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Modeling small-scale spatially distributed influences on the development of infectious diseases

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In this paper, the small-scale spatially distributed influences on the infectious disease development are proposed to be modeled by means of diffuse disturbance of the corresponding degenerate model problems. We represent the asymptotic expansions of the solutions of the corresponding singularly-disturbed problems with a time-delay that are reduced to a sequence of problems without a time-delay. The results of numerical experiments that characterize the spatially distributed diffuse influences on the infectious disease development are presented. The decrease in the maximum concentration level of pathogenic antigens due to their diffuse "redistribution" from the locus of infection into less infected areas of the target organ is illustrated.

Keywords: *infectious disease model, stationary solutions for dynamic systems, stability of solution.*

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1. Introduction

The universality of the immune defense processes of the organism against pathogenic bacteria and viruses prompted the development and wide application of mathematical modeling methods to their study. Today, there is a various spectrum of mathematical models of the immune defence of the organism constructed according to different principles [1–5].

In particular, in [1] the simplest mathematical model of infectious disease of G. I. Marchuk is presented as a system of nonlinear differential equations with time-delay

$$\begin{aligned}
&\frac{dV}{dt} = (\beta - \gamma F)\, V,\\
&\frac{dC}{dt} = \xi(m)\, \alpha V(t-\tau)\, F(t-\tau) - \mu_C (C - C^*),\\
&\frac{dF}{dt} = \rho C - (\mu_f + \eta\gamma V)\, F,\\
&\frac{dm}{dt} = \sigma V - \mu_m m
\end{aligned} \tag{1}$$

for conditions

$$C(t_0) = C^0, \quad m(t_0) = m^0, \quad V(\tilde{t}) = V^0(\tilde{t}), \quad F(\tilde{t}) = F^0(\tilde{t}), \quad t_0 - \tau \leqslant \tilde{t} \leqslant t_0, \tag{2}$$

where $V(t)$ is the concentration of pathogenic antigens, $C(t)$ is the concentration of plasma cells that are carriers and producers of antibodies, $F(t)$ is the concentration of antibodies that neutralize antigens, $m(t)$ is the relative characteristic (measure of contagion) of the infected organ. The model also assumes

that for the uninfected organ m is zero and for the fully infected it is a unit. (see [1]). With significant damage to the organism, the production efficiency of antibodies decreases, which, in general, can lead to death. The function that we introduced in model (1)–(2)

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

allows us to account of the reducing of the production efficiency of antibodies with significant damage to important target organs. On the interval $0 \leqslant m < m^*$ the function $\xi(m)$ equals a unity, it means that functionality of the immunological organs is complete and does not depend on the severity of the disease. Further, for $m^* \leqslant m < 1$, the functionality efficiency of the organ rapidly decreases.

The system of equations (1) has stationary solutions, one of that describes the state of a healthy organism:

$$V = 0, \quad C = C^*, \quad F = F^* = \rho C^*/\mu_f, \quad m = 0. \tag{3}$$

This means that the concentration of pathogenic antigens and the infected proportion of the target organ is zero, and the number of plasma cells C and antibodies F correspond to the immunological status of a healthy person. In [1] it is shown that this state is asymptotically stable for $\beta < \gamma F^*$ and maintains such resistance when a healthy organism is infected by a dose of antigen V^0 that does not exceed some level V^* of the immunological barrier:

$$V^0 < V^* = \mu_f(\gamma F^* - \beta)/(\beta\eta\gamma). \tag{4}$$

The other stationary solution

$$\bar{V} = \frac{\mu_C\mu_f\,(\beta - \gamma F^*)}{\beta\,(\alpha\rho - \mu_C\eta\gamma)}, \quad \bar{C} = \frac{\alpha\beta\mu_f - \eta\mu_C\gamma^2 C^*}{\gamma\,(\alpha\rho - \mu_C\eta\gamma)}, \quad \bar{F} = \frac{\beta}{\gamma}, \quad \bar{m} = \frac{\sigma\bar{V}}{\mu_m} = \frac{\sigma\mu_C\mu_f\,(\beta - \gamma F^*)}{\mu_m\beta\,(\alpha\rho - \mu_C\eta\gamma)},$$

that describes the so-called chronic process of the disease, is obtained for $V > 0$ and $\xi(m) \equiv 1$ is also stable [1].

According to the assumptions of the basic infectious disease model with significant lesions of the target organ value of the relative characteristics of the extent of such lesions $m^* < m < 1$, then, in particular $\xi(m) = (m-1)/(m^*-1)$ [1]. Taking into account that the second equation of system (1) $(m-1)/(m^*-1)\alpha VF - \mu_C(C - C^*) = 0$, which describes the change in the number of plasma cells under steady state, we get stationary solutions in a situation of significant damage to the target organ

$$\bar{\bar{V}}_{1,2} = \mu_m\bar{\bar{m}}_{1,2}/\sigma, \quad \bar{\bar{C}}_{1,2} = \beta\eta\bar{\bar{V}}_{1,2}/\rho + \mu_f\beta/\,(\rho\gamma), \quad \bar{\bar{F}}_{1,2} = \beta/\gamma,$$

$$\bar{\bar{m}}_{1,2} = \frac{1}{2\alpha\rho}\left[\alpha\rho + \mu_C(m^*-1)\left(\eta\gamma \pm \sqrt{\left(\frac{\alpha\rho + \eta\gamma\mu_C(m^*-1)}{\mu_C(m^*-1)}\right)^2 - \frac{4\alpha\rho\sigma\mu_f(\gamma F^* - \beta)}{\beta\mu_m\mu_C(m^*-1)}}\right)\right]. \tag{5}$$

Let us note according to the infectious disease model (1)–(2) described above, the response of the immune system to the existing of foreign pathogenic antigens begins from the moment t_0. For that, a certain initial level of concentration of presented antigens in the organism V^0 is established.

The processes of spatial distribution of antigens after their entry and reproduction in the organism in the models are not specified. As noted in [6], for any pathogenic antigen in the organism there are lymphocytes that can recognize it. However, for each antigen, the number of lymphocytes with their corresponding specific receptors is small. In addition, the activity of lymphocytes is less than the activity of pathogenic antigen. So, it is considered that antigens that enter the organism externally prior to their recognition by the immune system are able to spread in the organism, infect the target organ cells in different spatially distributed places. Thus, several centers of infection with significantly higher antigenic pathogens are created. Further, the newly-formed antigens spread from high concen-

tration places to lower concentration places, expanding the target organ lesion area and reducing the concentration of available antigens in the area itself.

