Numerical Investigation of Adaptive Immune Response to Viral Infection

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Abstract. In this paper we present a new mathematical model describing acquired immune response to viral infection. The model is formulated as a system of six ordinary differential equations (ODE). Conditions for existence, uniqueness and non-negativity of the solutions are studied. Numerical simulations for the case of dominating cellular immunity and various initial values of concentrations of virus particles are presented and discussed.

Keywords: Numerical simulations · Differential equations · Nonlinear dynamics · Kinetic model · Virus · Immune system

1 Introduction

The use of mathematical models for investigations of the behavior of immune system of organisms infected by pathogens such as viruses or organisms suffering from cancer, can be effective tool for determining the tendencies of the disease under medical treatments or without them [4–6,8–10,12].

An organism that meets a specific antigen for the first time possesses only a small amount of lymphocytes able to recognize and neutralize the pathogen. That is why the acquired immune system needs at least several days while bigger amount of specific lymphocytes are produced and activated. During this period of time the fight against the pathogen is performed by the innate immunity, which functions quickly but does not possess specificity and efficiency. As a result the infection can become strong and difficult to eradicate [1]. That is why the acquired (or adaptive) immune mechanisms are often needed in order to clean the infection.

When foreign antigens enter an organism, both humoral and cellular types of acquired immunity start to function. Their mechanisms of functioning are different. The humoral immunity applies antibodies, which neutralize free viral particles. The cellular immunity system employs cytotoxic T lymphocytes (CTL), which destroy infected host cells [1].

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In our paper we present a model, which is a generalization of a basic model proposed by G. Marchuk [10] and a model proposed by D. Wodarz [12]. In our model we assume that the growth of the virus depends on the amount of the infected cells as well as on the amount of the free viral particles that have entered the organism. Additionally, we suppose that the production of antibodies and CTL depends on the degree of the damage of the target organ: the higher is the damage, the weaker is the production of antibodies and CTL.

The purpose of this paper is to illustrate the application of mathematical and computational methods to immunology. The contents of our work are organized as follows. In Sect. 2 we describe our mathematical model of acquired immune response to viral infection. The model is a complicated system of ordinary differential equations. Theorem for existence, uniqueness and non-negativity of its solution is proved. In Sect. 3 we present some results of our simulations and comment their biological meaning.

2 Mathematical Model

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;
- $z(t)$ - concentration of CTL specific for the virus;
- $w(t)$ - concentration of antibodies (immunoglobulins) specific for the virus;
- $m(t)$ - degree of the target organ damage.

The proposed model describing the time dynamics of the considered variables consists of the following six ordinary differential equations (ODE):

$$\dot{x}(t) = L - dx(t) - \beta x(t)v(t), \tag{1}$$

$$\dot{y}(t) = \beta x(t)v(t) - ay(t) - py(t)z(t), \tag{2}$$

$$\dot{v}(t) = ky(t)v(t) - qv(t)w(t), \tag{3}$$

$$\dot{z}(t) = c\xi(m)v(t)z(t) - \delta(z(t) - \bar{z}) - by(t)z(t), \tag{4}$$

$$\dot{w}(t) = \gamma\xi(m)v(t)w(t) - h(w(t) - \bar{w}) - rv(t)w(t), \tag{5}$$

$$\dot{m}(t) = sv(t) - nm(t). \tag{6}$$

We suppose that the parameters of the model (1) - (6) are non-negative constants and parameters $L, \bar{z}$ and $\bar{w}$ are positive. We look for solution such that the unknown functions are continuously differentiable with non-negative initial conditions.

Equation (1) describes the dynamics of the population of the susceptible uninfected cells. The meaning of its parameters is the following: L describes the production of uninfected cells; d - the rate of decrease of uninfected cells due

to their natural death; β - the rate of decrease of uninfected cells due to their infection by virus.

Equation (2) describes the dynamics of the population of the infected cells. Parameter a characterizes the decrease of concentration of infected cells due to their natural death; p denotes the rate of decrease of infected cells due to their destruction by CTL.

