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MATHEMATICAL MODELING OF INFECTIOUS DISEASE
МАТЕМАТИЧНЕ МОДЕЛЮВАННЯ ІНФЕКЦІЙНОГО ЗАХВОРЮВАННЯ

K. Zelensky/Зеленський К.Х.,
Doctor of Technical Sciences, as prof/д.т.н., доц.
ORCID: 0000-0003-1501-8214
J. Fomin/Фомін Я.В.,
S. Kochkarev/Кочкарьов С.В.,
Undergraduates/магіст.
National Technical University of Ukraine," Igor Sikorsky Kyiv Polytechnic Institute",
department of biomedical cybernetics,
37 Peremohy Avenue, 03056, Kyiv, Ukraine.
Національний технічний університет України "Київський політехнічний інститут імені Ігоря Сікорського", кафедра біомедичної кібернетики,
Проспект Перемоги, 37, 03056, Київ, Україна.

Summary. *The problem of mathematical modeling of the immune response to viral infections is considered. The mathematical model of the process is described by a system of nonlinear differential equations with delay. The solution of this system of equations is carried out by an iterative numerical-analytical method using the Laplace integral transformation. The obtained results of mathematical modeling provide an opportunity to solve problems of research and prediction of infectious diseases and to apply the simulation results for the diagnosis of personalized patients.*

Key words: *Cauchy problem, infectious diseases, immune system, integral transformation, iterative schemes, nonlinear differential equations.*

Introduction

For the analysis of the most important physiological processes in infectious diseases, mathematical modeling is widely used, when various diseases are considered from a single standpoint as a process of interaction of the immune system with pathogens. Mathematical models of infectious diseases are nonlinear systems of differential equations and contain a significant number of parameters that characterize the immune status of the organism and the properties of the antigen. The basis of mathematical models of the immune response is the fundamental work of G.I. Marchuk, [2-4,6,7,18] whose models reflect the most significant patterns of functioning of the immune system in infectious diseases.

Traditional tasks in the field of mathematical modeling in immunology are to build and study models of the immune response and immune defense of the body in infectious diseases.

Infectious disease is seen as a conflict between the immune system and a population of pathogens.

The following essential characteristics of the disease are considered as phase variables of the model [18]:

1. The concentration of antigens in the affected organ [parts/ml].
2. Plasma cell concentration, [cell/ml], is a population of producers and carriers of antibodies (immunocompetent cells).
3. The concentration of antibodies in the blood. They neutralize antigens.
4. Relative characteristics of the affected organ, which can be interpreted as a

proportion of antigen-destroyed cells of the body. This is a generalized characteristic of the damage that the antigen inflicts on the target organ,, where is the number of cells of the target organ at the time, the number of cells is normal.

Formulation of the problem

The model is a system of differential equations with a delayed argument. It describes the general patterns inherent in all infectious diseases.

$$\frac{dV_f}{dt}+(\gamma_{VM}M^0+\gamma_{VC}C^0)V_f(t)-\nu C_V(t)=N[V_f(t)]; \quad (1)$$

$$N[V_f(t)]=nb_{CE}C_V(t)E(t)+V_f(t)[\gamma_{VC}(C_V(t)+m(t))-\gamma_{VF}F(t)]; \quad (2)$$

$$\frac{dC_V}{dt}+b_mC_V(t)-\sigma C^0V_f(t)=b_mC^0-N[C_V(t)]; \quad (3)$$

$$N[C_V(t)]=\sigma\xi(m)V_f(t-\tau)[C_V(t-\tau)-m(t)]+nb_{CE}C_V(t-\tau)E(t). \quad (4)$$

$$\frac{dm}{dt}+\alpha_m m(t)-b_mC_V(t)=N[m(t)]=b_{CE}C_V(t)E(t),\ \ \xi(m)=1-m/C^0; \quad (5)$$

$$\frac{dF}{dt}+\alpha_F F(t)-\rho_F P(t)=-\gamma_{FV}F(t)V_f(t). \quad (6)$$

The values γ_{VM}, γ_{VF}, γ_{VC} characterize the inverse values of the interaction time of free viruses with macrophages, antibodies and healthy cells, respectively.

The function $m(t)$ is defined as [15]:

$$m(t)=\frac{M_0-M_1(t)}{M_0},$$

where M_0 - the characteristics of a healthy organ (mass or volume); $M_1(t)$ - characteristics of the healthy part of the body at the time.

