a). These results demonstrate the expected decrease in the "severity". of the disease with increasing intensity of diffusion redistribution and thermal conductivity. Fig. 2, b) presents the dynamics of body temperature at different values of the parameter β_1 in the reproduction rate of antigens. The presented results confirm the expected efficiency increase of the body's temperature response during self-defense against pathogens with a higher sensitivity to an increase in ambient temperature.

The change in the model concentration of antigens in the epicenter of

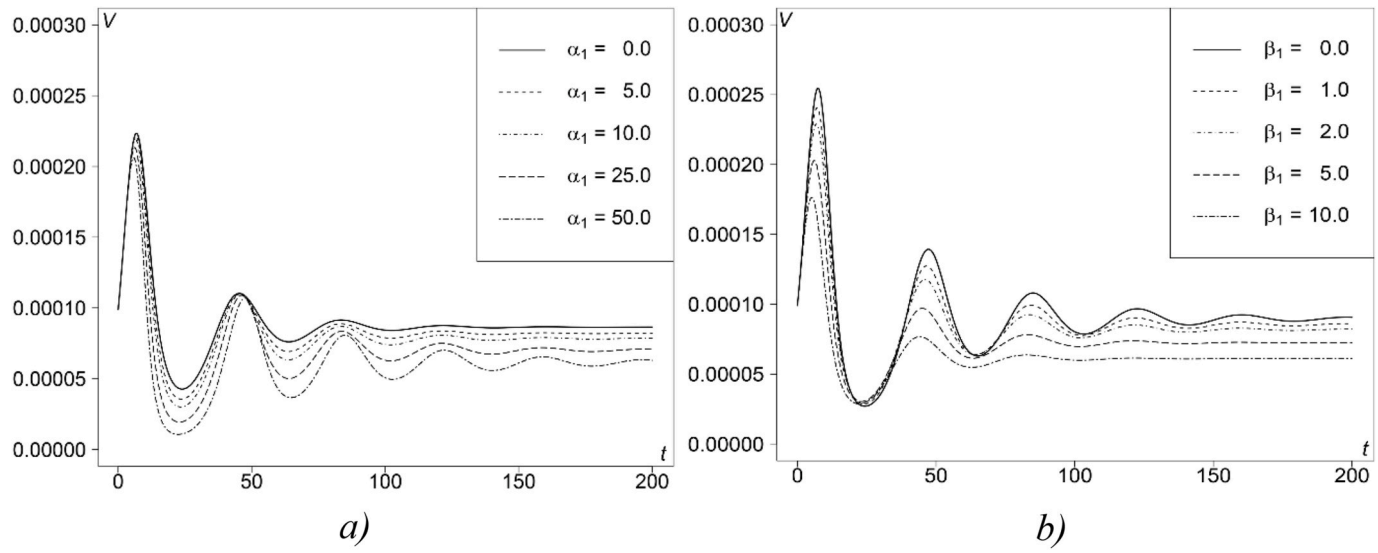

Fig. 3. The model dynamics of the antigens concentration in a chronic form disease:
a) at the different values α_1 in the coefficient of stimulation of protein synthesis; *b*) at the different values β_1 in the reproduction rate of antigens.

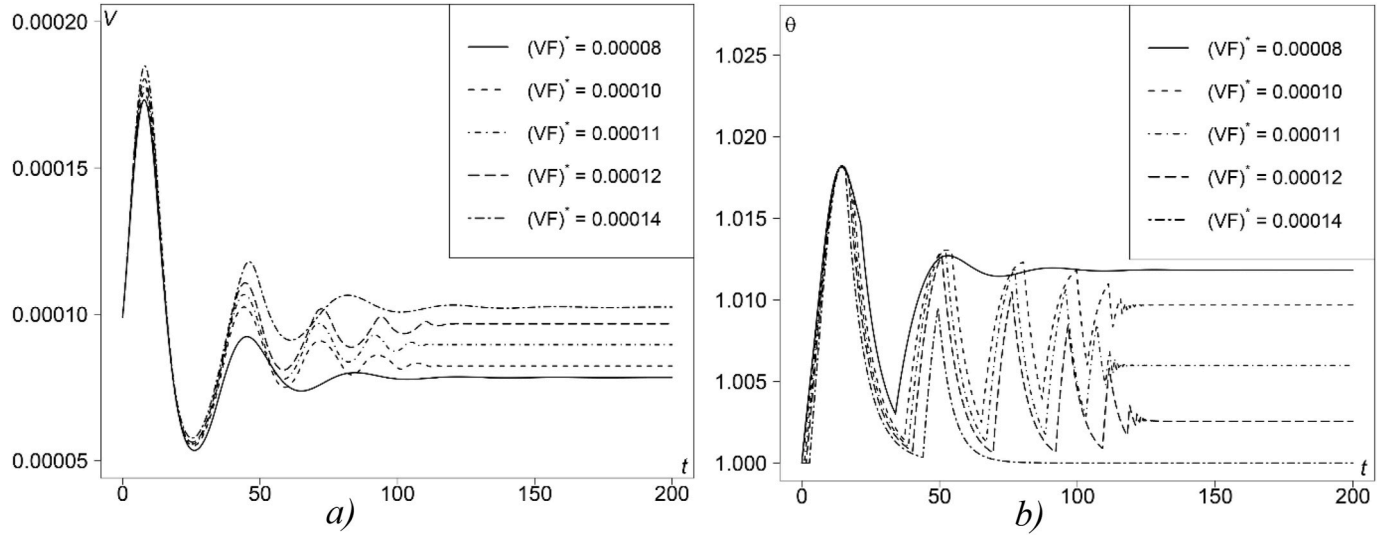

Fig. 4. Model dynamics of the antigen concentration *a*) and the temperature *b*) at different threshold value $(VF)^*$ concentrations of *VF*-complexes.

