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A brief look at the mathematical modelling of the immune response

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Abstract Many advances in clinical immunology have been made in the last twenty years. They have also led to the appearance of a significant number of mathematical models that are trying to capture some of the most important behaviours of the immune process. However, the immune system has a dynamic structure and a lot of components that interact with each other at various levels. So, a mathematical model may capture only some features of the complex immune response.

In this paper, we aim to give just an introduction to the field of mathematical immunology with a brief description of some mathematical models.

Keywords mathematical models · numerical simulations · immune system

Mathematics Subject Classification (2010) 35Q92 · 34A34 · 92B05 · 92D30

1 Introduction

The immune system consists of cells, tissues and organs that work together to protect the host organism against invading pathogens like bacteria, viruses, parasites, fungi as well as the body's own abnormal cells. Also, the immune system plays an important role in allergies or autoimmune disease. The pathogen factors trigger an immune response by presenting a foreign antigen on their surface. In order to be able to interpret the received signals and for coordination, the immune cells use receptors and adhesion molecules. Once they receive information about the existence of a pathogen inside of the body, they begin to fight against it by releasing soluble proteins (antibodies) via B-cells or inducing apoptosis via cytotoxic T-cells. The first process occurs in the case of free extracellular pathogens and the second happens in the case of pathogen-infected cells. Once initiated, the immune response must maintain a balance between destroying foreign cells and defending those of the host body.

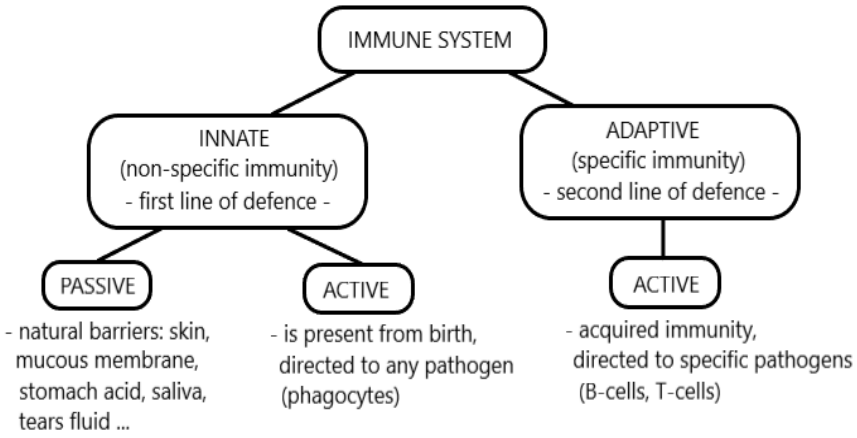

Fig. 1 Diagram of immune response.

The immune system, in the case of a typical infection, give successive, highly coordinated responses in order to eliminate the pathogen factors and protect the host body (Figure 1).

The fast response is the innate one and after that the adaptive immune response is initiated. The innate immunity include natural barriers (like skin, mucous membrane, stomach acid, saliva, tears fluid etc.) as a first line of the body defense. Their role is not allowing the pathogens to get into the body, but if this thing is happening, the immune system activates the non-specific immune cells. Now, these cells (phagocytes) start to inactivate and destroy the potential pathogens, no matter what type.

Sometimes, this is enough to eliminate the pathogens, but if it is not the case, the adaptive immune response is activated. The adaptive immunity, based on memory of encountered diseases, involves cells which are able to recognize the physical structure of a specific pathogen (B-cells, T-cells). B-cells bind the pathogens by specific receptors. After that, under the action of the cytokines released by the helper T-cells, the B-cells begin to replicate and also differentiate in memory B-cells and effector B-cells (plasma cells). Now, the plasma cells are able to produce the antibodies which will start to attach to the extracellular pathogens and neutralize them. Let us mention that the helper T-cells play a key role in activating and amplifying the immune response. The cytokines released by them are a very important factor of the connection between humoral (antibody-mediated) and cellular (cell-mediated) immune response.

