Numerical Modelling of the Competition between the Adaptive Immune System and Virus

Abstract. We present a mathematical model of the interactions between adaptive immune system and viral infection. The model is a bilinear system of partial integro-differential equations of Boltzmann type. We use the capabilities of specialized software to solve complicated system of equations, present the results of computer simulations and explain their immunological meaning.
Key words: numerical modelling, kinetic theory, active particles, partial integro-differential equations, nonlinear dynamics, virus, acquired immune system.

1 Introduction

Over the past decades computer technologies have become a significant part of the research in many fields. Often computer simulations are used together with mathematical methods for analysis, management, prediction, and visualization of various data related to phenomena and processes under investigation. The usefulness of mathematical modelling and computer simulations might be understood through their ability to describe and predict the temporal dynamics of interactions between entities, which may be very complicated and nonlinear [6, 28, 37, 42]. The use of mathematical and computational approaches in conjunction with experimental methods facilitates the understanding of the mechanisms of the studied processes and the discovery of new phenomena [29]. Examples of successful application of the methods of numerical simulations and mathematical modelling to applied and life sciences are works in such areas as complex biological systems [5, 7, 11, 16, 17], cancer modelling [13, 15, 35, 38], psychological interactions [8, 20], politics and social sciences [18, 19, 33, 34], traffic flow [21, 24], population dynamics [3] etc.

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 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 for development of treatment strategies, which are usually lengthy and expensive [4, 14].

The purpose of the present paper is to analyze numerically a mathematical model that describes the adaptive immune response to viral infection [1, 39]. The model is a generalization of the recently proposed in [27, 30] model of humoral immune response to virus and the model describing the cellular immune response to viruses that has been proposed in [31].

The organization of the paper is as follows. In Section 2 we present briefly the interacting populations and describe the mathematical model. Results of numerical simulations of the model are presented in Section 3. Finally, Section 4 includes our concluding remarks and future 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 virus particles that may leave the infected cells. The virus can destroy some of the host cells [42, 43, 45].

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 immune cells. The humoral response is performed by immunoglobulins (antibodies), which are produced by B lymphocytes. The humoral response helps in the eradication of the free virus particles [32, 36].

In this paper we generalize the models proposed in [27, 30] (describing the humoral response to virus) and [31] (that describes the interactions between CMI and viral infection). We consider five interacting populations that play a significant role in the interaction between the adaptive immune system and a virus, which are denoted by the corresponding subscript i and are described in Table 1.

Table 1. Virus-acquired immune system dynamics variables.

Variable i	Abbreviation	Population	Activation state $u \in [0,1]$
1	Uninfected T_h	Uninfected helper T cells	not relevant
2	Infected T_h	Infected helper T cells	virus replication, T_h destruction
3	Virus	Free virus particles	rate of infection of T_h
4	AB	Antibodies	destruction, deactivation of virus
5	CTLs	Cytotoxic T lymphocytes	destruction of infected T_h

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 [2, 9, 10, 12, 22, 23] is called activation state (or activity). 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 helper cells infected by cytopathic viruses (i.e. viruses able to shorten the life-span of the host cells at a higher rate [26, 44]) 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 denotes 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 denote 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 denotes their ability to destroy the infected T_h cells.

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

The meaning of the activation states of the considered populations participating in the competition between virus and adaptive immunity is presented in Table 1.

Further, we introduce the following notation. Let

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

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

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

Our generalized mathematical model of the competition between the virus and the adaptive immunity describes the dynamics of the distribution densities of the interacting populations. Respective gain, loss and conservative terms corresponding to the most important processes of production, destruction and change of activity of the individuals are included in the following system of partial integro-differential equations.

