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Numerical modelling of the competition between the adaptive immune system and virus*†

by

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Abstract: We present and analyze numerically a mathematical model of interactions between adaptive immune system and viral infection. The model is a bilinear system of partial integro-differential equations of Boltzmann type. It is a generalization of the recently proposed kinetic models that consider particular (namely, the cell-mediated and the humoral) immune mechanisms used in the fight against viral infections. We use Matlab to solve complicated system of equations, present the results of computer simulations and explain their immunological meaning. The results show that the model can describe in a better way (in comparison with the previous kinetic models) real biological situations and is able to illustrate various methods of therapy.

Keywords: numerical modelling, kinetic theory, active particles, integro-differential equations of Boltzmann type, nonlinear dynamics, virus, adaptive immune system.

1. Introduction

In this paper we present an application of computational methods to immunology. In this field mathematical methods are extensively used for the quantification of the time dynamics of interacting populations of immune cells and pathogens, for example between lymphocytes and viruses. Many immunological processes involve very complex interactions and dynamics. Mathematical and computer models are powerful tools for interpretation and understanding of experimental and clinical data and allow to obtain interesting and valuable insights into possible outcomes of interactions between foreign antigens and immune system. The application of computational approach to immunology

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facilitates the clarification of the factors that are necessary to explain experimental and clinical observations, the determination of these factors in precise terms and the evaluation of the smallest number of factors needed to explain the observed data. Moreover, computational methods can suggest new investigations for calculations of these significant factors providing in this way a basis for the design of new experiments. This may influence the development of new directions of immunological research. In addition, analysis and simulations of mathematical models can reduce the amounts of experiments (which are usually lengthy and expensive) for development of treatment strategies (see, e.g., Bellomo and Preziosi, 2000, and Asquith and Bangham, 2003).

The purpose of the present paper is to analyze numerically a mathematical model that describes the adaptive immune response to viral infection (see, e.g., Pinchuk, 2002, and Abbas and Lichtman, 2004, for more immunological details and references). The model is a generalization of the recently proposed in Kolev (2008a,b) model of humoral immune response to virus and the model describing the cellular immune response to viruses that has been proposed in Kolev (2009).

These models are formulated within the framework of the so-called "kinetic theory for active particles" (see, e.g., Bellouquid and Delitala, 2005, 2006; Bellomo, 2008; Bellomo and Forni, 2008; Bellomo et al., 2009). A characteristic feature of this theory is that, in addition to geometrical and mechanical variables used for the description of multi-particle systems in the mathematical kinetic theory, a variable describing the biological activity of interacting cellular and molecular populations is introduced in the kinetic theory for active particles. More details on the latter approach can be found, for instance, in Bellomo and Forni (2008), as well as in Section 2 of the present paper, where we describe the mathematical structure of the model. The usefulness of the kinetic theory for active particles in immunology (cancer research) can be illustrated by the model of Jackiewicz et al. (2009), which has been shown to fit well the laboratory data from Calvo et al. (2002) for prostate tumor progression *in vivo*. Another example is the paper by Drucis et al. (2010), devoted to the application of a model formulated in terms of Boltzmann type equations to clinical data of patients with breast cancer.

Papers by Kolev (2008a,b) present a kinetic model that describes the immune response performed by one of the two main adaptive defense mechanisms of a higher biological organism, namely the *humoral* immune response, to virus infections. In the model the interactions between virus particles and the populations of uninfected cells, infected cells and antibodies (which are able to destroy free viral particles (see, e.g., Abbas and Lichtman, 2004) are taken into account. In Kolev (2008a) the role of the ability of virus to kill infected cells is studied numerically. In Kolev (2008b) some conditions for existence and uniqueness of the solution to the Cauchy problem corresponding to the model of humoral immune response to virus are presented. The influence of the rate of viral replication inside infected cells on the outcome of the interaction between the virus and the host body is analyzed numerically.

The second important part of the adaptive immunity called *cellular* (or *cell-mediated*) immunity (see, e.g., Lydyard et al., 2000) is considered in Kolev (2009). The kinetic model presented there gives an account of the interactions between virus particles and the populations of uninfected cells, infected cells and cytotoxic T lymphocytes (CTLs), which are able to destroy infected cells (see, e.g., Kuby, 1997).