If in the case of the humoral immunity, B-cells play a major role, in the case of the cellular immunity, T-cells are the important players. After activation, T-cells turn into cytotoxic T-cells that are able to induce apoptosis

in the cells that have the pathogen inside (infected cells) or cells foreign to the host organism.

Many of the interaction features between the two components of the immune system (innate and adaptive) have been revealed in the last twenty years. These recent developments in immunology have generated a large number of mathematical studies describing different steps of the immunological process.

In order to construct a viable mathematical model, it is important to focus on the general laws and regularities that characterize the immune system. We must take into account that inside of the immune response there are fast and very slow processes (from fractions of a second to days), so different timescales. Also, from spatial point of view we have different scales (from intra-cellular level to whole body). Often it is difficult to decide which process involves molecules, cells or organs and where are the boundaries between the different scales. Broadly, the spatial scales are classified in three levels [4]: the microscopic level ($10^{-9}-10^{-7}m$), the mesoscopic level ($10^{-6}-10^{-4}m$) and the macroscopic level ($10^{-3}-1m$). The models at the microscopic level deal with intracellular events such as signal transduction, or gene expression. At the mesoscopic scale processes like proliferation, differentiation, apoptosis, cell-cell interaction or chemotaxis are described. The macroscopic scale includes the models dedicated to the function of the organs (wound healing, vascular network). The multiscale models represent mathematical models that describe biological processes at different spatial scales and they contain compartments of single-scale models.

The mathematical models have variables representing immunological components (cell populations, citokines density etc.) and a set of parameters which describe the connections between them. In general, the models which describe a biological phenomena involve a large number of variables and many parameters. As the number of variables and parameters increases, the mathematical model becomes closer to the reality, but, in the same time, harder to be analyzed. Usually, the number of the variables can be reduced by focusing on some sub-systems, for example if we take in account the different timescales. Regarding the estimation of the kinetic parameters, they are often difficult to be determined experimentally in the laboratories. Sometimes, it is necessary to made reasonable assumptions on some parameters included in a model, where the clinical immunology does not yet have a final answer.

The mathematical approach used in immunology can be quantitative or qualitative. With the help of quantitative models it is possible to predict the behaviour of the system, for example, at a certain check point time. Nevertheless, these models can involve a small number of equations and all system parameters must be known. On the other hand, qualitative models can take into account more biological variables, but they provide less details about the dynamics of the system.

The most common mathematical models of the immune processes are based on ordinary differential equations with linear and non-linear kinetics.

Their analysis is simpler than in the case of other models and they can be computationally simulated in an efficient manner. So, good qualitative information can be obtained about the behaviour of solutions.

Delay differential equations are used in immunology in order to simulate the delayed feedback in biological processes, like, for example, the delayed response to a stimulus. These models are infinite-dimensional systems, so their study and computational analysis are more complex than in the case of ordinary differential equations.

The mathematical models based on partial differential equations capture the widest range of the features of the biological processes. Nevertheless, the study of such models requires the use of advanced analysis techniques and they are computationally demanding. Usually, partial differential equations are used in age-structured and spatio-temporal models.

The previous types of models deal with populations (of molecules, cells etc.). Unlike these, the agent-based models deal with discrete variables (like isolated molecules or cells). Despite of their advantage on the modelling at the microcellular level, these models are often difficult to implement computationally.

Apart to the models presented above, in mathematical modelling for the immune response other models are also used. For example, stochastic differential equations are used in modelling of some genetic disorders, not to mention also the hybrid models. For a large bibliography about various mathematical models in immunology, see [1], [5], [11], [17], [24], [29].