$$\tfrac{d}{dt} n_1(t) = S_1(t) - d_{11} n_1(t) - d_{13} n_1(t) \int_0^1 v f_3(t,v) dv, \tag{2}$$

$$\begin{aligned} \tfrac{\partial f_2}{\partial t}(t,u) = & p_{13}^{(2)} (1-u) n_1(t) \int_0^1 v f_3(t,v) dv - d_{25} f_2(t,u) \int_0^1 v f_5(t,v) dv \\ & - d_{22} u f_2(t,u) + c_{22} \left(2 \int_0^u (u-v) f_2(t,v) dv - (1-u)^2 f_2(t,u) \right), \end{aligned} \tag{3}$$

$$\tfrac{\partial f_3}{\partial t}(t,u) = p_{22}^{(3)} \int_0^1 v f_2(t,v) dv - d_{33} f_3(t,u) - d_{34} f_3(t,u) \int_0^1 v f_4(t,v) dv, \tag{4}$$

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

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

with nonnegative initial conditions

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

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

The function $S_1(t)$ denotes the proliferation rate of uninfected T helper cells. The parameter d_{11} describes the natural death of the uninfected cells. They become infected by the virus with a rate proportional to their concentration as well as to the activation state of the virus. The temporal evolution of the population $i = 1$ of the uninfected cells is described by equation (2).

The equation (3) of the system model the dynamics of the distribution function of the population of the infected cells. The factor $(1-u)$ in its gain term describes our assumption that the activity of the newly infected T helper cells is low. This is connected with the experimental observations demonstrating that the virus needs some time to replicate after entering the host cell. During this period the virus particle uncoats and the viral genome is exposed. Subsequently, the viral genome is replicated and viral proteins are made. New virus particles are produced after the association of the newly generated viral proteins with

the viral genomes [42]. The rate of killing of the infected cells by the virus is assumed to be higher for cells with higher activitation states. It is described by the loss term

$$d_{22} u f_2(t,u).$$

The parameter d_{25} characterizes the rate of destruction of infected cells by CTLs which is assumed to be proportional to the state of activity of CTLs. The replication of the virus particles inside the infected cells leads to an increase in the probability of the destruction of the infected cells by the virus. This is described by the conservative term

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

which corresponds to an increase in the activation states of the infected cells (cf. equation (3)).

The equation (4) describes the temporal evolution of the distribution function of the population of the viral particles. The parameter $p_{22}^{(3)}$ characterizes the rate of replication of the virus inside the host cells, which is supposed to be proportional to the activation state of the infected cells. The parameter d_{33} characterizes the natural death of viruses. The parameter d_{34} describes the rate of killing of free viruses by antibodies.

The equation (5) of the system model the dynamics of the distribution function of the population of the antibodies. The parameter $p_{34}^{(4)}$ describes the rate of production of AB, while the parameter d_{44} characterizes the natural death of AB.

There is experimental evidence that the newly produced AB and CTLs need time for their development and activation [32]. The factor $(1-u)$ in the gain terms of equation (5) and equation (6) describes our assumption that the activity of the newly generated ABs and CTLs is low.

The equation (6) describes the temporal evolution of the distribution function of the population of CTLs. The production rate of the CTLs is supposed to be proportional to the concentrations of the uninfected helper T cells and of the virus, both of which stimulate the proliferation of cytotoxic T lymphocytes [36]. The parameter d_{55} characterizes the natural death of CTLs.

3 Numerical simulations

The initial value problem corresponding to the model (2)-(6) consisting of 5 nonlinear partial integro-differential equations is solved numerically. In the first step, we discretize the system (2)-(6) in the activation state variable $u \in [0,1]$ by constructing a uniform grid

$$u_i = i\Delta u, \quad i = 0, 1, \ldots, N, \tag{7}$$

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 $4N + 4$ ordinary differential equations allowing to find approximate solutions to the model (2)-(6).

This system of ordinary differential equations corresponding to the discretized model (2)-(6) is solved by using the code `ode15s` from the Matlab ODE suite [40] with $RelTol = 10^{-3}$ and $AbsTol = 10^{-4}$. The participating integrals are approximated by the use of the composite Simpson's rule [25, 41]. 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 (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:

$$S_1(t) = 100, \quad t \geq 0,$$

$$d_{22} = d_{25} = 50, \quad c_{22} = 10,$$

$$d_{11} = d_{33} = p_{22}^{(3)} = p_{13}^{(5)} = 100.$$

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 AB 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 [31]. There, the role of the parameter d_{13} for the dynamics of the solutions to the system (2)-(6) 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 [42]. The computational experiments presented in [31] 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 AB and change the following parameters related to the functions of the AB (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 to 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.