These previous models consider *only one* of the two main components of the adaptive immunity. The purpose of the paper is to present and analyze numerically a generalized kinetic model that describes *both* the cellular and the humoral immune mechanisms in the fight against viral infections.

The organization of the paper is as follows. In Section 2 we present briefly the interacting populations and describe the mathematical model. Conditions for existence and uniqueness of the solution to the corresponding initial value problem are considered. Results of numerical simulations for the model are presented in Section 3. Finally, Section 4 includes our concluding remarks and future research directions.

2. Interacting populations and mathematical model

Various viruses cause diseases, some of which, like AIDS, hepatitis etc. are very dangerous. Viruses are intracellular pathogens. In order to reproduce, they must enter susceptible cells and use the metabolic machinery of the host cells. The viruses can replicate inside the infected cells, thus producing new viral particles that may leave the infected cells. The virus can destroy some of the host cells (see, e.g., Wodarz and Bangham, 2000; Wodarz et al., 2000, and Wodarz, 2007).

The immune system can apply innate and adaptive responses against the viruses. The adaptive immunity may be subdivided into two main types, called cell-mediated (or cellular) immunity (CMI) and humoral immunity.

The main immune cells involved in the CMI are T lymphocytes. They include cytotoxic T lymphocytes (CTLs) and T helper (T_h) cells. The CTLs can destroy infected cells. T helper cells produce cytokines and signals inducing the proliferation and activation of the immune cells.

The humoral response is performed by immunoglobulins (antibodies (ABs)), which are produced by B lymphocytes. The humoral response helps in the eradication of the free virus particles (see, e.g., Kuby, 1997, and Lydyard et al., 2000).

In this paper we present a model that generalizes the models proposed in Kolev (2008a,b) (describing the humoral response to virus) and Kolev (2009) (that describes the interactions between CMI and viral infection). We consider five interacting populations, namely the populations of uninfected T helper cells, infected T helper cells, free virus particles, antibodies and cytotoxic T lymphocytes. These populations play a significant role in the interaction between the

adaptive immune system and viral infection. They are denoted by corresponding subscripts $i = 1, 2, ..., 5$.

The interacting individuals are characterized by a microscopic state variable $u \in [0, 1]$, that describes the specific biological function of each individual, which in the kinetic theory for active particles is called *activation state* (or *activity*) (see, e.g., Bellomo and Forni, 1994; Arlotti et al., 2003; De Lillo et al., 2007; Bellomo and Delitala, 2008; Bellomo et al., 2008; De Angelis and Lodz, 2008). In our model we introduce the following meaning of activity for the populations $i = 2, 3, 4, 5$.

The state of activity for the population $i = 2$ of infected helper T cells denotes the virus mediated killing rate of the infected cells as well as the rate of viral reproduction inside the host cell. We assume that the T_h cells infected by cytopathic viruses, i.e. viruses able to shorten the life-span of the host cells at a higher rate (see, e.g., Kagi et al., 1995; Wodarz and Krakauer, 2000), possess higher activation states. Moreover, the infected cells with higher states of activity are supposed to produce larger amount of virus particles.

The activation state for the population $i = 3$ of free virus particles describes their ability to infect the susceptible T_h cells. The higher the ability of a virus to enter a cell, the higher the activity of the virus.

The activation state for the population $i = 4$ of antibodies is supposed to describe their ability to kill the viruses and to lower their states of activity.

We assume also that the activity for the population $i = 5$ of the CTLs describes their ability to destroy the infected T_h cells.

In our model, the presence of internal degree of freedom of the population $i = 1$ of the uninfected T_h cells is neglected. As a simplification of reality, we suppose that the population $i = 1$ is independent of their activation states.

Further, we introduce the following notation. Let

$$f_i(t, u), \quad f_i : [0, \infty) \times [0, 1] \to R_+, \quad i = 1, \ldots, 5,$$

denote the distribution density of the i-th population with state of activity $u \in [0, 1]$ at time $t \geq 0$. Moreover, we denote by

$$n_i(t) = \int_0^1 f_i(t, u)du, \quad n_i : [0, \infty) \to R_+, \quad i = 1, \ldots, 5, \tag{1}$$

the concentration of the i-th population at time $t \geq 0$.