In the mathematical, as well as in biological literature, there is a significant number of low dimensional models. The simplest ones do not distinguish between humoral and cell-mediated response. They describe a general immunologic model, not some particular characteristics of a disease. It is only assumed that the defense response is given by certain components of immune systems (usually called generically "effectors" and they can be, for example, B-cells, cytotoxic T-cells or certain antibodies) directed to target cells (which can be viruses, bacteria or immunogenic tumor cells susceptible to an immune response). The dynamics of such models is based on the interaction between effectors and target cells and describes the equilibrium relations between them. More nonlinear a model is, more it is able to produce a richness of behaviours. Even in this simplified form, the low dimensional models are able to simulate some phenomena and particularities observed at the immune response. On the other hand, the high dimensional models may provide more accurately information about the pattern observed in the dynamics of the immune system. However, they require a deep mathematical analysis and complex computational techniques.

The mathematical modelling of the immune response can provide sometimes the understanding of some mechanisms of the disease processes and methods for an effective medical treatment. However, it is difficult to predict which kind of mathematical model is most suitable in order to describe a biological process. Usually, it starts with a system based on the principal features of the process, despite the fact that many others, maybe important,

are neglected. Gradually, other components are introduced in system such that the model becomes closer to the biological process. The new system can have a completely new structure and will require a new analysis. The idea is to keep the essential features of the immune response dynamics.

In the following, we discuss about the modelling of the immune response via ordinary differential equations and partial differential models.

2 Low dimensional models of the immune response

2.1 Two variables model

Mathematical models based on the ordinary differential equations were widely used for modelling the immune response. They have been used for modelling B-cells, T-cells or NK-cells (natural killer) responses, as well as immunotherapy ([3], [6], [22], [12], [13], [15], [18], [20]), just to mention a few results.

Our first example comes from [18]. The idea of the authors was to find a mathematical model, as simple as possible, but able to provide a good simulation for the immune response. The dynamics of the kinetic system is based on the nonlinear interactions between the target cells T and specific immune component E. After non-dimensionalization, the proposed mathematical model is:

$$\begin{aligned} \frac{dT}{dt} &= rT - kTE \\ \frac{dE}{dt} &= p\frac{T^u}{1+T^v} + s\frac{E^n}{1+E^n} - E \end{aligned} \tag{2.1}$$

with non-negative rate constants r, k and positive constants $n, p, u, v, u \leqslant v$.

It is assumed that the reproduction rate of the target cells is proportional to the target size and the elimination rate of them is proportional to the contact rate between the target cells and the effector cells. Thus, the temporal change of the target population size T is considered to be the difference between their reproduction and their elimination. The immune competence E represents the density of some effector component of the immune system able to eliminate target cells. By their presence inside of the body, the target cells initiate trigger processes in the immune system which lead to their elimination. The velocity of this action is described by the first term which appears in the dynamics of E. Let us notice that this term is bounded as T gets large accounting for the fact that there are limitations in the rate of temporal change of E. The second term represents the autocatalytic and/or cooperation effect of the immune responses. The last term represents the finite lifetime of E.

This is a rather simple mathematical model and many details about the immune system are neglected. Nevertheless, depending on the values of the parameters and due to interplay between the nonlinear kinetics, this model

exhibits many types of behaviours. An advantage of the ODEs systems is that an overview of the qualitative aspects can be obtained by phase plane analysis and we briefly present some of them here, for more details see [18]. If $n = 1$ and $s > 1 + r/k$, the system has exactly two steady states, namely $(0, 0)$ and $(0, E^*)$, where $E^* = s - 1$. The first one is unstable and the second one is globally attractive in the domain $T \geqslant 0$, $E > 0$. In Figure 2 two solutions of the system (2.1) are presented, in the phase plane, starting from two different initial conditions $(T_1, 0)$, $(T_2, 0)$. At the time of infection $(t = 0)$ it is assumed that no effector cells E are present, $E(0) = 0$. Both solutions converge to the "immune" stable steady state $(0, E^*) = (0, s - 1)$, so a complete elimination of the target cells was reached.

