

The diffusion scattering parameters identification for a modified model of viral infection in the conditions of logistic dynamics of immunological cells

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Based on the modification of the infectious disease model, taking into account diffusion disturbances and logistic dynamics of immunological cells, separate approaches to the diffusion scattering parameters identification for different types of functional dependence of diffusion coefficients and given redefinition conditions are proposed. A special step-by-step procedure for numerically asymptotic approximation of the solution to the corresponding singularly perturbed model problem with a delay has been improved. The results of computer experiments on identifying the unknown diffusion scattering parameters are presented. It is noted that the identification and application of variable diffusion coefficients will provide a more accurate prediction of the dynamics of an infectious disease, which is significant in decision-making regarding the use of various medical procedures.

Keywords: *infectious disease model; parameter identification; dynamic systems with delay; asymptotic method; singularly perturbed problem; logistic dynamics.*

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1. Introduction

The availability of a well-developed mathematical modeling toolkit for predicting the dynamics of infectious diseases, taking into account a wide range of potential internal and external influencing factors, is a significant and relevant precondition for the high-quality assessment of the possible response of the organism to disease pathogens, the strength of the immune response, and the development of effective and personalized treatment programs involving special therapeutic procedures to prevent critical exacerbations of the disease, accelerate the recovery process, and eliminate toxins and viral elements from the body.

The classical models of infectious diseases, antiviral and antibacterial immune responses described in [1] allow for the prediction of general trends in viral infections, taking into account the mechanisms of humoral and cellular types of an immune response. Despite being some of the earliest mathematical models of an immune response, these models remain powerful tools for investigating various aspects of immune system function, as well as serving as a basis for improvement and creation of new modifications and generalizations that take into account various aspects of immune response to infections, oncology, immunodeficiency states, and immunotherapy. Examples of such modifications and generalizations of basic models are provided, in particular, in [2]. The general approaches for constructing models of viral infections developed in [1] were used in [3] to model antitumor immunity. An integrated model was proposed in [4] to predict processes of local tissue inflammation, in which the Marchuk approach was applied to describe the systemic immune response. Using the same methodology, a mathematical model was developed in [5] to predict the dynamics of the immune response to COVID-19 coronavirus infection under conditions of immunotherapy.

In [6], an approach is proposed that allows taking into account the influence of diffusion disturbances of active factors on the development of infectious diseases in the body, and it is shown that reducing

the concentration of active factors in the infection center due to their diffusion scattering provides a general decrease in the predicted severity of the disease. In addition, in [7, 8], this approach is generalized to account for various concentrated influences, which allows studying the course of viral infection when injecting solutions of pharmacological or immunobiological preparations by injection or through a dropper, and to take into account the conditions of the body's temperature reaction [9].

The course of infectious diseases, during which periods of rapid exacerbation of the disease often occur, is determined by the influence of many factors, and depending on the state of the immune system of a particular organism and the strength of its reaction, it can develop according to different, difficult to predict scenarios. In order to improve the quality of forecasting the dynamics of viral infection, in addition to the development of modifications and generalizations of basic models, it is also necessary to develop a reliable toolkit for determining personalized parameters of corresponding forecasting models.

The objective of this study is to identify the parameters of the diffusion scattering of active factors in a modified model of infectious disease under the conditions of logistic dynamics of immunological cells.

2. Modified model of viral infection with consideration of diffusion scattering and logistic dynamics

The dynamics of the model components of the viral infection process, taking into account their small diffusive scattering [6–9] and the logistic dynamics of immunological cells, for the convenience of presenting the main provisions, will be described in a simple canonical domain $G = \{(x, t): -\infty < x < +\infty; 0 < t < +\infty\}$ by the following singularly perturbed system of nonlinear differential equations with delays:

$$\begin{aligned}\frac{\partial V}{\partial t} &= (\beta - \gamma F) V + \varepsilon \frac{\partial}{\partial x} \left(D^V \frac{\partial V}{\partial x} \right), \\ \frac{\partial C}{\partial t} &= \xi(m) \alpha V(x, t - \tau) F(x, t - \tau) - \mu_C (C - C^*) + \varepsilon^2 \frac{\partial}{\partial x} \left(D^C \frac{\partial C}{\partial x} \right), \\ \frac{\partial F}{\partial t} &= \omega^F + \rho C \left(1 - \frac{C}{C^{**}} \right) - (\mu_f + \eta \gamma V) F + \varepsilon \frac{\partial}{\partial x} \left(D^F \frac{\partial F}{\partial x} \right), \\ \frac{\partial m}{\partial t} &= \sigma V - \mu_m m + \varepsilon^2 \frac{\partial}{\partial x} \left(D^m \frac{\partial m}{\partial x} \right)\end{aligned}\tag{1}$$

under the conditions:

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

where $V = V(t, x)$, $F = F(t, x)$, $C = C(t, x)$, $m = m(t, x)$ are the concentrations of antigens (pathogenic viruses, bacteria, etc.), their corresponding immune agents (antibodies, cell receptors, etc.), immunological cells that produce immune agents, the value of the relative characteristic of damage to the target organ by antigens ($0 \leq m \leq 1$) at the moment t at the point x ; β is the rate of reproduction of antigens; γ is the coefficient that takes into account the result of the interaction of antigens with immune agents; τ is the time delay (the time required for the formation of a cascade of immunological cells, which are stimulated by FV -complexes); μ_C are the values inverse of the life span of immunological cells; α is the coefficient of stimulation of the immune system by VF -complexes; C^* is the concentration of immunological cells in a healthy body, and C^{**} is the maximum possible concentration of these cells; μ_f is the value inverse of the duration of existence of immune agents; η are costs of immune agents for neutralization of a single antigen; σ is the rate of damage to cells of the target organ by antigens; μ_m is a velocity of recovery of the target organ after its damage by antigens; ρ is the rate of production of immune agents by one immunological cell; $C^0(x)$, $m^0(x)$, $V^0(x, \tilde{t})$, $F^0(x, \tilde{t})$ are sufficiently smooth and bounded functions; εD^V , εD^F , $\varepsilon^2 D^C$, $\varepsilon^2 D^m$ are diffusion coefficients of antigens, immune agents, immunological cells, and affected cells of the target organ, respectively, ε is a small parameter that

determines the degree of smallness of the influence of the corresponding diffusion components on the process in comparison with others. The function $\xi(m)$ takes into account the effect of reducing the intensity of plasma cell production in case of significant damage to an immunological organ, and the function $\omega^F(x, t)$ serves to describe, in particular, concentrated changes in the concentration of immune agents [7, 8].

