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ANALYSIS OF A MATHEMATICAL MODEL OF ADAPTIVE IMMUNE RESPONSE TO VIRUS INFECTION

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Abstract: A mathematical model of adaptive immune response to a viral infection is formulated by five nonlinear ordinary differential equations. The model describes the interactions between a virus, uninfected cells, infected cells, and the adaptive immune response represented by the antibodies and cytotoxic T lymphocytes. Theorems of existence, uniqueness and non-negativity of solution are proven. Numerical simulations of the model are presented.

AMS Subject Classification: 03H10
Key Words: mathematical model, ordinary differential equations, numerical simulations

1. Introduction

The use of mathematical models for investigations of the behavior of immune system of organisms infected by pathogens such as viruses, can be an effective tool for determining the tendencies of the disease with or without medical treatment. An organism that meets a specific antigen for the first time possesses only a small amount of lymphocytes that are able to recognize and neutralize the pathogen. That is why the acquired immune system needs at least several

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days to produce and activate a bigger amount of specific lymphocytes, see [1].

When foreign antigens enter an organism, the adaptive type of acquired immunity starts to function. The humoral immunity applies antibodies, which neutralize free viral particles, and cytotoxic T lymphocytes (CTL) destroy the infected cells. In the paper we present a model, which is a generalization of a basic model proposed by G. Marchuk [3] and a model proposed by D. Wodarz [7]. Similar mathematical models has been investigated in [4] and [5]. In our model we assume that the growth of the virus depends on the amount of the free viral particles that have entered the organism, and on the infected cells, wherein the viruses have propagated. The purpose of this paper is to illustrate the application of the mathematical and computational methods to the study of immunological processes.

2. Model Description

The interacting populations included in our model and their notations are the following: $x(t)$ - concentration of the susceptible uninfected cells of the target organ; $y(t)$ - concentration of the infected cells; $v(t)$ - concentration of the free virus particles; $w(t)$ - concentration of antibodies (immunoglobulins) specific for the virus; $z(t)$ - concentration of the CTLs. By $\overline{w}$ and $\overline{z}$ means the concentrations of the circulating antibodies and CTLs in the healthy organism, that are specific for the virus.The proposed model describes the time dynamics of the considered unknown functions, is represented by a system of the following five nonlinear ordinary differential equations (ODE):

$$\frac{dx(t)}{dt} = l - d \cdot x(t) - b_1 \cdot x(t) \cdot v(t), \tag{1}$$

$$\frac{dy(t)}{dt} = b_1 \cdot x(t) \cdot v(t) - a \cdot y(t) - p \cdot y(t) \cdot z(t), \tag{2}$$

$$\frac{dv(t)}{dt} = k \cdot y(t) \cdot v(t) - q \cdot v(t) \cdot w(t), \tag{3}$$

$$\frac{dw(t)}{dt} = g \cdot v(t) \cdot w(t) - h \cdot (w(t) - \overline{w}), \tag{4}$$

$$\frac{dz(t)}{dt} = c \cdot v(t) \cdot z(t) - b \cdot (z(t) - \overline{z}). \tag{5}$$

We suppose that the parameters d, b_1,a, p, k, q, g, h, c, b of the model (1)-(5) are non-negative, and $l > 0$, $\overline{w} > 0$, $\overline{z} > 0$.

Equation (1) describes the dynamics of the population of the susceptible uninfected cells.

Table 1: Individual parameter, units, biologically relevant description.

Parameter	Units	Relevant Biological Description
l	$\frac{cells}{(ml \times days)}$	Growth Rate (Uninfected cells)
d	$\frac{1}{days}$	Death Rate (Uninfected cells)
b_1	$\frac{ml}{(cells \times days)}$	Interaction Rate (Virus and Uninfected cells)
a	$\frac{1}{days}$	Death Rate (Infected cells)
p	$\frac{ml}{(cells \times days)}$	Interaction Rate (Infected cells and CTLs)
k	$\frac{ml}{(cells \times days)}$	Interaction Rate (Infected cells and Vi-ruses)
q	$\frac{ml}{(cells \times days)}$	Interaction Rate (Viruses and Antibodies)
g	$\frac{ml}{(cells \times days)}$	Interaction Rate (Infected cells and Vi-ruses)
h	$\frac{1}{days}$	Death Rate (Antibodies)
c	$\frac{ml}{(cells \times days)}$	Interaction Rate (Viruses and CTLs)
b	$\frac{1}{days}$	Death Rate (CTLs)

Equation (2) describes the dynamics of the population of the infected cells.

