Modification of Infection Disease Model to Take into account Diffusion Perturbation in the Conditions of Temperature Reaction of the Organism

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Abstract

The mathematical model of the infectious disease modified to take into account the impect of diffuse perturbations on the infectious disease dynamics under conditions of a temperature reaction of the body. The solution of a singularly perturbed model problem with a delay is reduced to a sequence of solutions of problems without delay, for which the sought functions are obtained in the asymptotic expansions form as perturbations of solutions of the corresponding degenerate problems. Using computer simulations, we present results that show influences of diffusion "redistributions" on infection disease dynamics in the conditions of temperature reaction of organism. They illustrate that decrease of model antigen concentrations in the infection locus to a non-critical level caused by diffusion "redistribution" for a relatively short period may contribute to their further neutralization by presence antibodies in the organism or require injection with a lower concentration of donor antibodies.

Keywords 1

Infectious disease model, dynamic systems, dynamic systems with delay, singularly perturbed problems.

1. Introduction

Today, there are many mathematical models of different detail levels that are based on the clonal selection theory of F. Burnett (see [1,2,3]) and that are proposed for study and prediction of the interaction process between the immune system and pathogens. In particular, the most general patterns of the humoral immune response are studied here and they are based on the so-called simplest model of infectious disease, which is represented by a system of four nonlinear differential equations with time-delay. To take into account the cell type immunity more advanced mathematical models of antiviral and antibacterial immune response are proposed in [1,2]. Such kind of basic models adequacy is sufficiently substantiated in [1,2,5-9].

In [4] it is indicated that the simplest infectious disease model and the antiviral model, antibacterial immune response model and other immunological models [5-9] do not provide for taking into account the spatially distributed influences caused by uneven distribution of active factors in the body. Also, the simplest model of an infectious disease have been modified [10] to take into account diffusion perturbations in pharmacotherapy and immunotherapy, and in [11,12] the model was generalized to take into account various kinds of point-pulse, in particular, external therapeutic influences.

Apart from the humoral and cellular type of immunity, the mechanism of temperature rise is a more important element in the organism defense system. It starts causing by pathogenic microorganisms in the organism. In [1,2] it is known that an increase in body temperature leads to a

IDDM-2021: 4th International Conference on Informatics & Data-Driven Medicine, November 19-21, 2021, Valencia, Spain
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decrease in the reproduction intensity of pathogenic microorganisms and reduce their ability to penetrate into cells, and to increase the activity of enzymes that stimulate immunological reactivity. In particular, studies of the biochemical mechanisms of temperature effect on the immune response dynamics are presented in [13, 14, 15]. It should be noted that the kind of problems which consider the dynamics disturbance of the main factors by thermal phenomena, have not been solved previously.

The object of this work is the modification of the simplest infectious disease model to take into account diffusion perturbations in case of the temperature reaction of the organism.

2. Modification of infection disease model to take into account diffusion perturbation in the conditions of temperature reaction of the organism

Let us describe the corresponding spatio-temporal dynamics of infectious disease process taking into account diffusion perturbation in the conditions of temperature reaction of the organism in the set $G=\{(x,t): x\in R, t\in R_+\}$ as the singularly disturbed system of nonlinear differential equations with time-delay τ:

$$\begin{aligned}
&\frac{\partial u_1}{\partial t}=w_1+(\beta(u_5)-\gamma u_3)u_1+\varepsilon D_1\frac{\partial^2 u_1}{\partial x^2},\\
&\frac{\partial u_2}{\partial t}=\xi(u_4)\alpha(u_5)u_3(t-\tau)u_1(t-\tau)-\mu_C(u_2-u_2^*)+\varepsilon^2 D_2\frac{\partial^2 u_2}{\partial x^2},\\
&\frac{\partial u_3}{\partial t}=w_2+\rho u_2-(\mu_f+\eta\gamma u_1)u_3+\varepsilon D_3\frac{\partial^2 u_3}{\partial x^2},\\
&\frac{\partial u_4}{\partial t}=\sigma u_1-\mu_m u_4+\varepsilon^2 D_4\frac{\partial^2 u_4}{\partial x^2},\\
&\frac{\partial u_5}{\partial t}=\alpha_T u_1 u_3-\mu_T(u_5-u_5^*)+\varepsilon D_5\frac{\partial^2 u_5}{\partial x^2}
\end{aligned} \tag{1}$$