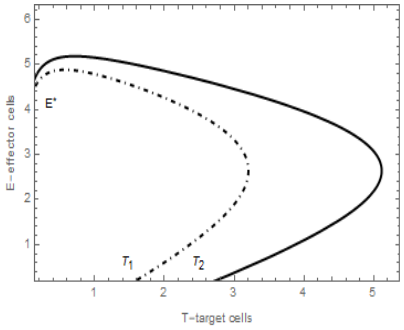

Fig. 2 Two solutions of the system (2.1) starting from two different initial conditions $(T_1, 0)$, $(T_2, 0)$ and converging to the "immune" steady state $(0, E^*) = (0, s - 1)$.

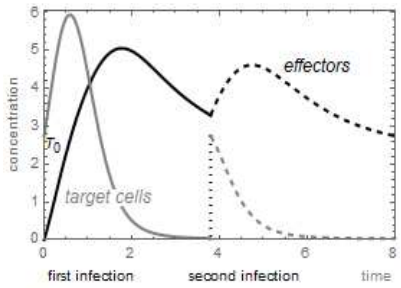

Fig. 3 The time behaviour for T-target cells and E-effectors cells. The immune response is faster in a second infection.

In the same regime of parameters, in Figure 3, the time behaviour of the immune system in the case of the first and second response to a infection is illustrated.

In the case of the second infection, the trajectories start in (T_0, E^*), meaning that some effector components (memory cells) are present. The immune response is faster. Due to the large number of parameters, many situations can occur. In Figure 4 a case when a complete elimination of the pathogen cells is not possible is presented, so target and immune cells coexist. This could be the case of the chronic diseases.

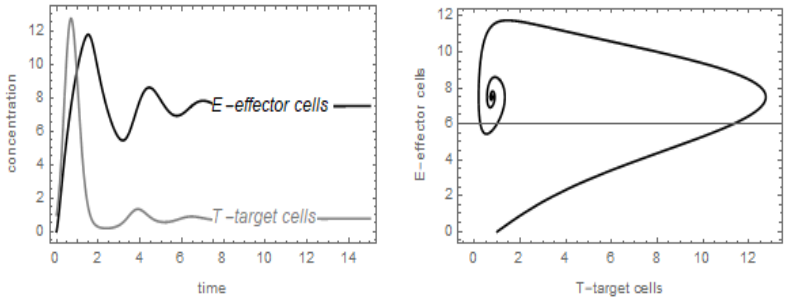

Fig. 4 T-target cells and E-effectors cells coexist in a equilibrium. In this case the target cells are not completely eliminated.

2.2 Three variables model

As we mentioned before, the cytokines have a key role in the immune response by activating the immune cells. So, besides the dynamics of target and immune cells, it is natural to consider their behaviour in a mathematical model. In [12], the authors propose a mathematical model for the study of the tumor-immune cells dynamics. They describe the interaction between the effector cells E, target cells T (tumor cells) and the cytokines I_L (interleukin IL-2) by the system

$$\frac{dE}{dt} = \underbrace{cT}_{\text{recruitment}} - \underbrace{\mu_2 E}_{\text{lifespan}} + \underbrace{\frac{p_1 E I_L}{g_1 + I_L}}_{\text{proliferation}} + \underbrace{s_1}_{\text{external source}}$$

$$\frac{dT}{dt} = \underbrace{r_2 T(1 - bT)}_{\text{logistic grow}} - \underbrace{\frac{aET}{g_2 + T}}_{\text{immune response}}$$

$$\frac{dI_L}{dt} = \underbrace{\frac{p_2 ET}{g_3 + T}}_{\text{stimulation}} - \underbrace{\mu_3 I_L}_{\text{degradation}} + \underbrace{s_2}_{\text{treatment}}$$

where the parameters are positive numbers. The dynamics of this model are complex. Depending on the parameters values there exist multiple, positive steady states. A key role in the behaviour of this system is played by the parameter c (antigenicity factor). In a parameter value regime, we can observe a limit cycle where T-target cells and E-immune cells oscillate around an unstable steady state (Figure 5). This can be the case of a chronic disease when both types of cells coexist for a long period of time.