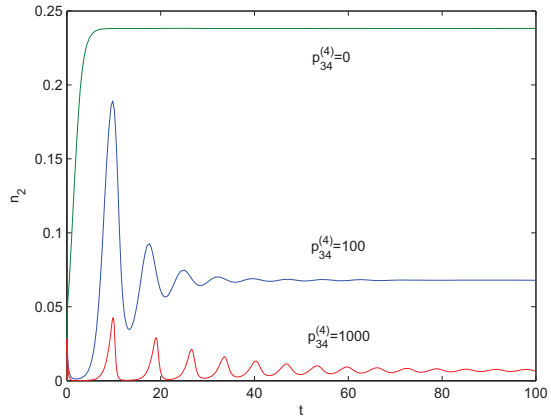

Fig. 1. Dynamics of the infected cells in cases of "cellular-only" and "cellular-and-humoral" responses.

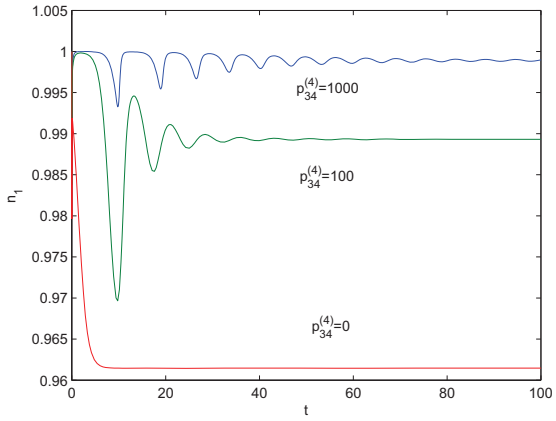

Fig. 2. Dynamics of the uninfected cells in cases of "cellular-only" and "cellular-and-humoral" responses.

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 Fig.1, Fig.2, Fig.3 and Fig.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 $p_{34}^{(4)} = 1000$.

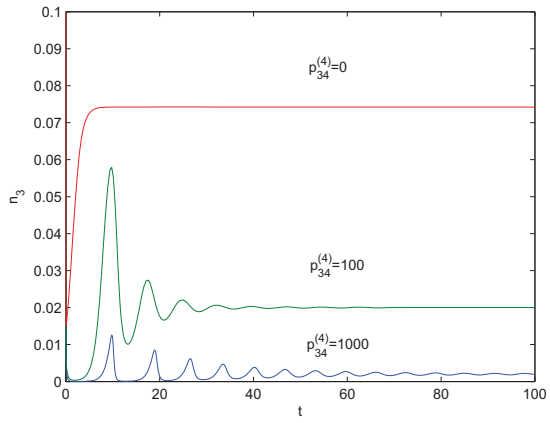

Fig. 3. Dynamics of the free viral particles in cases of "cellular-only" and "cellular-and-humoral" responses.

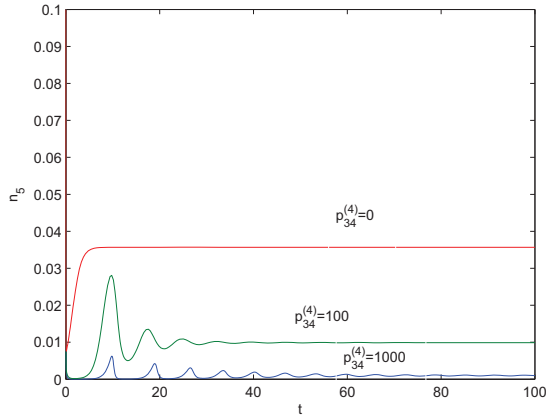

Fig. 4. Dynamics of the CTLs in cases of "cellular-only" and "cellular-and-humoral" responses.

The 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, the 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, the close collaboration between cellular and humoral

immunity can be very important in the fight against aggressive viruses and lead to a successful eradication of the infection.

4 Concluding remarks and future 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.

Numerical simulations utilizing mathematical models may lead to a reduction in the quantity of experimental studies performed in virology. Our future work will address the influence of other parameters of the model (2)-(6) 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.

