Trakia Journal of Sciences, Vol. 8, Suppl. 2, pp 49-55, 2010

Available online at:
http://www.uni-sz.bg

ISSN 1313-7050 (print)
ISSN 1313-3551 (online)

APPLICATION OF MATHEMATICAL MODELING TO IMMUNOLOGICAL PROBLEMS

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ABSTRACT

PURPOSE. The purpose of our paper is to investigate the interactions between the immune system of vertebrates and infectious pathogens such as viruses. METHODS. We use methods of mathematical modeling and computer simulations in order to study the dynamics of the interacting populations. RESULTS. The numerical results present possible outcomes of the competition between viruses and immune cells. The immunological meaning of the computational results is explained. CONCLUSIONS. The results of the numerical analysis of the investigated mathematical model illustrate typical types of behavior of viral infections and confirm the usefulness of mathematical methods in the field of the immunology.

Key words: acquired immune system, virus, computer simulations, integro-differential equations; not used in the title should be included (up to 8)

INTRODUCTION

The immune system is a remarkably adaptive defense system that has evolved in vertebrates to protect them from invading pathogenic microorganisms and cancer. The most important features of any immune system are: (i) the ability to distinguish host cells, tissues and organs from foreign cells, molecules, particles etc., called "nonself", that might enter the body of the host; (ii) the ability of eradication of foreign invaders, some of which are very dangerous; (iii) the ability of recognition and destruction of altered self-substances that have been modified by injury or disease like cancer (1).

Immunity has both nonspecific and specific components. With respect to this, the immune system may be subdivided into natural (also called innate or nonspecific) immune system and adaptive (called also acquired or specific) immune system (2). Innate, or nonspecific, immunity refers to the basic resistance to disease that an individual is born with. The innate immunity reacts in nonspecific ways by the use of various physical barriers and changes as well as immune cells that possess no memory and have low level of specificity. Most of the microorganisms encountered by a healthy individual are readily cleared within a few days by nonspecific defense mechanisms without enlisting a specific immune response. When an invading microorganism or tumor eludes the nonspecific host defense mechanisms, a specific immune response is enlisted. Innate defense mechanisms provide the first line of host defense against invading pathogens until the acquired immune response develops. Acquired, or specific**,** immunity has evolved in vertebrates. It requires the activity of a functional immune system, involving cells called lymphocytes and their products. The acquired immunity specifically recognizes the physical structure of the invading pathogens and cancer cells. It is able to improve its reaction and functions in a better way against second and every following encounter with the same antigen. That is why it is also called adaptive immunity (3). The acquired immunity plays

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the major role in the defense against foreign pathogens (1-5).

The key cells in adaptive immunity are B lymphocytes (B cells) and T lymphocytes (T cells). Two major populations of T cells exist: T helper cells (Th) and cytotoxic T lymphocytes (CTLs). Both populations of T cells are involved in the first form of acquired immunity called cell-mediated (or cellular) immunity (4,5). CTLs are able to destroy altered self-cells, including virus-infected cells and cancer cells. Th cells secrete numerous cytokines, which are required for activation and proliferation of T cells, B cells and antigen presenting cells (APCs). B cells give rise to the second form of the acquired immunity called humoral immunity (4,5). On contact with antigens, B cells proliferate and differentiate. Some of them produce secreted antibodies (Abs) (immunoglobulins), which bind to and help eliminate the antigens or cancer cells. Interactions between T and B cells as well as APCs, are critical to the development of the specific immunity. In experimental and clinical observations foreign antigens have been shown to induce both humoral and cell-mediated immune responses.

These two types of adaptive immunity have been developed in higher organisms due to the existence of two different kinds of pathogens that are able to infect the host body. Some of pathogens are intracellular and other are extracellular pathogens. Examples of the first type of pathogens are viruses and intracellular bacteria. They are able to enter the host cells and use their metabolic machinery in order to replicate. On the other side, extracellular microorganisms, toxins, extraneous chemicals etc. are located outside the host cells and therefore they belong to the group of extracellular pathogens. The fight against intracellular pathogens is performed primarily by the cell-mediated acquired immunity. The elimination of extracellular pathogens is a function of the humoral acquired immunity (2-5).

