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Modeling the Influence of Small-Scale Diffusion Perturbations on the Development of Infectious Diseases under Immunotherapy

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***Abstract*—The article proposes a modification to the mathematical model of the immunotherapy influence on the immune response dynamics considering small-scale diffusion perturbations. The corresponding singularly perturbed model problem with time-delay solution is reduced to a sequence of solutions without time-delay. Sought functions are represented in the form of asymptotic series as perturbations of solutions to the corresponding degenerate problems. We present the results of numerical modeling that illustrate the influence of diffusion redistribution of active factors on the infectious disease dynamics under immunotherapy. The results demonstrate the decrease in the maximum concentration level of antigens in the locus of infection as a result of their diffusion redistribution.**

Keywords—infectious disease model; dynamic systems; asymptotic methods; singularly perturbed problems

I. Introduction

The known simplest model of infectious disease of G.I. Marchuk [2] has been modified in [1] to take into account the impact of immunotherapy. In particular, it proposes to describe the dynamics of native and donor antibodies in the organism separately and to introduce an additional function of the donor antibodies concentration $K(t)$. The modified model of the immunotherapy effect on the dynamics of immune response in infectious disease is presented in [1] by the following differential equations system (with a time-delay):

$$\begin{aligned} V_t' &= \beta V - \gamma FV - \gamma_1 KV, \\ C_t' &= \xi(m)\alpha\left(F(t-\tau)+K(t-\tau)\right)V(t-\tau) - \mu_C\left(C-C^*\right), \\ F_t' &= \rho C - \eta\gamma FV - \mu_f F, \\ K_t' &= u(t) - \eta_1\gamma_1 KV - \mu_k K, \\ m_t' &= \sigma V - \mu_m m, \end{aligned} \tag{1}$$

under conditions (for $-\tau \le \tilde{t} \le 0$)

$$\begin{aligned} C(\tilde{t}) = C^*,\ m(\tilde{t}) = 0,\ V(\tilde{t}) = V_0\theta(\tilde{t}), \\ F(\tilde{t}) = \rho C^* / \mu_f = F^*,\ K(\tilde{t}) = 0, \end{aligned} \tag{2}$$

where $V(t)$ is the antigens concentration, particles/mL; $C(t)$ is the plasma cells concentration that are carriers and producers of their native specific antibodies, cells/ mL; $F(t)$ is the native specific antibodies concentration that neutralize the corresponding antigens, particles/mL; $m(t)$ is relative characteristics of the lesion of the target organ; $\theta(t)$ is the Heaviside function; β is the rate of reproduction of antigens, day^{-1}; γ, γ_1 are coefficients that take into account the interaction result of antigens with native and donor specific antibodies, respectively, mL/(particles ·day); τ is the period of time (delay) required to form a cascade of plasma cells, days; μ_c is the inverse value of the plasma cells lifespan, day^{-1}; α is the coefficient of immune system stimulation, cell·mL/(particles·molecule·day); C^* is the level of plasma cells in a healthy organism, cells/mL; ρ is the production speed of native specific antibodies by one plasma cell, molecule/(cell·day); μ_f, μ_k are the inverse values of the existence duration of their native and donor specific antibodies, respectively, day^{-1}; η, η_1 are the consumption of native and donor specific antibodies to neutralize one antigen, respectively, molecule/particles; σ is the damage rate of cells of the target organ, mL/(particles·day); μ_m is the recovery rate of target organ, day^{-1}. The function $\xi(m)$ takes into account the effect of decreased antibody production while the target organ is significantly damaged. On the interval $0 \le m \le m^*$ the value of $\xi(m)$ equals one, i.e., the immunological organs fully function, regardless of the disease severity. Under $m^* \le m < 1$, the efficiency of the organism is rapidly declining. The function $u(t)$ describes the rate of the introduction of donor antibodies into the organism and satisfies restrictions $0 \le u(t) \le B$, $0 \le t \le T$ [1].