In a situation where the parameters D^V, D^F, D^C, D^m are unknown, in order to find them together with the sought functions V, F, C, m , the original model problem (1)–(2) must be supplemented with some additional conditions (so-called “overdetermination conditions”) [10]. We note that such additional conditions can generally have a different form, which means that there is a need to apply different methods of finding the solution of the corresponding inverse problems.

3. Identification of diffusion scattering parameters and numerical asymptotic solution approximation procedure

3.1. First, consider the case $D^V = D^V(t), D^F = D^F(t), D^C = D^C(t), D^m = D^m(t)$, and additional conditions (overdetermination conditions) have the form:

$$\begin{aligned} \varepsilon D^V(t) \frac{\partial V}{\partial x} \Big|_{x=x^*} &= \varepsilon V_*^*(t), & \varepsilon^2 D^C(t) \frac{\partial C}{\partial x} \Big|_{x=x^*} &= \varepsilon^2 C_*^*(t), \\ \varepsilon D^F(t) \frac{\partial F}{\partial x} \Big|_{x=x^*} &= \varepsilon F_*^*(t), & \varepsilon^2 D^m(t) \frac{\partial m}{\partial x} \Big|_{x=x^*} &= \varepsilon^2 m_*^*(t), \end{aligned} \tag{3}$$

where $\varepsilon D^V \frac{\partial V}{\partial x}, \varepsilon^2 D^C \frac{\partial C}{\partial x}, \varepsilon D^F \frac{\partial F}{\partial x}, \varepsilon^2 D^m \frac{\partial m}{\partial x}$ are densities of the corresponding diffusion flows, x^* is a given point (for example, a spot where the taking of biomaterials for laboratory research is carried out); $V_*^*(t), C_*^*(t), F_*^*(t)$ are sufficiently smooth and bounded functions. Hereafter, we will accept $x^* = 0$, which is quite natural.

Let us represent the inverse problem (1)–(3) obtained in this way with a delay τ , similarly to [6–9], in the form of the following sequence of problems on the intervals $k\tau \leq t \leq (k + 1)\tau$ ($k = 0, 1, \dots$):

$$\begin{aligned} \frac{\partial V_k}{\partial t} &= (\beta - \gamma F_k) V_k + \varepsilon D_k^V(t) \frac{\partial^2 V_k}{\partial x^2}, \\ \frac{\partial C_k}{\partial t} &= \xi(m) \alpha \Psi_k - \mu_C (C_k - C^*) + \varepsilon^2 D_k^C(t) \frac{\partial^2 C_k}{\partial x^2}, \\ \frac{\partial F_k}{\partial t} &= \omega_k^F + \rho C_k \left(1 - \frac{C_k}{C^{**}} \right) - (\mu_f + \eta \gamma V_k) F_k + \varepsilon D_k^F(t) \frac{\partial^2 F_k}{\partial x^2}, \\ \frac{\partial m_k}{\partial t} &= \sigma V_k - \mu_m m_k + \varepsilon^2 D_k^m(t) \frac{\partial^2 m_k}{\partial x^2} \end{aligned} \tag{4}$$

under the conditions:

$$\begin{aligned} C_k(x, k\tau) &= C_{k-1}(x, k\tau), & m_k(x, k\tau) &= m_{k-1}(x, k\tau), \\ V_k(x, k\tau) &= V_{k-1}(x, k\tau), & F_k(x, k\tau) &= F_{k-1}(x, k\tau), \\ D_k^V \frac{\partial V_k}{\partial x} \Big|_{x=0} &= V_{*k}^*, & D_k^C \frac{\partial C_k}{\partial x} \Big|_{x=0} &= C_{*k}^*(t), & D_k^F \frac{\partial F_k}{\partial x} \Big|_{x=0} &= F_{*k}^*, & D_k^m \frac{\partial m_k}{\partial x} \Big|_{x=0} &= m_{*k}^*, \end{aligned} \tag{5}$$

where $C_{-1}(x, 0) = C^0(x), m_{-1}(x, 0) = m^0(x), V_{-1}(x, 0) = V^0(x, 0), F_{-1}(x, 0) = F^0(x, 0), \Psi_k(x, t) = V_{k-1}(x, t - \tau) F_{k-1}(x, t - \tau)$ ($k = 1, 2, \dots$), $\Psi_0(x, t) = V^0(x, t - \tau) F^0(x, t - \tau)$. As a result, if the solution to problem (4)–(5) is found for the previous interval, at the next stage we obtain the problem without delay. At the same time, the necessary level of smoothness of the solution of the model problem at the moments of time $\tau, 2\tau, \dots$ will be ensured, as in [6–9], by imposing additional conditions for the agreement of the corresponding partial solutions.