The majority of the intracellular pathogens are viruses. Their life cycle can include intracellular as well as extracellular stages. Viruses consist of genetic material wrapped up in a protein coat (6). In order to reproduce, viruses have to enter susceptible cells (usually via surface cell receptors) and use the metabolic machinery of the host cells. After being taken in the host cell, the virus uncoats (i.e. it loses the protein coat) and the viral genome is expressed. Then this genome is both replicated and expressed thus generating new viral proteins. The further association of the newly produced viral proteins with viral genomes results in building of new viral particles. They can leave the infected cells or destroy them (6).

MATERIALS AND METHODS

Various methods such as detailed molecular studies, *in vitro* and *in vivo* experiments *etc.* have been successfully used in immunology for investigation of the interactions between immune system and foreign pathogens (6). In the present paper we apply methods of mathematical modeling and computer simulations for analysis of the acquired immune response to viral infection.

In the field of immunology mathematical models have been utilized for clarifying the factors that are important to explain experimental and clinical data. Furthermore, mathematical modeling methods have been used for defining these factors in precise terms as well as for suggesting experiments for calculation of these factors (7). Analyses and simulations of mathematical models have contributed to reduction of the amounts of experiments needed for successful drug design (8-10). Very useful is the ability of mathematical models to describe and predict the time dynamics of the populations of infections and immune cells, the interactions between which are very complicated and nonlinear (11,12).

In this paper we analyze numerically the recently proposed mathematical model describing the interactions between the virus and the acquired immune system (13,14), which is a generalization of a model of humoral response (15,16) and of a model of cellular immune response to virus (17). The mathematical model is developed in the framework of the so called “kinetic theory for active particles” (10,11). This approach in the context of biological processes has been used for the first time by Jager and Segel (18) being related to a certain population of interacting insects. Jager and Segel have introduced and utilized the concept of dominance of different individuals. The application of the kinetic theory of active

particles to immunology has been introduced by Bellomo and Forni for modeling the growth of cancer (19). This modeling approach utilizes a variable u that describes the biological activity of the interacting populations, i.e. the ability of the cells to express their main functions (according to their role in the organism). The interactions between different cells and particles can either change the existing state or cause proliferation or destruction. The physical system consists of cells or particles that belong to N interacting populations denoted by the subscript i. The activation state of each cell or particle is denoted by the variable u whose value spans in the interval $[0,1]$. The statistical state of the whole system can be described by the function

$$f = (f_1, f_2, ..., f_N)$$

where the functions $f_i(t,u)$, $f_i : [0,T] \times [0,1] \to R^+$ denote the distribution densities of the populations labelled by the index i at time t belonging to some interval $[0,T]$. The concentrations of individuals from the corresponding populations are denoted by

$$n_i(t) = \int_0^1 f_i(t,u)du \qquad (1)$$

The mathematical model proposed in (13,14) describes the interactions between the following five important populations: (i) the population of uninfected T helper cells, denoted by the subscript $i=1$; (ii) the population of infected T helper cells, denoted by the subscript $i=2$; (iii) the population of virus, denoted by the subscript $i=3$; (iv) the population of antibodies, denoted by the subscript $i=4$; (v) the population of CTLs, denoted by the subscript $i=5$.

For simplicity, the distribution function of uninfected T helper cells is assumed to be independent of their activation states:

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

The activation state of the infected T helper cells denotes the virus mediated killing rate of the infected cells as well as the rate of the reproduction of the virus inside the host cell. The activation state of free viruses denotes their ability to infect the susceptible T helper cells. The activation state of the antibodies is supposed to denote their capability to destroy free viruses and to lower their activation states. The state of activity of the CTLs is assumed to denote their ability to destroy the infected T helper cells.

The considered mathematical model is the following system of partial integro-differential equations.