The use of immunotherapy is effective in the treatment of acute forms of infectious disease. In the absence of antigens ($V = 0$), the introduction of donor bodies, of course, is not carried out, i.e. $u(t)=0$ and $K(t)=0$. The values V, C, F, m of the stationary solution to the system (1) that corresponds to the state of a healthy organism are the same as in the stationary solution to the basic model of infectious disease. Reference [2] shows that the condition $\beta<\gamma\rho C^*/\mu_f$ is asymptotically stable during the infection with a dose of antigens V^0 that does not exceed a certain level of the immunological barrier V^*

$$V^0<V^*=\left(\gamma\rho C^*-\beta\mu_f\right)/(\beta\eta\gamma). \tag{3}$$

Let us note that the construction of various mathematical models of immune response dynamics with different levels of detail is based on general principles that relate to the mechanisms of interaction of the immune system with pathogens [3-5]. As in the simplest model of an infectious disease and in its modification described above, we assume that the environment of the "organism" is homogeneous, and all its process components are immediately mixed.

According to generally accepted notions of immune defense today, the immune response triggering does not occur immediately after antigens enter the organism, but begins after the recognition of a foreign antigen by binding to a specific receptor on the membrane of a mature lymphocyte. After stimulating the immune system, a cascade population of plasma cells is formed over a period of time, which synthesize the appropriate type of antibody that is able to bind the recognized antigens. Although the above mechanism of the immune response is quite simplified, it allows for antigens that are not immediately neutralized by the immune system, spread by the organism, infect cells and reproduce. As a result, certain foci of infection with a higher concentration of antigens are formed in the organism. It is natural to assume that the generated antigens in the organism are redistributed over time from the infection foci to the surrounding uninfected areas, then the infected area is increasing and the concentration of antigens at the epicenter of infection is decreasing.

The aim of this work is taking into account small-scale diffusion perturbations in the research.

II. Problem Statement

We modify the immune response dynamic model in the conditions of immunotherapy (1) - (2) by introducing additional terms that describe small-scale diffusion effects ("redistributions"). The corresponding spatio-temporal dynamics of the model components of the infectious disease process in the set $G_Z=\{(x,t):\ -\infty<x<+\infty;\ 0<t<+\infty\}$ is described by the following system of differential equations with time-delay:

$$\begin{aligned}
&V_t'(x,t)=(\beta-\gamma F(x,t)-\gamma_1 K(x,t))V(x,t)+\varepsilon D_V V_{xx}''(x,t),\\
&C_t'(x,t)=\xi(m)\alpha\left(F(x,t-\tau)+K(x,t-\tau)\right)V(x,t-\tau)-\\
&\qquad -\mu_C\left(C(x,t)-C^*\right)+\varepsilon^2 D_C C_{xx}''(x,t),\\
&F_t'(x,t)=\rho C(x,t)-\left(\mu_f+\eta\gamma V(x,t)\right)F(x,t)+\varepsilon D_F F_{xx}''(x,t),\\
&K_t'(x,t)=u(x,t)-(\mu_k+\eta_1\gamma_1 V(x,t))K(x,t)+\varepsilon D_K K_{xx}''(x,t),\\
&m_t'(x,t)=\sigma V(x,t)-\mu_m m(x,t)+\varepsilon^2 D_m m_{xx}''(x,t),
\end{aligned} \tag{4}$$

for conditions

$$\begin{aligned}
&C(x,0)=C^0(x),\ m(x,0)=m^0(x),\ K(x,\tilde t)=K^0(x,\tilde t),\\
&V(x,\tilde t)=V^0(x,\tilde t),\ F(x,\tilde t)=F^0(x,\tilde t),\ -\tau\le\tilde t\le 0,
\end{aligned} \tag{5}$$

where $V(x,t)$, $C(x,t)$, $F(x,t)$, $K(x,t)$, $m(x,t)$ are concentrations of antigens, plasma cells, native and donor antibodies and the value of the relative characteristics of the lesion of the target organ at point x at time t, respectively, εD_V, εD_F, εD_K, $\varepsilon^2 D_C$, $\varepsilon^2 D_m$ are coefficients of spatial diffusion redistribution of antigens, native and donor antibodies, plasma and affected cells, respectively, ε is a small parameter that characterizes the small-scale influence of the respective components in comparison with other (dominant) components of the process.