Due to the supposed independency of the distribution function $f_1(t, u)$ of the activation state u

$$f_1(t, u) = n_1(t), \quad \forall u \in [0, 1], \quad t \geq 0.$$

The kinetic theory of active particles studies the evolution of a system of n interacting populations presented by their distribution functions f_i. The dynamics

of the system can be described by Boltzmann type equations of the following general form (see Arlotti et al., 2000 and 2002):

$$\frac{\partial f_i}{\partial t}(t,u) = J_i[f](t,u), \quad i = 1,...,n, \quad f = (f_1, f_2, ..., f_n),$$
$$J_i[f](t,u) = G_i[f](t,u) - L_i[f](t,u) + S_i[f](t,u),$$

where G_i is the gain term due to binary interactions that drive cells into the $i-$th population with state of activity u:

$$G_i[f](t,u) = \sum_{j,k=1}^{n} \int_0^1 \int_0^1 a_{jk}(v,w) A_{jk}^{(i)}(v,w;u) f_j(t,v) f_k(t,w) dv dw;$$

the operator L_i is the loss term due to binary interactions that change the activation state u or drive cells out of the $i-$th population:

$$L_i[f](t,u) = f_i(t,u) \sum_{j=1}^{n} \int_0^1 a_{ij}(u,v) f_j(t,v) dv;$$

S_i is the term describing the production of cells of the $i-$th population with state of activity u due to any artificial inlet.

The interactions between pairs of cells/particles may change their states of activity, as well as the size of the populations by destroying or creating cells/particles. They may be described by the following functions:

$a_{ij}(u,v)$ - the rate of interaction between the cells/particles of the $i-$th population with state of activity u and the cells/particles of the $j-$th population with state of activity v, and the function

$A_{jk}^{(i)}(v,w;u)$ - describing the transition into the $i-$th population with state of activity u due to the interaction of an individual from the $j-$th population with state of activity v an individual from the $k-$th population with state of activity w.

Now we proceed with the description of our generalized mathematical model of the competition between the virus and the adaptive immunity. The following important processes of production, destruction and change of activity of the individuals are taken into account.

As a result of the interactions between free viral particles and susceptible uninfected T helper cells the latter may become infected. Therefore, they move from the population denoted by $i = 1$ into the population denoted by $i = 2$. The corresponding encounter rate is assumed to be

$$a_{13}(v,w) = d_{13} w, \quad \text{for } v, w \in [0,1].$$

From this assumption it follows that the uninfected T_h cells become infected by the virus with a rate proportional to their concentration as well as to the

activation state of the virus. Another assumption in our model is that uninfected T_h cells are produced by the organism at a rate described by the function $S_1(t)$. The last factor influencing the size of the population $i = 1$, taken into account in our model, is the assumed natural death of the uninfected cells at the rate described by the parameter d_{11}. The resulting Boltzmann equation for the temporal evolution of the population $i = 1$ of the uninfected cells is:

$$\frac{d}{dt}n_1(t) = S_1(t) - d_{11}n_1(t) - d_{13}n_1(t)\int_0^1 vf_3(t,v)dv \tag{2}$$

This equation is exactly the same as the equation for the dynamics of the uninfected T helper cells proposed in the simpler models of cellular immune response by Kolev (2009) and of humoral response to viral infection by Kolev (2008a,b).

The following processes and factors are assumed to influence the size of population $i = 2$. The number of infected T helper cells increases due to the viral infection of susceptible cells from population $i = 1$. The corresponding transition probability density is supposed to be

$$A_{13}^{(2)}(v,w;u) = \frac{p_{13}^{(2)}(1-u)}{d_{13}}.$$

From this assumption it follows that the increase in the number of infected cells is proportional to the activity of the viruses. The activity of the newly infected T_h cells is supposed to be low in accordance with the experimental observations that some time is needed for the viral replication after entering the host cell (see, e.g., Wodarz, 2007). In order to assure the equality between the corresponding loss term in equation (2) and gain term in equation (2) describing the number of cells shifted out of population $i = 1$ into population $i = 2$ due to the process of infection, the condition $p_{13}^{(2)} = 2d_{13}$ should be satisfied.

