Adaptive immunity and CTL differentiation - a kinetic modeling approach

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Abstract. In this paper we present a mathematical model formulated within the framework of the kinetic theory for active particles. The model is a bilinear system of integro-differential equations of Boltzmann type and it describes the interactions between virus population and the adaptive immune system. The population of cytotoxic T lymphocytes is additionally divided into precursor and effector cells. The effects of the parameters describing the proliferation and differentiation of cytotoxic T lymphocytes are studied numerically.

1 Introduction

Mathematical models have been widely used in the last decades for the description and prediction of the structures and behavior of complex biological systems. They play a significant role in understanding the functioning of living systems. Recent scientific investigations are devoted to the challenging project of creating a mathematical theory of living systems by the use of mathematical methods, see the review papers [1, 2] and the references therein, the recent book [3] and papers [4, 5]. This is a challenging and difficult project, considering that biological systems possess features, which are radically different from the features of the inert matter [6]. Characteristic properties of living systems are their abilities for metabolism, reproduction and/or destruction action, competition, learning, interaction with other entities, evolution, survival, and many others [3, 7]. Some scientists like E. Schrödinger explain the specificities of the living entities through the aperiodicity of their elementary constitutive elements (genes), other like the vitalists - through some special vital principle and “life

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force” [8, 9]. Independently of the reason for this distinction, it is clear that there is a need of different mathematical approach for the description of living systems in comparison with those used for studying the inanimate matter [1]. In recent works (see for example [1, 2, 3]) a new systems biology approach is proposed. It is based on reduction of the complexity of overall living systems by their splitting into subsystems performing specific biological functions. The authors propose mathematical methods suitable to describe the common features of complex biological systems. They are based on the so-called “kinetic theory for active particles” (KTAP). This approach has been successfully applied to model social dynamics and economic systems, mutations and immune competition, wound healing process, crowds and swarms, and many others [1, 2, 3, 4, 10].

In this paper we present an application of computational methods to immunology. Mathematical and computational methods are widely used in this field (see e.g. [11, 12]) for the quantification of the time dynamics of interacting populations. Mathematical modeling of viral infections may be very useful in understanding the course of interactions between the adaptive immune system and virus. It is used to clarify main factors influencing the acute phase and outcome of infection, as well as to interpret data from experiments (in vivo and in vitro) and clinical observations. Apart from verifying immunological hypotheses, simulations and analyzes of mathematical models may also reduce the amount of experiments [13], which are usually lengthy and expensive, and indicate new directions of immunological research [14].

Viruses are intracellular pathogens. In order to reproduce, they have to enter susceptible host cells and use their metabolic machinery (viruses do not have their own metabolism - see e.g. [12, 15]). Newly produced virus particles leave the infected cells and spread the infection to different tissues and organs of the infected individual. Excessive virus production inside the infected cells may, in many cases, lead to significant reduction in longevity of the cells due to the virus-mediated killing of the cells. This is why many diseases caused by viral infections (e.g. influenza, hepatitis C, AIDS) can be very dangerous (or even lethal) for the infected individual.

The defense (immune) mechanisms of the infected individual can apply innate and adaptive (acquired) responses to fight the infection (see e.g. [15, 16]). The innate response is non-specific, i.e. it is not directed against any specific virus strain. Innate defense mechanisms include physical barriers (e.g. skin, stomach acid), changes (inflammation) and immune cells with no immunological memory (e.g. macrophages, dendritic cells).

The adaptive (acquired) response is virus-specific, i.e. it can specifically recognize the physical structure of virus particles (thus recognizing certain virus strains). Apart from responses directed against virus particles and infected cells, the adaptive mechanisms also establish immunological memory (this means better responses in future encounters with the same virus strain). There are two branches of adaptive immunity: humoral and cell-mediated immunity.

The humoral immunity is carried out by B lymphocytes (see e.g. [17]). Effector B lymphocytes (plasma cells) produce antibodies that destroy free virus particles. Antibody response can be very effective in suppressing the virus population, but it is helpless against virus particles inside infected cells. Despite the ongoing humoral response, virus particles may still reproduce.

