Generalizing the Antiviral Immune Response Model to Account for Adsorption, Diffusion Perturbations, and Temperature

Serhii Baranovsky[a], Andrii Bomba [a], Oksana Pryshchepa[a]

[a] *National University of Water and Environmental Engineering, 11 Soborna Str., Rivne, 33028, Ukraine*

Abstract

The antiviral immune response model has been generalized to take into account the effect of adsorption therapy on the development of disease process under conditions of small diffuse scattering of acting factors based on the synthesis of perturbation theory and modeling ideas of the adsorption mass transfer process. A computational technology of step-by-step asymptotic approximation of the solution to the corresponding model problem with time delay as a perturbation of solutions to degenerate problems without delay has been developed. The numerical experiment results demonstrate a predictive decrease in the concentration of viral elements in the target organ through their neutralization into the organism by adsorbents introduced. It is noted that the efficiency of adsorption drugs depends, in particular, on the moment of time for their introduction, which must be considered when making decisions on the formation of complex treatment programs using appropriate therapy.

Keywords 1

Antiviral immune response model, adsorption, dynamic systems with delay, asymptotic methods, singularly perturbed problems.

1. Introduction

The practice of using adsorption agents for detoxification of the organism has a very long history [1]. Charcoal, clay, ground tuffs and burnt horn were used to treat poisoning, dysentery, jaundice and other diseases even in the time of Ancient Egypt, India, and Greece. The ability of adsorbents to bind, retain and naturally remove from the organism not only various types of toxins, metabolic products and heavy metals, but also pathogenic microorganisms and products of their vital activity ensures an increase in the therapeutic effect with the complex application of traditional therapeutic procedures and adsorption drugs. As is known, adsorption drugs, unlike pharmacological ones, have a different mechanism of action [1, 2]. It is associated with the absorption of the substance as a result of its diffusion into the pores of these adsorbents. At the same time, most of these drugs are not specific to certain types of toxins or microorganisms. Adsorbents can connect only those substances whose molecules can penetrate their internal pores. Considering the specifics of adsorption therapy application is important for forecasting the infectious disease dynamics in decision-making systems in the development of effective individual treatment programs.

The basic model of infectious disease and models of antiviral and antibacterial immune responses [3] are proven and already classical tools for predicting the general patterns of infectious disease courses. These models consider the antiviral humoral and cellular immune response and are the basis of their new modifications and generalizations that make it possible to consider other factors and mechanisms of the organism's defence. Examples of effective application of viral and bacterial infection mathematical models that are built according to the methodology described in [3] to consider

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EMAIL: svbaranovsky@gmail.com (S. Baranovsky); abomba@ukr.net (A. Bomba); o.v.pryshchepa@nuwm.edu.ua (O. Pryshchepa)
ORCID: 0000-0002-8056-2980 (S. Baranovsky); 0000-0001-5528-4192 (A. Bomba); 0000-0001-8032-1223 (O. Pryshchepa)

various protection mechanisms and features of various disease courses are given in [4]. Adaptation of the simplest model of a viral disease to tumor-immune system interactions considering the role of interleukins in immune processes was proposed in [5]. The basic model of the immune response was modified to consider the features of the COVID-19 course and the conditions of the use of immunotherapy [6]. The authors in [7] proposed to take into account the antigens' spatial dispersion and other factors of the model as a diffuse perturbation of the process. This approach was used for modifying the infectious disease model to consider the organism's temperature response in [8] and for generalizing the antiviral immune response model to comprehensively consider diffusion perturbations, the temperature and the logistic dynamics of antigens in [9].

Let us note that the wide use of various micro- and nanoporous catalytic environments in many industries turned to the active study of adsorption processes and the development of corresponding mathematical models. In particular, in [10, 11] the single-component adsorption process in a certain catalytic medium of l length of microporous structure particles of the radius R is described by the following model problem: $c_t'=\mathrm{D}_{inter}c_{xx}''-\theta_{intra}(q_r')|_{r=R}$, $q_t'=\mathrm{D}_{intra}(q_{rr}''+2q_r'/r)$ under conditions $c(0,x)=0$, $c(t,l)=c_\infty$, $c_x'(t,0)=0$, $q(0,x,r)=0$, $q(t,x,R)=\kappa\cdot c(t,x)$, $q_r'(t,x,0)=0$. This approach is based on the idea of taking into account the interaction of mass transfer in the interparticle space (first equation) and mass transfer into the interior of particles with concentration $q(t,x,r)$ (second equation), which is related to concentration $c(t,x)$. This approach (in [12]) has been used for modifying the basic model of viral infection to consider adsorption therapy and diffuse scattering effects, which makes it possible to predict an additional decrease in the antigens' concentration due to their absorption by adsorbents.

This work aims to generalize the antiviral immune response model to consider the effect of adsorbing substances on the disease dynamics in the conditions of diffusion perturbations and temperature of the organism.