The purpose of this work is to take into account the small spatially distributed diffuse influences on the development of the infectious disease for its study that is based on the basic model of G. I. Marchuk (1)–(2).

2. Modeling infectious disease process taking into account of small diffuse disturbance (problem statement)

We assume that small-scale spatially distributed influences on the development of the infectious disease process have diffusive character. Let us describe the corresponding spatio-temporal dynamics of model factors of infectious disease in the set $G_Z = \{(x,t)\colon -\infty < x < +\infty; t_0 < t < +\infty\}$ as the system of differential equations with time-delay generalized according to (1)–(2):

$$\begin{aligned}
&\frac{\partial V(x,t)}{\partial t} = (\beta - \gamma F(x,t))\, V(x,t) + \varepsilon D_V \frac{\partial^2 V(x,t)}{\partial x^2},\\
&\frac{\partial C(x,t)}{dt} = \xi(m(x,t))\, \alpha V(x,t-\tau)\, F(x,t-\tau) - \mu_C (C(x,t) - C^*) + \varepsilon D_C \frac{\partial^2 C(x,t)}{\partial x^2},\\
&\frac{\partial F(x,t)}{dt} = \rho C(x,t) - (\mu_f + \eta\gamma V(x,t))\, F(x,t) + \varepsilon^2 D_F \frac{\partial^2 F(x,t)}{\partial x^2},\\
&\frac{\partial m(x,t)}{dt} = \sigma V(x,t) - \mu_m m(x,t) + \varepsilon^2 D_m \frac{\partial^2 m(x,t)}{\partial x^2}
\end{aligned} \tag{6}$$

for conditions

$$\begin{gathered}
C(x,t_0) = C^0(x), \quad m(x,t_0) = m^0(x), \quad V(x,\tilde{t}) = V^0(x,\tilde{t}),\\
F(x,\tilde{t}) = F^0(x,\tilde{t}), \quad t_0 - \tau \leqslant \tilde{t} \leqslant t_0,
\end{gathered} \tag{7}$$

where εD_V, εD_C, $\varepsilon^2 D_F$, $\varepsilon^2 D_m$ are the coefficients of space-diffusion "redistribution" of antigens, antibodies, plasma and affected cells respectively.

In cases, when the spatially distributed diffuse influences on the dynamic of infectious disease are small compared to other components of the process (parameter ε is small) the use of asymptotic methods for solving the corresponding singularly disturbed model problems [7, 8] is effective. In particular, the solutions of problems (3)–(5) can be formally represented as asymptotic series $V(x,t) = \sum_{i=0}^{N} \varepsilon^i V_i(x,t) + R_N^V(x,t,\varepsilon)$, $C(x,t) = \sum_{i=0}^{N} \varepsilon^i C_i(x,t) + R_N^C(x,t,\varepsilon)$, $F(x,t) = \sum_{i=0}^{N} \varepsilon^i F_i(x,t) + R_N^F(x,t,\varepsilon)$, $m(x,t) = \sum_{i=0}^{N} \varepsilon^i m_i(x,t) + R_N^m(x,t,\varepsilon)$ as disturbance of the solution to the corresponding degenerate problem [9], where $V_i(x,t)$, $C_i(x,t)$, $F_i(x,t)$, $m_i(x,t)$ are the members of regular part of asymptotes, $R_N^V(x,t,\varepsilon)$, $R_N^C(x,t,\varepsilon)$, $R_N^F(x,t,\varepsilon)$, $R_N^m(x,t,\varepsilon)$ are the corresponding remainders. After substituting the asymptotic series and performing the standard procedure of equating the coefficients with the same powers of ε, we obtain such problems to find the functions $V_i(x,t)$, $C_i(x,t)$, $F_i(x,t)$, $m_i(x,t)$ $(i = 0, 1, \ldots, N)$:

$$\begin{cases}
\dfrac{dV_0(x,t)}{dt} = (\beta - \gamma F_0(x,t))\, V_0(x,t)\,,\\
\dfrac{dC_0(x,t)}{dt} = \alpha V_0(x,t-\tau) F_0(x,t-\tau) - \mu_C (C_0(x,t) - C^*)\,,\\
\dfrac{dF_0(x,t)}{dt} = \rho C_0(x,t) - (\mu_f + \eta\gamma V_0(x,t))\, F_0(x,t),\\
\dfrac{dm_0(x,t)}{dt} = \sigma V_0(x,t) - \mu_m m_0(x,t),\\
V_0(x,\tilde{t}) = V^0(x,\tilde{t}), \quad F_0(x,\tilde{t}) = F^0(x,\tilde{t}), \quad t_0 - \tau \leqslant \tilde{t} \leqslant t_0,\\
C_0(x,t_0) = C^0(x), \quad m_0(x,t_0) = m^0(x);
\end{cases} \tag{8}$$

$$\begin{cases} \dfrac{dV_1(x,t)}{dt} = \beta V_1(x,t) - \gamma\left(a_0(x,t)F_1(x,t) + b_0(x,t)V_1(x,t)\right) + \Phi_{V1}(x,t), \\ \dfrac{dC_1(x,t)}{dt} = \alpha\left(a_0(x,t-\tau)F_1(x,t-\tau) + b_0(x,t-\tau)V_1(x,t-\tau)\right) - \mu_C C_1(x,t) + \Phi_{C1}(x,t), \\ \dfrac{dF_1(x,t)}{dt} = \rho C_1(x,t) - \mu_f F_1(x,t) - \eta\gamma\left(a_0(x,t)F_1(x,t) + b_0(x,t)V_1(x,t)\right), \\ \dfrac{dm_1(x,t)}{dt} = \sigma V_1(x,t) - \mu_m m_1(x,t), \\ V_1(x,\tilde{t}) = 0, \quad F_1(x,\tilde{t}) = 0, \quad t_0 - \tau \leqslant \tilde{t} \leqslant t_0, \\ C_1(x,t_0) = 0, \quad m_1(x,t_0) = 0; \end{cases} \tag{9}$$