Cell-mediated (cellular) immunity is in turn directed against the infected cells (see e.g. [18]). Cellular response is carried out by T lymphocytes (see e.g. [12]) - T helper cells (T_h) and cytotoxic T lymphocytes (CTL). T helper cells are responsible for the regulation of cellular and humoral immune responses, while the main role of CTL is to identify and kill infected cells.

There are two subpopulations of CTL: precursor (CTL_P) and effector (CTL_E) cells. When there is no antigen stimulation, all CTL’s exist as precursors. The population of CTL_P proliferates upon contact with antigen, establishing CTL memory (higher concentrations of virus-specific CTL_P) and
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differentiating into effector cytotoxic T lymphocytes ($CTL_E$). Effector cells are responsible for recognition and destruction of infected cells.

In this paper we present a mathematical model for the interactions between the adaptive immune system and virus particles. The model is an improved version of the model proposed by one of the authors in [17]. It includes the additional division of the CTL population (as in [12]) into precursor ($CTL_P$) and effector ($CTL_E$) cytotoxic T lymphocytes. The presented model is then analyzed numerically to examine the influence of CTL proliferation and differentiation on the course and outcome of viral infection.

The model presented in this paper is formulated within the framework of KTAP previously mentioned. Mathematical structures concerning the kinetic theory for active particles can be found in [19]. In this theory, an additional variable (“activity”, “activation”, “state of activity”) is introduced. It describes the specific biological function of individuals of interacting populations. Applications of this approach in immunology can be found, for example, in [20, 21].

The organization of the paper is as follows. In Section 2 we introduce the interacting populations (Section 2.1) and the mathematical model (Section 2.2) of the adaptive immune response. In Section 3 we construct the approximate numerical solution (Section 3.1) of the model. Further we present and interpret the results of our numerical simulations (Section 3.2). In the concluding Section 4 we summarize the results and present some future research directions.

2 Mathematical model of adaptive immune response to virus

2.1 Interacting populations

Following the ideas from [12, 17, 18], we consider the following interacting populations (see Table 1): susceptible uninfected cells, infected cells, free virus particles, antibodies, cytotoxic T lymphocytes (precursor and effector cells). Each population is denoted by the corresponding subscript $i = 1, \ldots, 6$. The microscopic state of the individuals of the considered populations are characterized by a variable $u \in [0, 1]$ describing the specific biological function (activity) of each individual.

<table>
<thead>
<tr>
<th>$i$</th>
<th>Abbreviation</th>
<th>Population</th>
<th>Activation state $u \in [0, 1]$</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>—</td>
<td>Susceptible uninfected cells</td>
<td>Not considered</td>
</tr>
<tr>
<td>2</td>
<td>—</td>
<td>Infected cells</td>
<td>Virus production, virus-mediated destruction of infected cells</td>
</tr>
<tr>
<td>3</td>
<td>Virus</td>
<td>Free virus particles</td>
<td>Rate of infection of susceptible cells</td>
</tr>
<tr>
<td>4</td>
<td>$ABs$</td>
<td>Antibodies</td>
<td>Destruction of free virus particles</td>
</tr>
<tr>
<td>5</td>
<td>$CTL_P$</td>
<td>Precursor cytotoxic T lymphocytes</td>
<td>Proliferation of precursor cytotoxic T lymphocytes</td>
</tr>
<tr>
<td>6</td>
<td>$CTL_E$</td>
<td>Effector cytotoxic T lymphocytes</td>
<td>Destruction of infected cells</td>
</tr>
</tbody>
</table>

We neglect the presence of internal degree of freedom of the population $i = 1$ (uninfected cells). This population is assumed to be independent of its activation states.

The activity of the population $i = 2$ (infected cells) denotes both: (i) rate of viral replication inside the infected cell and (ii) rate of virus-mediated killing of the cell. Infected cells with higher states of activity are assumed to be more effective in production of virus particles, at the cost of faster destruction of the cell (due to excessive virus production - see e.g. [17]).
The activity of the population $i = 3$ (free virus particles) describes its ability to infect susceptible uninfected cells. We assume that virus particles with higher states of activity are more effective in entering susceptible host cells.

Population $i = 4$ (antibodies) takes part in humoral immune response. The main biological function of $\text{ABs}$ is to destroy free virus particles. Thus, we assume that $\text{ABs}$ with higher activation states will be more effective in suppressing the population $i = 3$ (free virus particles).