2. Generalizing the antiviral immune response model to consider adsorption, diffusion perturbations and temperature

To predict the viral disease process development considering adsorption therapy we will generalize the modification of the immune response model to viral pathogens (in [9]) by introducing additional components that describe the diffusion mass transfer of antigens inside the adsorbent particles and its relationship with the mass transfer of antigens in the environment of the target organ. We will describe the corresponding immune response dynamics taking into account the effect of adsorbents under conditions of diffusion scattering and temperature of the organism, in the set $G=\{(t,x): t\in R_+, x\in R\}$ by such a singularly perturbed system of nonlinear differential equations with small parameter μ:

$$\begin{aligned}
\frac{\partial V_f}{\partial t}&=\omega_V+h_1(\Theta)\cdot C_V\left(1-\frac{C_V}{C_V^{**}}\right)+\nu h_2(\Theta)\cdot C_V E-h_3(\Theta)\cdot FV_f-h_4(\Theta)\cdot MV_f-\\
&-h_5V_f(C^*-m-C_V)+\mu D_V\frac{\partial^2 V_f}{\partial x^2}-\mu D_W^*\left(\frac{\partial W_f}{\partial r}\right|_{r=R},\\
\frac{\partial W_f}{\partial t}&=\mu^2 D_W\left(\frac{\partial^2 W_f}{\partial r^2}+\frac{2}{r}\frac{\partial W_f}{\partial r}\right),\\
\frac{\partial M_V}{\partial t}&=h_4(\Theta)M\cdot V_f-h_6M_V+\mu^2 D_{M_V}\frac{\partial^2 M_V}{\partial x^2},\\
\frac{\partial H_E}{\partial t}&=h_7(\Theta)\xi(m)H_E(t-t_1^o,x)M_V(t-t_1^o,x)-h_8(\Theta)M_VH_E-\\
&-h_9(\Theta)M_VH_EE+h_{10}(H_E^*-H_E)+\mu^2 D_{H_E}\frac{\partial^2 H_E}{\partial x^2},\\
\frac{\partial H_B}{\partial t}&=h_{11}(\Theta)\xi(m)H_B(t-t_2^o,x)M_V(t-t_2^o,x)-h_{12}(\Theta)M_VH_B-
\end{aligned}\tag{1}$$

$$-h_{13}(\Theta)M_V H_B B+h_{14}(H_B^*-H_B)+\mu^2 D_{H_B}\frac{\partial^2 H_B}{\partial x^2},$$

$$\frac{\partial E}{\partial t}=h_{15}(\Theta)\xi(m)E(t-t_3^{\circ},x)H_E(t-t_3^{\circ},x)M_V(t-t_3^{\circ},x)-h_{16}(\Theta)M_V H_E E-$$

$$-h_2(\Theta)C_V E+h_{17}(E^*-E)+\mu^2 D_E\frac{\partial^2 E}{\partial x^2},$$

$$\frac{\partial B}{\partial t}=h_{18}(\Theta)\xi(m)B(t-t_4^{\circ},x)H_B(t-t_4^{\circ},x)M_V(t-t_4^{\circ},x)-$$

$$-h_{19}(\Theta)M_V H_B B+h_{20}(B^*-B)+\mu^2 D_B\frac{\partial^2 B}{\partial x^2},$$

$$\frac{\partial P}{\partial t}=h_{21}(\Theta)\xi(m)B(t-t_5^{\circ},x)H_B(t-t_5^{\circ},x)M_V(t-t_5^{\circ},x)+h_{22}(P^*-P)+\mu^2 D_P\frac{\partial^2 P}{\partial x^2},$$

$$\frac{\partial F}{\partial t}=\omega_F+h_{23}P\left(1-\frac{P}{P^{**}}\right)-h_3(\Theta)\cdot V_f F-h_{24}F+\mu D_F\frac{\partial^2 F}{\partial x^2},$$

$$\frac{\partial C_V}{\partial t}=h_{25}V_f(C^*-m-C_V)-h_2(\Theta)EC_V-h_{26}C_V+\mu^2 D_{C_V}\frac{\partial^2 C_V}{\partial x^2},$$

$$\frac{\partial m}{\partial t}=h_2(\Theta)C_V E+h_{26}C_V-h_{27}m+\mu^2 D_m\frac{\partial^2 m}{\partial x^2},$$

$$\frac{\partial \Theta}{\partial t}=h_{28}F(t-t_6^{\circ},x)V_f(t-t_6^{\circ},x)(1-h_{29}F(t-t_6^{\circ},x)V_f(t-t_6^{\circ},x))-h_{30}(\Theta-\Theta^*)+\mu D_\Theta\frac{\partial^2\Theta}{\partial x^2}$$