$$\begin{cases} \dfrac{dV_i(x,t)}{dt} = \beta V_i(x,t) - \gamma\left(a_0(x,t)F_i(x,t) + b_0(x,t)V_i(x,t)\right) + \Phi_{Vi}(x,t), \\ \dfrac{dC_i(x,t)}{dt} = \alpha\left(a_0(x,t-\tau)F_i(x,t-\tau) + b_0(x,t-\tau)V_i(x,t-\tau)\right) - \mu_C C_i(x,t) + \Phi_{Ci}(x,t), \\ \dfrac{dF_i(x,t)}{dt} = \rho C_i(x,t) - \mu_f F_i(x,t) - \eta\gamma\left(a_0(x,t)F_i(x,t) + b_0(x,t)V_i(x,t)\right) + \Phi_{Fi}(x,t), \\ \dfrac{dm_i(x,t)}{dt} = \sigma V_i(x,t) - \mu_m m_i(x,t) + \Phi_{mi}(x,t), \\ C_i(x,t_0) = 0, \quad m_i(x,t_0) = 0, \quad V_i(x,\tilde{t}) = 0, \quad F_i(x,\tilde{t}) = 0, \quad t_0 - \tau \leqslant \tilde{t} \leqslant t_0, \\ i = 2,3,\ldots,N, \end{cases} \tag{10}$$

where

$$\begin{aligned} &a_0(x,t) = V_0(x,t), \quad b_0(x,t) = F_0(x,t); \\ &\Phi_{V1}(x,t) = D_V\frac{\partial^2 V_0(x,t)}{\partial x^2}, \quad \Phi_{C1}(x,t) = D_C\frac{\partial^2 C_0(x,t)}{\partial x^2}; \\ &\Phi_{Vi}(x,t) = -\gamma\sum_{k=1}^{i-1} V_k(x,t)F_{i-k}(x,t) + D_V\frac{\partial^2 V_{i-1}(x,t)}{\partial x^2}, \\ &\Phi_{Ci}(x,t) = \alpha\sum_{k=1}^{i-1} V_k(x,t-\tau)F_{i-k}(x,t-\tau) + D_C\frac{\partial^2 C_{i-1}(x,t)}{\partial x^2}, \\ &\Phi_{Fi}(x,t) = -\eta\gamma\sum_{k=1}^{i-1} V_k(x,t)F_{i-k}(x,t) + D_F\frac{\partial^2 C_{i-2}(x,t)}{\partial x^2}, \\ &\Phi_{mi}(x,t) = D_m\frac{\partial^2 C_{i-2}(x,t)}{\partial x^2}, \quad i = 2,3,\ldots,N. \end{aligned}$$

Let us note that the equations (8)–(10) are ordinary differential equations for variable t, where variable x is a parameter. The solution to problems (8), (9), (10) with time-delay is reduced to the sequence of problems without time-delay [10]:

$$\begin{cases} \dfrac{dV_{0,0}(x,t)}{dt} = \left(\beta - \gamma F_{0,0}(x,t)\right)V_{0,0}(x,t), \\ \dfrac{dC_{0.0}(x,t)}{dt} = \alpha V^0(x,t-\tau)F^0(x,t-\tau) - \mu_C\left(C_{0,0}(x,t) - C^*\right), \\ \dfrac{dF_{0,0}(x,t)}{dt} = \rho C_{0,0}(x,t) - \left(\mu_f + \eta\gamma V_{0,0}(x,t)\right)F_{0,0}(x,t), \\ \dfrac{dm_{0,0}(x,t)}{dt} = \sigma V_{0,0}(x,t) - \mu_m m_{0,0}(x,t), \\ V_{0,0}(x,t_0) = V^0(x,t_0), \quad F_{0,0}(x,t_0) = F^0(x,t_0), \\ C_{0,0}(x,t_0) = C^0(x), \quad m_{0,0}(x,t_0) = m^0(x), \quad t_0 \leqslant t \leqslant t_0 + \tau, \end{cases} \tag{11}$$

$$\begin{cases} \dfrac{dV_{0,1}(x,t)}{dt} = (\beta - \gamma F_{0,1}(x,t))\, V_{0,1}(x,t), \\ \dfrac{dC_{0.1}(x,t)}{dt} = \alpha V_{0,0}(x,t-\tau)F_{0,0}(x,t-\tau) - \mu_C\left(C_{0,1}(x,t) - C^*\right), \\ \dfrac{dF_{0,1}(x,t)}{dt} = \rho C_{0,1}(x,t) - (\mu_f + \eta\gamma V_{0,1}(x,t))\, F_{0,1}(x,t), \\ \dfrac{dm_{0,1}(x,t)}{dt} = \sigma V_{0,1}(x,t) - \mu_m m_{0,1}(x,t), \\ V_{0,1}(x,t_0+\tau) = V_{0,0}(x,t_0+\tau), \quad F_{0,1}(x,t_0+\tau) = F_{0,0}(x,t_0+\tau), \\ C_{0,1}(x,t_0+\tau) = C_{0,0}(x,t_0+\tau), \quad m_{0,1}(x,t_0+\tau) = m_{0,0}(x,t_0+\tau), \\ t_0+\tau \leqslant t \leqslant t_0+2\tau, \end{cases} \tag{12}$$

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$$\begin{cases} \dfrac{dV_{0,n}(x,t)}{dt} = (\beta - \gamma F_{0,n}(x,t))\, V_{0,n}(x,t), \\ \dfrac{dC_{0.n}(x,t)}{dt} = \alpha V_{0,n-1}(x,t-\tau)F_{0,n-1}(x,t-\tau) - \mu_C\left(C_{0,n}(x,t) - C^*\right), \\ \dfrac{dF_{0,n}(x,t)}{dt} = \rho C_{0,n}(x,t) - (\mu_f + \eta\gamma V_{0,n}(x,t))\, F_{0,n}(x,t), \\ \dfrac{dm_{0,n}(x,t)}{dt} = \sigma V_{0,n}(x,t) - \mu_m m_{0,n}(x,t), \\ V_{0,n}(x,t_0+n\tau) = V_{0,n-1}(x,t_0+n\tau), \quad F_{0,n}(x,t_0+n\tau) = F_{0,n-1}(x,t_0+n\tau), \\ C_{0,n}(x,t_0+n\tau) = C_{0,n-1}(x,t_0+n\tau), \quad m_{0,n}(x,t_0+n\tau) = m_{0,n-1}(x,t_0+n\tau), \\ t_0+n\tau \leqslant t \leqslant t_0+(n+1)\tau, \end{cases} \tag{13}$$