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

$$\frac{\partial f_2}{\partial t}(t,u) = p_{13}^{(2)}(1-u)n_1(t)\int_0^1 vf_3(t,v)dv - d_{25}\, f_2(t,u)\int_0^1 vf_5(t,v)dv$$

$$- d_{22}uf_2(t,u) + c_{22}\left(2\int_0^u (u-v)\, f_2(t,v)dv - (1-u)^2\, f_2(t,u)\right), \qquad (3)$$

$$\frac{\partial f_3}{\partial t}(t,u) = p_{22}^{(3)}\int_0^1 vf_2(t,v)dv - d_{33}\, f_3(t,u) - d_{34}\, f_3(t,u)\int_0^1 vf_4(t,v)dv \qquad (4)$$

$$\frac{\partial f_4}{\partial t}(t,u) = p_{34}^{(4)}(1-u)\int_0^1 f_3(t,v)dv \int_0^1 f_4(t,v)dv - d_{44}\, f_4(t,u)\,, \qquad (5)$$

$$\frac{\partial f_5}{\partial t}(t,u) = p_{13}^{(5)}(1-u)n_1(t)\int_0^1 f_3(t,v)dv - d_{55}\, f_5(t,u), \qquad (6)$$

complemented by nonnegative initial conditions

$$n_1(0) = n_1^{(0)},\ f_i(0,u) = f_i^{(0)}(u),\ i = 2,3,4,5. \qquad (7)$$

All parameters included in the model are assumed to be nonnegative and $p_{13}^{(2)} = 2d_{13}$.
The equation (2) of the model describes the dynamics of the susceptible uninfected cells. The function $S_1(t)$ characterizes the rate of production of uninfected T helper cells by the organism. The parameter d_{11} characterizes their natural death rate. The parameter d_{13} characterizes the rate of viral infectivity of uninfected T helper cells.

The equation (3) of the model describes the dynamics of the infected cells. The parameter $p_{13}^{(2)}$ characterizes the rate of viral infectivity of uninfected T helper cells. The parameter d_{22} characterizes the rate of killing of the infected cells by the virus. The parameter d_{25} characterizes the rate of killing of the infected cells by CTLs. The parameter c_{22} characterizes the possible increase in the activation states of the infected cells.

The equation (4) of the model describes the dynamics of the free virus particles. The parameter $p_{22}^{(3)}$ characterizes the rate of viral replication inside the infected cells. The parameter d_{33} characterizes the natural death rate of the free virus particles. The parameter d_{34} characterizes the rate of killing of the free viruses by antibodies.

The equation (5) of the model describes the dynamics of the antibodies. The parameter $p_{34}^{(4)}$ characterizes the rate of their production. The parameter d_{44} characterizes the natural death rate of antibodies.
The equation (6) of the model describes the dynamics of the CTLs. The parameter $p_{13}^{(5)}$ characterizes the rate of their generation. The parameter d_{55} characterizes the natural death rate of CTLs.
The model (2)-(7) has been solved after its discretization with respect to the activity variable u. The resulting system of ordinary differential equations has been solved by the use of *ode15s* code from the Matlab ODE suite (20) with $\mathrm{Re}lTol = 10^{-3}$ and $AbsTol = 10^{-4}$. The concentrations $n_i(t)$ of populations $i = 2,...,5$ have been computed from the obtained approximate solutions for $f_i(t,u)$ by using Eq. (1).

RESULTS

As initial conditions for the model system (2)-(6) we assume the presence of uninfected T helper cells, antibodies, free virus particles, and the absence of infected T helper cells and CTLs, setting $n_1(0) = 1$, $f_3(0) = f_4(0) = 0.1$, $f_2(0) = f_5(0) = 0$. In addition, it is assumed that $S_1(t) = 100$.

In the first part of our simulation we study the interactions between virus infection and acquired immunity when only its humoral part is active while the cellular immunity is passive. We model this particular case by setting $d_{25} = d_{55} = p_{13}^{(5)} = 0$. The role of the rate of killing of the infected cells by the virus and of the possible increase in the activation states of the infected cells modeled by the parameters d_{22} and c_{22} respectively is analyzed in (15). In (21) we have analyzed the role of the rate of viral infectivity of uninfected T helper cells modeled by parameter d_{13}. We have shown that when the value of d_{13} is not very high, the humoral immune response can be successful in the fight against the infection even in the absence of cellular immune responce. When the value of d_{13} is high, the humoral immune response is not able to clean the infection alone. More susceptible cells become infected. This results in a higher replication of the virus, which can be released and infect new host cells. These two cases are illustrated in **Figure 1** presenting the dynamics of infected cells for values $d_{13} = 100$ and $d_{13} = 108$. The remaining parameters are set as follows: $c_{22} = 15$,