On each of the intervals $k\tau \leq t \leq (k + 1)\tau$ ($k = 0, 1, \dots$), to approximate the solution of problem (4)–(5) with a small parameter ε , as in [6–9], we apply the perturbation method. For this purpose, we

present the formally corresponding solutions in the form of the following asymptotic series:

$$\begin{aligned} V_k &= V_{(k,0)}(x, t) + \sum_{i=1}^n \varepsilon^i V_{(k,i)}(x, t) + R_{(k,n)}^V(x, t, \varepsilon), \\ C_k &= C_{(k,0)}(x, t) + \sum_{i=1}^n \varepsilon^i C_{(k,i)}(x, t) + R_{(k,n)}^C(x, t, \varepsilon), \\ F_k &= F_{(k,0)}(x, t) + \sum_{i=1}^n \varepsilon^i F_{(k,i)}(x, t) + R_{(k,n)}^F(x, t, \varepsilon), \\ m_k &= m_{(k,0)}(x, t) + \sum_{i=1}^n \varepsilon^i m_{(k,i)}(x, t) + R_{(k,n)}^m(x, t, \varepsilon), \end{aligned} \quad (6)$$

$$\begin{aligned} D_k^V &= D_{(k,0)}^V(t) + \sum_{i=1}^n \varepsilon^i D_{(k,i)}^V(t) + R_{(k,n)}^{D^V}(t, \varepsilon), & D_k^C &= D_{(k,0)}^C(t) + \sum_{i=1}^n \varepsilon^i D_{(k,i)}^C(t) + R_{(k,n)}^{D^C}(t, \varepsilon), \\ D_k^F &= D_{(k,0)}^F(t) + \sum_{i=1}^n \varepsilon^i D_{(k,i)}^F(t) + R_{(k,n)}^{D^F}(t, \varepsilon), & D_k^m &= D_{(k,0)}^m(t) + \sum_{i=1}^n \varepsilon^i D_{(k,i)}^m(t) + R_{(k,n)}^{D^m}(t, \varepsilon), \end{aligned} \quad (7)$$

where $R_{(k,n)}^V$, $R_{(k,n)}^C$, $R_{(k,n)}^F$, $R_{(k,n)}^m$, $R_{(k,n)}^{D^V}$, $R_{(k,n)}^{D^C}$, $R_{(k,n)}^{D^F}$, $R_{(k,n)}^{D^m}$ are the corresponding residual terms (for $0 < t \leq T < \infty$); $V_{(k,i)}$, $C_{(k,i)}$, $F_{(k,i)}$, $m_{(k,i)}$, $D_{(k,i)}^V$, $D_{(k,i)}^C$, $D_{(k,i)}^F$, $D_{(k,i)}^m$ ($i = 0, \dots, n$) are the sought functions (terms of asymptotics). Similarly to [6–9], after substituting (6), (7) into (4)–(5) and implementing the standard “equation procedure”, for example, in the case $\xi(m) = 1$ for finding the functions $V_{(k,0)}(x, t)$, $C_{(k,0)}(x, t)$, $F_{(k,0)}(x, t)$, $m_{(k,0)}(x, t)$, we obtain the following degenerate with respect to the original problem:

$$\begin{aligned} \frac{\partial V_{(k,0)}}{\partial t} &= \beta V_{(k,0)} - \gamma F_{(k,0)} V_{(k,0)}, \\ \frac{\partial C_{(k,0)}}{\partial t} &= \alpha \Psi_k - \mu_C (C_{(k,0)} - C^*), \\ \frac{\partial F_{(k,0)}}{\partial t} &= \omega_k^F + \rho \left(1 - \frac{C_{(k,0)}}{C^{**}} \right) C_{(k,0)} - \mu_f F_{(k,0)} - \eta \gamma F_{(k,0)} V_{(k,0)}, \\ \frac{\partial m_{(k,0)}}{\partial t} &= \sigma V_{(k,0)} - \mu_m m_{(k,0)}, \end{aligned} \quad (8)$$

$$\begin{aligned} C_{(k,0)}(x, k\tau) &= C_{k-1}(x, k\tau), & m_{(k,0)}(x, k\tau) &= m_{k-1}(x, k\tau), \\ V_{(k,0)}(x, k\tau) &= V_{k-1}(x, k\tau), & F_{(k,0)}(x, k\tau) &= F_{k-1}(x, k\tau), & k\tau \leq t \leq (k+1)\tau, \end{aligned}$$

and for finding $V_{(k,i)}(x, t)$, $C_{(k,i)}(x, t)$, $F_{(k,i)}(x, t)$, $m_{(k,i)}(x, t)$ ($i = 1, \dots, n$), which ensure taking into account the effect of diffusion scattering of active factors, the following problems:

$$\begin{aligned} \frac{\partial V_{(k,1)}}{\partial t} &= \beta V_{(k,1)} - \gamma (a_{(k,0)} F_{(k,1)} + b_{(k,0)} V_{(k,1)}) + \Phi_{(k,1)}^V, \\ \frac{\partial C_{(k,1)}}{\partial t} &= -\mu_C C_{(k,1)}, \\ \frac{\partial F_{(k,1)}}{\partial t} &= \rho d_{(k,0)} C_{(k,1)} - \mu_f F_{(k,1)} - \eta \gamma (a_{(k,0)} F_{(k,1)} + b_{(k,0)} V_{(k,1)}) + \Phi_{(k,1)}^F, \\ \frac{\partial m_{(k,1)}}{\partial t} &= \sigma V_{(k,1)} - \mu_m m_{(k,1)}, \\ C_{(k,1)}(x, k\tau) &= 0, & m_{(k,1)}(x, k\tau) &= 0, & V_{(k,1)}(x, k\tau) &= 0, & F_{(k,1)}(x, k\tau) &= 0, & k\tau \leq t \leq (k+1)\tau; \\ & \dots \end{aligned} \quad (9)$$

$$\begin{aligned}
 \frac{\partial V_{(k,i)}}{\partial t} &= \beta V_{(k,i)} - \gamma (a_{(k,0)} F_{(k,i)} + b_{(k,0)} V_{(k,i)}) + \Phi_{(k,i)}^V, \\
 \frac{\partial C_{(k,i)}}{\partial t} &= -\mu_C C_{(k,i)} + \Phi_{(k,i)}^C, \\
 \frac{\partial F_{(k,i)}}{\partial t} &= \rho d_{(k,0)} C_{(k,i)} - \mu_f F_{(k,i)} - \eta \gamma (a_{(k,0)} F_{(k,i)} + b_{(k,0)} V_{(k,i)}) + \Phi_{(k,i)}^F, \\
 \frac{\partial m_{(k,i)}}{\partial t} &= \sigma V_{(k,i)} - \mu_m m_{(k,i)} + \Phi_{(k,i)}^m, \quad i = 2, \dots, n;
 \end{aligned}
 \tag{10}$$

