Kinetic Modelling of Autoimmune Diseases

M. Piedade M. Ramos, C. Ribeiro, and Ana Jacinta Soares

Abstract In this paper, we review previous results obtained by the authors, concerning the mathematical modelling of autoimmune diseases when the kinetic theory approach is used in order to describe the microscopic interactions between cells. Three cell populations are considered and the distribution function of each population depends on the biological activity variable defining the functional state relevant for that population. We revisit the wellposedness of the kinetic system and focus our study on the numerical simulations with the kinetic system in view of investigating the sensitivity of the solution to certain parameters of the model with biological significance.

Keywords Mathematical modelling · Kinetic theory · Cellular interactions · Autoimmune diseases

1 Introduction

The main job of the immune system is to protect the organism against disease whether caused by external factors such as bacteria and viruses, or internal aspects such as the existence of cancerous tumour cells in the human body. In order to provide this protection, the main players of the immune system must distinguish between pathogens and healthy tissue.

An autoimmune disease is an illness in which the immune system wrongly attacks healthy cells by reacting to self-antigens. In many cases it is chronic, and patients alternate between periods of relapse, having suffering symptoms, and periods of remittance, in which symptoms are absent.

Autoimmune diseases can affect just about any part of the body, and depending on which part of the body is affected by the such a perverse mechanism, a different

M. P. M. Ramos · C. Ribeiro · A. J. Soares (✉)
Centre of Mathematics (CMAT), Universidade do Minho, Braga, Portugal
e-mail: mpr@math.uminho.pt; cribeiro@math.uminho.pt; ajsoares@math.uminho.pt

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autoimmune disease can be identified. The consequence of this is that over one hundred types of autoimmune diseases exist, some of the most common include type 1 diabetes, rheumatoid arthritis, multiple sclerosis, lupus, psoriasis, thyroid diseases, and inflammatory bowel disease. Although these diseases are not, in general, deadly, they are, in most cases, chronic. The chronic nature of autoimmunity can have serious implications on the quality of life of patients suffering from these diseases. Unfortunately, in spite of a significant increase in the number of patients suffering from these conditions, particularly in the developed world, much about the process of autoimmunity remains a mystery, although environmental changes associated with industrialization have been long suspected as well as genetic factors. See, for example, papers [1–4].

Motivated by the idea of developing a mathematical model in order to describe, in a rigorous way, the complex dynamics of the variables involved in some autoimmune disease, we have initiated a research project with this objective in mind. We have proposed in paper [5] a rather simple, but mathematically robust, model with the aim of describing the immune system interactions in the context of autoimmune disease. The interacting populations are self-antigen presenting cells, self reactive T cells and the set of immunosuppressive cells consisting of Regulatory T (Treg) cells and Natural Killer (NK) cells. In paper [5], we have developed a rather complete qualitative analysis of the model equations and investigated the existence of biologically realistic solutions. Then, in paper [6], a new model has been proposed by considering a further population of IL-2 cytokines and an artificial inlet of external drug therapy with the aim of studying optimal policies for the immunotherapeutic treatment of autoimmune diseases. Paper [6] focus on the macroscopic formulation of this new model, whereas paper [7] introduces the kinetic system approach and exploits the corresponding cellular dynamics. We believe that the kinetic approach, where the model is developed at the cellular scale, can give some insights concerning the biological processes involved in autoimmunity.

In these proceedings, we revisit the model proposed in [5] and summarize the results there obtained. Then we further develop a sensitivity analysis of the parameters involved in the model equations in order to investigate which trends and outcomes, that are common in autoimmune diseases, can be replicated with our numerical simulations. On the one hand, the sensitivity analysis presented here studies the effect of immunotolerance on the evolution of the main populations of cells involved in autoimmunity by, for example, decreasing or increasing certain proliferative parameters defined in the model and on the other hand it shows the effect of immunosupression in the evolution of the same populations by changing certain destructive parameters appearing in the model. A sensitivity analysis of the model to certain conservative parameters is also given, showing the effect of increasing or decreasing these parameters on the number of more active cells participating in the process.

To the best of our knowledge, only few contributions are known on the mathematical modelling of the process of autoimmunity. Some examples of these models prior to our work can be found in [8–10]. On the other hand, several well-known

studies on the mathematical modeling of the tumour-immune system interactions can be found in [11–15].