For beginning we consider the case when the immune system mechanism is fully complete and does not depend on the disease severity ($\xi(m)=1$). Using the steps method [6], we reduce the solution of the problem (4) - (5) with a time-delay to a sequence of solutions of problems without time-delay (we assume that the system (4) is dimensionless):

$$\begin{cases}
V_{0\,t}'=(\beta-\gamma F_0-\gamma_1 K_0)V_0+\varepsilon D_V V_{0\,xx}'',\\
C_{0\,t}'=\alpha\left(F^0(x,t-\tau)+K^0(x,t-\tau)\right)V^0(x,t-\tau)-\mu_C\left(C_0-C^*\right)+\\
+\varepsilon^2 D_C C_{0\,xx}'',\\
F_{0\,t}'=\rho C_0-\left(\mu_f+\eta\gamma V_0\right)F_{0\,xx}''+\varepsilon D_F F_{0\,xx}'',\\
K_{0\,t}'=u-(\mu_k+\eta_1\gamma_1 V_0)K_0+\varepsilon D_K K_{0\,xx}'',\\
m_{0\,t}'=\sigma V_0-\mu_m m_0+\varepsilon^2 D_m m_{0\,xx}'',\\
C_0(x,0)=C^0(x),\ m_0(x,0)=m^0(x),K_0(x,0)=K^0(x,0),\\
V_0(x,0)=V^0(x,0),\ F_0(x,0)=F^0(x,0),\ 0\le t\le\tau;
\end{cases} \tag{6}$$

$$\begin{cases}
V_{n\,t}'=(\beta-\gamma F_n-\gamma_1 K_n)V_n+\varepsilon D_V V_{n\,xx}'',\\
C_{n\,t}'=\alpha\left(F_{n-1}(x,t-\tau)+K_{n-1}(x,t-\tau)\right)V_{n-1}(x,t-\tau)-\mu_C\left(C_n-\right.\\
\left.-C^*\right)+\varepsilon^2 D_C C_{n\,xx}'',\\
F_{n\,t}'=\rho C_n-\left(\mu_f+\eta\gamma V_n\right)F_n+\varepsilon D_F F_{n\,xx}'',\\
K_{n\,t}'=u-(\mu_k+\eta_1\gamma_1 V_n)K_n+\varepsilon D_K K_{n\,xx}'',\\
m_{n\,t}'=\sigma V_n-\mu_m m_n+\varepsilon^2 D_m m_{n\,xx}'',\\
C_n(x,n\tau)=C_{n-1}(x,n\tau),\ m_n(x,n\tau)=m_{n-1}(x,n\tau),\\
K_n(x,n\tau)=K_{n-1}(x,n\tau),\ V_n(x,n\tau)=V_{n-1}(x,n\tau),\\
F_n(x,n\tau)=F_{n-1}(x,n\tau),\ n\tau\le t\le(n+1)\tau,\ n=1,2,....
\end{cases} \tag{7}$$

Let us note that the required order of smoothness of the corresponding solutions for $t=\tau$, $t=2\tau$, …, $t=n\tau$, … is provided by consistency conditions for $t=-\tau$, $t=0$, … [7], besides the usual conditions of smoothness with respect to functions (5) of the initial conditions of the model. In particular, the following condition must be satisfied

$$C_{0\,t}'(x,0)=\alpha\left(F^0(x,-\tau)+K^0(x,-\tau)\right)V^0(x,-\tau)-$$
$$-\mu_C\left(C_0(x,0)-C^*\right)+\varepsilon^2 D_C C_{0\,xx}''(x,0).$$

Taking into account that we consider small-scale diffusion redistributions of the active components of immune response in comparison with other components, we use the asymptotic method to solve the corresponding singularly perturbed model problems (6) - (7) [7,8]. In particular, the solutions of problems (6) - (7) are presented in the form of asymptotic series $V_j(x,t)=$ $=\sum_{i=o}^{N}\varepsilon^i V_{ij}(x,t)+R_{Nj}^V(x,t,\varepsilon)$, $C_j(x,t)=\sum_{i=o}^{N}\varepsilon^i C_{ij}(x,t)+R_{Nj}^C(x,t,\varepsilon)$, $F_j(x,t)=\sum_{i=o}^{N}\varepsilon^i F_{ij}(x,t)+R_{Nj}^F(x,t,\varepsilon)$, $K_j(x,t)=\sum_{i=o}^{N}\varepsilon^i K_{ij}(x,t)+$ $+R_{Nj}^K(x,t,\varepsilon)$, $m_j(x,t)=\sum_{i=o}^{N}\varepsilon^i m_{ij}(x,t)+R_{Nj}^m(x,t,\varepsilon)$ as perturbation of the solutions of the corresponding degenerate problems [9], where $j=0,1,...,n,...$, $V_{ij}(x,t)$, $C_{ij}(x,t)$, $F_{ij}(x,t)$, $K_{ij}(x,t)$, $m_{ij}(x,t)$ are sought functions (members of asymptotes), $R_{Nj}^V(x,t,\varepsilon)$, $R_{Nj}^C(x,t,\varepsilon)$, $R_{Nj}^F(x,t,\varepsilon)$, $R_{Nj}^K(x,t,\varepsilon)$, $R_{Nj}^m(x,t,\varepsilon)$ are the corresponding remainders. Performing the standard procedure of equating the coefficients with the same power of ε, we obtain such following problems of finding functions $V_{ij}(x,t)$, $C_{ij}(x,t)$, $F_{ij}(x,t)$, $K_{ij}(x,t)$, $m_{ij}(x,t)$ $(i=0,1,...,N$, $j=0,1,...,n,...)$:

$$\begin{cases}
V_{0,0\,t}'=(\beta-\gamma F_{0,0}-\gamma_1 K_{0,0})V_{0,0},\\
C_{0,0\,t}'=\alpha\left(F^0(x,t-\tau)+K^0(x,t-\tau)\right)V^0(x,t-\tau)-\mu_C\left(C_{0,0}-\right.\\
\left.-C^*\right),\\
F_{0,0\,t}'=\rho C_{0,0}-\left(\mu_f+\eta\gamma V_{0,0}\right)F_{0,0},\\
K_{0,0\,t}'=u-\left(\mu_k+\eta_1\gamma_1 V_{0,0}\right)F_{0,0},\\
m_{0,0\,t}'=\sigma V_{0,0}-\mu_m m_{0,0},\\
C_{0,0}(x,0)=C^0(x),\ m_{0,0}(x,0)=m^0(x),\\
K_{0,0}(x,0)=K^0(x,0),\ V_{0,0}(x,0)=V^0(x,0),\\
F_{0,0}(x,0)=F^0(x,0),\ 0\le t\le\tau,
\end{cases} \tag{8}$$

. . . . . .

$$\begin{cases}
V_{i,0\,t}'=\beta V_{i,0}-\gamma\left(a_{0,0}F_{i,0}+b_{0,0}V_{i,0}\right)-\gamma_1\left(a_{0,0}K_{i,0}+c_{0,0}V_{i,0}\right)+\\
+\Phi_{V\,i,0},\\
C_{i,0\,t}'=\alpha\left(a_{0,0}(x,t-\tau)\left(F_{i,0}(x,t-\tau)+K_{i,0}(x,t-\tau)\right)+\right.\\
\left.+\left(b_{0,0}(x,t-\tau)+c_{0,0}(x,t-\tau)\right)\right)V_{i,0}(x,t-\tau)-\mu_C C_{i,0}+\Phi_{C\,i,0},\\
F_{i,0\,t}'=\rho C_{i,0}-\mu_f F_{i,0}-\eta\gamma\left(a_{0,0}F_{i,0}+b_{0,0}V_{i,0}\right)+\Phi_{F\,i,0},\\
K_{i,0\,t}'=\mu_k K_{i,0}-\eta_1\gamma_1\left(a_{0,0}K_{i,0}+c_{0,0}V_{i,0}\right)+\Phi_{K\,i,0},\\
m_{i,0\,t}'=\sigma V_{i,0}-\mu_m m_{i,0}+\Phi_{m\,i,0},\\
C_{i,0}(x,0)=0,\ m_{i,0}(x,0)=0,\ K_{i,0}(x,0)=0,\ V_{i,0}(x,0)=0,\\
F_{i,0}(x,0)=0,\ 0\le t\le\tau,
\end{cases} \tag{9}$$

$$\begin{cases}
V_{0,n\,t}'=(\beta-\gamma F_{0,n}-\gamma_1 K_{0,n})V_{0,n},\\
C_{0,n\,t}'=\alpha\left(F_{0,n-1}(x,t-\tau)+K_{0,n-1}(x,t-\tau)\right)V_{0,n-1}(x,t-\tau)-\\
-\mu_C\left(C_{0,n}-C^*\right),\\
F_{0,n\,t}'=\rho C_{0,n}-\left(\mu_f+\eta\gamma V_{0,n}\right)F_{0,n},\\
K_{0,n\,t}'=u-\left(\mu_k+\eta_1\gamma_1 V_{0,n}\right)F_{0,n},\\
m_{0,n\,t}'=\sigma V_{0,n}-\mu_m m_{0,n},\\
C_{0,n}(x,n\tau)=C_{0,n-1}(x,n\tau),\ m_{0,n}(x,n\tau)=m_{0,n-1}(x,n\tau),\\
K_{0,n}(x,n\tau)=K_{0,n-1}(x,n\tau),\ V_{0,n}(x,n\tau)=V_{0,n-1}(x,n\tau),\\
F_{0,n}(x,n\tau)=F_{0,n-1}(x,n\tau),\ n\tau\le t\le(n+1)\tau,
\end{cases} \tag{10}$$