under

$$V_f(0,x)=V_f^0(x),\ M_V(0,x)=M_V^0(x),\ H_B(0,x)=H_B^0(x),\ H_E(0,x)=H_E^0(x),\ E(0,x)=E^0(x),$$
$$P(0,x)=P^0(x),\ B(0,x)=B^0(x),\ F(0,x)=F^0(x),\ C_V(0,x)=C_V^0(x),\ m(0,x)=m^0(x),\ \Theta(0,x)=\Theta^0(x),$$
$$H_E(\tilde{t},x)M_V(\tilde{t},x)=\varphi_1(\tilde{t},x),\ -t_1^{\circ}\le\tilde{t}<0,\ H_B(\tilde{t},x)M_V(\tilde{t},x)=\varphi_2(\tilde{t},x),\ -t_2^{\circ}\le\tilde{t}<0,\ E(\tilde{t},x)H_E(\tilde{t},x)\times \quad (2)$$
$$\times M_V(\tilde{t},x)=\varphi_3(\tilde{t},x),\ -t_3^{\circ}\le\tilde{t}<0,\ B(\tilde{t},x)H_B(\tilde{t},x)M_V(\tilde{t},x)=\varphi_4(\tilde{t},x),\ -\tilde{t}^{\circ}\le\tilde{t}<0,\ \tilde{t}^{\circ}=\max\{t_4^{\circ},t_5^{\circ}\},$$
$$F(\tilde{t},x)V_f(\tilde{t},x)=\varphi_5(\tilde{t},x),\ -t_6^{\circ}\le\tilde{t}<0,\ W_f(0,x,r)=W_f^0(x,r),\ W_f(t,x,R)=\kappa\cdot V_f(t,x),\ \frac{\partial W_f(t,x,0)}{\partial r}=0$$

where $V_f=V_f(t,x)$, $W_f=W_f(t,x)$, $M_V=M_V(t,x)$, $H_E=H_E(t,x)$, $H_B=H_B(t,x)$, $E=E(t,x)$, $B=B(t,x)$, $P=P(t,x)$, $F=F(t,x)$, $C_V=C_V(t,x)$, $m=m(t,x)$, $\Theta=\Theta(t,x)$ are accordingly the number of antigens that are present in the intercellular space of the target organ, the number of antigens in the middle of particles of the adsorbent, the number of stimulated macrophages, the number of *T*-helper-lymphocytes of cellular immunity, the number of *T*-helper-lymphocytes of humoral immunity, the number of *T*-cell-effectors, the number of *B*-lymphocytes, the number of plasma cells, the number of antibodies, the number of viruses infected cells, non-functional part of the damaged target organ and temperature at the moment of time *t* at point *x*; *M* is the number of all macrophages in the organism, determined by homeostasis; $h_1(\Theta)=h_1^0/(1+h_1^*(\Theta-\Theta^*))$ is temperature dependent parameter ($h_1^*=const>0$), which is related to antigen reproduction rate; $h_l(\Theta)=h_l(1+h_l^*(\Theta-\Theta^*))$, $l=\{2,3,4,7,8,9,11,12,13,15,16,18,19,21\}$ are temperature dependent parameters ($h_l^*=const>0$), which are related to the immune system. The parameter h_{28} characterizes the mechanism for increasing the organism's temperature, which is related to the number of $V_f F$-complexes: if their number does not exceed the certain threshold value $(V_f F)^*$, then the temperature does not increase and $h_{28}=0$. If the value of $V_f F$ exceeds this threshold, then the temperature increases $h_{28}=h_{28}^*=const>0$. The other parameters h_i of the model are determined according to [3]. C^*, H_E^*, H_B^*, E^*, B^*, P^*, Θ^* are the number of the target organ cells, immunological cells of the corresponding type and the temperature value maintained in the organism by homeostasis respectively; C_V^{**}, P^{**} are the maximum numbers of damaged and plasma cells respectively that produce antibodies; $V_f^0(x)$, $M_V^0(x)$, $H_E^0(x)$, $H_B^0(x)$, $E^0(x)$, $B^0(x)$, $P^0(x)$, $F^0(x)$, $C_V^0(x)$, $m^0(x)$,

$\Theta^0(x)$, $\varphi_1(\tilde{t},x)$, $\varphi_2(\tilde{t},x)$, $\varphi_3(\tilde{t},x)$, $\varphi_4(\tilde{t},x)$, $\varphi_5(\tilde{t},x)$, $W_f^0(x,r)$ is smooth limited functions of necessary order. The function $\xi(m)$ considers the effect of productivity decrease on the immune system due to damage to the target organ, $0\le\xi(m)\le1$. And εD_V, $\varepsilon^2 D_W$, $\varepsilon^2 D_{M_V}$, $\varepsilon^2 D_{H_E}$, $\varepsilon^2 D_{H_B}$, $\varepsilon^2 D_E$, $\varepsilon^2 D_B$, $\varepsilon^2 D_P$, εD_F, $\varepsilon^2 D_{C_V}$, $\varepsilon^2 D_m$ are diffusion coefficients of the corresponding components of the process; μD_Θ is the thermal conductivity coefficient of the target organ medium; εD_W^* is the coefficient that characterizes the interaction of the diffusion redistribution of antigens in micropores of the adsorbent particles on their diffusional scattering in the intercellular space; μ is a parameter intended to describe the small influence of diffusion components compared to the influence of other process components. Functions $\omega_V(t,x)$, $\omega_F(t,x)$ are intended to describe changes concentrated in space and time according to the number of antigens and antibodies [9].