$$C_{(k,i)}(x, k\tau) = 0, \quad m_{(k,i)}(x, k\tau) = 0, \quad V_{(k,i)}(x, k\tau) = 0, \quad F_{(k,i)}(x, k\tau) = 0, \quad k\tau \leq t \leq (k+1)\tau,$$

where

$$\begin{aligned}
 a_{(k,0)}(x, t) &= V_{(k,0)}(x, t), \quad b_{(k,0)}(x, t) = F_{(k,0)}(x, t), \quad d_{(k,0)}(x, t) = \left(1 - \frac{2C_{(k,0)}(x, t)}{C^{**}}\right), \\
 \Phi_{(k,1)}^V &= D_{(k,0)}^V \frac{\partial^2 V_{(k,0)}^V}{\partial x^2}, \quad \Phi_{(k,1)}^F = D_{(k,0)}^F \frac{\partial^2 F_{(k,0)}^F}{\partial x^2}, \\
 \Phi_{(k,i)}^V &= \sum_{r=0}^{i-1} D_{(k,r)}^V \frac{\partial^2 V_{(k,i-r-1)}^V}{\partial x^2} - \gamma \sum_{r=1}^{i-1} F_{(k,r)} V_{(k,i-r)}, \quad \Phi_{(k,i)}^C = \sum_{r=0}^{i-2} D_{(k,r)}^C \frac{\partial^2 C_{(k,i-r-2)}^C}{\partial x^2}, \\
 \Phi_{(k,i)}^F &= \sum_{r=0}^{i-1} D_{(k,r)}^F \frac{\partial^2 F_{(k,i-r-1)}^F}{\partial x^2} - \frac{\rho}{C^{**}} \sum_{r=1}^{i-1} C_{(k,i-r)} C_{(k,r)} - \eta \gamma \sum_{r=1}^{i-1} F_{(k,i-r)} V_{(k,r)}, \\
 \Phi_{(k,i)}^m &= \sum_{r=0}^{i-2} D_{(k,r)}^m \frac{\partial^2 m_{(k,i-r-2)}^m}{\partial x^2}.
 \end{aligned}$$

Here, the unknown functions $D_{(k,i)}^V, D_{(k,i)}^C, D_{(k,i)}^F, D_{(k,i)}^m$ ($i = 0, \dots, n$) are expressed through the previously found asymptotic terms, namely:

$$\begin{aligned}
 D_{(k,0)}^V(t) &= \frac{V_{(k,0)}^*(t)}{V_{(k,0)x}(0, t)}, \quad D_{(k,0)}^F(t) = \frac{F_{(k,0)}^*(t)}{F_{(k,0)x}(0, t)}, \quad D_{(k,1)}^V(t) = -\frac{D_{(k,0)}^V V_{(k,1)x}(0, t)}{V_{(k,0)x}(0, t)}, \\
 D_{(k,0)}^C(t) &= \frac{C_{(k,0)}^*(t)}{C_{(k,0)x}(0, t)}, \quad D_{(k,1)}^F(t) = -\frac{D_{(k,0)}^F(t) F_{(k,1)x}(0, t)}{F_{(k,0)x}(0, t)}, \quad D_{(k,0)}^m(t) = \frac{m_{(k,0)}^*(t)}{m_{(k,0)x}(0, t)}, \\
 D_{(k,i-1)}^V(t) &= -\frac{\sum_{r=0}^{i-2} D_{(k,r)}^V(t) V_{(k,i-r-1)x}(0, t)}{V_{(k,0)x}(0, t)}, \quad D_{(k,i-1)}^C(t) = -\frac{\sum_{r=0}^{i-3} D_{(k,r)}^C(t) C_{(k,i-r-2)x}(0, t)}{C_{(k,0)x}(0, t)}, \\
 D_{(k,i-1)}^F(t) &= -\frac{\sum_{r=0}^{i-2} D_{(k,r)}^F(t) F_{(k,i-r-1)x}(0, t)}{F_{(k,0)x}(0, t)}, \quad D_{(k,i-1)}^m(t) = -\frac{\sum_{r=0}^{i-3} D_{(k,r)}^m(t) m_{(k,i-r-2)x}(0, t)}{m_{(k,0)x}(0, t)}.
 \end{aligned}$$

When considering the model problem in bounded domains and with the presence (in addition to the conditions (2)) of boundary conditions, the solution of the corresponding inverse problem can be found similarly to, for example, [11].

3.2. In the cases where the values of the unknown diffusion scattering parameters in the model problem (1)–(2) depend on the spatial coordinate: $D^V = D^V(x), D^F = D^F(x), D^C = D^C(x), D^m = D^m(x)$, then we can implement different methods to find them. For example, let the values of the derivatives of the sought functions be set as the conditions of overdetermination at the initial moment of time, namely:

$$\left. \frac{\partial V}{\partial t} \right|_{t=0} = V_{\Delta}(x), \quad \left. \frac{\partial C}{\partial t} \right|_{t=0} = C_{\Delta}(x), \quad \left. \frac{\partial F}{\partial t} \right|_{t=0} = F_{\Delta}(x), \quad \left. \frac{\partial m}{\partial t} \right|_{t=0} = m_{\Delta}(x), \tag{11}$$

where $V_{\Delta}(x), C_{\Delta}(x), F_{\Delta}(x), m_{\Delta}(x)$ are sufficiently smooth functions, as well as the values of these unknown parameters at a certain characteristic point, for example, at the point of selection of biomaterials x^* :

$$D^V(x^*) = D_{*}^V, \quad D(x^*) = D_{*}^C, \quad D^F(x^*) = D_{*}^F, \quad D^m(x^*) = D_{*}^m. \tag{12}$$