. . . . . .

$$\begin{cases}
V_{i,n\,t}'=\beta V_{i,n}-\gamma\left(a_{0,n}F_{i,n}+b_{0,n}V_{i,n}\right)-\gamma_1\left(a_{0,n}K_{i,n}+c_{0,n}V_{i,n}\right)+\\
+\Phi_{V\,i,n},\\
C_{i,n\,t}'=\alpha\left(a_{0,n}(x,t-\tau)\left(F_{i,n-1}(x,t-\tau)+K_{i,n-1}(x,t-\tau)\right)+\right.\\
\left.+\left(b_{0,n}(x,t-\tau)+c_{0,n}(x,t-\tau)\right)\right)V_{i,n-1}(x,t-\tau)-\mu_C C_{i,n}+\Phi_{C\,i,n},\\
F_{i,n\,t}'=\rho C_{i,n}-\mu_f F_{i,n}-\eta\gamma\left(a_{0,n}F_{i,n}+b_{0,n}V_{i,n}\right)+\Phi_{F\,i,n},\\
K_{i,n\,t}'=\mu_k K_{i,n}-\eta_1\gamma_1\left(a_{0,n}K_{i,n}+c_{0,n}V_{i,n}\right)+\Phi_{K\,i,n},\\
m_{i,n\,t}'=\sigma V_{i,n}-\mu_m m_{i,n}+\Phi_{m\,i,n},\\
C_{i,n}(x,n\tau)=C_{i,n-1}(x,n\tau),\ m_{i,n}(x,n\tau)=m_{i,n-1}(x,n\tau),\\
K_{i,n}(x,n\tau)=K_{i,n-1}(x,n\tau),\ V_{i,n}(x,n\tau)=V_{i,n-1}(x,n\tau),\\
F_{i,n}(x,n\tau)=F_{i,n-1}(x,n\tau),\ n\tau\le t\le(n+1)\tau,
\end{cases} \tag{11}$$

where

$a_{0,j}(x,t)=V_{0,j}(x,t)$, $b_{0,j}(x,t)=F_{0,j}(x,t)$, $c_{0,j}(x,t)=K_{0,j}(x,t)$;

$\Phi_{V1,j}(x,t)=D_V V_{0,j\,xx}''(x,t)$, $\Phi_{F1,j}(x,t)=D_F F_{0,j\,xx}''(x,t)$,

$\Phi_{K1,j}(x,t)=D_K K_{0,j\,xx}''(x,t)$;

$\Phi_{Vi,j}(x,t)=-\gamma\sum_{k=1}^{i-1}V_{k,j}(x,t)F_{i-k,j}(x,t)+D_V V_{i-1,j\,xx}''(x,t)$,

$\Phi_{Ci,j}(x,t)=\sum_{k=1}^{i-1}\alpha V_{k,j}(x,t-\tau)\left(F_{i-k,j}(x,t-\tau)+K_{i-k,j}(x,t-\tau)\right)+$

$+D_C C_{i-2,j\,xx}''(x,t)$,

$\Phi_{Fi,j}(x,t)=-\sum_{k=1}^{i-1}\eta\gamma V_{k,j}(x,t)F_{i-k,j}(x,t)+D_F F_{i-1,j\,xx}''(x,t)$,

$\Phi_{Ki,j}(x,t)=-\sum_{k=1}^{i-1}\eta_1\gamma_1 V_{k,j}(x,t)K_{i-k,j}(x,t)+D_K K_{i-1,j\,xx}''(x,t)$,

$\Phi_{mi,j}(x,t)=D_m m_{i-2,j\,xx}''(x,t)$, $i=2,3,...,N$, $j=0,1,...,n,...$.

Let us note that the proposed approach can be easily "transferred" to other sets G_Z, including finite ones. In this case you need to use more complex series instead of the ones used here (see, for example, [7,8,9]).