Equation (3) describes the time dynamics of the concentration of the free virus particles.

Equation (4) describes the dynamics of the concentration of the antibodies. Their production depends on the amount of the viruses.

Equation (5) describes the dynamics of the cytotoxic T lymphocytes.

3. Analysis of the Model

Theorem 1. *If the system (1)-(5) with initial conditions* $x(t_0) = x_0 > 0$,$y(t_0) = y_0 \geq 0$,$v(t_0) = v_0 \geq 0$,$w(t_0) = w_0 \geq 0$,$z(t_0) = z_0 \geq 0$, *possesses solution, then this solution is non-negative for every* $t \geq 0$.

Proof. Let us assume that there exist values of $t \geq 0$ such that $x(t) < 0$. From the initial condition $x(0) > 0$ and the continuity of the function $x(t)$ it follows that there exists an instant in time t_1 at which $x(t)$ changes its sign i.e. $x(t_1) = 0$, and let t_1 is the smallest value of t, for which $x(t_1) = 0$. From here we would have $\frac{dx}{dt} \leq 0$ when $t = t_1$. This would be a contradiction with

equation (1) giving

$$\frac{dx(t)}{dt} \mid_{t=t_1} = l - d \cdot x(t_1) - b_1 \cdot x(t_1) \cdot v(t_1) = l > 0.$$

Therefore the assumption about the possible negativity of $x(t)$ is incorrect.

From equation (3)

$$v(t) = v(0) \cdot e^{\int_0^t (k \cdot y(u) - q \cdot w(u)) du} \geq 0$$

when $t \geq 0$.

From equation (2)

$$y(t) = e^{-\int_0^t (p \cdot z(u) + a) du} \cdot [y(0) + \int_0^t b_1 \cdot x(u) \cdot v(u) \cdot e^{\int_0^t (p \cdot z(u) + a) du} du] \geq 0$$

as $y(0) \geq 0$, $x(t) \geq 0$ and $v(t) \geq 0$ when $t \geq 0$. From equation (4) we obtain

$$w(t) = e^{\int_0^t (g \cdot v(u) - h) du} \cdot [w(0) + \int_0^t h \cdot \overline{w} \cdot e^{-\int_0^t (g \cdot v(u) - h) du} du] \geq 0$$

when $t \geq 0$, as $w(0) \geq 0$ and $v(t) \geq 0$.

From(5)

$$z(t) = e^{\int_0^t (c \cdot v(u) - b) du} [z(0) + \int_0^t b \cdot \overline{z} \cdot e^{-\int_0^t (c \cdot v(u) - b) du} du] \geq 0$$

when $t \geq 0$.

So it has been proven that when the initial conditions are non-negative, if the model has a solution, this solution is non-negative. □

Theorem 2. *For every $T > 0$, on the interval [0; T] there exists an unique continuously differentiable solution to the system (1) - (5) with initial conditions $x(t_0) = x_0 > 0$, $y(t_0) = y_0 \geq 0$, $v(t_0) \geq 0$, $w(t_0) = w_0 \geq 0$, $z(t_0) = z_0 \geq 0$.*

Proof. The local existence of the solution follows from the continuity of the right hand sides [2]. The uniqueness of the solution follows from the continuity of the partial derivatives of the right-hand sides with respect to the unknown functions [2].

The functions $x(t)$, $y(t)$, $v(t)$, $w(t)$ and $z(t)$ are bounded on [0; T], therefore they receive their maximal and minimal values on [0; T]. It is trivial to prove that the nonlinear system (1) - (5) behaves not worse than a linear system. Therefore a global solution on [0; T] exists. □

4. Numerical Simulations of the Role of the Vaccination

Vaccines learn our immune system to produce specific antibodies and CTLs by mimicking a natural infection. Traditionally, there are two main types of vaccines: live virus vaccines and inactivated virus vaccines. Our simulations relate to the second type. With this type of vaccines, the immune response is humoral. The numerical simulations reflect the immune response of a vaccinated and an unvaccinated organism to a viral infection. The numerical simulations were made with ode15s of Matlab and $RelTol = 1 \cdot e^{-3}$ and $AbsTol1 \cdot e^{-6}$ that provides precision 0.001 for each point in time [6]. The parameter and initial values are chosen as follows :$l = 2$,$d = 0.2$,$b1 = 0.02$,$a = 0.2$,$k = 55$,$u = 1$, $q = 1.5$, $g = 0.1$, $h = 0.4$, $c = 0.1$, $b = 0.4$, $\overline{z} = 1$, $p = 0.1$, $x(0) = 1$, $y(0) = 0$, $v(0) = 0.151$, $w(0) = 0.0001$, $z(0) = 0.0001$. Fig.1 is obtained for $\overline{w} = 1$, and fig=2 for $\overline{w} = 10$.