The level of antigen concentration $V_f(t)$ is the main indicator of the dynamics of the disease and the functioning of the immune system. Since in equation (5) there is an expression $b_{CE}C_V(t)E(t)$, that contains a function defined in the block T-cellular immune response to make independent solutions of equations that describe the dynamics of processes in these blocks, we consider only the linear part of the equation:

$$\frac{dE^{(0)}(t)}{dt}+\alpha_E E^{(0)}(t)=\alpha_E E^0; \qquad \frac{dP(t)}{dt}+\alpha_P P=\alpha_P.$$

A large number of scientific papers, for example, [2,9,13], are devoted to the search for solutions of systems of differential equations with a deviating argument, in the vast majority of which difference schemes of the Runge-Kutta type are used [11,12,14,19] relative to the linear part of the system of differential equations.

The aim of the work is to develop a method for solving systems of nonlinear differential equations with a deviating argument based on an iterative numerical-analytical method [5].

Solving the problem

Denote by $y_1=V_f(t)$, $y_2=C_V(t)$, $y_3=m(t)$, $y_4=F(t)$, $y_5(t)=P(t)$. We have the following system of equations to determine the functions that simulate the block of the target organ:

$$\frac{dy(t)}{dt} + Ay(t) = y_0(t) + N(y); \tag{7}$$

$$A = \begin{bmatrix} a_{v_f} & -\nu & 0 & 0 & 0 \\ -\sigma C^0 & b_m & 0 & 0 & 0 \\ 0 & -b_m & \alpha_m & 0 & 0 \\ 0 & 0 & 0 & \alpha_F & \rho_F \\ 0 & 0 & 0 & 0 & \alpha_P \end{bmatrix}; \tag{8}$$

$$y_0 = [0 \;\; b_m C^0 \;\; 0 \;\; 0 \;\; \alpha_P P^0]^T; \tag{9}$$

$$N = [N_{y_1} \; N_{y_2} \; N_{y_3} \; N_{y_4} \; N_{y_5}]^T; \tag{10}$$

$$N_{y_1} = nb_1^C y_2(t)\cdot E^{(0)}(t) + y_1(t)[\gamma_1^C(y_2(t)+y_3(t)) - \gamma_2^C y_4(t)];$$

$$N_{y_2} = \sigma y_1(t-\tau)[y_2(t-\tau) - y_3(t)] + nb_1^C y_2(t-\tau)E^{(0)}(t);$$

$$N_{y_3} = b_1^C y_2(t)E^{(0)}(t); \quad N_{y_4} = \gamma_2^C y_1(t) y_4(t);$$

Initial conditions for this system of equations:

$$y_1(0) = V_f(0) = V_f^0; \;\; y_2(0) = C_V(0) = C_0; \;\; y_3(0) = m(0) = m_0;$$

$$y_4(0) = \frac{\rho_F}{\alpha_F}\cdot P^0, \; P(0) = 1. \tag{11}$$

We have a Cauchy problem for the vector-matrix equation (7) with initial conditions (11)

We apply to the problem (7), (11) the integral Laplace transform. Let us denote $\mathbf{y}(p)$ the Laplace transform of the desired function. Then we have

$$A(p)\mathbf{y}(p) = \mathbf{y}_0/p + \mathbf{y}(0) + \mathcal{L}[\mathbf{N(y)}].$$

$$\mathbf{y}(p) = A^{-1}(p)[\mathbf{y}_0/p + \mathbf{y}(0)] + A^{-1}(p)\mathcal{L}[\mathbf{N(y)}]. \tag{12}$$

$$A(p) = \begin{bmatrix} p + a_{V_f} & -\nu & 0 & 0 & 0 \\ -\alpha C^0 & p + b_m & 0 & 0 & 0 \\ 0 & -b_m & p+\alpha_m & 0 & 0 \\ 0 & 0 & 0 & p+\alpha_F & \rho_F \\ 0 & 0 & 0 & 0 & p+\alpha_P. \end{bmatrix}. \tag{13}$$

Since the Laplace transform is a linear transformation, the search for a solution to this problem is carried out by an iterative procedure. Denote the solution of the linear part of the problem, ie without taking into account.