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$$\begin{cases} \dfrac{dV_{1,0}(x,t)}{dt} = \beta V_{1,0}(x,t) - \gamma\left(a_{0,0}(x,t)F_{1,0}(x,t) + b_{0,0}(x,t)V_{1,0}(x,t)\right) + \Phi_{V1,0}(x,t), \\ \dfrac{dC_{1,0}(x,t)}{dt} = \alpha\left(a_{0,0}(x,t-\tau)F_1(x,t-\tau) + b_{0,0}(x,t-\tau)V_1(x,t-\tau)\right) - \mu_C C_{1,0}(x,t) \\ \qquad +\Phi_{C1,0}\left(x,t\right), \\ \dfrac{dF_{1,0}(x,t)}{dt} = \rho C_{1,0}(x,t) - \mu_f F_{1,0}(x,t) - \eta\gamma\left(a_{0,0}(x,t)F_{1,0}(x,t) + b_{0,0}(x,t)V_{1,0}(x,t)\right), \\ \dfrac{dm_{1,0}(x,t)}{dt} = \sigma V_{1,0}(x,t) - \mu_m m_{1,0}(x,t), \\ V_{1,0}(x,t_0) = V_1(x,t_0), \quad F_{1.0}(x,t_0) = F_1(x,t_0), \\ C_{1,0}(x,t_0) = 0, \quad m_1(x,t_0) = 0, \quad t_0 \leqslant t \leqslant t_0+\tau; \end{cases} \tag{14}$$

$$\begin{cases} \dfrac{dV_{1,1}(x,t)}{dt} = \beta V_{1,1}(x,t) - \gamma\left(a_{0,1}(x,t)F_{1,1}(x,t) + b_{0,1}(x,t)V_{1,1}(x,t)\right) + \Phi_{V1,1}(x,t), \\ \dfrac{dC_{1,1}(x,t)}{dt} = \alpha\left(a_{0,1}(x,t-\tau)F_{1,1}(x,t-\tau) + b_{0,1}(x,t-\tau)V_{1,1}(x,t-\tau)\right) - \mu_C C_{1,1}(x,t) \\ \qquad +\Phi_{C1,1}(x,t), \\ \dfrac{dF_{1,1}(x,t)}{dt} = \rho C_{1,1}(x,t) - \mu_f F_{1,1}(x,t) - \eta\gamma\left(a_{0,1}(x,t)F_{1,1}(x,t) + b_{0,1}(x,t)V_{1,1}(x,t)\right), \\ \dfrac{dm_{1,1}(x,t)}{dt} = \sigma V_{1,1}(x,t) - \mu_m m_{1,1}(x,t), \\ V_{1,1}(x,t_0+\tau) = V_{1,0}(x,t_0+\tau), \quad F_{1,1}(x,t_0+\tau) = F_{1,0}(x,t_0+\tau), \\ C_{1,1}(x,t_0+\tau) = C_{1,0}(x,t_0+\tau), \quad m_{1,1}(x,t_0+\tau) = m_{1,0}(x,t_0+\tau), \quad t_0+\tau \leqslant t \leqslant t_0+2\tau, \end{cases} \tag{15}$$

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$$\begin{cases} \dfrac{dV_{1,n}(x,t)}{dt} = \beta V_{1,n}(x,t) - \gamma\left(a_{0,n}(x,t)F_{1,n}(x,t) + b_{0,n}(x,t)V_{1,n}(x,t)\right) + \Phi_{V1,n}(x,t), \\ \dfrac{dC_{1,n}(x,t)}{dt} = \alpha\left(a_{0,n}(x,t-\tau)F_{1,n}(x,t-\tau) + b_{0,n}(x,t-\tau)V_{1,n}(x,t-\tau)\right) - \mu_C C_{1,n}(x,t) \\ \qquad +\Phi_{C1,n}(x,t), \\ \dfrac{dF_{1,n}(x,t)}{dt} = \rho C_{1,n}(x,t) - \mu_f F_{1,n}(x,t) - \eta\gamma\left(a_{0,n}(x,t)F_{1,n}(x,t) + b_{0,n}(x,t)V_{1,n}(x,t)\right), \\ \dfrac{dm_{1,n}(x,t)}{dt} = \sigma V_{1,n}(x,t) - \mu_m m_{1,n}(x,t), \\ V_{1,n}(x,t_0+n\tau) = V_{1,n-1}(x,t_0+n\tau), \quad F_{1,n}(x,t_0+n\tau) = F_{1,n-1}(x,t_0+n\tau), \\ C_{1,n}(x,t_0+n\tau) = C_{1,n-1}(x,t_0+n\tau), \quad m_{1,n}(x,t_0+n\tau) = m_{1,n-1}(x,t_0+n\tau), \\ t_0+n\tau \leqslant t \leqslant t_0+(n+1)\tau; \end{cases} \tag{16}$$

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$$\begin{cases} \dfrac{dV_{i,0}(x,t)}{dt} = \beta V_{i,0}(x,t) - \gamma\left(a_{0,0}(x,t)F_{i,0}(x,t) + b_{0,0}(x,t)V_{i,0}(x,t)\right) + \Phi_{Vi,0}(x,t), \\ \dfrac{dC_{i,0}(x,t)}{dt} = \alpha\left(a_{0,0}(x,t-\tau)F_i(x,t-\tau) + b_{0,0}(x,t-\tau)V_i(x,t-\tau)\right) - \mu_C C_{i,0}(x,t) \\ \qquad +\Phi_{Ci,0}(x,t), \\ \dfrac{dF_{i,0}(x,t)}{dt} = \rho C_{i,0}(x,t) - \mu_f F_{i,0}(x,t) - \eta\gamma\left(a_{0,0}(x,t)F_{i,0}(x,t) + b_{0,0}(x,t)V_{i,0}(x,t)\right) \\ \qquad +\Phi_{Fi,0}(x,t), \\ \dfrac{dm_{i,0}(x,t)}{dt} = \sigma V_{i,0}(x,t) - \mu_m m_{i,0}(x,t) + \Phi_{m\,i,0}(x,t), \\ V_{i,0}(x,t_0) = V_i(x,t_0), \quad F_{i.0}(x,t_0) = F_i(x,t_0), \\ C_{i,0}(x,t_0) = 0, \;\; m_i(x,t_0) = 0, \quad t_0 \leqslant t \leqslant t_0+\tau; \end{cases} \tag{17}$$