At the same time, two of them, namely $V_\Delta(x)$ and $F_\Delta(x)$ can be determined as one-sided derivatives of known (given) functions:

$$V_\Delta(x) = \left. \frac{\partial V^0(x, t)}{\partial t} \right|_{t=0-0}, \quad F_\Delta(x) = \left. \frac{\partial F^0(x, t)}{\partial t} \right|_{t=0-0}. \quad (13)$$

By substituting (2) and (11) into (1), we obtain the system for the instant of time $t = 0$:

$$\begin{aligned} V_\Delta(x) &= (\beta - \gamma F^0(x, 0)) V^0(x, 0) + \varepsilon \frac{\partial}{\partial x} \left(D^V(x) \frac{\partial V^0(x, 0)}{\partial x} \right), \\ C_\Delta(x) &= \xi(m) \alpha V^0(x, -\tau) F^0(x, -\tau) - \mu_C (C^0(x) - C^*) + \varepsilon^2 \frac{\partial}{\partial x} \left(D^C(x) \frac{\partial C^0(x)}{\partial x} \right), \\ F_\Delta(x) &= \omega^F + \rho C^0(x) \left(1 - \frac{C^0(x)}{C^{**}} \right) - (\mu_f + \eta \gamma V) F^0(x, 0) + \varepsilon \frac{\partial}{\partial x} \left(D^F(x) \frac{\partial F^0(x, 0)}{\partial x} \right), \\ m_\Delta(x) &= \sigma V - \mu_m m^0(x) + \varepsilon^2 \frac{\partial}{\partial x} \left(D^m(x) \frac{\partial m^0(x)}{\partial x} \right), \end{aligned} \quad (14)$$

after solving which we will find the values of the unknown parameters of diffusion scattering. Further, using the already found functions $D^V(x)$, $D^F(x)$, $D^C(x)$, $D^m(x)$, as in the previous case, we gradually find numerical asymptotic approximations of the sought functions $V_k(x, t)$, $C_k(x, t)$, $F_k(x, t)$, $m_k(x, t)$ for each of the intervals $k\tau \leq t \leq (k+1)\tau$ ($k = 0, 1, \dots$) using the perturbation method.

If at the initial moment of time, in addition to conditions (2), local densities of diffusion flows are also given, namely

$$\begin{aligned} D^V(x) \left. \frac{\partial V}{\partial x} \right|_{t=0} &= V_o^\circ(x), & D^C(x) \left. \frac{\partial C}{\partial x} \right|_{t=0} &= C_o^\circ(x), \\ D^F(x) \left. \frac{\partial F}{\partial x} \right|_{t=0} &= F_o^\circ(x), & D^m(x) \left. \frac{\partial m}{\partial x} \right|_{t=0} &= m_o^\circ(x), \end{aligned} \quad (15)$$

then, using the given initial conditions (2), we first find the values of the derivatives of concentrations of the active factors on the left sides of (15):

$$\left. \frac{\partial V}{\partial x} \right|_{t=0} = \frac{\partial V^0(x, 0)}{\partial x}, \quad \left. \frac{\partial C}{\partial x} \right|_{t=0} = \frac{\partial C^0(x)}{\partial x}, \quad \left. \frac{\partial F}{\partial x} \right|_{t=0} = \frac{\partial F^0(x, 0)}{\partial x}, \quad \left. \frac{\partial m}{\partial x} \right|_{t=0} = \frac{\partial m^0(x)}{\partial x}, \quad (16)$$

and then, substituting (16) into (15), we find the sought parameters of diffusion scattering:

$$D^V(x) = \frac{V_o^\circ(x)}{\frac{\partial V^0(x, 0)}{\partial x}}, \quad D^C(x) = \frac{C_o^\circ(x)}{\frac{\partial C^0(x)}{\partial x}}, \quad D^F(x) = \frac{F_o^\circ(x)}{\frac{\partial F^0(x, 0)}{\partial x}}, \quad D^m(x) = \frac{m_o^\circ(x)}{\frac{\partial m^0(x, 0)}{\partial x}}. \quad (17)$$

Further, with already found parameters of diffusion scattering, similar to the previous one, we successively find the numerical asymptotic approximation of the unknown functions $V_k(x, t)$, $C_k(x, t)$, $F_k(x, t)$, $m_k(x, t)$ on each of the intervals $k\tau \leq t \leq (k+1)\tau$ ($k = 0, 1, \dots$).

It is also possible that in order to find the unknown parameters $D^V(x)$, $D^F(x)$, $D^C(x)$, $D^m(x)$ as overdetermination conditions, from the point of view of practical application, it is appropriate to set the values of the sought functions $V(x, t)$, $C(x, t)$, $F(x, t)$, $m(x, t)$ at some following moment in time $t = \bar{t}$, namely:

$$V(x, \bar{t}) = \bar{V}(x), \quad C(x, \bar{t}) = \bar{C}(x), \quad F(x, \bar{t}) = \bar{F}(x), \quad m(x, \bar{t}) = \bar{m}(x). \quad (18)$$

For the convenience of exposition, further we assume that $0 < \bar{t} < \tau$. Note that the functions $\bar{V}(x)$, $\bar{C}(x)$, $\bar{F}(x)$, $\bar{m}(x)$ in a certain sense must be ‘‘close’’ to the solution of the corresponding degenerate problem when $t = \bar{t}$, for example, they can be represented in the form:

$$\begin{aligned} \bar{V}(x) &= \bar{V}_0(x) + \varepsilon \bar{V}_1(x) + \varepsilon^2 \bar{V}_2(x), & \bar{C}(x) &= \bar{C}_0(x) + \varepsilon \bar{C}_1(x) + \varepsilon^2 \bar{C}_2(x), \\ \bar{F}(x) &= \bar{F}_0(x) + \varepsilon \bar{F}_1(x) + \varepsilon^2 \bar{F}_2(x), & \bar{m}(x) &= \bar{m}_0(x) + \varepsilon \bar{m}_1(x) + \varepsilon^2 \bar{m}_2(x), \end{aligned} \quad (19)$$