Populations $i = 5$ (precursor CTL) and $i = 6$ (effector CTL) take part in the cellular immune response. Upon contact with antigen, precursor CTL ($i = 5$) proliferate. This results in establishment of CTL memory and creation of effector cells ($i = 6$). Hence, the activity of precursor CTL will denote the rate of $\text{CTL}_p$ proliferation.

Since the main biological function of population $i = 6$ (effector CTL) is to recognize and destroy infected cells, the activity of population of $\text{CTL}_E$ denotes their ability to kill infected cells. Effector CTL with higher activation states will be more efficient in suppressing the population $i = 2$ (infected cells).

### 2.2 The mathematical model

We introduce the following notation. Let

$$f_i = f_i(t, u) : [0, \infty] \times [0, 1] \to \mathbb{R}_+, \quad i = 1, \ldots, 6.$$ be the distribution function of the $i$-th population with activity state $u \in [0, 1]$ at time $t \geq 0$. The concentration of the $i$-th population at time $t \geq 0$ is then equal to:

$$n_i(t) = f_i(t, u), \quad \forall u \in [0, 1], \quad t \geq 0,$$

$$n_i(t) = \int_0^1 f_i(t, u) du : [0, \infty) \to \mathbb{R}_+, \quad i = 2, \ldots, 6.$$ (2.1)

Note that in Eqs. (2.1) a different equation for $n_1(t)$ is used. This is due to the assumed independency of the population $i = 1$ (uninfected cells) of its’ activation states $u$. Moreover, we denote:

$$n_i^*(t) = \int_0^1 u f_i(t, u) du : [0, \infty) \to \mathbb{R}_+, \quad i = 2, \ldots, 6.$$ (2.2)

The model of virus - adaptive immune system interactions is given by the following system of partial integro-differential equations:

$$\frac{dn_1}{dt} = S_1(t) - d_{11}n_1(t) - d_{13}n_1(t)n_3^*(t),$$ (2.3)

$$\frac{df_2}{dt}(t, u) = p_{13}^{(2)}(1 - u)n_1(t)n_3^*(t) - d_22uf_2(t, u) - \underbrace{d_{26}f_2(t, u)n_6^*(t)}_{\text{cellular immunity}}$$

$$+c_{22}\left(2 \int_0^u (u - v)f_2(t, v) dv - (1 - u)^2f_2(t, u)\right),$$

$$\frac{df_3}{dt}(t, u) = p_{22}^{(3)}n_2^*(t) - d_{33}f_3(t, u) - \underbrace{d_{34}f_3(t, u)n_4^*(t)}_{\text{humoral immunity}},$$ (2.5)
\[
\frac{\partial f_i}{\partial t}(t,u) = p^{(3)}_{23} (1-u)n_3(t)n_4(t) - d_{44}f_i(t,u), \tag{2.6}
\]
\[
\frac{\partial f_3}{\partial t}(t,u) = p^{(5)}_{25} (1-u)n_2(t)n_5'(t) - d_{55}f_3(t,u), \tag{2.7}
\]
\[
\frac{\partial f_6}{\partial t}(t,u) = p^{(6)}_{26} (1-u)n_2(t)n_6'(t) - d_{66}f_6(t,u), \tag{2.8}
\]

with the following initial conditions
\[
n_1(0) = n_1^{(0)}, \quad f_i(0,u) = f_i^{(0)}(u), \quad i = 2,\ldots,6.
\]

The initial conditions and all parameters of the model are assumed to be nonnegative. Moreover, we assume that \(p_{13}^{(2)} = 2d_{13}.

The equation (2.3) describes the dynamics of the population of susceptible uninfected cells. The function \(S_1(t)\) denotes the rate of production of uninfected cells, while the parameter \(d_{11} \) describes the rate of their natural death. Host cells become infected at the rate proportional to the parameter \(d_{13} \) (virus infectivity rate) as well as to the concentration and activity of free virus particles.

The parameter \(p_{13}^{(2)} \) in Eq. (2.4) denotes the gain in the concentration of population \(i = 2 \) (infected cells). The rate of natural death of infected cells is denoted by the parameter \(d_{22} \). We assume that the virus replication shortens the longevity of the infective cells (hence the rate of natural death is also proportional to the activity of the infected cells). The parameter \(d_{26} \) describes the cell-mediated immune response - it characterizes the CTL-mediated destruction of infected cells. Note that the cellular response is also proportional to the concentration and activity of the population of effector CTL.