In our model we consider two possible causes of destruction of infected T_h cells: due to the killing ability of the virus and of the CTLs. The rate of destruction of the infected cells by the virus is assumed to be proportional to the states of activity of the cells. In our model it is described by the loss term $d_{22}uf_2(t,u)$. The encounter rate of CTLs with infected cells is assumed to be

$$a_{25}(v,w) = d_{25}w, \quad \text{for } v,w \in [0,1].$$

From this assumption it follows that the rate of destruction of infected cells by CTLs is proportional to the state of activity of the CTLs.

In addition, we consider possible increase in the activation state of the infected cells due to the replication of the viral particles inside the infected cells, described by the conservative term

$$CA_2(t,u) = c_{22}\left(2\int_0^u (u-v)f_2(t,v)dv - (1-u)^2 f_2(t,u)\right). \tag{3}$$

The resulting Boltzmann equation for the temporal evolution of the population $i = 2$ of the infected cells is:

$$\frac{\partial f_2}{\partial t}(t,u) = p_{13}^{(2)}(1-u)n_1(t)\int_0^1 v f_3(t,v)dv - \overbrace{d_{25}f_2(t,u)\int_0^1 v f_5(t,v)dv}^{\text{cell-mediated immunity}}$$
$$-d_{22}u f_2(t,u) + c_{22}\left(2\int_0^u (u-v)f_2(t,v)dv - (1-u)^2 f_2(t,u)\right). \qquad (4)$$

Equation (2) is exactly the same as the corresponding equation in the model of cell-mediated response to virus by Kolev (2009). It is more general than the equation describing the dynamics of the infected cells in the model of humoral immune response by Kolev (2008a,b) where the overbraced term in equation (2) expressing the destruction of cells by CTLs is absent.

The following processes and factors are assumed to influence the size of the population $i = 3$. The viruses are intracellular pathogens that need the metabolic machinery of the host cells in order to reproduce (see, e.g., Wodarz, 2007). The rate of viral replication inside the host cells is supposed to be proportional to the activation state of the infected cells and is characterized by parameter $p_{22}^{(3)}$.

We consider two possible causes of destruction of free viruses: due to their natural death (characterized by parameter d_{33}) and due to their destruction by antibodies. The encounter rate of viruses with ABs is assumed to be

$$a_{34}(v,w) = d_{34}w, \quad \text{for } v,w \in [0,1].$$

From this assumption it follows that the rate of destruction of viruses by ABs is proportional to the state of activity of the ABs.

The resulting Boltzmann equation for the temporal evolution of the population $i = 3$ of the free viruses is:

$$\frac{\partial f_3}{\partial t}(t,u) = p_{22}^{(3)}\int_0^1 v f_2(t,v)dv - d_{33}f_3(t,u) - \underbrace{d_{34}f_3(t,u)\int_0^1 v f_4(t,v)dv}_{\text{humoral immunity}}. \qquad (5)$$

Equation (5) is similar to the corresponding equation in the model of humoral response to virus by Kolev (2008a,b) where additional terms for possible change of activity of the virus are present. Equation (5) is more general than the equation describing the dynamics of the virus in the model of cell-mediated immune response by Kolev (2009), where the underbraced term expressing the destruction of viruses by ABs is absent.

The following processes and factors are assumed to influence the size of the populations $i = 4$ and $i = 5$.

We assume that the interactions between viruses and antibodies lead to the production of ABs. The corresponding encounter rate is supposed to be

$$a_{34}(v,w) = p_{34}^{(4)} w, \quad \text{for } v,w \in [0,1].$$

The corresponding transition probability density is assumed to be

$$A_{34}^{(4)}(v,w;u) = \frac{(1-u)}{w}.$$

The activity of the newly produced ABs is supposed to be low in accordance with the experimental evidence that they need time for development and activation (see, e.g., Kuby, 1997).

We assume that the interactions between viruses and uninfected cells lead to the production of CTLs (see, e.g., Lydyard et al., 2000). The corresponding encounter rate is supposed to be

$$a_{13}(v,w) = p_{13}^{(5)} w, \quad \text{for } v,w \in [0,1].$$

The corresponding transition probability density is assumed to be

$$A_{13}^{(5)}(v,w;u) = \frac{(1-u)}{w}.$$

The activity of the newly produced CTLs is supposed to be low (see, e.g., Kuby, 1997).