By applying similar to the one described for case 3.1 standard ‘‘equation procedure’’, we obtain the problem (8) for finding the solution of the corresponding degenerate problem, and also, taking into account Eq. (19), we establish that $\bar{V}_0(x) = V_{(0,0)}(x, \bar{t})$, $\bar{C}_0(x) = C_{(0,0)}(x, \bar{t})$, $\bar{F}_0(x) = F_{(0,0)}(x, \bar{t})$,

$\bar{m}_0(x) = m_{(0,0)}(x, \bar{t})$. At the same time, to find the unknown parameters D^V , D^F , and the sought functions $V_{(0,1)}$, $C_{(0,1)}$, $F_{(0,1)}$, $m_{(0,1)}$, taking into account Eq. (19), we obtain the following problem:

$$\begin{aligned} \frac{\partial V_{(0,1)}}{\partial t} &= \beta V_{(0,1)} - \gamma (a_{(0,0)} F_{(0,1)} + b_{(0,0)} V_{(0,1)}) + \frac{\partial}{\partial x} \left(D^V \frac{\partial V_{(0,0)}}{\partial x} \right), \\ \frac{\partial C_{(0,1)}}{\partial t} &= -\mu_C C_{(0,1)}, \quad \frac{\partial m_{(0,1)}}{\partial t} = \sigma V_{(0,1)} - \mu_m m_{(0,1)}, \\ \frac{\partial F_{(0,1)}}{\partial t} &= \rho d_{(0,0)} C_{(0,1)} - \mu_f F_{(0,1)} - \eta \gamma (a_{(0,0)} F_{(0,1)} + b_{(0,0)} V_{(0,1)}) + \frac{\partial}{\partial x} \left(D^F \frac{\partial F_{(0,0)}}{\partial x} \right), \\ \bar{C}_1 &= C_{(0,1)}(x, \bar{t}), \quad \bar{m}_1 = m_{(0,1)}(x, \bar{t}), \\ \frac{\partial \bar{V}_0}{\partial x} \frac{\partial D^V}{\partial x} + \frac{\partial^2 \bar{V}_0}{\partial x^2} D^V &= \frac{\partial V_{(0,1)}(x, \bar{t})}{\partial t} - \beta \bar{V}_1 + \gamma (\bar{V}_0 \bar{F}_1 + \bar{F}_0 \bar{V}_1), \\ \frac{\partial \bar{F}_0}{\partial x} \frac{\partial D^F}{\partial x} + \frac{\partial^2 \bar{F}_0}{\partial x^2} D^F &= \frac{\partial F_{(0,1)}(x, \bar{t})}{\partial t} - \rho \left(1 - \frac{2\bar{C}_0}{C^{**}} \right) \bar{C}_1 + \mu_f \bar{F}_1 + \eta \gamma (\bar{V}_0 \bar{F}_1 + \bar{F}_0 \bar{V}_1), \\ C_{(0,1)}(x, 0) &= 0, \quad m_{(0,1)}(x, 0) = 0, \quad V_{(0,1)}(x, 0) = 0, \quad F_{(0,1)}(x, 0) = 0, \\ D^V(x^*) &= \bar{D}_*^V, \quad D^F(x^*) = \bar{D}_*^F, \end{aligned} \tag{20}$$

and for the parameters D^C , D^m and functions $V_{(0,2)}$, $C_{(0,2)}$, $F_{(0,2)}$, $m_{(0,2)}$ we obtain such a problem:

$$\begin{aligned} \frac{\partial V_{(0,2)}}{\partial t} &= \beta V_{(0,2)} - \gamma (a_{(0,0)} F_{(0,2)} + b_{(0,0)} V_{(0,2)}) + \frac{\partial}{\partial x} \left(D^V \frac{\partial V_{(0,1)}}{\partial x} \right), \\ \frac{\partial C_{(0,2)}}{\partial t} &= -\mu_C C_{(0,2)} + \frac{\partial}{\partial x} \left(D^C \frac{\partial C_{(0,0)}}{\partial x} \right), \\ \frac{\partial F_{(0,2)}}{\partial t} &= \rho d_{(0,0)} C_{(0,2)} - \mu_f F_{(0,2)} - \eta \gamma (a_{(0,0)} F_{(0,2)} + b_{(0,0)} V_{(0,2)}) + \frac{\partial}{\partial x} \left(D^F \frac{\partial F_{(0,1)}}{\partial x} \right), \\ \frac{\partial m_{(0,2)}}{\partial t} &= \sigma V_{(0,2)} - \mu_m m_{(0,2)} + \frac{\partial}{\partial x} \left(D^m \frac{\partial m_{(0,0)}}{\partial x} \right), \\ \bar{V}_2 &= V_{(0,2)}(x, \bar{t}), \quad \bar{F}_2 = F_{(0,2)}(x, \bar{t}), \\ \frac{\partial \bar{C}_0}{\partial x} \frac{\partial D^C}{\partial x} + \frac{\partial^2 \bar{C}_0}{\partial x^2} D^C &= \frac{\partial C_{(0,2)}(x, \bar{t})}{\partial t} + \mu_C \bar{C}_2, \\ \frac{\partial \bar{m}_0}{\partial x} \frac{\partial D^m}{\partial x} + \frac{\partial^2 \bar{m}_0}{\partial x^2} D^m &= \frac{\partial m_{(0,2)}(x, \bar{t})}{\partial t} - \sigma \bar{V}_2 + \mu_m \bar{m}_2, \\ C_{(0,2)}(x, 0) &= 0, \quad m_{(0,2)}(x, 0) = 0, \quad V_{(0,2)}(x, 0) = 0, \quad F_{(0,2)}(x, 0) = 0, \\ D^C(x^*) &= \bar{D}_*^C, \quad D^m(x^*) = \bar{D}_*^m. \end{aligned} \tag{21}$$

Here $a_{(0,0)}(x, t) = V_{(0,0)}(x, t)$, $b_{(0,0)}(x, t) = F_{(0,0)}(x, t)$, $d_{(0,0)}(x, t) = (1 - 2C_{(0,0)}(x, t)/C^{**})$.