3. Computing technology of numerical-asymptotic approximation of the problem solution

Let us come to building a procedure for a step-by-step numerical asymptotic approximation of the solution to the problem (1)-(2). We represent the delay values specified in the model as $t_i^o = s_i \cdot \tau$, where $s_i \in N$, $i=\overline{1,6}$, $\tau>0$. It should be noted that according to the results of the parameter identification of the immune response model to viral infection in [3] using the data of clinical observations, the duration of formation periods of new helper cells H_E, H_B and *T*-effectors and *B*-lymphocytes are practically the same. Therefore, we will assume that $s_1=s_2$, $s_3=s_4$ ($t_1^o=t_2^o$ and $t_3^o=t_4^o$) and $s_6<s_1<s_3<s_5$.

We will also assume that equations in the system (1) is dimensionless [7-9, 12]. Then, similarly to [7-9,12], we will find a solution to the model problem (1)-(2) with delay as a sequence of solutions to problems without delay on the intervals $(s-1)\tau\le t\le s\tau$, $s=1,2,...$. To ensure the necessary order of smoothness of partial solutions for $t=\tau$, $t=2\tau$, … we add conditions for their consistency in the same way as was done in [7-9,12]. According to a [7-9,12], we find the approximation of solutions obtained as a result of singularly perturbed problems on each of the intervals $(s-1)\tau\le t\le s\tau$ $(s=1,2,...)$, by the asymptotic method, formally presenting them as asymptotic series: $V_{f(s)}=\sum_{i=0}^{n}\mu^i V_{f(s,i)}+R_{n(s)}^{Vf}$, $W_{f(s)}=\sum_{i=0}^{n}\mu^i W_{f(s,i)}+R_{n(s)}^{Wf}$, $M_{V(s)}=\sum_{i=0}^{n}\mu^i M_{V(s,i)}+R_{n(s)}^{M_V}$, $H_{E(s)}=\sum_{i=0}^{n}\mu^i H_{E(s,i)}+R_{n(s)}^{H_E}$, $H_{B(s)}=\sum_{i=0}^{n}\mu^i H_{B(s,i)}+R_{n(s)}^{H_B}$, $E_{(s)}=\sum_{i=0}^{n}\mu^i E_{(s,i)}+R_{n(s)}^{E}$, $B_{(s)}=\sum_{i=0}^{n}\mu^i B_{(s,i)}+R_{n(s)}^{B}$, $P_{(s)}=\sum_{i=0}^{n}\mu^i P_{(s,i)}+R_{n(s)}^{P}$, $F_{(s)}=\sum_{i=0}^{n}\mu^i F_{(s,i)}+R_{n(s)}^{F}$, $C_{V(s)}=\sum_{i=0}^{n}\mu^i C_{V(s,i)}+R_{n(s)}^{C_V}$, $m_{(s)}=\sum_{i=0}^{n}\mu^i m_{(s,i)}+R_{n(s)}^{m}$, $\Theta_{(s)}=\sum_{i=0}^{n}\mu^i \Theta_{(s,i)}+R_{n(s)}^{\Theta}$, where $V_{f(s,i)}=V_{f(s,i)}(t,x)$, $W_{f(s,i)}=W_{f(s,i)}(t,x)$, $M_{V(s,i)}=M_{V(s,i)}(t,x)$, $H_{E(s,i)}=H_{E(s,i)}(t,x)$, $H_{B(s,i)}=H_{B(s,i)}(t,x)$, $E_{(s,i)}=E_{(s,i)}(t,x)$, $B_{(s,i)}=B_{(s,i)}(t,x)$, $P_{(s,i)}=P_{(s,i)}(t,x)$, $F_{(s,i)}=F_{(s,i)}(t,x)$, $C_{V(s,i)}=C_{V(s,i)}(t,x)$, $m_{(s,i)}=m_{(s,i)}(t,x)$, $\Theta_{(s,i)}=\Theta_{(s,i)}(t,x)$ $(i=0,1,...,n)$ required functions, $R_{n(s)}^{Vf}=R_{n(s)}^{Vf}(t,x,\mu)$, $R_{n(s)}^{Wf}=R_{n(s)}^{Wf}(t,x,\mu)$, $R_{n(s)}^{M_V}=R_{n(s)}^{M_V}(t,x,\mu)$, $R_{n(s)}^{H_E}=R_{n(s)}^{H_E}(t,x,\mu)$, $R_{n(s)}^{H_B}=R_{n(s)}^{H_B}(t,x,\mu)$, $R_{n(s)}^{E}=R_{n(s)}^{E}(t,x,\mu)$, $R_{n(s)}^{B}=R_{n(s)}^{B}(t,x,\mu)$, $R_{n(s)}^{P}=R_{n(s)}^{P}(t,x,\mu)$, $R_{n(s)}^{F}=R_{n(s)}^{F}(t,x,\mu)$, $R_{n(s)}^{C_V}=R_{n(s)}^{C_V}(t,x,\mu)$, $R_{n(s)}^{m}=R_{n(s)}^{m}(t,x,\mu)$, $R_{n(s)}^{\Theta}=R_{n(s)}^{\Theta}(t,x,\mu)$ are relevant residual members. We will perform a regularizing transformation $\tilde{r}=r/\mu$ $(0\le\tilde{r}\le\tilde{R}=R/\mu)$ [12] since the sizes of adsorption particles are small. We will obtain problems for finding unknown functions (asymptotics) as a result of the "procedure of equalization" [7-9, 12]. For example, for the period $0\le t\le t_6^o$, at $\xi(m)=1$ problems for finding corrections to solutions of degenerate problems that take into account the effects of diffusion scattering in the intercellular space and adsorption of antigens look as:

$$\frac{\partial V_{f(s,i)}}{\partial t}=[a^{V_f}_{C_V(s)}C_{V(s,i)}+a^{V_f}_{\Theta(s)}\Theta_{(s,i)}]+\nu h_2[b^{V_f}_{E(s)}E_{(s,i)}+b^{V_f}_{C_V(s)}C_{V(s,i)}+b^{V_f}_{\Theta(s)}h^*_2\Theta_{(s,i)}]-h_3[d^{V_f}_{V_f(s)}V_{f(s,i)}+$$
$$+d^{V_f}_{F(s)}F_{(s,i)}+d^{V_f}_{\Theta(s)}\Theta_{(s,i)}]-h_4M[q^{V_f}_{V_f(s)}V_{f(s,i)}-q^{V_f}_{\Theta(s)}\Theta_{(s,i)}]-h_5[g^{V_f}_{V_f(s)}V_{f(s,i)}-g^{V_f}_{C_V(s)}(C_{V(s,i)}+m_{(s,i)})]+\Psi^{V_f}_{(s,i)},$$
$$\frac{\partial W_{f(s,i)}}{\partial t}=D_W\left(\frac{\partial^2 W_{f(s,i)}}{\partial\tilde{r}^2}+\frac{2}{\tilde{r}}\frac{\partial W_{f(s,i)}}{\partial\tilde{r}}\right),$$
$$\frac{\partial M_{V(s,i)}}{\partial t}=h_4M(q^{V_f}_{V_f(s)}V_{f(s,i)}+q^{V_f}_{\Theta(s)}\Theta_{(s,i)})-h_6M_{V(s,i)},$$
$$\frac{\partial H_{E(s,i)}}{\partial t}=h_7\Phi^{H_E}_{(s)}\Theta_{(s,i)}-h_8[a^{H_E}_{H_E(s)}H_{E(s,i)}+a^{H_E}_{M_V(s)}M_{V(s,i)}+a^{H_E}_{\Theta(k)}\Theta_{(s,i)}]-h_9[b^{H_E}_{E(s)}E_{(s,i)}+b^{H_E}_{H_E(s)}H_{E(s,i)}+$$
$$+b^{H_E}_{M_V(s)}M_{V(s,i)}+b^{H_E}_{\Theta(s)}\Theta_{(s,i)}]-h_{10}H_{E(s,i)}+\Psi^{H_E}_{(s,i)},$$
$$\frac{\partial H_{B(s,i)}}{\partial t}=h_{11}\Phi^{H_B}_{(s)}\Theta_{(s,i)}-h_{12}[a^{H_B}_{H_B(s)}H_{B(s,i)}+a^{H_B}_{M_V(s)}M_{V(s,i)}+a^{H_B}_{\Theta(s)}\Theta_{(s,i)}]-h_{13}[b^{H_B}_{B(s)}B_{(s,i)}+b^{H_B}_{H_B(s)}H_{B(s,i)}+$$
$$+b^{H_B}_{M_V(s)}M_{V(s,i)}+b^{H_B}_{\Theta(s)}\Theta_{(s,i)}]-h_{14}H_{B(s,i)}+\Psi^{H_B}_{(s,i)},$$
$$\frac{\partial E_{(s,i)}}{\partial t}=h_{15}\Phi^{E}_{(s)}\Theta_{(s,i)}-h_{16}[a^{E}_{E(s)}E_{(s,i)}+a^{E}_{H_E(s)}H_{E(s,i)}+a^{E}_{M_V(s)}M_{V(s,i)}+a^{E}_{\Theta(s)}\Theta_{(s,i)}]-h_2[b^{V_f}_{E(s)}E_{(s,i)}+$$