Equation (3) describes the time dynamics of the concentration of free virus particles. The viruses are produced inside the infected cells. The meaning of its parameters is the following: k denotes the rate of production of virus particles inside the infected cells; q - the decrease of virus particles due to their neutralization by antibodies.

Equation (4) describes the dynamics of CTL. The meaning of its parameters is the following: c characterizes the production of CTL; δ - the natural death of CTL; b - the decrease of concentration of CTL due to their killing activity against infected cells; $\bar{z}$ is the amount of CTL circulating in a healthy organism.

Equation (5) describes the dynamics of the concentration of antibodies. Their production depends on the amount of viruses and on the degree of target organ damage. The meaning of its parameters is the following: γ characterizes the production of antibodies; h - the rate of their natural death; r - the decrease of concentration of antibodies due to their antiviral activity; $\bar{w}$ is the amount of antibodies circulating in a healthy organism.

Equation (6) describes the degree of target organ damage. The damage depends on the amount of virus particles and can decrease due to repair processes in the organism. The meaning of its parameters is the following: s denotes the rate of damage of the target organ by viruses; n - the rate of recovery of the target organ.

$\xi(m)$ (participating in Eqs. (4) and (5)) is assumed to be non-increasing non-negative continuous function that accounts for the violation of the normal functioning of the immune system due to the damage of the target organ [1]. We assume that there exists its limit value $\bar{m} \in (0, 1)$. If the value of m is less than $\bar{m}$ we suppose that the damage of the infected organ is small and it does not affect the efficiency of the immune system. On the other hand, if m is greater than $\bar{m}$, we suppose that the damage of the infected organ is considerable and the immune response is weakened. The form of the function $\xi(m)$ is not uniquely defined. It can be chosen such that $\xi(m) = 1$ for $m \leq \bar{m}$ and $\xi(1) = 0$. For example it can be defined as follows:

$$\xi(m) = \begin{cases} 1 & \text{for } 0 \leq m \leq \bar{m}, \\ \frac{m-1}{\bar{m}-1} & \text{for } \bar{m} < m \leq 1. \end{cases} \tag{7}$$

Now we formulate theorems for non-negativity, existence and uniqueness of the solution to model (1) - (6).

Theorem 1. *If the system (1) - (6) with initial conditions* $x(0) = x_0 > 0$, $y(0) = y_0 \geq 0$, $v(0) = v_0 \geq 0$, $z(0) = z_0 = \bar{z} > 0$, $w(0) = w_0 = \bar{w} > 0$, $m(0) = m_0 \geq 0$ *possesses solution then this solution is non-negative for every* $t \geq 0$.

Proof. Consider Eq. (1). Let us assume that that there exist values of $t > 0$ 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. $x(t) > 0$ for $t < t_1$, $x(t_1) = 0$ and $x(t) < 0$ for $t > t_1$). From here we would have $\dot{x}(t_1) < 0$. This would be a contradiction with Eq. (1) giving $\dot{x}(t_1) = L > 0$. Therefore the assumption about the possible negativity of $x(t)$ is incorrect.

The solution to Eq. (3) can be written in the form:

$$v(t) = v(0)e^{\int_0^t [ky(u) - qw(u)]du} \geq 0 \text{ for } t \geq 0.$$

From the non-negativity of $x(t)$ and $v(t)$ the non-negativity of $y(t)$ follows, since from Eq. (2) we obtain:

$$y(t) = e^{-\int_0^t [pz(u)+a]du} \left[y(0) + \int_0^t \beta x(u)v(u)e^{\int_0^t [pz(u)+a]du} du \right].$$

From Eq. (4) the non-negativity of $z(t)$ follows, since

$$z(t) = e^{\int_0^t [c\xi(m)v(u) - \beta - by(u)]du} \left[z(0) + \int_0^t \delta \bar{z} e^{-\int_0^t [c\xi(m)v(u) - \beta - by(u)]du} du \right].$$