In our model we include also linear terms describing the natural death of ABs and CTLs characterized by parameters d_{44} and d_{55}, respectively.

The resulting Boltzmann equation for the temporal evolution of the population $i = 4$ of antibodies is:

$$\frac{\partial f_4}{\partial t}(t,u) = p_{34}^{(4)}(1-u)\int_0^1 f_3(t,v)dv \int_0^1 f_4(t,v)dv - d_{44} f_4(t,u). \tag{6}$$

Equation (6) is similar to the corresponding equation in the model of humoral response to virus by Kolev (2008a,b) where additional terms for possible change of activity of the ABs are present. Equation (6) is absent in the model of cell-mediated immune response by Kolev (2009), which does not consider the role of the ABs.

The resulting Boltzmann equation for the temporal evolution of the population $i = 5$ of CTLs is:

$$\frac{\partial f_5}{\partial t}(t,u) = p_{13}^{(5)}(1-u) n_1(t) \int_0^1 f_3(t,v)dv - d_{55} f_5(t,u). \tag{7}$$

This equation is exactly the same as the equation for the dynamics of the CTLs proposed in the simpler models of cellular immune response by Kolev (2009). Equation (7) is absent in the model of humoral response to virus by Kolev (2008a,b), which does not consider the role of the CTLs.

The presented generalized model (2), (2)-(7) has to be supplemented with nonnegative initial conditions

$$n_1(0) = n_1^{(0)}, \quad f_i(0,u) = f_i^{(0)}(u), \quad i = 2,3,4,5. \tag{8}$$

All parameters of the system (2), (2)-(7) denoted by $p_{ij}^{(k)}$, d_{ij} and c_{ij} are supposed to be nonnegative and $p_{13}^{(2)} = 2d_{13}$.

Now, let us consider some properties of the solution to the initial value problem (2), (2)-(8). We introduce the following notation:

$$\mathbf{X} = \big\{\mathbf{f} = (n_1, f_2, ..., f_5) : |n_1| < \infty, \text{ and } f_i \in L_1(0,1)\,, \text{ for } i = 2,3,4,5\big\},$$
$$\mathbf{X}^+ = \big\{\mathbf{f} = (n_1, f_2, ..., f_5) \in \mathbf{X} : n_1 \geq 0, \text{ and } f_i \geq 0\,,\ i = 2,3,4,5, \text{a.e.}\big\}\,.$$

We have the following theorem.

THEOREM 1 *Let $S_1 \in C^0\big([0,\infty); R_+\big)$. For every $T > 0$ there exists a unique solution*

$$\mathbf{f} \in C^0\big([0,T]; \mathbf{X}\big) \cap C^1\big((0,T); \mathbf{X}\big)$$

to system (2), (2)-(7) with the initial datum $\mathbf{f}^{(0)} = (n_1^{(0)}, f_2^{(0)}, ..., f_5^{(0)})$, $\mathbf{f}^{(0)} \in \mathbf{X}^+$. The solution satisfies $\mathbf{f}(t) \in \mathbf{X}^+\,, \forall\, t \in [0,T]$.

Proof. It is easy to check that the operators defined by the right-hand sides of Eqs. (2), (2)-(7) are Lipschitz–continuous in $\mathbf{X}$. Therefore, local existence and uniqueness follows. Standard proof can be carried out for instance by transforming system (2), (2)-(7) into corresponding integral system and applying the Banach fixed point theorem, similarly to a proof of Picard's theorem, see, e.g., Kolmogorov and Fomin (1975) and Belleni-Morante (1979).

The nonnegativity of the solution can be easily proved by the use of the successive approximation method (see, e.g., Arkeryd, 1972; Arlotti and Lachowicz; 1996, and Arlotti et al., 2000).

It remains to find *a priori* estimates for the solution. From the continuity of $S_1(t)$ and Eq. (2) it follows that:

$$\frac{d}{dt} n_1(t) \leq \sup_{[0,T]} S_1(t), \quad n_1(t) \leq t \sup_{[0,T]} S_1(t). \tag{9}$$

Therefore, the concentration $n_1(t)$ of uninfected cells is bounded on each finite time interval $[0,T]$.