$$+b^{V_f}_{C_V(s)}C_{V(s,i)}+b^{V_f}_{\Theta(s)}\Theta_{(s,i)}]-h_{17}E_{(s,i)}+\Psi^{E}_{(s,i)},\qquad(3)$$
$$\frac{\partial B_{(s,i)}}{\partial t}=h_{18}\Phi^{B}_{(s)}\Theta_{(s,i)}-h_{19}[a^{B}_{B(s)}B_{(s,i)}+a^{B}_{H_B(s)}H_{B(s,i)}+a^{B}_{M_V(s)}M_{V(s,i)}+a^{B}_{\Theta(s)}\Theta_{(s,i)}]-h_{20}B_{(s,i)}+\Psi^{B}_{(s,i)},$$
$$\frac{\partial P_{(s,i)}}{\partial t}=h_{21}\Phi^{P}_{(s)}\Theta_{(s,i)}-h_{22}P_{(s,i)}+\Psi^{P}_{(s,i)},$$
$$\frac{\partial F_{(s,i)}}{\partial t}=h_{23}a^{F}_{P(s)}P_{(s,i)}-h_3[d^{V_f}_{V_f(s)}V_{f(s,i)}+d^{V_f}_{F(s)}F_{(s,i)}+d^{V_f}_{\Theta(s)}\Theta_{(s,i)}]-h_{24}F_{(s,i)}+\Psi^{F}_{(s,i)},$$
$$\frac{\partial C_{V(s,i)}}{\partial t}=h_{25}[g^{V_f}_{V_f(s)}V_{f(s,i)}-g^{V_f}_{C_V(s)}(C_{V(s,i)}+m_{(s,i)})]-h_2[b^{V_f}_{E(s)}E_{(s,i)}+b^{V_f}_{C_V(s)}C_{V(s,i)}+b^{V_f}_{\Theta(s)}\Theta_{(s,i)}]-$$
$$-h_{26}C_{V(s,i)}+\Psi^{C_V}_{(s,i)},$$
$$\frac{\partial m_{(s,i)}}{\partial t}=h_2[b^{V_f}_{E(s)}E_{(s,i)}+b^{V_f}_{C_V(s)}C_{V(s,i)}+b^{V_f}_{\Theta(s)}\Theta_{(s,i)}]+h_{26}C_{V(s,i)}-h_{27}m_{(s,i)}+\Psi^{m}_{(s,i)},$$
$$\frac{\partial\Theta_{(s,i)}}{\partial t}=-h_{30}\Theta_{(s,i)}+\Psi^{\Theta}_{(s,i)},$$
$$V_{f(s,i)}((s-1)\tau,x)=0,\ M_{V(s,i)}((s-1)\tau,x)=0,\ H_{E(s,i)}((s-1)\tau,x)=0,\ H_{B(s,i)}((s-1)\tau,x)=0,$$
$$E_{(s,i)}((s-1)\tau,x)=0,\ B_{(s,i)}((s-1)\tau,x)=0,\ P_{(s,i)}((s-1)\tau,x)=0,\ F_{(s,i)}((s-1)\tau,x)=0,$$
$$C_{V(s,i)}((s-1)\tau,x)=0,\ m_{(s,i)}((s-1)\tau,x)=0,\ \Theta_{(s,i)}((s-1)\tau,x)=0,\ W_{f(s,i)}((s-1)\tau,x,r)=0,\qquad(4)$$
$$\frac{\partial W_{f(s)}(t,x,0)}{\partial r}=0,\ W_{f(s,i)}(t,x,R)=\kappa\cdot V_{f(s,i)}(t,x),\ (s-1)\tau\le t\le s\tau,\ s=1,2,...,s_6,$$