Similarly, from Eq. (5) the non-negativity of $w(t)$ follows, since

$$w(t) = e^{\int_0^t [\gamma\xi(m)v(u) - h - rv(u)]du} \left[w(0) + \int_0^t h\bar{w} e^{-\int_0^t [\gamma\xi(m)v(u) - h - rv(u)]du} du \right].$$

Finally, from Eq. (6) the non-negativity of $m(t)$ follows, since

$$m(t) = e^{-nt} \left[m(0) + \int_0^t sv(u)e^{nu} du \right].$$

Theorem 2. *For every $T > 0$ on the interval $[0, T]$ there exists a unique continuously differentiable solution to the system (1) – (6) with initial conditions $x(0) = x_0 > 0$, $y(0) = y_0 \geq 0$, $v(0) = v_0 \geq 0$, $z(0) = z_0 = \bar{z} > 0$, $w(0) = w_0 = \bar{w} > 0$, $m(0) = m_0 \geq 0$.*

Proof. The local existence of the solution follows from the continuity of the right-hand sides (Peano theorem [7]). The uniqueness of the solution follows from the continuity of the partial derivatives of the right-hand sides with respect to the unknown functions [7].

It can be shown that the functions $x(t)$, $y(t)$ and $v(t)$ are bounded on $[0, T]$. Let us denote their maximal values with X, Y and V respectively. The following a priory bounds can be established for the solution on $[0, T]$:

$$\dot{x}(t) \leq L - dx(t), \tag{8}$$

$$\dot{y}(t) \leq \beta X v(t) - ay(t), \tag{9}$$

$$\dot{v}(t) \leq kYv(t), \tag{10}$$

$$\dot{z}(t) \leq cVz(t) - \delta(z(t) - \bar{z}), \tag{11}$$

$$\dot{w}(t) = \gamma Vw(t) - h(w(t) - \bar{w}), \tag{12}$$

$$\dot{m}(t) = sv(t) - nm(t). \tag{13}$$

By the estimations (8) -(13) we see that, the nonlinear system (1) – (6) behaves not worse than a linear system. Therefore a global solution on $[0, T]$ exists.

3 Numerical Experiments and Discussion

The Cauchy problem (1)–(6) consisting of six nonlinear ODE is solved numerically. The system is solved by using the code `ode15s` from the Matlab ODE suite with $RelTol = 10^{-3}$ and $AbsTol = 10^{-4}$. `ode15s` is a multistep solver using numerical differential formulae (see, e.g. [11]).

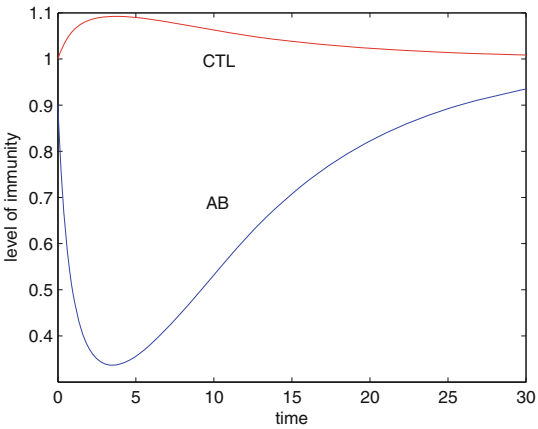

Fig. 1. Concentrations of antibodies (AB) and CTL at $v_0 = 0.1$ (low initial virus load).

The aim of our numerical experiments is to study the role of the magnitude v_0 of the initial virus load for the outcome of the competition between the immune system and the viral infection in the case when both parts of the immune systems (the cellular and the humoral immunity) are strong.