for conditions

$$u_2|_{t=0}=u_2^0(x), u_4|_{t=0}=u_4^0(x), u_5|_{t=0}=u_5^0(x), u_1|_{t=\tilde{t}}=u_1^0(x,\tilde{t}), u_3|_{t=\tilde{t}}=u_3^0(x,\tilde{t}), -\tau\le\tilde{t}\le 0, \tag{2}$$

where $u_1(x,t)$, $u_2(x,t)$, $u_3(x,t)$, $u_4(x,t)$, $u_5(x,t)$ are the antigens, plasma cells, antibodies concentrations, the relative characteristic of target organ damage, the temperature in point x in time t respectively, $\beta(u_5)=\beta_0/(1+\beta_1(u_5-u_5^*))$ is the reproduction rate of antigens, which decreases if the organism temperature increases, $\beta_1=const>0$; γ - the coefficient which is connected with antigens neutralization probability at their antibodies interaction; μ_c is the value inverse to the plasma cells lifespan; $\alpha(u_5)=\alpha_0(1+\alpha_1(u_5-u_5^*))$ is the coefficient of immune system stimulation, $\alpha_1=const>0$; u_2^* is the level of plasma cells in a healthy organism; ρ is the antibody production rate by a single plasma cell; μ_f is the values inverse to antibodies lifespan; η is the antibodies amount required to neutralize one antigen; σ is the cells damage rate of the target organ; μ_m is the affected organ recovery rate; $u_5^*(x)$ is temperature distribution in a healthy organism;

$$\alpha_T=\begin{cases}0, & u_1u_3<(u_1u_3)^*,\\ \alpha_T^*, & u_1u_3\ge(u_1u_3)^*;\end{cases}$$

$(u_1u_3)^*$ is the threshold value of u_1u_3-complexes when temperature increase is not stimulated yet, $\alpha_T^*=const>0$; εD_1, εD_3, $\varepsilon^2 D_2$, $\varepsilon^2 D_4$, εD_5 is the spatial diffusion scattering coefficients of antigens, antibodies, plasma and damaged cells, thermal conductivity respectively, ε is a small parameter that characterizes respective components small impact compared to other components of the process; $u_2^0(x)$, $u_4^0(x)$, $u_1^0(x,\tilde{t})$, $u_3^0(x,\tilde{t})$, $u_5^0(x)$ are limited enough smooth functions. The function

$$\xi(u_4)=\begin{cases}1, & 0\le u_4\le u_4^*,\\ \xi^*(u_4), & u_4^*<u_4\le 1\end{cases}$$

allow us to take account effect of decreasing of the immune organ efficiency in a significant damage, where u_4^* is the maximum value of contagion measure of the immune organ in which the normal functionality of the immune system is provided, $\xi^*(u_4)$ is the monotonically non-decreasing continuously differentiable on the interval $(u_4^*;1)$ function and $\xi^*(u_4^*)=1$, $\xi^*(1)=0$ (for example, $\xi(u_4)=(1-u_4)/(1-u_4^*)$). Functions $w_1(x,t)$, $w_2(x,t)$ allow us to describe, in particular, the concentrated changes in antigen and antibodies concentrations [11,12]. We present them as point-pulse functions of source with maximum values in points x_s^1, x_s^2 in time t_s^1 and t_s^2:

$$w_1(x,t)=\sum_{s=1}^{n_1}A_s^1 e^{-\alpha_s^1(x-x_s^1)^2}e^{-\beta_s^1(t-t_s^1)^2},\ w_2(x,t)=\sum_{s=1}^{n_2}A_s^2 e^{-\alpha_s^2(x-x_s^2)^2}e^{-\beta_s^2(t-t_s^2)^2}. \tag{3}$$

3. Asymptotics of the solution

We assume that system (1) is nondimensional [11,12]. Using step method [16], we reduce solution to problem with time-delay (1)-(2) to sequence of solutions of the problem without time-delay. So, on the intervals $r\tau<t\le(r+1)\tau$ $(r=0,1,2,...)$ we have:

$$\begin{cases}
\dfrac{\partial u_{1(0)}}{\partial t}=w_1+(\beta(u_{5(0)})-\gamma u_{3(0)})u_{1(0)}+\varepsilon D_1\dfrac{\partial^2 u_{1(0)}}{\partial x^2},\\
\dfrac{\partial u_{2(0)}}{\partial t}=\xi(u_{4(0)})\alpha(u_{5(0)})u_3^0(t-\tau)u_1^0(t-\tau)-\mu_C(u_{2(0)}-u_2^*)+\varepsilon^2 D_2\dfrac{\partial^2 u_{2(0)}}{\partial x^2},\\
\dfrac{\partial u_{3(0)}}{\partial t}=w_2+\rho u_{2(0)}-(\mu_f+\eta\gamma u_{1(0)})u_{3(0)}+\varepsilon D_3\dfrac{\partial^2 u_{3(0)}}{\partial x^2},\\
\dfrac{\partial u_{4(0)}}{\partial t}=\sigma u_{1(0)}-\mu_m u_{4(0)}+\varepsilon^2 D_4\dfrac{\partial^2 u_{4(0)}}{\partial x^2},\\
\dfrac{\partial u_{5(0)}}{\partial t}=\alpha_T u_{1(0)}u_{3(0)}-\mu_T(u_{5(0)}-u_5^*)+\varepsilon D_5\dfrac{\partial^2 u_{5(0)}}{\partial x^2},\\
u_{2(0)}\big|_{t=0}=u_2^0(x),u_{4(0)}\big|_{t=0}=u_4^0(x),u_{5(0)}\big|_{t=0}=u_5^0(x),\\
u_{1(0)}\big|_{t=0}=u_1^0(x,0),u_{3(0)}\big|_{t=0}=u_3^0(x,0),0<t\le\tau;
\end{cases} \tag{4}$$

. . . . . .

$$\begin{cases}
\dfrac{\partial u_{1(r)}}{\partial t}=w_1+(\beta(u_{5(r)})-\gamma u_{3(r)})u_{1(r)}+\varepsilon D_1\dfrac{\partial^2 u_{1(r)}}{\partial x^2},\\
\dfrac{\partial u_{2(r)}}{\partial t}=\xi(u_{4(r)})\alpha(u_{5(r)})u_{3(r-1)}(t-\tau)u_{1(r-1)}(t-\tau)-\mu_C(u_{2(r)}-u_2^*)+\varepsilon^2 D_2\dfrac{\partial^2 u_{2(r)}}{\partial x^2},\\
\dfrac{\partial u_{3(r)}}{\partial t}=w_2+\rho u_{2(r)}-(\mu_f+\eta\gamma u_{1(r)})u_{3(r)}+\varepsilon D_3\dfrac{\partial^2 u_{3(r)}}{\partial x^2},\\
\dfrac{\partial u_{4(r)}}{\partial t}=\sigma u_{1(r)}-\mu_m u_{4(r)}+\varepsilon^2 D_4\dfrac{\partial^2 u_{4(r)}}{\partial x^2},\\
\dfrac{\partial u_{5(r)}}{\partial t}=\alpha_T u_{1(r)}u_{3(r)}-\mu_T(u_{5(r)}-u_5^*)+\varepsilon D_5\dfrac{\partial^2 u_{5(r)}}{\partial x^2},\\
u_{2(r)}\big|_{t=r\tau}=u_{2(r-1)}(x,r\tau),u_{4(r)}\big|_{t=r\tau}=u_{4(r-1)}(x,r\tau),u_{5(r)}\big|_{t=r\tau}=u_{5(r-1)}(x,r\tau),\\
u_{1(r)}\big|_{t=r\tau}=u_{1(r-1)}(x,r\tau),u_{3(r)}\big|_{t=r\tau}=u_{3(r-1)}(x,r\tau),r\tau<t\le(r+1)\tau.
\end{cases} \tag{5}$$

To ensure sufficient smoothness of the corresponding solutions at $t=0$, $t=\tau$, …, $t=r\tau$, … , is provided by the imposition of additional conditions of consistency of the functions of the initial conditions of the model problem at $t=-\tau$ and $t=0$ [11,12]. In particular, the condition

$$\frac{\partial u_{2(0)}(x,0)}{\partial t}=\xi(u_{4(0)})\cdot\alpha_0\cdot u_3^0(x,-\tau)\cdot u_1^0(x,-\tau)-\mu_C(u_{2(0)}(x,0)-u_2^*)+\varepsilon^2 D_2\frac{\partial^2 u_{2(0)}(x,0)}{\partial x^2}. \quad (6)$$

must be satisfied.