References

1. A.K. Abbas and A.H.Lichtman. *Basic Immunology. Functions and Disorders of the Immune System.* Philadelphia: Elsevier, 2004.
2. L. Arlotti, N. Bellomo, E. De Angelis and M. Lachowicz. *Generalized Kinetic Models in Applied Sciences*. New Jersey: World Sci., 2003.
3. L. Arlotti, N. Bellomo and K. Latrach. From the Jäger and Segel model to kinetic population dynamics: Nonlinear evolution problems and applications. *Math. Comput. Modelling*, 30, 15–40, 1999.
4. B. Asquith and Ch.R.M. Bangham. An introduction to lymphocyte and viral dynamics: the power and limitations of mathematical analysis, *Proc. R. Soc. Lond. B*, 270, 1651–1657, 2003.
5. N. Bellomo. *Modelling complex living systemsa kinetic theory and stochastic game approach.* Boston: Birkhäuser, 2008.
6. N. Bellomo and A. Bellouquid. On the onset of nonlinearity for diffusion models of binary mixtures of biological materials by asymptotic analysis, *Internat. J. Nonlinear Mech.*, 41(2), 281–293, 2006.
7. N. Bellomo, C. Bianca and M. Delitala. Complexity analysis and mathematical tools towards the modelling of living systems, *Physics of Life Reviews*, 6, 144–175, 2009.
8. N. Bellomo and B. Carbonaro B. On the complexity of multiple interactions with additional reasoning about Kate, Jules and Jim. *Math. Comput. Modelling*, 47 (1-2), 168–177, 2008.
9. N. Bellomo and M. Delitala. From the mathematical kinetic, and stochastic game theory to modelling mutations, onset, progression and immune competition of cancer cells, *Physics of Life Reviews*, 5, 183–206, 2008.
10. N. Bellomo and G. Forni. Dynamics of tumor interaction with the host immune system, *Math. Comput. Modelling*, 20 (1), 107–122, 1994.
11. N. Bellomo and G. Forni. Complex multicellular systems and immune competition: New paradigms looking for a mathematical theory. *Curr. Top. Dev. Biol.*, 81, 485–502, 2008.