This system of equations can be reduced to three equations, because the equations are relative to $y_4(t)$ and $y_5(t)$ do not depend on the first three variables. Then instead of (12) we will have

$$\mathbf{y}(p) = B^{-1}(p)[\mathbf{y}_0/p + \mathbf{y}(0)] + B^{-1}(p)\mathcal{L}[\mathbf{N(y)}]. \tag{14}$$

$$B(p)=\begin{bmatrix} p+a_{V_f} & -\nu & 0 \\ -\alpha C^0 & p+b_m & 0 \\ 0 & -b_m & p+\alpha_m \end{bmatrix}.$$

We have a linear approximation:

$$\mathbf{y}^{(0)}(p)=B^{-1}(p)[\mathbf{y}_0/p+\mathbf{y}(0)],$$

The determinant of the matrix $B(p)$ is obtained in the form

$$\Delta(p)=|B(p)|=(p^2+b_1p+b_2)(p+\alpha_m)=\Delta_1(p)(p+\alpha_m);$$

$$b_1=\alpha_m+b_m;\ b_2=a_{V_f}b_m-\nu\alpha C^0.$$

We have:

$$B^{-1}(p)=\frac{1}{\Delta(p)}\begin{bmatrix} (p+b_m)(p+\alpha_m) & \nu(p+b_m) & 0 \\ \alpha C^0(p+\alpha_m) & (p+a_{V_f})(p+\alpha_m) & 0 \\ \alpha C^0 b_m & b_m(p+a_{V_f}) & (p^2+b_1p+b_2) \end{bmatrix}. \quad (15)$$

We write in vector form the initial conditions (11) taking into account the perturbations (9).

$$\mathbf{d}(p)=[V_f^0\ \ b_mC^0/p\ \ 0]^T;$$

We have for the linear part of the vector equation (14):

$$\mathbf{y}^{(0)}(p)=B^{-1}(p)\mathbf{d}(p), \quad (16)$$

or in component form:

$$y_k^{(0)}(p)=\frac{f_0^k}{p}+\frac{f_1^k}{p+\alpha_m}+\frac{f_2^kp+f_4^k}{p^2+b1p+b2}.$$

$$y_k^{(0)}(t)=f_0^k+f_1^ke^{-\alpha_m t}+e^{-\beta t}\begin{cases}\left[f_2^k\cos\omega t+f_3^k\sin\omega t)\right], & \omega<0,\\ \left[f_2^k ch\omega t+f_3^k sh\omega t\right], & \omega>0,\end{cases}=g^{y_k}(t). \quad (17)$$

Numerical values f_j^k are determined after substitution into expressions for the coefficients of numerical values f_j^k of the corresponding parameters of the system of equations [12]:

$$a_{v_f}=2\cdot10^{-4};\nu=0{,}1;b_m=0{,}005;\alpha C^0=0{,}4;\alpha_m=0{,}12;\alpha_F=0{,}17;\rho_F=0{,}17;$$

Next, we use the obtained solution in a linear approximation to determine the nonlinear part **N(y)** of the problem.

Since the nonlinear parts include expressions for $E(t)$, and implicitly $P(t)$, we write the solutions of the linear approximations for for these functions.

$$E^{(0)}(t)=E^0\left(1-e^{-\alpha_E t}\right);P^{(0)}(t)=P^0\left(1-e^{-\alpha_P t}\right);$$

$$F^{(0)}(t)=y_4^{(0)}(t)=a_0^4+a_1^4e^{-\alpha_F t}+a_2^4e^{-\alpha_P t};$$

Taking into account the obtained solution of the system of equations in the linear approximation, we have the following expressions for the nonlinear components of this system:

$$N_{y_1} = nb_1^C y_2^{(0)}(t)\cdot E^{(0)}(t) + y_1^{(0)}(t)[\gamma_1^C(y_2^{(0)}(t)+y_3^{(0)}(t)) - \gamma_2^C y_4^{(0)}(t)]$$

$$= nb_1^C E^0[1-e^{-\alpha_E t}]g^2(t) + g^1(t)\{\gamma_1^C[c_1^3 e^{-\alpha_m t} + g^2(t)+g^3(t)] - \gamma_2^C g^4(t)\}. \quad (18)$$

Substitute the expressions for $g^1(t)$, $g^2(t)$, $g^3(t)$ (solution of the linear part of the system of equations) to (18) and perform the corresponding transformations. We get:

$$N_{y_1}^{(0)}(t) = r_0^1 + r_1^1 e^{-\alpha_m t} + r_6^1 e^{-2\beta t} + e^{-(\alpha_m+\beta)t}[r_4^1\cos\omega t + r_5^1 \sin\omega t]$$

$$+ e^{-\beta t}[r_2^1\cos\omega t + r_3^1\sin\omega t] + e^{-2\beta t}[r_7^1\cos 2\omega t + r_8^1 \sin 2\omega t]. \quad (19)$$