$d_{11} = d_{33} = d_{34} = d_{44} = p_{22}^{(3)} = p_{34}^{(4)} = 100.$

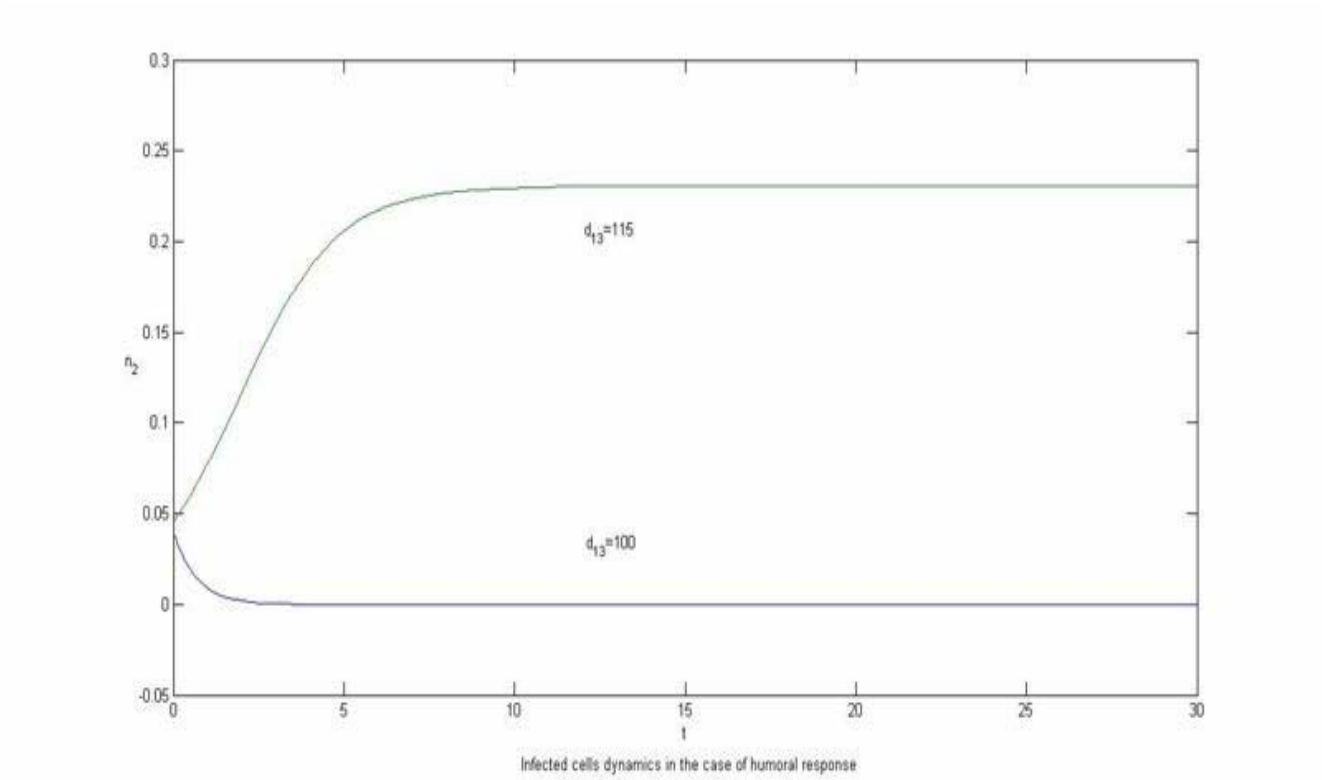

Fig. 1

In cases of high viral infectivity, additional cellular immune response may be needed for the successful clearance of the virus. The second part of our numerical analysis is devoted to the cooperative humoral and cellular acquired response against the infection. As initial conditions we assume additionally the presence of CTLs: $f_5(0) = 0.1$, and change the values of the following parameters: $d_{55} = p_{13}^{(5)} = 100$. We set $d_{13} = 108$ and investigate numerically the role of the rate of killing of the infected cells by CTLs described by parameter d_{25}. Low values of this parameter correspond to weak cellular immunity (or even its absence for $d_{25} = 0$). In such cases the acquired immunity is unable to fight off the infection. Possible dynamics of the population of infected cells is illustrated on Figure 2 by graphs corresponding to $d_{25} = 0$ and $d_{25} = 100$ when the impact of the