12. N. Bellomo, N.K. Li, and P.K. Maini. On the foundations of cancer modelling: Selected topics, speculations, and perspectives. *Math. Models Methods Appl. Sci.*, 18, 593–646, 2008.
13. N. Bellomo and P. Maini. Preface in: Cancer Modelling (II). *Math. Models Methods Appl. Sci.*, 16 (7b), iii–vii (special issue), 2006.
14. N. Bellomo and L. Preziosi. Modelling and mathematical problems related to tumor evolution and its interaction with the immune system, *Math. Comput. Modelling*, 32, 413–452, 2000.
15. N. Bellomo and B. Sleeman. Preface in: Multiscale Cancer Modelling. *Comput. Math. Meth. Med.*, 20 (2-3), 67–70 (special issue), 2006.
16. A. Bellouquid and M. Delitala. Mathematical methods and tools of kinetic theory towards modelling complex biological systems. *Math. Models Methods Appl. Sci.*, 15, 1639–1666, 2005.
17. A. Bellouquid and M. Delitala. *Modelling complex biological systems a kinetic theory approach*. Boston: Birkhäuser, 2006.
18. M.L. Bertotti and M. Delitala. From discrete kinetic theory and stochastic game theory to modelling complex systems in applied sciences. *Math. Models Methods Appl. Sci.*, 14, 1061–1084, 2004.
19. M.L. Bertotti and M. Delitala. Conservation laws and asymptotic behavior of a model of social dynamics. *Nonlin. Anal. RWA*, 9, 183-196, 2008.
20. B. Carbonaro B and C. Giordano. A second step towards mathematical models in psychology: A stochastic description of human feelings. *Math. Comput. Modelling*, 41, 587–614, 2005.
21. V. Coscia, M. Delitala and P. Frasca. On the mathematical theory of vehicular traffic flow models II. Discrete velocity kinetic models. *Internat. J. Nonlinear Mech.*, 42, 411–421, 2007.
22. E. De Angelis and B. Lodz. On the kinetic theory for active particles: A model for tumor-immune system competition. *Math. Comput. Modelling*, 47 (1-2), 196–209, 2008.
23. S. De Lillo, M.C. Salvatori and N. Bellomo. Mathematical tools of the kinetic theory of active particles with some reasoning on the modelling progression and heterogeneity. *Math. Comput. Modelling*, 45 (5-6), 564–578, 2007.
24. M. Delitala and A. Tosin. Mathematical modelling of vehicular traffic: A discrete kinetic theory approach. *Math. Models Methods Appl. Sci.*, 17, 901–932, 2007.
25. W. Gautschi. *Numerical Analysis: An Introduction*. Boston: Birkhäuser, 1997.
26. D. Kagi, P. Seiler, J. Pavlovic, B. Ledermann, K. Burki, R.M. Zinkernagel and H. Hengartner. The roles of perforin-dependent and Fas-dependent cytotoxicity in protection against cytopathic and noncytopathic viruses, *Eur. J. Immunol.*, 25, 3256, 1995.
27. M. Kolev. Mathematical modelling of the interactions between antibodies and virus, *Proc. of the IEEE Conf. on Human System Interactions*, Krakow, 365–368, 2008.
28. J. Keener, J. Sneyd. *Mathematical Physiology*. 2nd ed. New York: Springer-Verlag, 2001.
29. B.J. Kogan. *Introduction to Computational Cardiology: Mathematical Modeling and Computer Simulation*. New York: Springer-Verlag, 2010.
30. M. Kolev. Mathematical modelling of the humoral immune response to virus, *Proc. of the Fourteenth National Conf. on Application of Mathematics in Biology and Medicine*, Leszno (Poland), 63–68, 2008.
31. M. Kolev. Numerical modelling of cellular immune response to virus, *Lecture Notes Comput. Sci.*, 5434, 361–368, 2009.

32. J. Kuby. *Immunology*. New York: W.H. Freeman, 1997.
33. M. Lo Schiavo. The modelling of political dynamics by generalized kinetic (Boltzmann) models. *Math. Comput. Modelling*, 37, 261–281, 2003.
34. M. Lo Schiavo. A dynamical model of electoral competition. *Math. Comput. Modelling*, 43, 1288–1309, 2006.
35. P.L. Lollini, S. Motta and P. Pappalardo. Modeling tumor immunology, *Math. Models Methods Appl. Sci.*, 16(7b), 1091–1125, 2006.
36. P.M. Lydyard, A. Whelan and M.W. Fanger. *Instant Notes in Immunology*. Oxford: BIOS Sci. Publ. Ltd., 2000.
37. D.P.F.Moeller, *Mathematical and Computational Modeling and Simulation: Fundamental and Case Studies*. Berlin, New York: Springer, 2004.
38. A. d'Onofrio. Tumor–immune system interaction and immunotherapy: Modelling the tumor–stimulated proliferation of effectros, *Math. Models Methods Appl. Sci.*, 16(8), 1375–1402, 2006.
39. G. Pinchuk. *Schaum's Outline of Theory and Problems of Immunology*. New York: McGraw-Hill, 2002.
40. M.W. Shampine and M.W. Reichelt. The Matlab ODE suite, *SIAM J. Sci. Comput.*, 18, 1-22, 1997.
41. E.A. Volkov. *Numerical Methods*. New York/Moscow: Hemisphere/Mir, 1990.
42. D. Wodarz. *Killer Cell Dynamics*. New York, Berlin: Springer, 2007.
43. D. Wodarz and C.R. Bangham. Evolutionary dynamics of HTLV-I, *J. Mol. Evol.*, 50, 448–455, 2000.
44. D. Wodarz and D.C. Krakauer. Defining CTL-induced pathology: implication for HIV, *Virology*, 274, 94–104, 2000.
45. D. Wodarz, R. May and M. Nowak. The role of antigen-independent persistence of memory cytotoxic T lymphocytes, *Intern. Immun.*, 12, 467–477, 2000.