Further, it is easy to check that operator (3) is conservative in L_1 sense, i.e.:

$$\int_0^1 C A_2(t,u) du = 0.$$

Thus, integration of Eq. (2) from 0 to 1 with respect to u yields:

$$\frac{d}{dt}n_2(t) = 0.5p_{13}^{(2)}n_1(t)\int_0^1 vf_3(t,v)dv - n_2(t)\Big[d_{25}\int_0^1 vf_5(t,v)dv + 0.5d_{22}\Big]. \quad (10)$$

Taking into account the relation $p_{13}^{(2)} = 2d_{13}$, after summing up Eqs. (2) and (10) we obtain:

$$\frac{d}{dt}\big(n_1(t)+n_2(t)\big) = S_1(t) - d_{11}n_1(t) - n_2(t)\Big[d_{25}\int_0^1 vf_5(t,v)dv + 0.5d_{22}\Big]. \quad (11)$$

Due to the nonnegativity of $f_5(t,v)$, it follows from (11) that the sum of the concentrations of infected and uninfected cells $n_1(t)+n_2(t)$ is bounded on each finite time interval $[0,T]$. Since $n_1(t)$ is bounded, it follows that $n_2(t)$ is also bounded on $[0,T]$.

From the boundedness of $n_1(t)$ and $n_2(t)$, after integration of Eqs. (5)-(7) from 0 to 1 with respect to u, the boundedness of $n_3(t)$, $n_4(t)$ and $n_5(t)$ on $[0,T]$ follows. This proves the boundedness of $f_i(t)$, $i = 2,3,4,5$ on each finite time interval.

From the obtained *a priori* estimates it follows that the solution to the initial value problem (2), (2)-(8) exists and it is unique on each finite time interval $[0,T]$, which finishes the proof. ∎

3. Numerical simulations

The initial value problem corresponding to the model (2), (2)-(7) consisting of five nonlinear partial integro-differential equations is solved numerically. In the first step, we discretize the last four equations of the system (2), (2)-(7) in the activation state variable $u \in [0,1]$ by constructing a uniform grid

$$u_i = i\Delta u, \quad i = 0,1,\ldots,N, \quad (12)$$

where Δu and N are chosen in such a way that $N\Delta u = 1$ and N is a positive integer. This yields a system of $4N+5$ ordinary differential equations allowing to find approximate solutions to the model (2), (2)-(7).

This system of ordinary differential equations corresponding to the discretized model (2), (2)-(7) is solved by using the code `ode15s` from the Matlab ODE suite (see, e.g., Shampine and Reichelt, 1997) with $RelTol = 10^{-3}$ and $AbsTol = 10^{-4}$. The participating integrals are approximated by the use of the composite Simpson's rule (see, e.g., Volkov, 1990, and Gautschi, 1997). The obtained numerical solutions of the discretized system are then used to compute the approximations to the functions $n_2(t)$, $n_3(t)$, $n_4(t)$ and $n_5(t)$ by the use of Eq. (1).

The aim of our numerical experiments is to analyze the role of cellular and humoral immunity against viral infection.

The values of the parameters of the model are set as follows:

$$S_1(t) = 100, \quad t \geq 0,$$
$$d_{22} = d_{25} = 50, \quad c_{22} = 10, \quad p_{13}^{(2)} = 2d_{13},$$
$$d_{11} = d_{33} = d_{55} = p_{22}^{(3)} = p_{13}^{(5)} = 100.$$

As initial conditions we assume the presence of uninfected T helper cells, free virus particles, and CTL as well as the absence of infected T helper cells, setting for $t = 0$:

$$n_1(0) = 1, \quad f_2(0) = 0, \quad f_3(0) = 0.1, \quad f_5(0) = 0.1.$$

In the first part of our simulation we study the interactions between viral particles and adaptive immunity when only the cellular response is activated. We model this case assuming the absence of ABs at $t = 0$ and set additionally

$$d_{34} = d_{44} = p_{34}^{(4)} = 0, \quad f_4(0) = 0.$$

This particular case of adaptive immunity, when only cellular response is active and humoral response is passive, is analyzed numerically in Kolev (2009). There, the role of the parameter d_{13} for the dynamics of the solutions to the system (2), (4)-(7) is studied. This parameter describes the rate of viral infectivity, which is very important for the reproduction of the viruses because they need the metabolic machinery of the susceptible cells in order to replicate (see, e.g., Wodarz, 2007). The computational experiments presented in Kolev (2009) show that for lower values of the parameter d_{13} (e.g. $d_{13} = 100$) an effective, sustained cellular immune response becomes established. In such cases virus load is contained at low levels. For higher values of the parameter describing the viral infectivity (e.g. $d_{13} = 108$) the viral load is at high levels and an effective, sustained cellular immune response is not established.