$$\begin{cases} \dfrac{dV_{i,1}(x,t)}{dt} = \beta V_{i,1}(x,t) - \gamma\left(a_{0,1}(x,t)F_{i,1}(x,t) + b_{0,1}(x,t)V_{i,1}(x,t)\right) + \Phi_{Vi,1}(x,t), \\ \dfrac{dC_{i,1}(x,t)}{dt} = \alpha\left(a_{0,1}(x,t-\tau)F_{i,1}(x,t-\tau) + b_{0,1}(x,t-\tau)V_{i,1}(x,t-\tau)\right) - \mu_C C_{i,1}(x,t) \\ \qquad +\Phi_{Ci,1}\left(x,t\right), \\ \dfrac{dF_{i,1}(x,t)}{dt} = \rho C_{i,1}(x,t) - \mu_f F_{i,1}(x,t) - \eta\gamma\left(a_{0,1}(x,t)F_{i,1}(x,t) + b_{0,1}(x,t)V_{i,1}(x,t)\right) \\ \qquad +\Phi_{Fi,1}(x,t), \\ \dfrac{dm_{i,1}(x,t)}{dt} = \sigma V_{i,1}(x,t) - \mu_m m_{i,1}(x,t) + \Phi_{m\,i,1}(x,t), \\ V_{i,1}(x,t_0+\tau) = V_{i,0}(x,t_0+\tau), \quad F_{i,1}(x,t_0+\tau) = F_{i,0}(x,t_0+\tau), \\ C_{i,1}(x,t_0+\tau) = C_{i,0}(x,t_0+\tau), \quad m_{i,1}(x,t_0+\tau) = m_{i,0}(x,t_0+\tau), \quad t_0+\tau \leqslant t \leqslant t_0+2\tau; \end{cases} \tag{18}$$

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$$
\begin{cases}
\dfrac{dV_{i,n}(x,t)}{dt} = \beta V_{i,n}(x,t) - \gamma\left(a_{0,n}(x,t)F_{i,n}(x,t) + b_{0,n}(x,t)V_{i,n}(x,t)\right) + \Phi_{Vi,n}(x,t), \\
\dfrac{dC_{i,n}(x,t)}{dt} = \alpha\left(a_{0,n}(x,t-\tau)F_{i,n}(x,t-\tau) + b_{0,n}(x,t-\tau)V_{i,n}(x,t-\tau)\right) - \mu_C C_{i,n}(x,t) \\
\quad +\Phi_{Ci,n}(x,t), \\
\dfrac{dF_{i,n}(x,t)}{dt} = \rho C_{i,n}(x,t) - \mu_f F_{i,n}(x,t) - \eta\gamma\left(a_{0,n}(x,t)F_{i,n}(x,t) + b_{0,n}(x,t)V_{i,n}(x,t)\right) \\
\quad +\Phi_{Fi,n}(x,t), \\
\dfrac{dm_{i,n}(x,t)}{dt} = \sigma V_{i,n}(x,t) - \mu_m m_{i,n}(x,t) + \Phi_{m\,i,n}(x,t), \\
V_{i,n}\left(x,t_0+n\tau\right) = V_{i,n-1}(x,t_0+n\tau), \quad F_{i,n}(x,t_0+n\tau) = F_{i,n-1}(x,t_0+n\tau), \\
C_{i,n}(x,t_0+n\tau) = C_{i,n-1}(x,t_0+n\tau), \quad m_{i,n}(x,t_0+n\tau) = m_{i,n-1}(x,t_0+n\tau), \\
t_0+n\tau \leqslant t \leqslant t_0+(n+1)\tau,
\end{cases}
\tag{19}
$$

. . . . . ,

where

$$
\begin{aligned}
&a_{0,j}(x,t) = V_{0,j}\left(x,t\right), \quad b_{0,j}(x,t) = F_{0,j}(x,t); \\
&\Phi_{V1,j}(x,t) = D_V\frac{\partial^2 V_{0,j}(x,t)}{\partial x^2}, \quad \Phi_{C1,j}(x,t) = D_C\frac{\partial^2 C_{0,j}(x,t)}{\partial x^2}, \\
&\Phi_{Vi,j}(x,t) = -\gamma\sum_{k=1}^{i-1} V_{k,j}(x,t)F_{i-k,j}(x,t) + D_V\frac{\partial^2 V_{i-1,j}(x,t)}{\partial x^2}, \\
&\Phi_{Ci,j}(x,t) = \alpha\sum_{k=1}^{i-1} V_{k,j}(x,t-\tau)F_{i-k,j}(x,t-\tau) + D_C\frac{\partial^2 C_{i-1,j}(x,t)}{\partial x^2}, \\
&\Phi_{Fi,j}(x,t) = -\eta\gamma\sum_{k=1}^{i-1} V_{k,j}(x,t)F_{i-k,j}(x,t) + D_F\frac{\partial^2 C_{i-2,j}(x,t)}{\partial x^2}, \\
&\Phi_{mi,j}(x,t) = D_m\frac{\partial^2 C_{i-2,j}(x,t)}{\partial x^2}, \quad i = 2,3,\ldots,N, \quad j = 0,1,\ldots,n,\ldots.
\end{aligned}
$$

It should be noted that in order to ensure the proper smoothness of the corresponding solutions for $t=\tau$, $t=2\tau$, $t=3\tau$, ..., it is also necessary besides the traditional conditions of smoothness with respect to functions (7), to impose consistency conditions for $t=t_0-\tau$, $t=t_0$ [10]. In particular, the condition (for $\xi(m)=1$)

$$
\frac{\partial C(x,t_0)}{dt} = \alpha V^0(x,t_0-\tau)F^0(x,t_0-\tau) - \mu_C\left(C(x,t_0)-C^*\right) + \varepsilon D_C\frac{\partial^2 C(x,t_0)}{\partial x^2}
$$

must be satisfied.

Let us note that we consider an infinite set G_Z for the convenience of the presentation avoiding their complexity. The proposed approach is "without problems" transferred to other areas. Obviously, we should use more complex series instead of those described above.