The content of these proceedings is organized as follows. In Sect. 2 we briefly describe how the immune system can be represented within a mathematical framework, introducing the cellular populations considered in our model and their main role in the dynamics. Then, in Sects. 3 and 4, we revisit the model proposed in [5] and summarize the results concerning the wellposedeness of the kinetic system. Section 5 is devoted to the numerical simulations and their biological interpretation and contains a sensitivity analysis of the parameters involved in the model equations. Finally, in Sect. 6 we state our conclusions and present future ideas in terms of research perspectives.

2 The Mathematical Representation of the Immune System

The immune system can be considered, at the cellular level, as a system constituted by a large number of cells belonging to different interacting populations, and therefore a kinetic theory approach can be used to describe the dynamics of the populations.

In our model, we consider three interacting cell populations p_i, $i = 1, 2, 3$, that are involved in the development of autoimmunity, namely the population p_1 of SAPCs (self-antigen presenting cells), the population p_2 of SRTCs (self-reactive T cells), and the population p_3 of ISCs (immunosuppressive cells).

These populations interact at the cellular level, and the relevant effects that are considered in our description are the following.

- SAPCs transport self-antigens to their encounter with SRTCs.
- SRTCs are activated when they encounter a SAPC that has digested a self-antigen.
- ISCs regulate the activity of SRTCs and SAPCs.

2.1 The Functional Activity at the Cellular Level

The functional state of each population is described by a positive real variable $u \in [0, 1]$, called activation variable or activity, whose biological meaning is characterized as follows.

- The activity u of SAPCs is the ability to stimulate and activate SRTCs. When $u = 0$, SAPCs do not activate SRTCs and, therefore, any autoimmune response is induced in the body.
- The activity u of SRTCs is the ability of promoting the secretion of cytokines which, in turn, can induce an inflammatory process. When $u = 0$, SRTCs do

not produce cytokines, meaning that SRTCs are not sensitive to the stimulus by SAPCs and no inflammatory process is triggered.
- The activity u of ISCs is the ability to inhibit the autoimmune response by either suppressing the activity of SAPCs and SRTCs or eliminating SAPCs or SRTCs. When $u = 0$, the ISCs are neither able to inhibit the activity of SAPCs and SRTCs nor to eliminate SAPCs or SRTCs.

2.2 The Cellular Interactions

The dynamics at the cellular level is modelled under the following assumptions.

(i) Interactions are homogeneous in space and instantaneous modify the state of the participating cells.
(ii) Only binary interactions between cells of different populations are significant for the evolution of the system.
(iii) Interactions among cells of populations p_1 (SAPCs), p_2 (SRTCs) and p_3 (ISCs) can create SAPCs, SRTCs and ISCs (proliferative type), or destroy SAPCs and SRTCs (destructive type), and they can also simply change the activity of SAPCs and SRTCs (conservative type).
(iv) The population p_3 (ISCs) is homogeneous with respect to its biological activity, so that interactions involving ISCs can be only proliferative or destructive type.

Assumption (i) indicates that the interactions occur without time delay. Assumption (ii) is rather natural and common when modelling biological systems, and means that interactions involving more than two cells are not effective in our model. Assumption (iii) is motivated by the immunobiology associated to autoimmune diseases. We consider that interactions among cells of populations p_1 (SAPCs), p_2 (SRTCs) and p_3 (ISCs) can create SAPCs, SRTCs and ISCs (proliferative type), or destroy SAPCs and SRTCs (destructive type), and they can also simply change the activity of SAPCs and SRTCs (conservative type). In fact, during an immune response, a proliferation of both SRTCs and ISCs occurs and an increase of circulating APCs also occurs. Simultaneously, the role of ISCs is to control proliferation of both magenta SRTCs and SAPCs and, decrease their activity. Assumption (iv) results from the fact that we do not consider internal degrees of freedom for ISCs population. In fact, we do not consider the impact of the cellular interactions on the activity of both Treg and NK cells and, therefore, the population of ISCs is considered homogeneous with respect to its biological activity.

The admissible interactions in our model are described as follows.

- Interactions between SAPCs and SRTCs can be of conservative type, increasing the activity of both SAPCs and SRTCs, of proliferative type, enlarging the number of SRTCs and also that of SAPCs.