In the second part of our computer simulations we study the problem whether an additional humoral response is able to change the outcome of the competition between the viral infection and the adaptive immune system in cases when the cellular immunity alone is not able to control the infection, and set $d_{13} = 108$. We consider additionally an initial presence of ABs and change the following parameters related to the functions of the ABs (population $i = 4$):

$$d_{34} = 1000, \quad d_{44} = 1, \quad f_4(0) = 0.1.$$

The results of the numerical simulations show that humoral response can be helpful for the adaptive immunity, especially when the rate of production of antibodies (described by the parameter $p_{34}^{(4)}$) and their ability to destroy viruses (described by the parameter d_{34}) is high enough. In such cases immunoglobulins destroy large amounts of free viral particles and limit the growth of the infection.

The computational results for the case when only cellular response is functioning, as well as two cases of cooperative response of cellular and humoral immunity are presented in Figs. 1 through 4. Fig. 1 illustrates the dynamics of the infected cells, Fig. 2 — of the uninfected cells, Fig. 3 — the viral dynamics, and Fig. 4 — the temporal evolution of CTLs. The curves labeled by $p_{34}^{(4)} = 0$ describe the case when only cellular response is functioning, while the other two curves on each figure correspond to cases when humoral immunity is also active, with $p_{34}^{(4)} = 100$ and $p_{34}^{(4)} = 1000$.

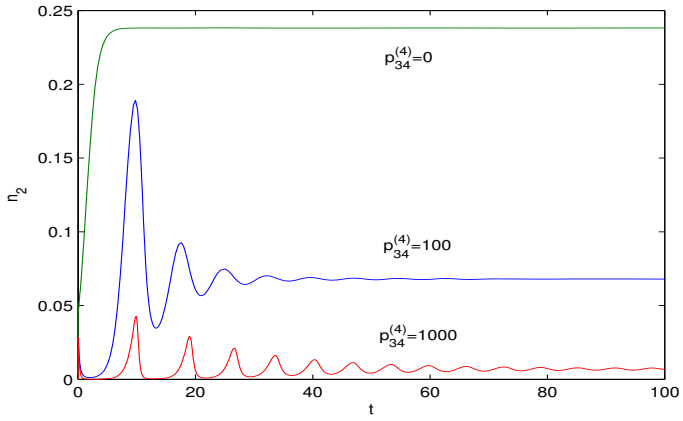

Figure 1. Dynamics of the infected cells in cases of "cellular-only" and "cellular-and-humoral" responses

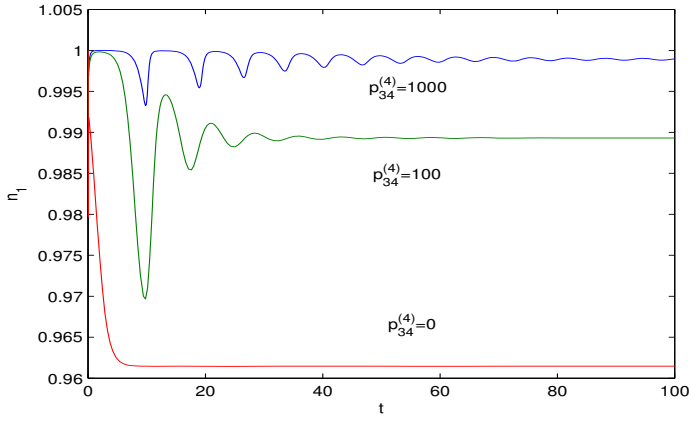

Figure 2. Dynamics of the uninfected cells in cases of "cellular-only" and "cellular-and-humoral" responses