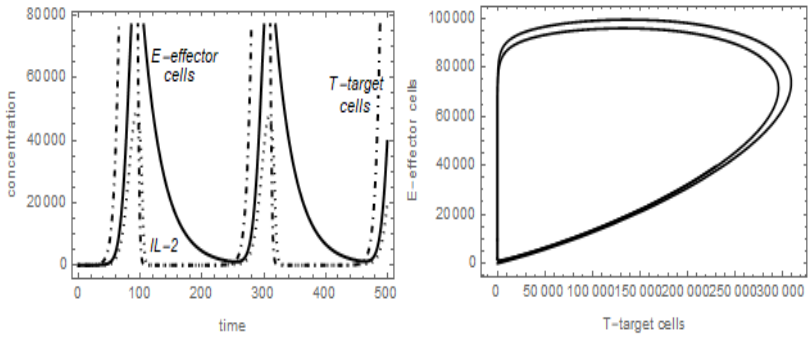

Fig. 5 T-target cells and E-immune cells oscillate around an unstable steady state.

As the value of c increases, the amplitude and period of the limit cycle decrease and the steady state bifurcates (Hopf bifurcation) from an unstable to stable spiral node (Figure 6).

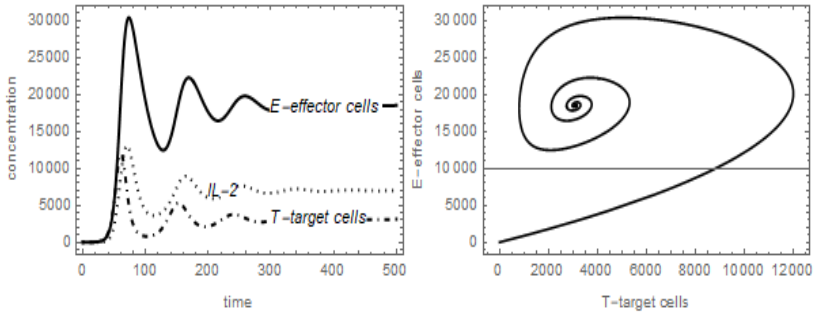

Fig. 6 T-target cells and E-immune cells coexist in a equilibrium. The "coexistence" steady state is globally attractive and the movement into this positive steady state is oscillatory.

If a treatment is not applied ($s_1 = s_2 = 0$), this model does not allow the complete removal of the target cells.

The Figure 7 presents the cases when, first, the system is considered without treatment term and after with treatment, the other parameters having the same values.

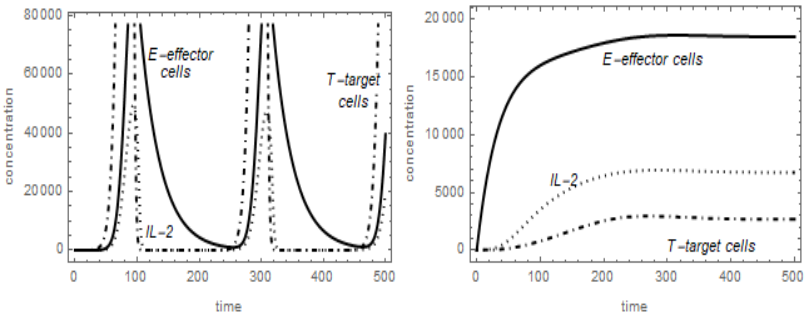

Fig. 7 In the first picture the treatment is not applied ($s_1 = s_2 = 0$), in the second picture the treatment is considered.

These two models, based on ordinary differential equations, show us that they are able to capture behaviours for the immune response.