The estimates of the remainders $R^V_{Nj}(x,y,t,\varepsilon)$, $R^C_{Nj}(x,y,t,\varepsilon)$, $R^F_{Nj}(x,y,t,\varepsilon)$, $R^m_{Nj}(x,y,t,\varepsilon)$ are similar to [7, 8].

3. Results of numerical experiments

Let us denote that one of the typical features of the basic infectious disease model of G. I. Marchuk (1)–(2) was using a differential equation with time-delay that allowed describing the rate of change of plasma cell concentration. And it allowed describing the immune response dynamics more accurately. Fig. 1

shows the dependence of the dynamics of the main infectious disease factors on the time-delay τ, during which the cascade of plasma cells is formed. As expected, if the time-delay τ increase then the maximum values of the current factors $V(t)$, $C(t)$, $F(t)$, $m(t)$ increases, that is, as a result of increasing the time-delay, the maximum concentration of pathogenic antigens increases in the organism. It causes an increase in the level of damage to the target organ and eventually leads to increase in the production and increase in the concentration of plasma cells and antibodies.

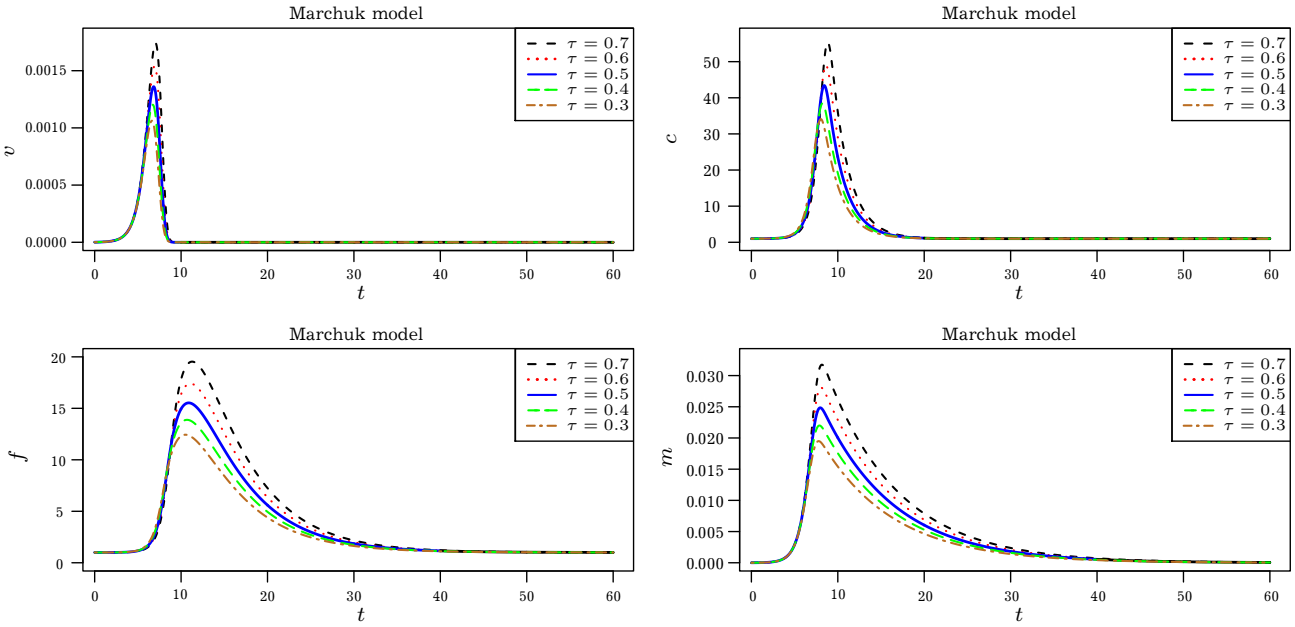

Fig. 1. Dynamics of the main acting factors of the basic infectious disease model of G. I. Marchuk with different values of time-delay τ.

Fig. 2 presents the spatial-temporal dynamics of the level of concentration of pathogenic antigens according to model (6)–(7), provided that they are uniform initial distribution $V(x,\tilde{t}) = V^0(\tilde{t})$, $t_0 - \tau \leqslant \tilde{t} \leqslant t_0$ in the space. The small-scale spatially distributed diffuse influences in this case do not cause changes in the dynamics of the infectious disease process.

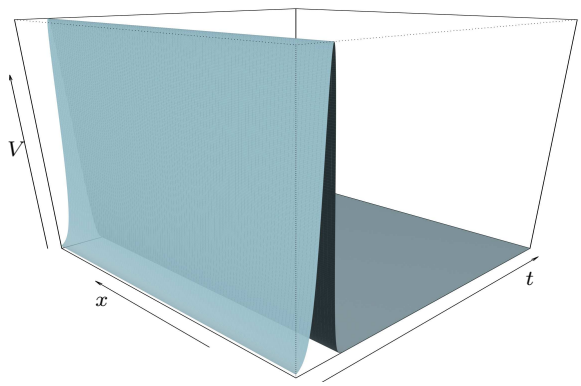

Fig. 2. Spatio-temporal dynamics of the level of the concentration of pathogenic antigens under condition $V(x,\tilde{t}) = V^0(\tilde{t})$, $t_0 - \tau \leqslant \tilde{t} \leqslant t_0$.

In the case when the distribution of pathogenic antigens at the initial time t_0 is spatially non-uniformly distributed $V(x,\tilde{t}) = V^0(x,\tilde{t})$, $t_0 - \tau \leqslant \tilde{t} \leqslant t_0$, taking into account the small-scale spatial distribution of diffuse influences in (6)–(7) leads to changes in the corresponding model dynamics of infectious disease processes. Fig. 3 presents the spatial-temporal dynamics of the concentration of pathogenic antigens in the organism in the case of a separate locus of infection when the small-scale spatially distributed diffuse influences are absent (Fig. 3*a*) and present (Fig. 3*b*). The results of numerical experiments show a decrease in the maximum level of concentration of pathogenic antigens in the infection locus in the case of diffuse influences. It is the result of "diffusion" spread of antigens from the places with their high concentration to places with lower concentration.