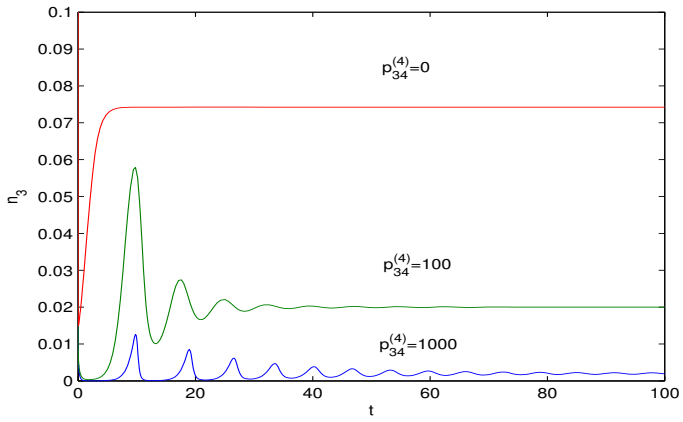

Figure 3. Dynamics of the free viral particles in cases of "cellular-only" and "cellular-and-humoral" responses

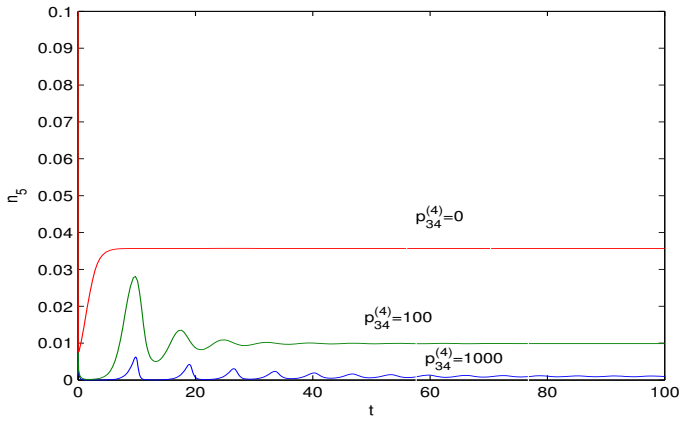

Figure 4. Dynamics of the CTLs in cases of "cellular-only" and "cellular-and-humoral" responses

Computer simulations show that while the cellular-only response is unable to fight off the infection in cases when the rate of infectivity of uninfected cells is very high, humoral immunity leads to an additional destruction of free viral particles and allows the immune system to control the viral load at sufficiently low levels. Thus, close collaboration between cellular and humoral immunity can be very important in the fight against aggressive viruses and lead to successful eradication of the infection.

4. Concluding remarks and future research directions

In the present paper, a generalized mathematical model of the competition between the adaptive immune system and the viruses is analyzed. It describes both the humoral and the cell-mediated immune mechanisms. The results of the numerical simulations confirm the importance of both parts of the adaptive immunity for clearance of the virus. The presented model improves the previously proposed kinetic models, which describe either the cell-mediated response (see Kolev, 2009) or the humoral response (see Kolev, 2008a,b) to virus. In particular, it is shown that in many cases with high rates of infectivity very important is the role of antibodies, which are able to destroy a large number of free viral particles and to clear the organism. The numerical results for high values of parameter $p_{34}^{(4)}$ presented in Section 3 may be considered as an illustration of possible antiviral therapy with neutralizing antibodies.

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 (2), (4)-(7) in order to fit existing experimental and clinical data, collected for instance from HIV infected patients or animal models (see, e.g., Wodarz, 2007). Then some therapeutic approaches could be modelled by the use of some modifications of the presented model. For instance, vaccination could be modelled by an additional source term in equation (5). Antiviral therapy with neutralizing antibodies could be also described by an additional source term in equation (6). Therapy with drugs that inhibit the replication cycle of viruses (e.g., used in the therapy of HIV) could be modelled by decreasing the reproduction rate of the virus (for instance, by setting low values of parameter $p_{22}^{(3)}$ in equation (5)).

Other future work will address the influence of other parameters of the model (2), (4)-(7) on the outcome of the competition between the viral infections and the adaptive immunity. It may lead to a better understanding of the mechanisms of these complex and highly nonlinear interactions.

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