3.3. In a situation where the unknown parameters of diffusion scattering can be represented by a product, namely:

$$D^V = \tilde{D}^V(x) \tilde{D}^V(t), \quad D^F = \tilde{D}^F(x) \tilde{D}^F(t), \quad D^C = \tilde{D}^C(x) \tilde{D}^C(t), \quad D^m = \tilde{D}^m(x) \tilde{D}^m(t),$$

and the overdetermination conditions are given in the form:

$$\begin{aligned} \tilde{D}^V(x) \frac{\partial V}{\partial x} \Big|_{t=0} &= \tilde{V}_0^\circ(x), \quad \tilde{D}^C(x) \frac{\partial C}{\partial x} \Big|_{t=0} = \tilde{C}_0^\circ(x), \\ \tilde{D}^F(x) \frac{\partial F}{\partial x} \Big|_{t=0} &= \tilde{F}_0^\circ(x), \quad \tilde{D}^m(x) \frac{\partial m}{\partial x} \Big|_{t=0} = \tilde{m}_0^\circ(x), \\ \tilde{D}^V(t) \frac{\partial V}{\partial x} \Big|_{x=x^*} &= \tilde{V}_*^*(t), \quad \tilde{D}^C(t) \frac{\partial C}{\partial x} \Big|_{x=x^*} = \tilde{C}_*^*(t), \\ \tilde{D}^F(t) \frac{\partial F}{\partial x} \Big|_{x=x^*} &= \tilde{F}_*^*(t), \quad \tilde{D}^m(t) \frac{\partial m}{\partial x} \Big|_{x=x^*} = \tilde{m}_*^*(t), \end{aligned} \tag{22}$$

$$\tag{23}$$

as in the corresponding situation in 3.2, using the initial conditions (2), first we find the following values of the diffusion scattering parameters depending on the spatial variable:

$$\tilde{D}^V(x) = \frac{\tilde{V}_0^o(x)}{\frac{\partial V^o(x)}{\partial x}}, \quad \tilde{D}^F(x) = \frac{\tilde{F}_0^o(x)}{\frac{\partial F^o(x)}{\partial x}}, \quad \tilde{D}^C(x) = \frac{\tilde{C}_0^o(x)}{\frac{\partial C^o(x)}{\partial x}}, \quad \tilde{D}^m(x) = \frac{\tilde{m}_0^o(x)}{\frac{\partial m^o(x)}{\partial x}}. \quad (24)$$

Further, by applying a step-by-step numerical asymptotic approximation procedure for the solution of the corresponding model problem similar to the one described in 3.1, we find the required functions $V_k(x, t)$, $C_k(x, t)$, $F_k(x, t)$, $m_k(x, t)$ for each of the intervals $k\tau \leq t \leq (k+1)\tau$ ($k = 0, 1, \dots$) and the values of the unknown parameters $\tilde{D}_{(k,i)}^V$, $\tilde{D}_{(k,i)}^C$, $\tilde{D}_{(k,i)}^F$, $\tilde{D}_{(k,i)}^m$ ($i = 0, \dots, n$), which are also expressed in terms of the previously found asymptotic terms, namely:

$$\begin{aligned} \tilde{D}_{(k,0)}^V(t) &= \frac{\tilde{V}_*^*(t)}{\tilde{D}^V(0) V_{(k,0)x}(0, t)}, & \tilde{D}_{(k,0)}^F(t) &= \frac{\tilde{F}_*^*(t)}{\tilde{D}^F(0) F_{(k,0)x}(0, t)}, \\ \tilde{D}_{(k,1)}^V(t) &= -\frac{\tilde{D}_{(k,0)}^V(t) V_{(k,1)x}(0, t)}{V_{(k,0)x}(0, t)}, & \tilde{D}_{(k,0)}^C(t) &= \frac{\tilde{C}_*^*(t)}{\tilde{D}^C(0) C_{(k,0)x}(0, t)}, \\ \tilde{D}_{(k,1)}^F(t) &= -\frac{\tilde{D}_{(k,0)}^F(t) F_{(k,1)x}(0, t)}{F_{(k,0)x}(0, t)}, & \tilde{D}_{(k,0)}^m(t) &= \frac{\tilde{m}_*^*(t)}{\tilde{D}^m(0) m_{(k,0)x}(0, t)}, \\ \tilde{D}_{(k,i-1)}^V(t) &= -\frac{\sum_{r=0}^{i-2} \tilde{D}_{(k,r)}^V(t) V_{(k,i-r-1)x}(0, t)}{V_{(k,0)x}(0, t)}, & \tilde{D}_{(k,i-1)}^C(t) &= -\frac{\sum_{r=0}^{i-3} \tilde{D}_{(k,r)}^C(t) C_{(k,s-r-2)x}(0, t)}{C_{(k,0)x}(0, t)}, \\ \tilde{D}_{(k,i-1)}^F(t) &= -\frac{\sum_{r=0}^{i-2} \tilde{D}_{(k,r)}^F(t) F_{(k,i-r-1)x}(0, t)}{F_{(k,0)x}(0, t)}, & \tilde{D}_{(k,i-1)}^m(t) &= -\frac{\sum_{r=0}^{i-3} \tilde{D}_{(k,r)}^m(t) m_{(k,i-r-2)x}(0, t)}{m_{(k,0)x}(0, t)}. \end{aligned}$$

Note that the solutions to problems (8)–(10) for each time interval $k\tau \leq t \leq (k+1)\tau$ ($k = 0, 1, \dots$) can be found by known numerical methods with the use of reliable packages of the corresponding software (see, for example, [12]) and using already found values of the sought functions for the previous interval. In the case when the basic functions are specified in a discrete form (in particular, as the results of laboratory methods of observation), for them we apply the procedure, for example, of the Chebyshev approximation of the function by the sum of a polynomial and an expression, similarly to [13, 14]. Establishing the space-time intervals of convergence and evaluating the residual terms is carried out similarly to [6–9, 15].