The virus particles inside a newly infected susceptible cell need some time to uncoat, expose the viral genome and start the replication process. Hence the initial activity of the infected cells is assumed to be low - this is expressed by the factor \((1-u)\) in the gain term of Eq. (2.4). The activity of the infected cells is also assumed to increase in time - this is expressed by the conservative term
\[
c_{22} \left(2 \int_0^u (u-v)f_2(t,v)dv - (1-u)^2 f_2(t,u) \right).
\]

The rate of the virus production inside the infected cells (proportional to the activity of the cell) is denoted by the parameter \(p_{31}^{(3)} \) in Eq. (2.5), while the rate of the natural death of the free virus particles is denoted by \(d_{33} \). The parameter \(d_{34} \) describes the humoral immune response - it characterizes the antibody-mediated destruction of the virus particles. Note that the humoral response is proportional to the concentration and activity of the population of antibodies.

The antibody proliferation (proportional to concentrations of virus and \textit{ABs} populations) is denoted by the parameter \(p_{34}^{(4)} \) in Eq. (2.6). We assume that the activity of the newly produced antibodies is low (this is expressed by the factor \((1-u)\) in the gain term of Eq. (2.6)). The natural death of the antibodies is denoted by parameter \(d_{44} \).

Equations (2.7) and (2.8) describe the dynamics of the cytotoxic T lymphocytes. Parameters \(p_{25}^{(5)} \) and \(p_{26}^{(6)} \) denote the rates of production of precursor and effector CTL, respectively. Note that the rates of production of both populations are proportional not only to the concentration of infected cells, but also to the concentration and activity of the precursor CTL. The activity of new CTL (both precursor and effector CTL) is assumed to be low. Parameters \(d_{55} \) and \(d_{66} \) denote the rate of natural death of
**3 Numerical simulations**

**3.1 Approximate solution of the model**

The initial value problem corresponding to the model of adaptive immune response (Eqs. (2.3) - (2.8)) has been solved numerically. The concentrations of the interacting populations \( n_i(t) \) for \( i = 1, \ldots, 6 \) can be computed from functions \( f_i(t, u) \) (using Eqs. (2.1)). To compute the numerical approximations of the functions \( f_i(t, u) \), we discretize Eqs. (2.4) - (2.8) of the model with respect to the activity states \( u \in [0, 1] \) by applying the uniform grid-points:

\[
u_j = j\Delta u, \quad j = 0, \ldots, N,
\]

where \( N \) is a positive integer and \( \Delta u = 1/N \). The values of \( f_i(t, u) \) can then be replaced by their approximations at the grid-points \( u_j \in [0, 1] \):

\[
f_i(t, u_j) \approx f_{i,j}(t), \quad i = 2, \ldots, 6.
\]

(3.1)

For every \( t > 0 \) and \( u_j \in [0, 1] \) (where \( j = 0, \ldots, N \)), we approximate the following integrals using the approximations from Eq. (3.1):

\[
\int_0^1 f_i(t, u) du \approx Q_0^N[f_i(t, u)], \quad i = 2, 3, 4,
\]

\[
\int_0^1 u f_i(t, u) du \approx Q_0^N[uf_i(t, u)], \quad i = 2, \ldots, 6,
\]

(3.2)

\[
\int_0^{u_j} (u_j - v)f_i(t, v) dv \approx Q_0^j[(u_j - v)f_i(t, v)], \quad i = 2.
\]

The approximations in Eqs. (3.2) represent arbitrary quadratures (see e.g. [22]).

Finally, we use Eqs. (3.1) and (3.2) to approximate the concentrations \( n_i(t) \) of the populations \( i = 1, \ldots, 6 \). Applying the approximations to the presented model (Eqs. (2.3) - (2.8)) yields a system of ordinary differential equations. In Section 3.2, this system was solved using the \texttt{ode15s} solver (with \( \text{RelTol} = 10^{-3} \) and \( \text{AbsTol} = 10^{-4} \)) from MatLAB ODE suite. The integrals were approximated by the use of the composite Simpson’s rule (see e.g. [22], [23]).