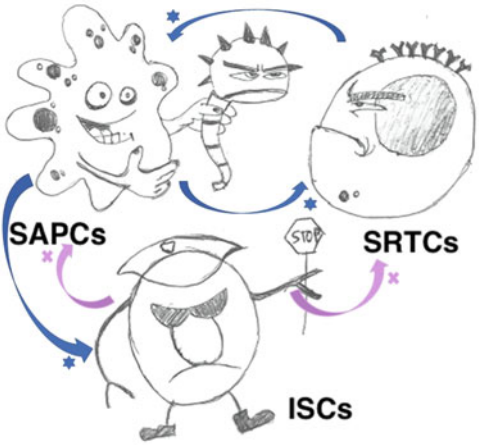

Fig. 1 *Illustration of the immune system interactions among SAPCs, SRTCs and ISCs.* Proliferative interactions are represented by blue starred arrows whereas destructive interactions are represented by purple crossed arrows

- Interactions between SAPCs and ISCs can be of conservative type, decreasing the activity of SAPCs, of proliferative type, enlarging the number of ISCs, as well as of destructive type, decreasing the number SAPCs.
- Interactions between SRTCs and ISCs can be of conservative type, decreasing the activity of SRTCs, and of destructive type, decreasing the number SRTCs.

The populations considered in our biological system and the non-conservative interactions among them are illustrated in Fig. 1. The proliferation of SRTCs by stimulation by SAPCs (blue starred arrow) induces an inflammatory response, in which the immune system mistakenly attacks the body. A cytokine storm produced by SRTCs increases the number of SAPCs (blue starred arrow) which, in turn, will activate more SRTCs. Additionally, ISCs, on the one hand, downgrade the function of both SAPCs (purple crossed arrow) and SRTCs (purple crossed arrow) and, on the other hand, eliminate both SAPCs and SRTCs.

3 The Kinetic Model for Autoimmune Diseases

The overall state of the biological system is described by the distribution functions associated to the populations p_1, p_2, p_3, namely $f_i : [0, \infty] \times [0, 1] \to \mathbb{R}^+$, $i = 1, 2, 3$, such that $f_i(t, u)$ gives the expected number of cells of population p_i with activity u at time t. Integration of each function f_i over the activity variable leads to the number density of p_i population,

$$n_i(t) = \int_0^1 f_i(t, u)\mathrm{d}u, \qquad i = 1, 2, 3, \tag{1}$$

which defines the expected number of cells of population p_i at time t.

Note that, as a consequence of Assumption D introduced in Sect. 2.2, the distribution function of the population p_3 is independent of its functional state, that is $f_3 = f_3(t)$.

The time evolution of the distribution functions f_i is described by the kinetic equations, that require a detailed description of the interaction balance operators, regarding the encounter rates and transition probability densities of cells in conservative interactions, as well as the proliferation rates and destructive rates of cell of different populations. See paper [5], where the complete structure of the kinetic system is explained in detail.

The kinetic system consists of the following coupled integro-differential equations

$$\begin{aligned}\frac{\partial f_1}{\partial t}(t,u) = {} & 2c_{12}\int_0^u (u-v)\,f_1(t,v)\mathrm{d}v\int_0^1 f_2(t,w)\mathrm{d}w - c_{12}(u-1)^2 f_1(t,u)\int_0^1 f_2(t,w)\mathrm{d}w \\ & + 2c_{13}f_3(t)\int_u^1 (v-u)\,f_1(t,v)\mathrm{d}v - c_{13}u^2 f_1(t,u)\,f_3(t) \\ & + p_{12}\,f_1(t,u)\int_0^1 f_2(t,w)\mathrm{d}w - d_{13}\,f_1(t,u)\,f_3(t), \end{aligned} \tag{2}$$

$$\begin{aligned}\frac{\partial f_2}{\partial t}(t,u) = {} & 2c_{21}\int_0^u (u-v)\,f_2(t,v)dv\int_{w^\star}^1 f_1(t,w)dw - c_{21}(u-1)^2 f_2(t,u)\int_{w^*}^1 f_1(t,w)dw \\ & + 2c_{23}f_3(t)\int_u^1 (v-u)\,f_2(t,v)dv - c_{23}u^2 f_2(t,u)\,f_3(t) \\ & + p_{21}f_2(t,u)\int_0^1 f_1(t,w)dw - d_{23}f_2(t,u)\,f_3(t), \end{aligned} \tag{3}$$

$$\frac{df_3}{dt}(t) = p_{31}f_3(t)\int_0^1 f_1(t,w)dw, \tag{4}$$

where parameters p_{ij}, d_{ij} and c_{ij} indicate constant rates of proliferative, destructive and conservative interactions, respectively, and parameter $w^\star \in]0,1[$ describes the tolerance of SRTCs towards self-antigens, in the sense that the greater the value of w^* the less efficient are SAPCs in increasing the activity of SRTCs after encounter. We have considered that during proliferative encounters, cloned cells inherit the same aggressive state as their mother cell, at a constant proliferation rate, and, additionally, that the destructive encounters occur at a constant destruction rate. See paper [5] for more details about the derivation of Eqs. (2)–(4).