where $a^{V_f}_{C_V(s)}=\dfrac{h^0_1(C^{**}_V-2C_{V(s,0)})}{C^{**}_V(1+h^*_1(\Theta_{(s,0)}-\Theta^*))}$; $a^{V_f}_{\Theta(s)}=-\dfrac{h^0_1h^*_1C_{V(s,0)}(C^{**}_V-C_{V(s,0)})}{C^{**}_V(1+h^*_1(\Theta_{(s,0)}-\Theta^*))^2}$; $b^{V_f}_{C_V(s)}=(h^*_2(\Theta_{(s,0)}-\Theta^*)+1)E_{(s,0)}$;

$b^{V_f}_{E(s)}=(1+h^*_2(\Theta_{(s,0)}-\Theta^*))C_{V(s,0)}$; $b^{V_f}_{\Theta(s)}=h^*_2C_{V(s,0)}E_{(s,0)}$; $d^{V_f}_{V_f(s)}=(1+h^*_3(\Theta_{(s,0)}-\Theta^*))F_{(s,0)}$;

$d^{V_f}_{F(s)}=(1+h^*_3(\Theta_{(s,0)}-\Theta^*))V_{f(s,0)}$; $d^{V_f}_{\Theta(s)}=h^*_3V_{f(s,0)}F_{(s,0)}$; $q^{V_f}_{V_f(s)}=(h^*_4(\Theta_{(s,0)}-\Theta^*)+1)$; $q^{V_f}_{\Theta(s)}=h^*_4V_{f(s,0)}$;

$g^{V_f}_{V_f(s)}=(C^*-m_{(s,0)}-C_{V(s,0)})$; $g^{V_f}_{C_V(s)}=V_{f(s,0)}$;

$$\Psi^{V_f}_{(s,i)}=\sum_{r=1}^{i-1}\left[\frac{T_{(s,r)}}{C^{**}_V}\left(C_{V(s,i-r)}(1-C_{V(s,0)})-\sum_{k=1}^{i-r}C_{V(s,k)}C_{V(s,i-r-k)}\right)-\frac{h^*_1C_{V(s,0)}(C^{**}_V-C_{V(s,0)})}{C^{**}_V(h^*_1(\Theta_{(s,0)}-\Theta^*)+1)}\Theta_{(s,i-r)}\times\right.$$
$$\left.\times T_{(s,r)}-\frac{T_{(s,0)}}{C^{**}_V}C_{V(s,r)}C_{V(s,i-r)}\right]+\nu h_2\left[\sum_{r=1}^{i-1}E_{(s,i-r)}\left(C_{V(s,r)}(h^*_2(\Theta_{(s,0)}-\Theta^*)+1)+h^*_2\sum_{k=1}^{r}\Theta_{(s,k)}C_{V(s,r-k)}\right)+h^*_2E_{(s,0)}\times\right.$$

$$\times\sum_{r=1}^{i-1}\Theta_{(s,r)}C_{V(s,i-r)}\Big]-h_3\Big[\sum_{r=1}^{i-1}V_{f(s,i-r)}\Big(F_{(s,r)}(h_3^*(\Theta_{(s,0)}-\Theta^*)+1)+h_3^*\sum_{k=1}^{r}\Theta_{(s,k)}F_{(s,r-k)}\Big)+h_3^*V_{f(s,0)}\sum_{r=1}^{i-1}\Theta_{(s,r)}F_{(s,i-r)}\Big]-$$

$$-h_4Mh_4^*\sum_{r=1}^{i-1}\Theta_{(s,r)}V_{f(s,i-r)}+h_5\sum_{r=1}^{i-1}V_{f(s,i-r)}(m_{(s,r)}+C_{V(s,r)})+D_V\frac{\partial^2V_{f(s,i-1)}}{\partial x^2}-D_W^*\left(\frac{\partial W_{f(s,i-1)}}{\partial r}\right)\Big|_{r=R},\quad T_{(s,i)}=$$

$$=-\frac{h_1^*\sum_{r=0}^{i-1}\Theta_{(s,i-r)}T_{(s,r)}}{h_1^*(\Theta_{(s,0)}-\Theta^*)+1},\ i=2,3,...;\quad T_{(s,0)}=\frac{h_1^0}{h_1^*(\Theta_{(s,0)}-\Theta^*)+1};\quad \Psi_{(s,1)}^{V_f}=D_V\frac{\partial^2V_{f(s,0)}}{\partial x^2}-D_W^*\left(\frac{\partial W_{f(s,0)}}{\partial r}\right)\Big|_{r=R};\ V_{f(s,0)},$$

$W_{f(s,0)}$, $M_{V(s,0)}$, $H_{B(s,0)}$, $H_{E(s,0)}$, $B_{(s,0)}$, $E_{(s,0)}$, $F_{(s,0)}$, $P_{(s,0)}$, $m_{(s,0)}$, $C_{V(s,0)}$, $\Theta_{(s,0)}$ are the known solutions of the corresponding degenerate problems. Other coefficients and involved functions in (3) are also known and expressed similarly through the previously found asymptotics. We apply numerical methods (for example, Runge-Kut methods) to find the solution of the corresponding degenerate problem for each interval $(s-1)\tau\le t\le s\tau$, $s=1,2,...$ and problems for finding corrections using already found values of the solutions to such problems at the previous stages. We establish the spatiotemporal intervals of convergence in predicting the dynamics of real viral diseases in a similar way [7-9,12].

4. Numerical experiment

As noted above, the introduction of adsorption agents can reduce the number of antigens in the organism as a result the severity of the viral infection will also decrease. Therefore, the assessment of the effect of certain drugs on the disease dynamics is an important task in developing a comprehensive treatment program using additional adsorption therapy. In general, we have focused the computer experiments on studying the features of the influence of adsorption agents on the predictive dynamics of the antiviral immune response.