From the graphs we can conclude that in the vaccinated organism, when too many specific for the virus antibodies circulate in the blood and lymph, the

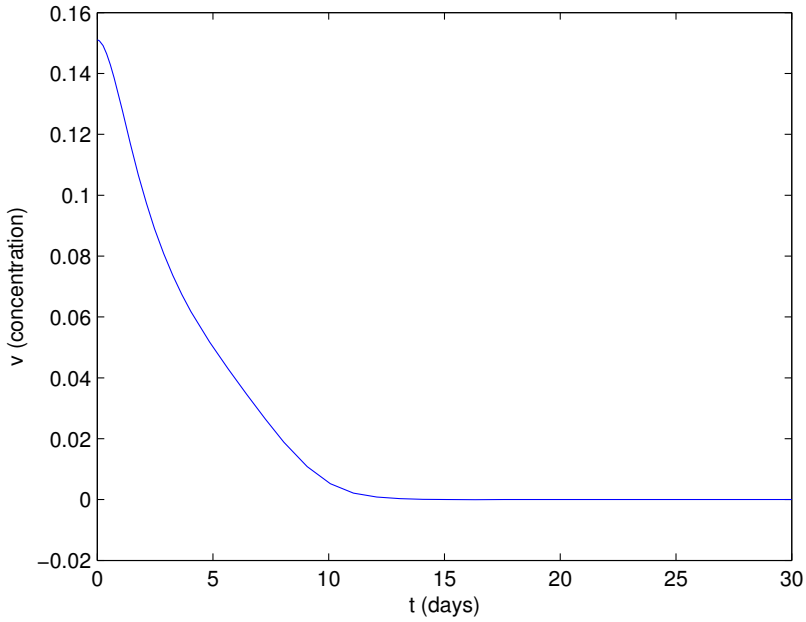

Figure 1: Dynamics of the populations of free viruses at infecting unvaccinated organism ($\overline{w} = 1$)

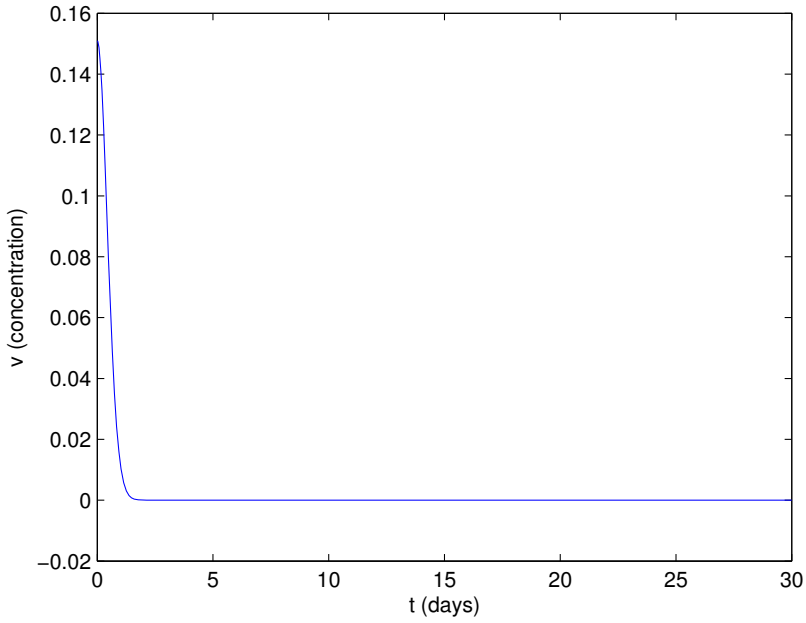

Figure 2: Dynamics of the populations of free viruses at infecting vaccinated organism ($\overline{w} = 10$)

free viruses are rapidly neutralized. This is a typical result, that is according with the medical data.

5. Conclusions

In the paper we have used a mathematical model to study some competition between a virus and the adaptive immune system. The new and the original one in our model is the assumption, that the growth of the virus depends on the amount of the free viral particles that have entered the organism, and on the infected cells, wherein the viruses have propagated. Our future research plans are related to application of the model to clinical data and development of the model for more detailed analysis of the immune reaction to viral infections.

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