The initial conditions for the system (2)–(4) are given by

$$f_1(0,u) = f_1^0(u), \quad f_2(0,u) = f_2^0(u), \quad f_3(0) = f_3^0. \tag{5}$$

The kinetic system (2)–(4) describes the microscopic dynamics at the cellular level starting from the initial data (5). The system reflects how the cellular interactions affect the activity of the various populations and how they contribute

to the evolution of the distribution functions f_i, $i = 1, 2, 3$. This system is used in the numerical simulations presented in Sect. 5.

4 The Mathematical Analysis of the Model

The mathematical analysis of the kinetic system (2)–(4) is in general a complex problem. Conversely, the mathematical analysis of the macroscopic system derived from kinetic equations is obviously an easier task, with the particularity that, under certain assumptions, relevant information on the solution to the kinetic system can be extracted from the mathematical analysis of the macroscopic equations. This is the case of our model. These observations motivate the content of the present section.

4.1 On the Initial Value Problem for the Kinetic System

The existence of a unique local solution to the initial value problem (2)–(4) and (5) can be stated, as follows.

Theorem 1 (Local Existence) *Assume initial data* $f_i^0(u)$ *in* $L^1[0, 1]$. *Then, there exists* $T_0 > 0$ *such that a unique positive solution to the Cauchy problem* (2)–(4) *and* (5) *exists in* $L^1[0, 1]$, *for* $t \in [0, T_0]$.

A general local result has been proven in paper [12] for a rather vast class of kinetic systems with conservative, proliferative and destructive interactions. The solution does not exist globally in time, since a blow-up can occur due to the proliferative interactions. However, a local result is enough when the system is solved numerically and an approximate solution is obtained in the considered biological context.

As it will become clear in the following, Theorem 1, together with the assumption of constant proliferation and destruction rates, assure that the basic information on the kinetic model is contained in the corresponding macroscopic system. Therefore, we introduce now the macroscopic model and present the main results concerning its qualitative analysis.

4.2 The Macroscopic Equations

From the kinetic equations (2)–(4), we formally derive the corresponding macroscopic balance equations describing the time evolution of the number of cells of each population, namely $n_i(t)$, $i = 1, 2, 3$, defined as in (1). These balance equations are obtained by integration of the kinetic equations (2)–(4) over the biological

activity variable $u \in [0, 1]$. As expected, conservative interactions do not give any contribution to the equations for $n_i(t)$, since they do not modify the number of cells of each population and are lost through the integration process. Therefore, the system of ordinary differential equations (ODEs) obtained in this way is

$$\frac{dn_1}{dt}(t) = p_{12}n_1(t)n_2(t) - d_{13}n_1(t)n_3(t), \tag{6}$$

$$\frac{dn_2}{dt}(t) = p_{21}n_2(t)n_1(t) - d_{23}n_2(t)n_3(t), \tag{7}$$

$$\frac{dn_3}{dt}(t) = p_{31}n_3(t)n_1(t). \tag{8}$$

For this system, we consider the following initial data

$$n_1(0) = n_1^0, \quad n_2(0) = n_2^0, \quad n_3(0) = n_3^0, \quad \text{with} \quad n_i^0 > 0 \quad \text{for} \quad i = 1, 2, 3. \tag{9}$$

The description obtained with the balance equations (6)–(8) gives information at a macroscopic scale and only reflects information concerning the changes on the number of cells of each population. All aspects related to the cellular activity are embedded in the macroscopic dynamics but are not directly recognizable in the balance equations.