The initial conditions and parameters of the model have been set to simulate a full adaptive (humoral and cellular) immune response to viral infection. We have assumed the initial presence of susceptible uninfected cells, virus particles, antibodies and precursor CTL, as well as the initial absence of infected cells and effector CTL. The initial values for populations and the parameters have been set as follows:

$$x(0) = 1, \quad y(0) = 0, \quad z(0) = 0.9, w(0) = 1, m(0) = 0,$$

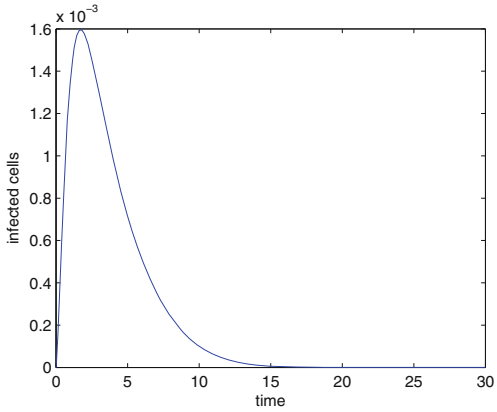

Fig. 2. Concentration of infected cells at $v_0 = 0.1$ (low initial virus load).

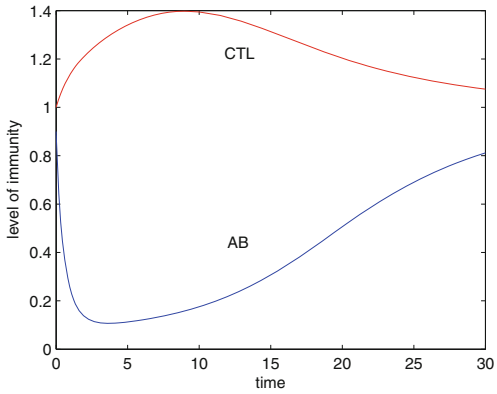

Fig. 3. Concentrations of antibodies and CTL at $v_0 = 0.2$ (high initial virus load).

$$L = 10, \quad d = 2, \beta = 0.01, \quad a = 0.1,$$
$$p = 1, \quad k = 1, \quad q = 1,$$
$$c = 1, \ \delta = 0.1, \ b = 10, \ \gamma = 0.5, \ h = 0.1,$$
$$r = 10, \ s = 10, \ n = 1.5.$$

Additionally, we assume that $\xi(m) = 1$ for every value of m and chose various values of the parameter v_0 specified in the captions of the figures.

Results of our numerical experiments are presented in Figs. 1–4. In the first part of our numerical experiments we consider the case of low initial virus load ($v_0 = 0.1$). The results for the dynamics of concentrations of antibodies and CTL as well as of infected cells are presented in Figs. 1 and 2 respectively.

In the second part of our numerical experiments we consider the case of high initial virus load ($v_0 = 0.2$). The results are presented in Figs. 3 and 4.

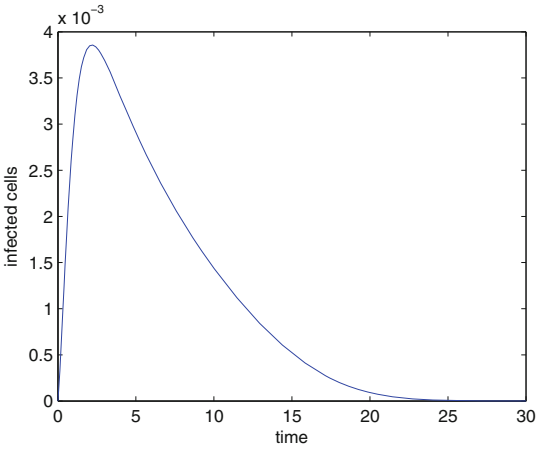

Fig. 4. Concentration of infected cells at $v_0 = 0.2$ (high initial virus load).

Our results show that in the presence of both cellular and humoral types of immunity, the strength and prolongation of infection does not depend significantly of the initial virus load. Strong cellular immunity kill the infected cells, which are needed for the viral replication. On the other hand, strong humoral response is able to destroy the free viral particles. Working in cooperation, the both adaptive immune mechanisms are able to eradicate the infection very effectively. Thus, the enhancement of the immune system is of crucial importance in the fight against viral infections.

We conclude that numerical simulations utilizing mathematical models may lead to a reduction in the quantity of experimental studies performed in virology. One of our future aims includes the determination of the parameters of the system (1)–(6) in order to fit existing experimental and clinical data. Another future plan is investigation of the role of function $\xi(m)$.

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