**3.2 Numerical experiments and discussion**

In our simulations, we study the role of CTL proliferation and differentiation into effector cells for the dynamics and outcome of viral infection. First, we set the initial conditions and parameters of the
model to simulate a viral infection with humoral-only immune response that is insufficient to achieve viral clearance.

We assume that the virus is cleared from the organism by the adaptive immune response if \( n_1(t) \geq 0.9 \) in equilibrium. Otherwise (if \( n_1(t) < 0.9 \) in equilibrium) persistent infection is established.

As initial conditions, we assume the presence of susceptible uninfected cells, virus particles, antibodies and precursor CTL, in the absence of infected cells and effector CTL. For every \( j = 0, \ldots, N \), we set the following initial values for populations:

\[
\begin{align*}
n_1(0) &= 1, & f_{2,j}(0) &= 0.0, & f_{3,j}(0) &= 0.1, & f_{4,j}(0) &= 0.1, & f_{5,j}(0) &= 0.1, & f_{6,j}(0) &= 0.0.
\end{align*}
\]

The parameters of the model were set as follows:

\[
\begin{align*}
S_1(t) &= 1, & d_{11} &= 1, & d_{13} &= 2.5, & d_{22} &= 1.5, & d_{26} &= 300, & c_{22} &= 0.1, \\
p_{(3)}^{(3)} &= 5, & d_{33} &= 1, & p_{(4)}^{(4)} &= 10, & d_{34} &= 10, & d_{44} &= 1, & d_{55} &= 0.1, & d_{66} &= 1.
\end{align*}
\]

Further, we include the cell-mediated response. We change the values of the parameters \( c \) (CTL proliferation) and \( q \) (CTL differentiation) to obtain the minimal and equilibrium values of \( n_1(t) \). The latter determines the outcome of the infection (viral clearance or persistent infection). The minimal value, in turn, shows us how dangerous the acute phase of the infection is (the lower the minimal value of \( n_1(t) \), the more onerous the acute phase).

Our simulations show that while the humoral-only response was unable to fight off the infection, the additional cell-mediated response can be very helpful in fighting the disease (see Fig. (1)).

![Fig. 1](image-url) Dynamics of the populations of uninfected and infected cells with (i) humoral-only \((c = 0)\) and (ii) full adaptive \((c = 11.5, q = 0.1)\) immune response.

Strong enough cellular response makes it possible to achieve viral clearance. Even if the immune control of the disease is not achieved, additional cell-mediated immunity will mitigate the acute phase of the infection. Our simulations show that the higher the rate of CTL proliferation (parameter \( c \)) the stronger the immune response is going to be. However, the strength of the immune response also depends on the rate of CTL differentiation into effector cells (parameter \( q \)).

In cellular-only immune response, the value of \( q \) is a tradeoff between less dangerous acute phase of infection and stronger CTL memory (see [24]). Lower values of \( q \) will result in low initial suppression of the virus population. This, in turn, results in: (i) more dangerous acute phase and (ii)
establishment of strong CTL memory (higher probability of virus clearance). High initial suppression
of virus population (higher values of $q$) may, on the other hand, block the growth of $CTLP$ population.
This means less onerous acute phase, but less chances for virus clearance.

The results of our simulations (see Fig. (2)) are similar to these from [24]. For a fixed CTL prolifera-
tion rate (parameter $c$), the equilibrium values of $n_1(t)$ are higher for lower values of $CTLE$
differentiation rates (parameter $q$). However, the minimal values of $n_1(t)$ are higher for higher values
of $q$.

![Equilibrium and minimal values of concentration of uninfected cells for (i) $q = 0.1$, (ii) $q = 0.6$.](image)

If the value of $c$ lies below a certain threshold $c_{MIN}$, the additional cellular immune response
will only affect the minimal value of $n_1(t)$. This means that it will mitigate the acute phase, but the
outcome of the infection will remain the same. If, on the other hand, $c \geq c_{MIN}$, the cellular response
will be able to affect the outcome of infection as well.

4 Conclusions

In this paper we have used a mathematical model developed within the kinetic theory for active
particles in order to study the competition between viral infection and adaptive immune system. In
particular, the role of CTL differentiation into precursors and effectors has been analyzed. Our future
research plans include application of the model to experimental data and development of the model
for more detailed analysis of the humoral immune response.

References