Figure 1 illustrates the model dynamics of viral infection antigens in the infection locus in various situational conditions: without taking into account the diffusion scattering and the absence of adsorption therapy (curve 1); taking into account the effect of diffusion scattering and the absence of adsorption antigens (curve 2); taking into account diffusion scattering and the effect of adsorption therapy (curve 3). Here, the number of antigens at the initial moment was equal to zero ($V_f^0(x)=0$), but at the moment $t_V=1$ at the point $x_V=0$ there is a concentrated increase in the model number of antigens: $\omega_V=A_Ve^{-\alpha_V(t-t_V)^2}e^{-\beta_V(x-x_V)^2}$. As expected, the lowest level of predicted growth of antigens is observed in a situation when we consider the effects of diffusion scattering and absorption of antigens by adsorbent. Thus, the presented results confirm the practicability of the adsorption drugs for additional neutralization of antigens, which makes it possible to reduce, in particular, the critical level of disease exacerbation. In addition, it should be noted that the timely introduction of adsorption drugs into the body can more effectively control the growth of the antigen population. Figure 2 shows the predicted

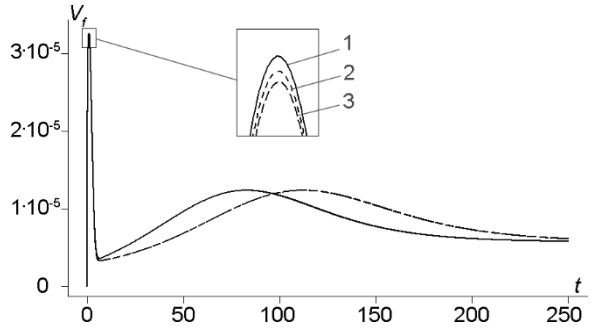

Fig. 1. Dynamics of antigens at: $\mu D_V=0.00$ and $\mu D_W^*=0.00$ (curve 1); $\mu D_V=0.05$ and $\mu D_W^*=0.00$ (curve 2); $\mu D_V=0.05$ and $\mu D_W^*=0.05$ (curve 3).

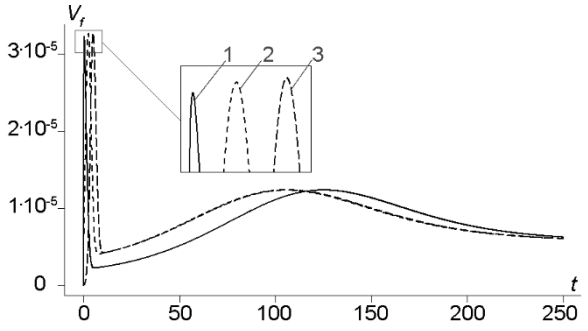

Fig. 2. Dynamics of antigens at: $t_V=0.0$ (curve 1); $t_V=2.5$ (curve 2); $t_V=5.0$ (curve 3).

dynamics of antigen concentration in cases if there is an increase in their number at different times: $t_V = 0.0$ (curve 1); $t_V = 2.5$ (curve 2); $t_V = 5.0$ (curve 3). According to the numerical experiments, the largest increase in the predicted number of antigens was obtained in the case when the interval between the introduction of the adsorption drug and the concentrated increase in the number of antigens was the largest. It means a decrease in the effectiveness of the corresponding therapy. Let us also note that the results presented concern cases of one-time introduction of adsorbents into the organism at the initial point in time. However, similar results will be expected even with repeated introduction of adsorption drugs.

5. Conclusions

Based on the synthesis of approaches to modeling adsorption in the medium of porous particles and the ideas of perturbation theory, the basic model of the immune response to viral pathogens is generalized, that considers the effect of adsorption therapy in conditions of diffusion perturbations. We have formed a step-by-step computational technology for asymptotically approximating the solution as a perturbation of corresponding solutions to the degenerate problems by reducing the original model singularly perturbed problem with delay to a sequence of problems without delay.

The results of computer modeling illustrate the effect of an additional reduction in the predicted number of antigens as a result of their removal and neutralization by adsorbents. It has been shown that the use of adsorption drugs, in particular during periods of disease exacerbation, provides an additional reduction in the supercritical amount of antigens and accordingly alleviates the disease course. At the same time, it is emphasized that an important condition for increasing the effectiveness of adsorption substances is the timeliness of their introduction into the organism. Taking into account features of adsorption influence is important for decision-making systems for the formation of complex treatment programs using adsorption drugs to increase the effectiveness of traditional therapeutic agents.

In our opinion, it is promising to adapt and expand the limits of application of the presented our approach to consider the conditions of competitive adsorption and diffusion, convection mass transfer, mixed infections and biostimulation. It is also promising to take into account random factors [13,14] and more complex function dependencies, which take into account the decrease in the immune system efficiency with a significant number of target organ cells affected by the virus, and conditions of quasi-periodic introduction of adsorption drugs.

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