infection with the development of infectious disease in the chronic form at different values of the parameter α_1 in the coefficient of stimulation of protein synthesis is presented in Fig. 3, a), and at different values of the parameter β_1- in Fig. 3, b). It is known that the degree of temperature response of different hosts to pathogenic microorganisms may differ, in addition, as evidenced by medical observations, the body's temperature response to antigens decreases with age. The presented results of numerical experiments in both situations are expected to show a decrease in the maximum values of antigen concentrations due to increasing body temperature, which in turn leads to a decrease in the characteristics of the target organ and reduces the "severity" of the disease.

Fig. 4, a) shows the model dynamics of the antigens concentration at the epicentre of infection in course of the infectious disease in a chronic form at different threshold levels of the $(VF)^*$ concentration of the "antigen-antibody" complexes. At lower $(VF)^*$ values, the temperature increase begins to be stimulated earlier, which, as expected, reduces to a faster decrease of model concentration of the antigens and provides a milder course of the disease. The model body temperature at such small threshold values $(VF)^*$ during the disease takes on higher values and sets at a higher level in the stationary state.

Fig. 5, a) and Fig. 5, b) shows the spatio-temporal dynamics of antigens concentration with the development of infectious disease process at a chronic form in cases with and without taking into account the body's temperature reaction, respectively. The initial values of the active factors of the process are the values of the stationary solution, which characterizes the state of a healthy organism. At different time points $(t_{V1} < t_{V2} < t_{V3})$ and at different points $(x_{V3} < x_{V1} < x_{V2})$ (in different infection cells), there are sharp, point-focused changes in antigen concentrations. The given results of numerical experiments also illustrate a model severity decrease of the infectious disease because of the self-protective action mechanism of body's temperature increasing.

Fig. 6 presents the spatio-temporal dynamics of antigen concentrations in the conditions of infectious disease in the chronic form in the presence of concentrated sources of antigens and donor antibodies at one point $(x_V = x_{F1} = x_{F2})$, but at different points in time $(t_V < t_{F1} < t_{F2})$ in cases without taking into account (Fig. 6, a)) and taking into account (Fig. 6, b)) diffuse redistribution ($\varepsilon = 0.05$). The obtained results illustrate the "localization" of the model course of the

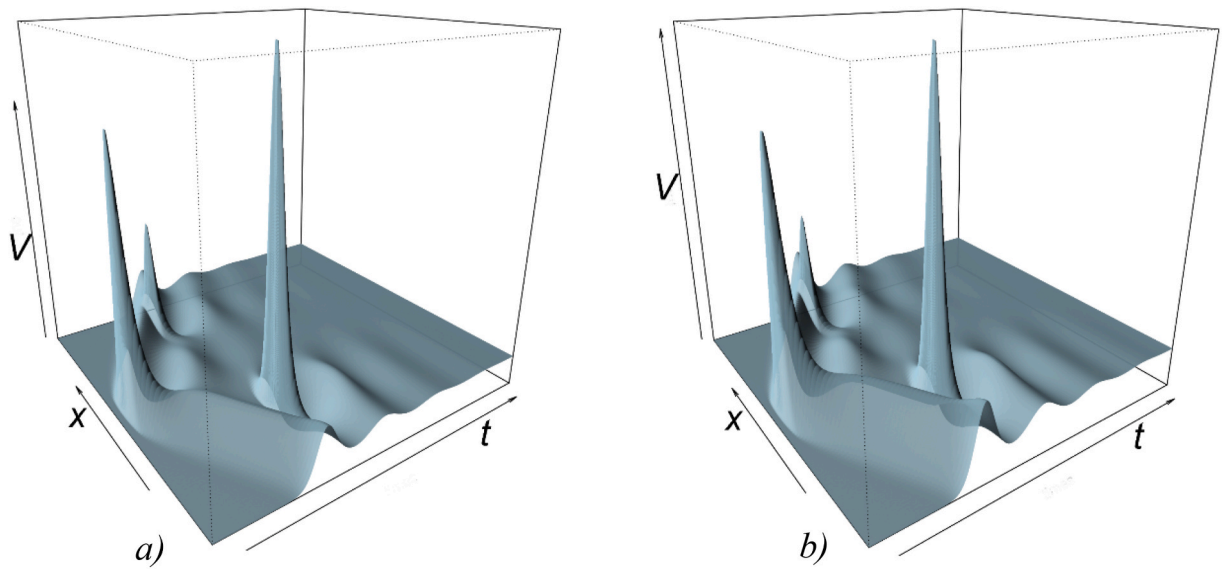

Fig. 5. Spatio-temporal dynamics of antigens concentration with availability of the several concentrated sources of antigens at: *a*) $\alpha_T = 50$; *b*). $\alpha_T = 0$.