Considering the small diffusion redistributions of active factors, we use the asymptotic method [4,11,12] to find problems solutions (4-5). Thus, the solutions of problems (4)-(5) are formally presented as asymptotic series $u_{1(r)}=\sum_{i=0}^{n}\varepsilon^i u_{1(i,r)}(x,t)+R^1_{n(r)}(x,t,\varepsilon)$, $u_{2(r)}=\sum_{i=0}^{n}\varepsilon^i u_{2(i,r)}(x,t)+\ +R^2_{n(r)}(x,t,\varepsilon)$, $u_{3(r)}=\sum_{i=0}^{n}\varepsilon^i u_{3(i,r)}(x,t)+R^3_{n(r)}(x,t,\varepsilon)$, $u_{4(r)}(x,t)=\sum_{i=0}^{n}\varepsilon^i u_{4(i,r)}(x,t)+R^4_{n(r)}(x,t,\varepsilon)$, $u_{5(r)}(x,t)=\sum_{i=0}^{n}\varepsilon^i u_{5(i,r)}(x,t)+$ $+R^5_{n(r)}(x,t,\varepsilon)$ as perturbation of the corresponding degenerate problems solutions [4,11,12], where $r=0,1,2,...$, $u_{1(i,r)}$, $u_{2(i,r)}$, $u_{3(i,r)}$, $u_{4(i,r)}$, $u_{5(i,r)}$ are members of the asymptotics, $R^1_{n(r)}$, $R^2_{n(r)}$, $R^3_{n(r)}$, $R^4_{n(r)}$, $R^5_{n(r)}$ are relevant residual members. Using standard «procedure of equalization » [4,11,12], we obtain functions $u_{1(i,r)}$, $u_{2(i,r)}$, $u_{3(i,r)}$, $u_{4(i,r)}$, $u_{5(i,r)}$. In case $\xi(u_{4(r)})=1$ we have:

$$\begin{cases}\frac{\partial u_{1(0,r)}}{\partial t}=w_1+(B_{(0,r)}-\gamma u_{3(0,r)})u_{1(0,r)},\\ \frac{\partial u_{2(0,r)}}{\partial t}=\alpha_0(1+\alpha_1(u_{5(0,r)}-u_5^*))\Psi^2_{(r)}-\mu_C(u_{2(0,r)}-u_2^*),\\ \frac{\partial u_{3(0,r)}}{\partial t}=w_2+\rho u_{2(0,r)}-(\mu_f+\eta\gamma u_{1(0,r)})u_{3(0,r)},\\ \frac{\partial u_{4(0,r)}}{\partial t}=\sigma u_{1(0,r)}-\mu_m u_{4(0,r)},\\ \frac{\partial u_{5(0,r)}}{\partial t}=\alpha_T u_{1(0,r)}u_{3(0,r)}-\mu_T(u_{5(0,r)}-u_5^*),\\ u_{2(0,r)}\big|_{t=r\tau}=u_{2(0,r-1)}(x,r\tau),u_{4(0,r)}\big|_{t=r\tau}=u_{4(0,r-1)}(x,r\tau),u_{5(0,r)}\big|_{t=r\tau}=u_{5(0,r-1)}(x,r\tau),\\ u_{1(0,r)}\big|_{t=r\tau}=u_{1(0,r-1)}(x,r\tau),u_{3(0,r)}\big|_{t=r\tau}=u_{3(0,r-1)}(x,r\tau),r\tau<t\le(r+1)\tau;\end{cases} \quad (7)$$

. . . . . .

$$\begin{cases}\frac{\partial u_{1(i,r)}}{\partial t}=a_{(0,r)}B_{(i,r)}+c_{(0,r)}u_{1(i,r)}-\gamma(a_{(0,r)}u_{3(i,r)}+b_{(0,r)}u_{1(i,r)})+\Phi^1_{(i,r)},\\ \frac{\partial u_{2(i,r)}}{\partial t}=\alpha_0\alpha_1 u_{5(i,r)}\Psi^2_{(r)}-\mu_C u_{2(i,r)}+\Phi^2_{(i,r)},\\ \frac{\partial u_{3(i,r)}}{\partial t}=\rho u_{2(i,r)}-\mu_F u_{3(i,r)}-\eta\gamma(a_{(0,r)}u_{3(i,r)}+b_{(0,r)}u_{1(i,r)})+\Phi^3_{(i,r)},\\ \frac{\partial u_{4(i,r)}}{\partial t}=\sigma u_{1(i,r)}-\mu_m u_{4(i,r)}+\Phi^4_{(i,r)},\\ \frac{\partial u_{5(i,r)}}{\partial t}=\alpha_T(a_{(0,r)}u_{3(i,r)}+b_{(0,r)}u_{1(i,r)})-\mu_T u_{5(i,r)}+\Phi^5_{(i,r)},\\ u_{2(i,r)}\big|_{t=r\tau}=0,u_{4(i,r)}\big|_{t=r\tau}=0,u_{5(i,r)}\big|_{t=r\tau}=0,u_{1(i,r)}\big|_{t=r\tau}=0,u_{3(i,r)}\big|_{t=r\tau}=0,\\ r\tau<t\le(r+1)\tau,i=1,2,...,n.\end{cases} \quad (8)$$