cell-mediated response to the adaptive immunity is not strong enough for the successful clearance of the infection. However for higher values of d_{25} the cellular immunity helps the acquired defense in reducing the virus load to very low levels. An example of such a case is presented by the graph corresponding to $d_{25} = 1000$ on **Figure 2.**

DISCUSSION

Our numerical experiments of the presented mathematical model of the competition between the acquired immunity and viral infection illustrate several typical outcomes of this complex interaction. They confirm the experimental observations of the failure of the humoral immunity in some cases to cope with the infection alone. Our numerical results show that in such cases an additional cell-mediated response can be very helpful. Therefore, mathematical models of immunological phenomena may be useful for better understanding of processes occurring in living organisms.

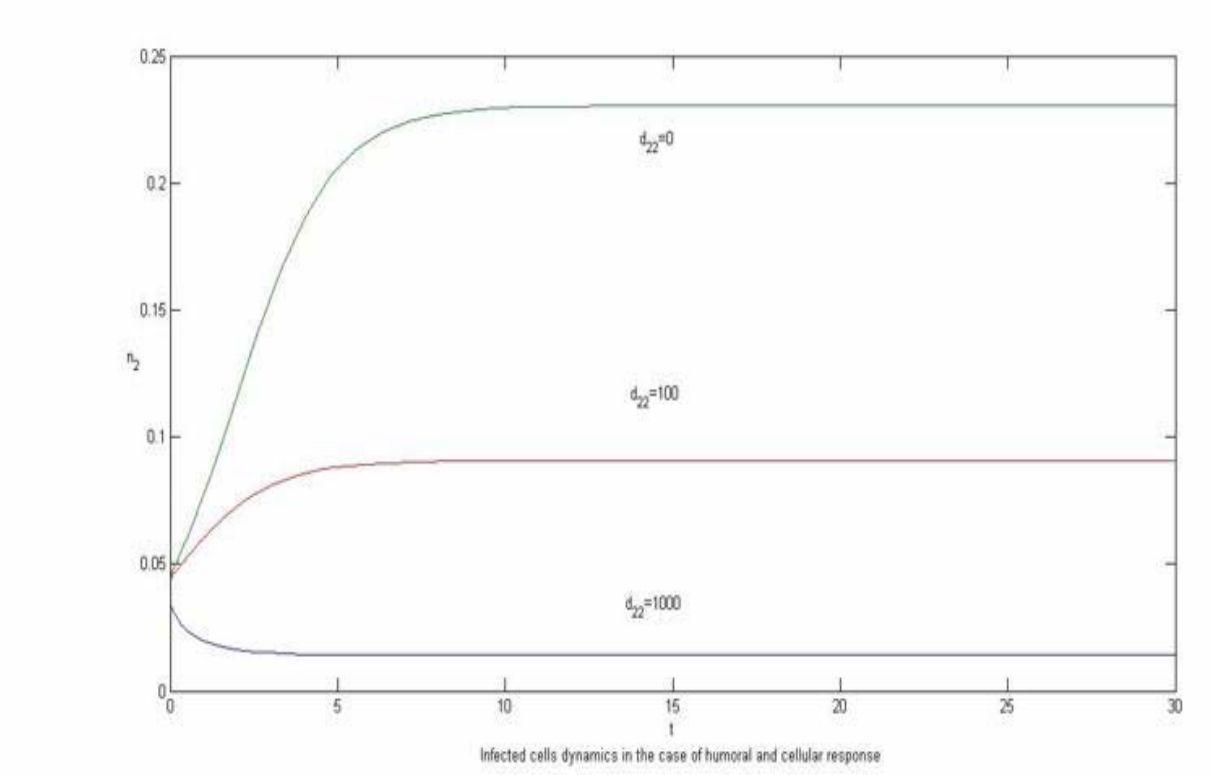

Fig. 2

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