Estimating the remainders R_{Nj}^V, R_{Nj}^C, R_{Nj}^F, R_{Nj}^W, R_{Nj}^m and establishing spatio-temporal intervals of convergence in the prediction of real processes is done using the maximum principle similarly to [7,8,9].

III. Numerical Experiments Results

Figure 1 shows the predicted dynamics of the antigen concentration in the case of infectious disease in the acute form in the locus of infection according to the model (4) - (5) with uneven initial distribution of antigens in the infected zone and different values of model intensity (parameter ε) of diffusion "redistribution". As in the previous case, we assume that the donor antibodies enter the organism at a constant rate ($u(x,t)=const$) and are evenly distributed.

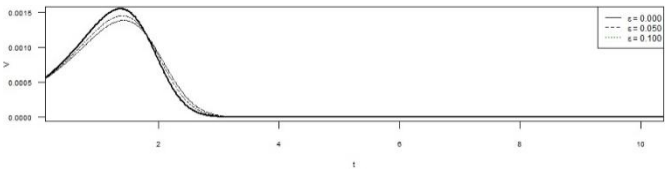

Figure 1. Dynamics of antigen concentration in the infection locus according to model (4) - (5) in the conditions of acute form of infectious disease at different intensity of diffusion effect

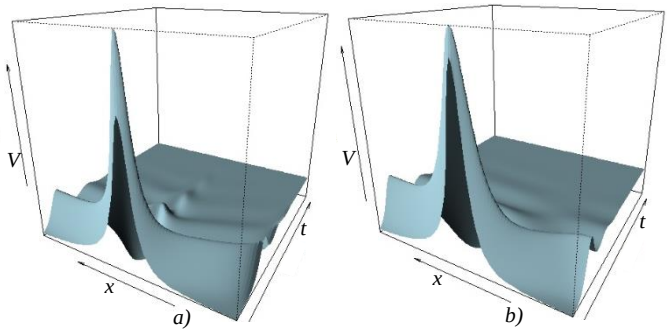

Figure 2. Spatio-temporal dynamics of antigen concentration on condition that $V^0(x,0)=\delta/(1+(x-\lambda)^2)$, $u(x,t)=const$ under *a*) $\varepsilon=0$; *b*) $\varepsilon=0.075$

These results show decrease of the maximum antigens concentration in the infection locus with increasing the diffusion "redistribution" intensity. Note that the dynamics of other active factors of the disease changes accordingly. Thus, considering the diffusion redistribution of active factors in the model predicts a less "acute" course of infectious disease, which is achieved by increasing the intensity of the introduction of donor antibodies in the traditional approach.

Figure 2 presents model spatio-temporal changes in antigen concentrations $V(x,t)$ with the development of infectious disease in the chronic form in cases when the small-scale diffusion effects is absent (Fig. 2, a)) and present (Fig. 2, b)). In both cases, it is assumed that we have the uneven initial distribution of antigen concentration $V(x,0)=V^0(x)$ (a separate source of infection is available), and the introduction of donor antibodies $u(x,t)$ is evenly distributed with a constant intensity. These results illustrate the simulated decrease of general "severity" in the course of disease, as well as the value of the maximum concentration of antigens in the locus of infection due to their diffusion redistribution.

IV. Conclusions

We present the approach for taking into account the influence of small-scale diffusion perturbations on the development of the infectious disease, based on the modification of the mathematical model of the immunotherapy influence on the immune response dynamics. The model problem with time-delay solution is reduced to a sequence of solutions of problems without time-delay that are presented in the form of asymptotic series as perturbations of the solutions of the corresponding degenerate problems.

In this paper, the presented results of numerical modelling illustrate the decrease in the value of the maximum antigen concentration in the locus of infection due to their diffusion "redistribution". We showed that the diffusion "redistribution" effect over time provides a decrease below the critical level of antigens concentration in the locus of infection. Therefore, their further neutralization will require fewer donor antibodies to be introduced into the organism. Thus, under this model, the "severity" of the infectious disease will decrease and the effectiveness of immunotherapy will increase. In this case, the sequence of solutions of the corresponding singularly perturbed problems (that determine a step-by-step (for delay τ) spatio-temporal prediction of the distribution of antigens, antibodies, plasma cells and measure of contagion) will lead to some stable (in particular, asymptotically stable) non-critical, less threatening stationary state.

It is a promising approach to take into account this kind of spatially distributed diffusion effects in the research of the process in terms of infectious disease immunotherapy based on more detailed models, in particular, models by Marchuk-Petrov [5].

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