3 Spatio-temporal models of the immune response

Beside the time evolution of the cells involved in the immune response, the spatio-temporal models pay attention also to the spatial distribution of them. In [14] the authors proposed a three reaction-diffusion equations model involving foreign antigens, chemokines and immune cells. Chemokines are chemotactic cytokines, meaning they have the ability to induce directed chemotaxis in nearby cells. Chemotaxis is the directed movement of cells in response to a chemical stimulus. They can move towards high concentration of the chemical (chemo-attraction), or cells may move in the direction of low concentration (chemo-repulsion).

Previously, mathematical models for the spatial dynamics of the innate and adaptive immune system, including chemotaxis, were proposed ([21], [25]). However, the large number of variables makes them difficult to analyze, and mainly numerical results were obtained.

In [14] the authors wanted to propose a mathematical model for the immune system with chemotaxis, as simple as possible, that would include a

minimal set of variables:

$$\begin{aligned}
\frac{\partial A}{\partial t} &= \underbrace{D_A \Delta A}_{\text{diffusion}} + \underbrace{s_A(x,t)}_{\text{antigen source}} - \underbrace{\lambda_A M A}_{\text{phagocytosis}} - \underbrace{\mu_A A}_{\text{degradation}}, \quad x \in \Omega, \quad t > 0 \\
\frac{\partial C}{\partial t} &= \underbrace{D_C \Delta C}_{\text{diffusion}} + \underbrace{s_C M A}_{\text{secretion by } M} - \underbrace{\mu_C C}_{\text{decay}}, \qquad x \in \Omega, \quad t > 0 \qquad (3.1) \\
\frac{\partial M}{\partial t} &= \underbrace{D_M \Delta M}_{\text{diffusion}} - \underbrace{\nabla(\chi M \nabla C)}_{\text{haptotaxis}} + \underbrace{s_M}_{\text{source}} - \underbrace{\lambda_M M A}_{\text{decay}} - \underbrace{\mu_M M}_{\text{apoptosis}}, x \in \Omega, \quad t > 0
\end{aligned}$$

where A is the concentration of the antigens, C the concentration of the chemokines, M the density of immune cells, all the parameters are positive and Ω is a smoothly bounded domain in $\mathbb{R}^n$ $(n = 1, 2)$. Considering the system (3.1) together with non-negative initial values and with homogeneous Neumann boundary conditions

$$\frac{\partial A}{\partial \nu} = \frac{\partial C}{\partial \nu} = \frac{\partial M}{\partial \nu} = 0, \qquad x \in \partial\Omega, \quad t > 0,$$

the stability and instability conditions for the uniform steady states are obtained in [14]. The stability of non-constant steady-states and existence of periodic orbits are established in [31], as well as the global existence and uniqueness of classical solutions (in one and two-dimensional space).

The system (3.1) is based on the well-known mathematical model proposed by Keller and Segel [10]. This model was proposed in order to describe the spatial aggregation of cellular slime molds which move toward high concentrations of some chemical substance secreted by the cells themselves. The classical Keller-Segel model, which is a system of two connected reaction-diffusion equations, has been subject of many papers (see, for example, the surveys of Horstmann [8], [9] and the references given therein). In the literature there are many theoretical results for the Keller-Segel model concerning existence and uniqueness as well as the qualitative behaviour of the solutions. Most of the results were focused on the global existence of solutions versus blow-up in finite time. Both behaviours strongly depend on the initial data and space dimension.

Because many biological processes are based on the chemotaxis, there are several mathematical models with similar equations as (3.1), but the dynamics can be quite different (see, for example, [2], [7], [16], [19], [23], [26], [27], [28], [30]).

4 Conclusions

Over the last few years, there has been an increasing interest in the mathematical modelling of the immune response. In order to formulate a mathematical model of the immune system, one requires an understanding of

the immune processes and the ability to work with different mathematical and computational techniques. Decisions must often be made regarding the choice of factors that play a fundamental role in describing the process, as well as the set of parameters that define the model.

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