Fig. 4 presents the dependence of the dynamics of active infectious disease factors on the intensity of diffuse influence (value of parameter ε) in the epicenter of infection. In particular, if the intensity of diffuse influences increase then the maximum level of concentration of pathogenic antigens decreases

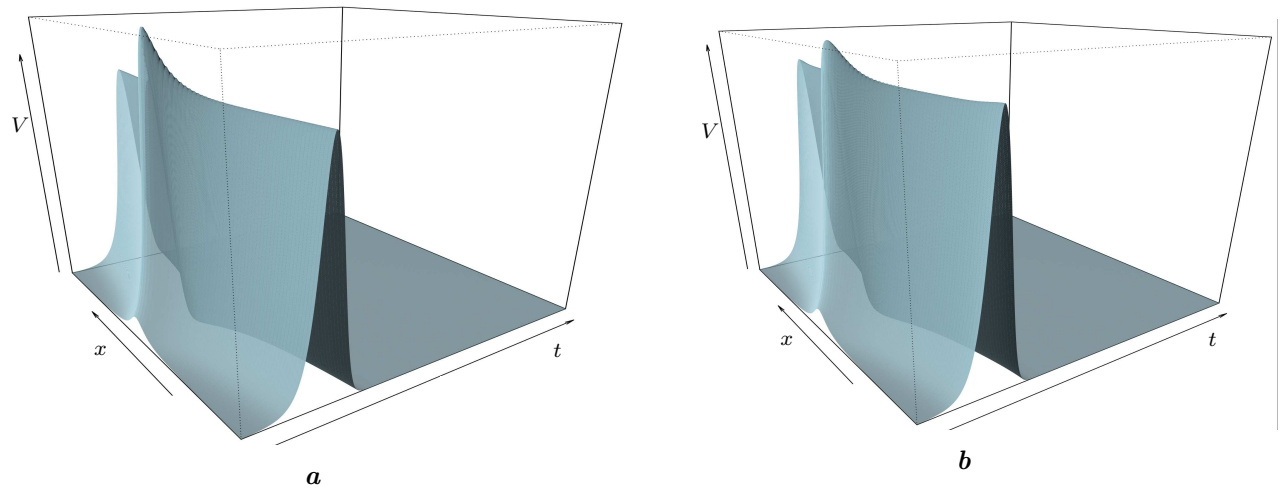

Fig. 3. Spatio-temporal dynamics of the level of the concentration of pathogenic antigens under condition $V^0(x,t_0)=\delta/(1+(x-\lambda)^2)$: (***a***) $\varepsilon=0$; (***b***) $\varepsilon=0.1$.

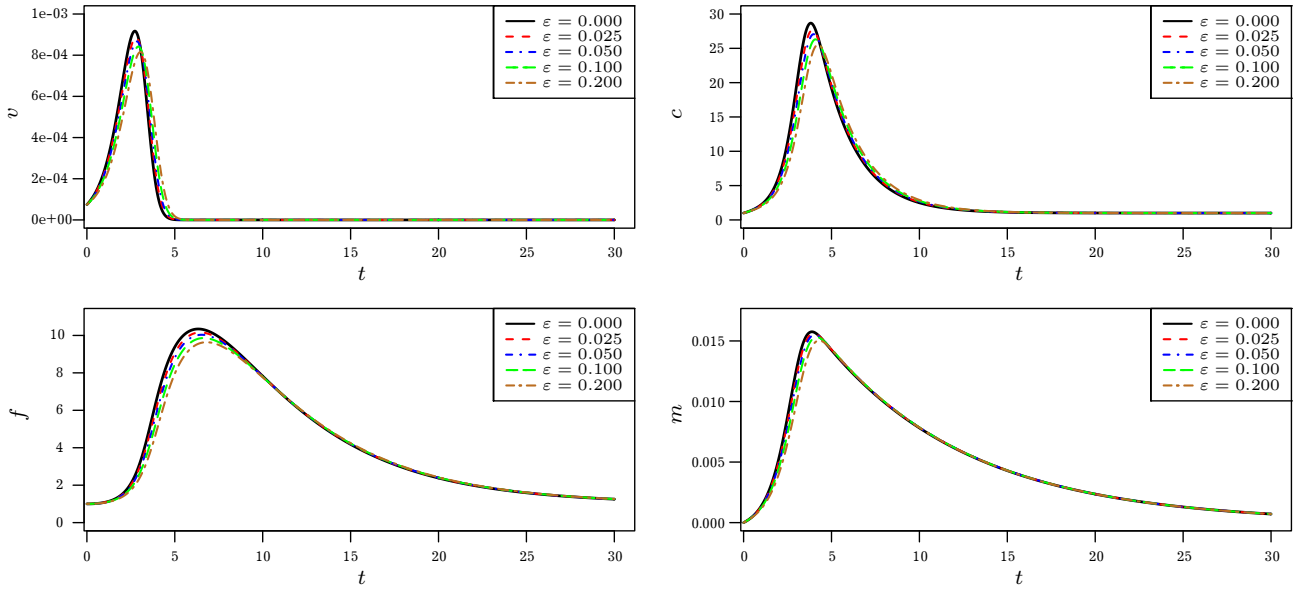

Fig. 4. Dynamics of the main acting factors of model (8)–(9) at different levels of diffuse influence.

in the epicenter of organ infection. It causes a decrease in the degree of target organ damage. The dynamics of other infectious disease factors (concentrations of plasma cells and antibodies) are similarly changing. Thus, the severity of infectious disease decreases if the intensity of diffuse influences increases.

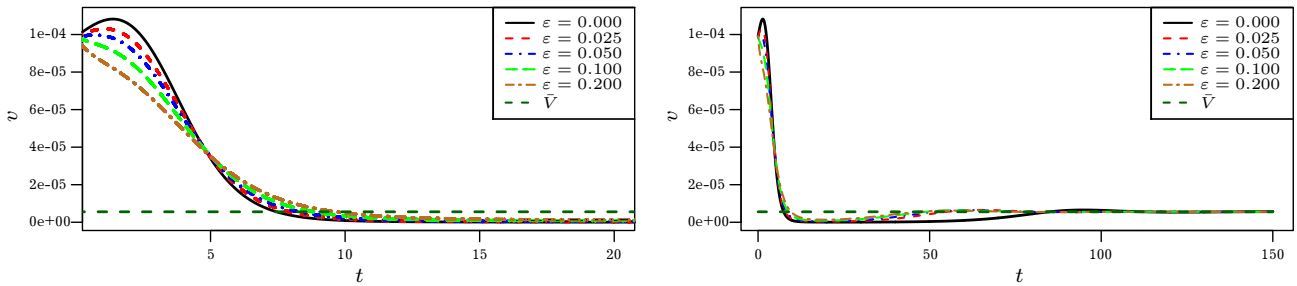

Fig. 5. Dynamics of the concentration of the pathogenic antigens at different intensity levels of the diffuse influence.