4. Results of numerical experiments

In the modifications and generalizations of the basic infectious disease models presented in [6–9], the proposed approach for taking spatial effects into account referred to the case when there is a diffusion dispersion of active factors with constant coefficients. When applying such an approach to practical situations, it is more expedient to assume the diffusion coefficient to be dependent on both spatial and temporal variables. For example, the dependence of diffusion coefficients on the biological structure of the target organ, as well as on the temperature in it, is quite natural. Therefore, an important condition for qualitative forecasting of the development of a viral infection and the development of effective personalized treatment programs, in addition to appropriate mathematical models, is the availability of reliable tools for identifying their personalized parameters.

In this regard, the computer experiments were focused on the study of the features of the practical application of the above-presented procedures for identifying the parameters of diffusion scattering of the active factors of an infectious disease in various situational conditions. In particular, in Figure 1, the model dynamics is presented for antigen concentration in the epicenter of infection for different values of the diffusion coefficient. As expected, the highest model severity of the disease occurred in the case when the influence of diffusion scattering of factors was not taken into account. For computer modeling of the situation when the diffusion coefficients of the active factors are known to be dependent

only on time, the density of the diffusion flow of antigens in the condition (3) was put according to the model dependence of the form $V_*^*(t) = a(\sin(b(t+c)))/(1+dt^\nu) - p$ (here $a = 6.12 \cdot 10^{-4}$, $b = 1.17 \cdot 10$, $c = 1.9 \cdot 10^{-1}$, $d = 5.7 \cdot 10^{-3}$, $\nu = 2.35$, $p = 0.5$). The values of the diffusion coefficient of the antigens for the model (1)–(2) being identified in accordance with 3.1 are presented in Figure 2. The intensity of the antigens concentration growth in this model case is the lowest, which causes the lowest severity of the course of the disease in the initial period of time. Such an effect is possible with a higher intensity of diffusion scattering of antigens in the infection zone, which is confirmed by correspondingly higher values of the identified diffusion coefficient in this period.

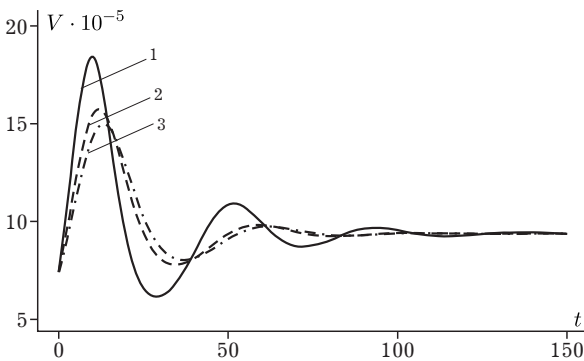


Fig. 1. Dynamics of antigens for different diffusion coefficients: $D^V = 0$ (curve 1); $D^V = 1$ (curve 2); $D^V = D^V(t)$ (curve 3).

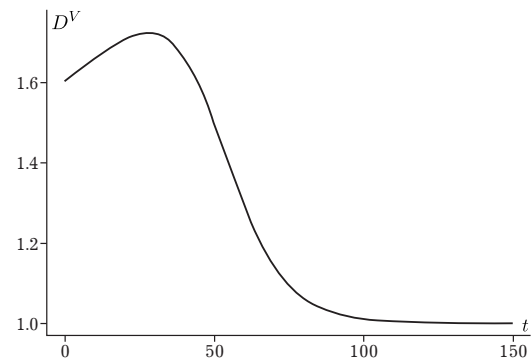


Fig. 2. The value of diffusion coefficient $D^V = D^V(t)$ at $\varepsilon = 0.025$.

5. Conclusions

In this work, based on the modification of the infectious disease model, which takes into account diffusion disturbances and logistic dynamics of immunological cells, individual approaches to the identification of unknown parameters of diffusion scattering of active factors are proposed for different types of functional dependence of the diffusion coefficient and given redefinition conditions. To find the solution to the original model singularly perturbed problem with delay and unknown parameters, a modernized step-by-step procedure of numerical asymptotic approximation of the corresponding sequence of problems without delay is proposed.

The presented results of computer modeling illustrate the effectiveness of the proposed approaches in identifying diffusion scattering parameters. It is shown that, under other identical conditions, a decrease in the concentration of antigens over a certain period of time leads to the observing higher values of the corresponding diffusion coefficient over this period. We should also emphasize that taking into account variable diffusion coefficients in models of infectious diseases provides a more accurate prediction of the course of the disease, and, therefore, the possibility of forming more effective treatment programs. At the same time, for the qualitative identification of unknown parameters of diffusion scattering, additional information is needed, which can be obtained by conducting additional laboratory studies according to an individual procedure.

A natural prospect for the development of the presented approach is its development for cases of infectious disease simulation taking into account convection, the body's temperature reaction, and mixed infections in the conditions of pharmacotherapy and immunotherapy. It is also promising to consider random factors [16, 17].

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Ідентифікація параметрів дифузійного розсіювання модифікованої моделі вірусної інфекції в умовах логістичної динаміки імунологічних клітин

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На основі модифікації моделі інфекційного захворювання з урахуванням дифузійних збурень та логістичної динаміки імунологічних клітин запропоновано окремі підходи щодо ідентифікації параметрів дифузійного розсіювання для різних типів функціональної залежності коефіцієнтів дифузії та заданих умов перевизначення. Модернізовано спеціальну покрокову процедуру для чисельно асимптотичного наближення розв'язку відповідної сингулярно збуреної модельної задачі із запізненням. Представлені результати комп'ютерних експериментів щодо ідентифікації невідомих параметрів дифузійного розсіювання. Зазначено, що ідентифікація та застосування змінних коефіцієнтів дифузійного розсіювання забезпечить більш точне прогнозування динаміки інфекційного захворювання, що є важливим у системі прийняття рішень щодо застосування різного роду лікувальних процедур.

Ключові слова: *модель інфекційного захворювання; ідентифікація параметрів; динамічні системи із запізненням; асимптотичні методи; сингулярно збурені задачі; логістична динаміка.*