Here $a_{(0,r)}=u_{1(0,r)}$, $b_{(0,r)}=u_{3(0,r)}$;

$c_{(0,r)}=B_{(0,r)}=\frac{\beta_0}{1+\beta_1(u_{5(0,r)}-u_5^*)}$, $B_{(i,r)}=-\frac{\beta_1}{1+\beta_1(u_{5(0,r)}-u_5^*)}\cdot\sum_{k=0}^{i-1}u_{5(i-k,r)}B_{(k,r)}$;

$\Psi^2_{(0)}=u_3^0(x,t-\tau)u_1^0(x,t-\tau)$; $\Psi^2_{(r)}=u_{3(r-1)}(x,t-\tau)u_{1(r-1)}(x,t-\tau)$;

$\Phi^1_{(1,r)}=D_1\frac{\partial^2 u_{1(0,r)}}{\partial x^2}$, $\Phi^2_{(1,r)}=0$, $\Phi^3_{(1,r)}=D_3\frac{\partial^2 u_{3(0,r)}}{\partial x^2}$, $\Phi^4_{(1,r)}=0$, $\Phi^5_{(1,r)}=D_5\frac{\partial^2 u_{5(0,r)}}{\partial x^2}$;

$$\Phi^1_{(i,r)}=\sum_{k=1}^{i-1}(B_{(k,r)}-\gamma u_{3(i-k,r)})u_{1(i-k,r)}+D_1\frac{\partial^2 u_{1(i-k,r)}}{\partial x^2},\ \Phi^2_{(i,r)}=D_2\frac{\partial^2 u_{2(i-2,r)}}{\partial x^2},$$

$$\Phi^3_{(i,r)}=-\eta\gamma\sum_{k=1}^{i-1}u_{1(k,r)}u_{3(i-k,r)}+D_3\frac{\partial^2 u_{3(i-1,r)}}{\partial x^2},\ \Phi^4_{(i,r)}=D_4\frac{\partial^2 u_{4(i-2,r)}}{\partial x^2},$$

$$\Phi^5_{(i,r)}=\alpha_T\sum_{k=1}^{i-1}u_{1(k,r)}u_{3(i-k,r)}+D_5\frac{\partial^2 u_{5(i-1,r)}}{\partial x^2},\ i=2,3,...,n.$$

On each interval $r\tau\le t\le(r+1)\tau$ we find solutions of the corresponding problems using numerical methods (for example, the Runge-Kutta method) and using obtained solutions of problems that was found on previous stage. Thus, the use of the asymptotic method provided the reduction of quiet complex initial problem to series of simpler ones. The technologies of numerical solution such problems have been already well studied and reliable packages of the corresponding software have been developed [17]. Estimation of the residual terms $R^1_{n(r)}$, $R^2_{n(r)}$, $R^3_{n(r)}$, $R^4_{n(r)}$, $R^5_{n(r)}$ is done the same to [4,11,12] on the basis of the maximum-type principle.

4. Numerical experiments

The implementation numerical experiments based on the proposed model's modifications (1) - (2) were focused on the study of the body's temperature reaction, taking into account the dissipation spatial effect on infection diseases development for different characteristic forms of their course.

Figure 1 a) shows model dynamics of the antigen concentration in the infection locus in chronic form of infectious disease focus at different values of temperature rise rate α_T that depend on the concentration of u_1u_3-complexes in the cases without taking account of diffusion perturbations. For the other model parameters the values were taken according to [1,2]: $\beta_0=1$, $\beta_1=10$; $\gamma=0.8$; $\mu_c=0.5$; $\alpha_0=1000$, $\alpha_1=25$; $u_2^*=1$; $\rho=0.17$; $\mu_f=0.17$; $\eta=10$; $\sigma=10$; $\mu_f=0.12$. As expected, if coefficient α_T increases that the value of the model antigens concentration in the infection focus with the development of the disease process and in the steady state decrease. So, the predicted "acuteness" of the infectious disease, in particular, in the chronic form will decrease due to the influence of the temperature reaction on the immune response.