Fig. 5 shows the dynamics of the concentration of pathogenic antigens in the acute form of the disease when the intensity of diffuse influences in the epicenter of infection is absent ($\varepsilon = 0$) and present. In the absence of diffusion, their concentration at the epicenter of infection increases to some maximum level triggering the mechanism of the immune response (increase in the concentration of plasma cells and antigens). As a result, over time the concentration of antigens is established at some stationary level. If the intensity of diffuse influence increases, the increasing rate of the concentration of pathogenic antigens in the epicenter of the infected organ decreases; then it causes a decrease in the severity of the immune response of the organism. And starting from a certain intensity level of diffuse influence, the concentration of pathogenic antigens in the epicenter of infection does not increase over time, i.e., before the infection, the available immune protection of an organism is able to reduce the concentration of pathogenic antigens to a steady-state level without the active response of the immune system. Fig. 6 shows the spatio-temporal dynamics of the concentration of pathogenic antigens of a certain locus of infection when the small-scale spatially distributed diffuse influences are absent (Fig. 6*a*) and present (Fig. 6*b*).

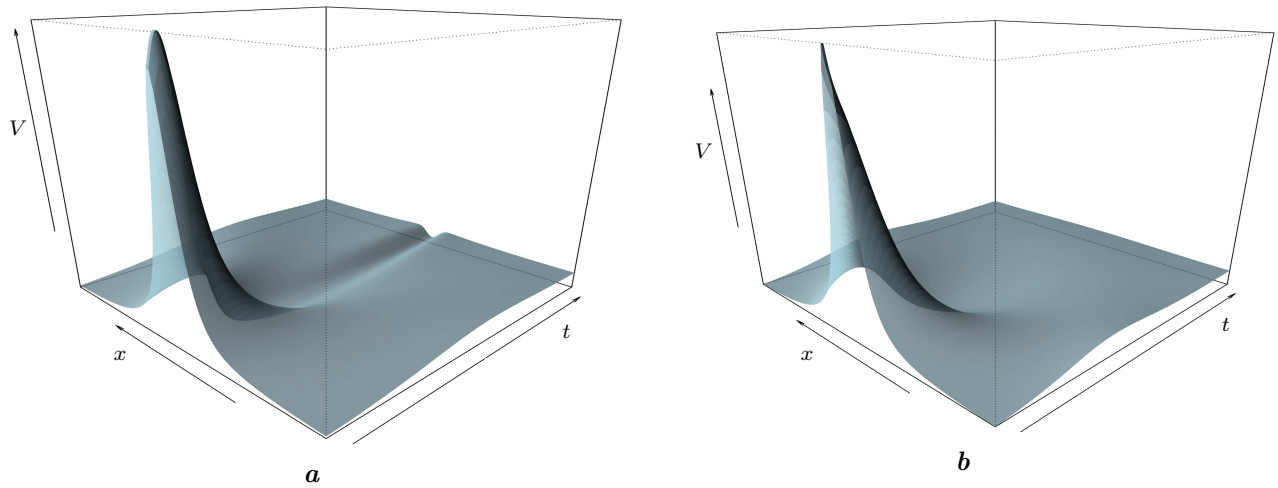

Fig. 6. Spatio-temporal dynamics of the level of the concentration of pathogenic antigens under condition (***a***) $\varepsilon = 0$; (***b***) $\varepsilon = 0.2$.

4. Conclusions

This paper presents an effective approach to take into account small-scale spatially distributed diffuse influences on the development of the studied process of the disease development and also a stepwise (by means of time-delay τ) representation of the required functions in the asymptotic series form as disturbance of the solution of the corresponding degenerate problem, on the example of the basic infectious disease model of G. I. Marchuk.

The results of numerical experiments illustrate the dynamics of reducing the maximum level of concentration of pathogenic antigens due to their diffusion "redistribution" from the locus of infection into less infected areas of the target-organ. This, in particular, influences the identification of the nature of the infectious disease in the model. If at the initial point of time the infection dose V^0 exceeds a certain critical value V^* in some area (in the zone of infection), as a result of diffusion "redistribution" over a certain period of time, the maximum concentration of pathogenic antigens in this area can be significantly reduced (in particular, to a level below critical one), and then the neutralization of antigens may be provided by the available antibody level F^* in the organism.

In this case, the solution of the corresponding singularly disturbed problem (that predicts the distribution in time and space of concentrations of antigens, antibodies, plasma cells, and the measure of contagion) leads to some stable, in particular, asymptotically stable, stationary value. That is, in

this case, in this model, the immune response is able to prevent the infection development, resulting in the nature of the infectious disease changes, for example, from acute to subclinical.

The developed computational procedure may serve the basis of a broader set of decision making: either we can completely rely on the immune self-protection of the organism or, otherwise, perform external influence (treatment) according to the values of the corresponding input data, in particular, data of the intensity of diffusion "redistribution" and the size of the infection zone.

In future studies, it is a possibility to take into account the spatially distributed diffuse influences in the investigation of the process of infectious disease that is based on the more general models, in particular, the Marchuk–Petrov's model of antiviral immune response [1].

It is perspective, to take into account the accumulation of plasma cells in lymph nodes, that is a certain analog of mathematical models of filtering-convection-diffusion-mass transfer in a two-porous (in particular, nanoporous) environment [11–14].

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Моделювання малих просторово розподілених впливів на розвиток процесу інфекційного захворювання

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Запропоновано малі просторово розподілені впливи на розвиток інфекційного захворювання досліджувати шляхом дифузійного збурення відповідних вироджених модельних задач. Побудовано представлення асимптотичних розвинень розв'язків відповідних сингулярно збурених задач із запізненням, які зведено до послідовності задач без запізнення. Наведені результати числових експериментів характеризують просторово розподілений дифузійний вплив на розвиток інфекційного захворювання. Проілюстровано зниження максимального рівня концентрації патогенних антигенів унаслідок їх дифузійного "перерозподілу" з осередку зараження у менш заражені зони органу-мішені.

Ключові слова: *модель інфекційного захворювання, стаціонарні розв'язки динамічних систем, стійкість розв'язку.*