4.3 The Qualitative Analysis of the Macroscopic Model Equations

The starting point of this analysis is the local existence result stated in Theorem 1. In fact, Theorem 1, together with the assumption of constant proliferation and destruction rates, assure that the boundedness of the solution to the macroscopic system (6)–(8) implies the boundedness of the L^1-norm $||f_i(t, \cdot)||_1$. See also paper [13]. This is an immediate consequence of the positivity of the local L^1-solution stated in Theorem 1. The estimates on the solution to the macroscopic system (6)–(8) provide a priori estimates on the solution to the kinetic system (2)–(4), due to the relationship kinetic-macro given by Eq. (1) of the population densities $n_i(t)$ in terms of the distribution functions $f_i(t, u)$.

Starting from Theorem 1, we prove in paper [5] the following results on the existence of a global, positive solution of the Cauchy problem for the macroscopic system (6)–(8) and (9).

Theorem 2 (Positivity) *Let $\underline{n}(t) = (n_1(t), n_2(t), n_3(t))$ be a solution of the Cauchy problem (6)–(8) and (9) defined on $[0, T]$, $0 < T < +\infty$. Then $n_1(t) > 0$, $n_2(t) > 0$, $n_3(t) > 0$, for $t \in [0, T]$.*

Theorem 3 (Global Solution and Asymptotic Behaviour) *Assume that* $p_{21} < p_{31}$. *Then the Cauchy problem* (6)–(8) *and* (9) *has a unique solution* $\underline{n}(t) = \big(n_1(t), n_2(t), n_3(t)\big)$ *defined on* $\mathbb{R}_+$, *satisfying the conditions*

$$\lim_{t\to+\infty} n_1(t) = 0, \quad \lim_{t\to+\infty} n_2(t) = 0, \quad \lim_{t\to+\infty} n_3(t) = \sigma < +\infty,$$

whatever are the corresponding initial data.

From the biological point of view, condition $p_{21} < p_{31}$, considered in Theorem 3, corresponds to assume that the proliferation of SRTCs resulting from the encounters with SAPCs is dominated by the proliferation of ISCs resulting from the encounters with SAPCs. In this case, the solution of the system does not possess blowups.

Theorems 2 and 3 are crucial to assure the consistency of the model and therefore to validate the numerical simulations to be performed with the kinetic system (2)–(4). These properties are important, not only from the mathematical point of view, but also from the biological point of view, to obtain solutions that are biologically significant. In particular, the positivity and the boundedness of the solution are essential features in the present context.

5 Numerical Simulations for the Biological System

In this section, we perform some numerical simulations with the kinetic system (2)–(4) in order to investigate the sensitivity of the solution to certain parameters of the model. Different scenarios are considered with the aim of analyzing if the solution is capable of describing the behavior of autoimmune diseases. The simulations show the evolution of the number density of the SRTCs, this being biologically the main indicator of an autoimmune reaction.

5.1 The Numerical Scheme

System (2)–(4) is solved numerically by discretizing the integro-differential equations in the activation variable u and using a trapezoidal quadrature rule to perform the numerical integration of the interaction terms.

More specifically, we choose a uniform discrete grid for the activation state variable $u \in [0, 1]$ and introduce the set U of $m + 1$ ($m \in \mathbb{N}$) equidistant grid points $u_k \in [0, 1]$, $k = 0, \ldots, m$, defined by

$$u_k = k\Delta u,$$

where $\Delta u = 1/m$ is the step size. We assume that parameter $w^\star$, describing the tolerance of SRTCs towards self-antigens and appearing in Eq. (3), coincides with the grid-point on the ℓ-position in U, that is $w^\star = u_\ell$.

Grid points u_k are used to approximate both the distribution function $f_i(t,u)$ and the integral collision terms in Eqs. (2)–(4). Therefore, we introduce the notation

$$f_i^k(t) = f_i(t,u_k), \tag{10}$$

where i stands for the population p_i and k indicates the localization of the activation state variable $u \in [0,1]$, with $i = 1,2$ and $k = 0,1,\ldots,m$. Moreover, we consider the integral approximations

$$\int_{u_\alpha}^{u_\beta} g(t,v)dv \approx \mathscr{Q}_\alpha^\beta[g(t,v)], \qquad 0 \le \alpha < \beta \le m, \tag{11}$$

with

$$\mathscr{Q}_\alpha^\beta[g(t,v)] = \frac{g(t,v_\alpha)+g(t,v_\beta)}{2}\Delta v + \sum_{s=\alpha+1}^{\beta-1} g(t,v_s)\Delta v, \qquad 0 \le \alpha < \beta \le m, \tag{12}$$