Laplace transform can now be applied to expression (24). We get:

$$\mathcal{L}[N_{y_1}] = \frac{r_0^1}{p} + \sum_{k=1}^{4}\frac{v_{6k-6}^1 p + v_{6k-5}^1}{p^2 + v_{6k-2}^1 p + v_{6k-3}^1}.$$

Applying to this expression an algorithm of equivalent simplification to the chain of the second order leads to the following expression:

$$\mathcal{L}[N_{y_1}^{(0)}] \approx \frac{v_0^1}{p} + \frac{\overline{v}_0^1 p + \overline{v}_1^1}{p^2 + \overline{v}_4^1 p + \overline{v}_3^1}$$

where through $\overline{v}_k^2$, $k=\overline{0,5}$, denote the coefficients obtained by simplifying the fractional-rational expression.

The nonlinear part is relatively $C_V(t)$ uniform

$$N_{y_2}^{(0)} = \sigma y_1^{(0)}(t-\tau)[y_2^{(0)}(t-\tau) - y_3^{(0)}(t)] + nb_1^C y_2^{(0)}(t-\tau)E^{(0)}(t)$$

$$= u_0^2 + \sum_{k=1}^{3}\{e^{-\beta^{(k)}t}[u_{3k-3}^2 + u_{3k-2}^2\cos(\omega^{(k)}t - \tau^{(k)}) + u_{3k-1}^2 \sin(\omega^{(k)}t-\tau^{(k)})]\};$$

In the image space, this expression corresponds

$$\overline{N}_{y_2}^{(0)}(p) = \frac{\overline{u}_0^2}{p} + \sum_{k=1}^{3} e^{-\tau^{(k)}p}\left[\frac{d_0^{(k)}}{p} + \frac{d_1^{(k)}(p+\beta^{(k)}) + d_2^{(k)}\omega^{(k)}}{(p+\beta^{(k)})^2 \pm (\omega^{(k)})^2}\right].$$

The presence of a delay $\beta^{(k)}$ leads to a nonlinear fractional-rational expression. We approximate [5] the multiplier $e^{-\tau p}$ also by a fractional-rational expression, limited to the second order of approximation:

$$e^{-\tau^{(k)}p} \approx \frac{12 - 6\tau^{(k)}p + (\tau^{(k)})^2 p^2}{12 + 6\tau^{(k)}p + (\tau^{(k)})^2p^2}.$$

Then we will have:

$$\overline{N}_{y_2}(p) = \frac{\overline{u}_0^2}{p} + \sum_{k=1}^{3}[\frac{-12/\tau^{(k)}u_0^{(k)}}{p^2 + 6/\tau^{(k)}p + 12/(\tau^{(k)})^2}$$

$$+\frac{p^2 - 6/\tau^{(k)}p + 12/(\tau^{(k)})^2}{p^2 + 6/\tau^{(k)}p + 12/(\tau^{(k)})^2}\cdot\frac{u_1^{(k)}p + [u_1^{(k)}\beta^{(k)}) + u_2^{(k)}\omega^{(k)}]}{p^2 + u_4^{(k)}p + u_3^{(k)}}].$$

Or

$$\overline{N}_{y_2}(p) = \frac{\overline{u}_0^2}{p} + \sum_{k=1}^{3}\frac{p^3 + r_1^{(k)}p^2 + r_2^{(k)}p + r_3^{(k)}}{p^4 + q_1^{(k)}p^3 + q_2^{(k)}p^2 + q_3^{(k)}p + q_4^{(k)}} \approx \frac{\overline{u}_0^2}{p} + \frac{\overline{v}_0^2 p + \overline{v}_1^2}{p^2 + \overline{v}_4^2 p + \overline{v}_3^2}. \quad (20)$$

We obtain the expression for the nonlinear part of the equation with respect to.

$$N_{y_3} = N_m = b_1^C C_v(t)E(t) = b_1^C C_V^{(0)}(t)E^{(0)}(t) = b_1^C[f_0^3 + f_1^3 e^{-\alpha_m t} + g_3(t)]E^0\left(1-e^{-\alpha_E t}\right)$$

$$= b_1^C E^0[f_0^3 - f_0^3 e^{-\alpha_E t} + f_1^3 e^{-\alpha_m t} + f_1^3 e^{-(\alpha_m+\alpha_E)t} + g_3(t) - e^{-\alpha_E t} g_3(t)$$