In addition, the effect of diffusion "redistribution" of active factors with their uneven distribution in the organism also leads to decrease of the disease "severity". Figure 1, b) illustrates model dynamics of the antigens concentration at the infection epicenter in the chronic form of the disease, taking into account the influence of the temperature reaction of the organism at different levels of the rate of

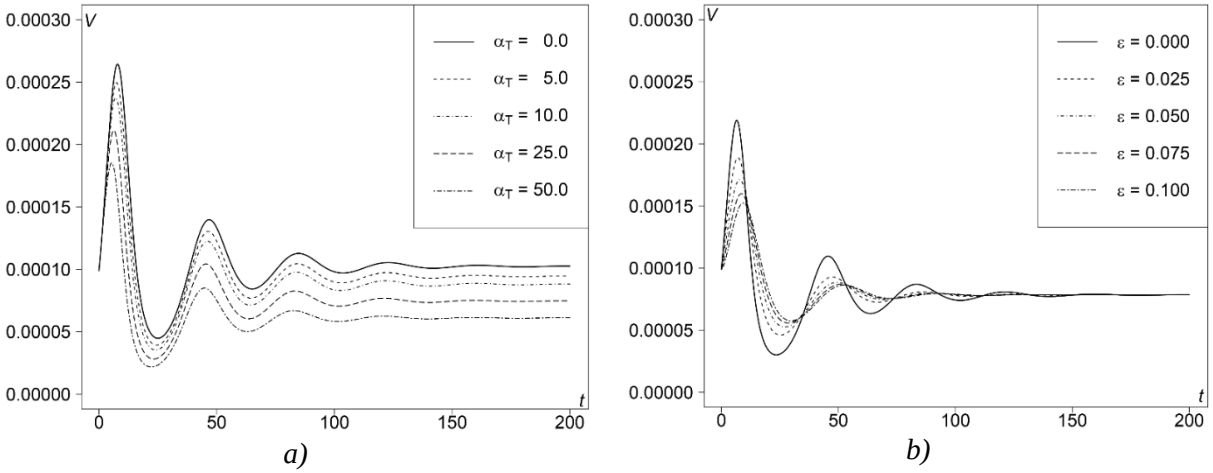

Figure 1: Model dynamics of the antigen concentration in the infection locus in chronic form of infectious disease: a) at different values of temperature rise rate α_T; b) at different intensity of diffuse "redistribution"

diffusion "redistribution". Note that the antigens predictive dynamic obtained on the basis of the modified model (1) - (2) without diffusion redistribution (ε=0) is consistent with the chronic disease dynamics accordance with the classical Marchuk model. It demonstrates the maximums and the change in the antigens' concentration rate at the infection epicenter during the disease development.

5. Conclusions

The presented of the mathematical model modification of a viral disease provides an opportunity to take into account diffuse perturbations and various concentrated influences on disease development in the conditions of the body's temperature reaction. The corresponding model problem solution with a delay is reduced to a sequence of singularly perturbed problems solutions without delay, for which the asymptotic method is applied. The advantage of this approach is the transition from "unperturbed" tasks to "perturbed" ones is carried out in such way that the regularities basic forms describing the viral disease process remain initially acceptable and the obtained basic "unperturbed" solutions are supplemented by various amendments.

The computer modeling presented results of the viral disease process under conditions of a temperature reaction of the body illustrate an amount decrease of antigens in the infection focus caused of their diffuse dispersion. It has been shown that the decrease caused by the influence of diffusion "redistribution", including supercritical values of antigen concentration, leads to more effective neutralization by exciting antibodies of the organism and, as a result, to a decrease in the infectious disease "severity". Thus, taking into account the body's temperature reaction and the influence of diffusion "redistribution" of active factors under forecasting of the viral disease dynamics and forming a treatment program allow to use more economical immunotherapy procedures and to establish the optimal concentration of donor antibodies in each injection.

It is a promising to development of the proposed approach to take into account the diffusion "redistribution" in terms of immunotherapy (pharmacotherapy). It is also very important to take into account logistical limitations of active factors and temperature reaction of the organism for forecasting of disease dynamics based on more general and detailed models.

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Informatics & Data-Driven Medicine (IDDM 2020): Proceedings of the 3rd International Conference (Växjö, Sweden, November 19-21, 2020). Växjö, Sweden, 2020. P. 119–128.
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