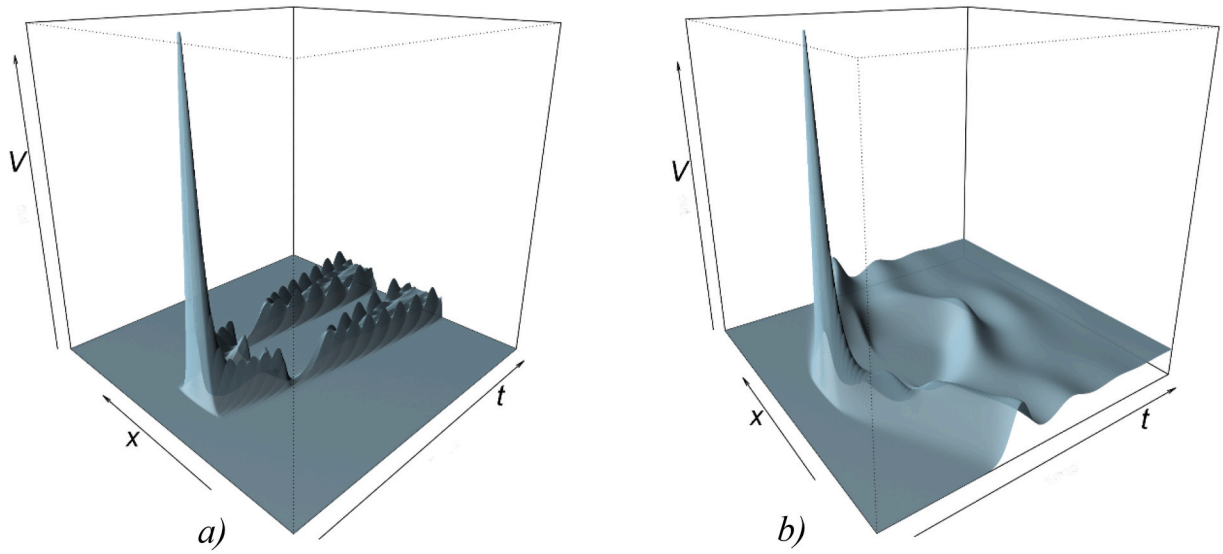

Fig. 6. Spatio-temporal dynamics of antigens concentration with availability of the several concentrated sources of antigens at: *a*) $\varepsilon = 0.00$; *b*) $\varepsilon = 0.05$.

disease in some area of infection (in particular, in the case of the introduction of donor antibodies) in the absence of diffuse redistribution. Taking into account the diffuse redistribution, the localization of the model process in the infection zone does not occur, and with the development of the disease, the distribution of active factors in the body is “aligned".

6. Conclusions

The presented approach takes into account the influence of diffuse perturbations and different kinds of concentrated influences on process development under conditions of a body’s self-protective temperature reaction is presented on the basis of mathematical model generalization of infectious disease. The solution singularly perturbed model problem with delay is introduced as sequence of problems without delay for which additional consistency conditions are determined that ensure the smoothness required order. The asymptotic method is applied to find solutions of problems at each time step, that makes it possible to construct an efficient computational procedure, according to which the known basic “unperturbed” solutions are supplemented by various corrections.

The presented results of predicting the model development of infectious disease in different situational conditions confirm the expected decrease in the growth rate of antigens, and, consequently, the “severity” of the disease due to increase of body temperature as a self-defense response to detected viral particles. The paper also presents the results of numerical experiments, which illustrate the decrease in the concentration of antigens in the epicenter of infection also due to their diffusion “redistribution”. It is shown that the reduction, including the supercritical amount of antigens as a result of temperature rise and diffusion “scattering” in the source of infection leads to even more effective neutralization of antibodies present in the body. Thus, taking into account the complex influence of diffusion “redistribution” of active factors, temperature response, as well as various concentrated influences in predicting the development of viral disease to form a rational treatment program allows more economical immunotherapy procedures and establish the optimal concentration of donor antibodies in each injection, method and rational frequency of its introduction.

In long term of research there is a development of the proposed approach to take into account spatially distributed diffusive "re-distributions" in immunotherapy (or pharmacotherapy) of different kinds concentrated influences, logistic limitations of acting factors and the body's temperature response when predicting the dynamics of diseases based on more general and detailed models, for example, the antiviral and antibacterial immune response of Marchuk-Petrov's models [1].

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Declaration of competing interest

The authors whose names are listed immediately below certify that they have NO affiliations with or involvement in any organization or entity with any financial interest (such as honoraria; educational grants; participation in speakers' bureaus; membership, employment, consultancies, stock ownership, or other equity interest; and expert testimony or patent-licensing arrangements), or non-financial interest (such as personal or professional relationships, affiliations, knowledge or beliefs) in the subject matter or materials discussed in this manuscript.

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