In the image space, this expression corresponds to:

$$\mathcal{L}[N_{y_3}(t)] = \frac{\overline{v}_0^3}{p} + \sum_{k=0}^{2} \frac{v_{6k}^3 p + v_{6k+1}^3}{p^2 + v_{6k+4}^3 p + v_{6k+3}^3} \approx \frac{\overline{v}1_0^3}{p} + \frac{\overline{v}_0^3 p + \overline{v}_1^3}{p^2 + \overline{v}_4^3 p + \overline{v}_3^3}.$$

Using the algorithm of equivalent simplification of fractional-rational functions [5], the expression $\mathcal{L}\{N_{y_1}\}$ for Laplace image space takes the form

$$\mathcal{L}\{N_{y_k}\} = N^k(p) = \frac{r_2^k}{p} + \frac{r_0^k + r_1^k p}{p^2 + r_4^k p + r_3^k}.$$

Substitute the obtained expressions in (14).

$$Y^{(m)}(p) = Y^{(0)}(p) + B^{-1}(p)N_y^{(m-1)}(p) = Y^{(0)}(p) + V(p),\ m = 0,1,2,\ldots \quad (21)$$

$$V(p) = \begin{bmatrix} \dfrac{p+b_m}{\Delta_1} & n\dfrac{p+b_m}{(p+\alpha_m)\Delta_1} & 0 \\ \dfrac{\alpha C^0}{\Delta_1} & \dfrac{p+a_{V_f}}{\Delta_1} & 0 \\ \dfrac{\alpha C^0 b_m}{(p+\alpha_m)\Delta_1} & \dfrac{b_m(p+b_m)}{(p+\alpha_m)\Delta_1} & \dfrac{1}{p+\alpha_m} \end{bmatrix} \cdot \begin{bmatrix} \dfrac{r_2^1}{p} + \dfrac{r_1^1 p + r_0^1}{p^2 + r_4^1 p + r_3^1} \\ \dfrac{r_2^2}{p} + \dfrac{r_1^2 p + r_0^2}{p^2 + r_4^2 p + r_3^2} \\ \dfrac{r_2^3}{p} + \dfrac{r_1^3 p + r_0^3}{p^2 + r_4^3 p + r_3^3} \end{bmatrix}. \quad (22)$$

After performing the appropriate actions in this expression, moving to the space of the originals and adding linear parts according to (21), (22), we obtain the solution of the system of equations in the first approximation in this form.

$$y_k^{(1)}(t) = q1^k + q2^k e^{\alpha_m t} + e^{-\beta t}[q_1^{(k)} \cos \omega t + q_2^{(k)} \sin \omega t] + e^{-\gamma_k t}[v_1^{(k)} \cos \omega_k t + v_2^{(k)} \sin \omega_k t].$$

These expressions take into account the solution of the system of equations in the linear approximation. Subsequent calculations are performed by similar algorithms, which contain the products of fractional-rational expressions in Laplace image space in the form of terms of the simplest chains (first and second degree), reduction of similar and record the results in the original space in a similar form.

Conclusions

The model of antiviral immune response of the target organ as a basic model of infectious disease is considered. An iterative numerical-analytical method for solving the Cauchy problem for a system of nonlinear differential equations is proposed, which makes it possible to obtain a solution in quadratures. The basis of this method is an iterative numerical-analytical method for solving nonlinear boundary value problems using algorithms for approximating fractional-rational expressions.

The proposed method for solving nonlinear boundary value problems can be used to solve a wide range of nonlinear problems in mathematical physics.

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Антотація. *Розглядається задача математичного моделювання імунної відповіді на вірусні інфекції. Математична модель процесу описується системою нелінійних диференційних рівнянь із запізненням. Розв'язання цієї системи рівнянь здійснюється ітераційним числово -аналітичним методом із застосуванням інтегрального перетворення Лапласа. Отримані результати математичного моделювання надають можливість вирішувати задачі дослідження і прогнозування розвитку інфекційних захворювань та застосовувати результати моделювання для діагностики персоніфикованих хворих.*

Ключові слова: *задача Коші, інфекційні захворювання, імунна система, інтегральне перетворення, ітераційні схеми, нелінійні диференційні рівняння.*