to obtain the quadrature approximations

$$\begin{aligned}
&\int_0^1 f_j(t,v)dv \approx \mathscr{Q}_0^m[f_j(t,v)], \quad \int_0^1 v f_j(t,v)dv \approx \mathscr{Q}_0^m[v f_j(t,v)], \quad j=1,2,\\
&\int_{u_k}^1 f_j(t,v)dv \approx \mathscr{Q}_k^m[f_j(t,v)], \quad \int_{u_k}^1 v f_j(t,v)dv \approx \mathscr{Q}_k^m[v f_j(t,v)], \quad j=1,2,\\
&\int_0^{u_k} f_j(t,v)dv \approx \mathscr{Q}_0^k[f_j(t,v)], \quad \int_0^{u_k} v f_j(t,v)dv \approx \mathscr{Q}_0^k[v f_j(t,v)], \quad j=1,2,\\
&\int_{w*}^1 f_1(t,v)dv \approx \mathscr{Q}_\ell^m[f_1(t,v)].
\end{aligned} \tag{13}$$

Proceeding in this way, we obtain the following system of $2(m+1)+1$ ODEs,

$$\begin{aligned}
\frac{df_1^k}{dt}(t) = {} & 2c_{13}f_3(t)\Big(\mathscr{Q}_k^m[v f_1(t,v)] - u_k\mathscr{Q}_k^m[f_1(t,v)]\Big) - c_{13}u_k^2 f_1^k(t) f_3(t) \\
& + c_{12}\Big[2\Big(u_k\mathscr{Q}_0^k[f_1(t,v)] - \mathscr{Q}_0^k[v f_1(t,v)]\Big) - (u_k-1)^2 f_1^k(t)\Big]\mathscr{Q}_0^m[f_2(t,v)] \\
& + p_{12}f_1^k(t)\mathscr{Q}_0^m[f_2(t,v)] - d_{13}f_1^k(t)f_3(t), \qquad k = 0,\ldots,m,
\end{aligned} \tag{14}$$

$$\frac{df_2^k}{dt}(t) = 2c_{23} f_3(t)\Big(\mathscr{Q}_k^m[vf_2(t,v)] - u_k \mathscr{Q}_k^m[f_2(t,v)]\Big) - c_{23} u_k^2 f_2^k(t) f_3(t) \tag{15}$$

$$+c_{21}\Big[2\Big(u_k \mathscr{Q}_0^k[f_2(t,v)] - \mathscr{Q}_0^k[vf_2(t,v)]\Big)\mathscr{Q}_\ell^m[f_1(t,v)]$$

$$-(u_k-1)^2 f_2^k(t)\mathscr{Q}_\ell^m[f_1(t,v)]\Big]$$

$$+p_{21} f_2^k(t)\mathscr{Q}_0^m[f_1(t,v)] - d_{23} f_2^k(t) f_3(t), \qquad k = 0, \ldots, m,$$

$$\frac{df_3}{dt}(t) = p_{31} f_3(t)\mathscr{Q}_0^m[f_1(t,v)]. \tag{16}$$

The ODE system (14)–(16) constitutes the numerical scheme to approximate the solution to the full kinetic system (2)–(4).

5.2 The Numerical Solution

We solve system (14)–(16) using the standard Maple dsolve command with the numeric option. A considerable number of simulations have been performed and we have selected a representative sample of figures to show the common features of the evolution of autoimmune diseases. These figures show the evolution of the number density of the SRTCs when different scenarios are considered.

In all simulations, the initial data are taken to be

$$f_i^0 = 10^{-2}, \quad \text{for} \quad i = 1, 2, 3. \tag{17}$$

The parameters that are not investigated in the present simulations are fixed as

$$c_{12} = 2 \quad \text{and} \quad c_{13} = 0.01. \tag{18}$$

They are associated to the SAPCs conservative interactions with SRTCs (c_{12}) and with ISCs (c_{13}).

All other parameters are varied in order to appreciate their influence on the solution to the kinetic system. In particular, parameters

$$w^\star, \quad p_{21}, \quad d_{23}, \quad c_{21} \quad \text{and} \quad c_{23} \tag{19}$$

have a direct influence on the number density of SRTCs, since they represent the tolerance parameter of the SRTCs with respect to SAPCs or, equivalently, the capacity of SAPCs to activate SRTCs ($w^\star$), the proliferative rate of SRTCs after interaction with SAPCs (p_{21}), the destructive rate of SRTCs after interaction with ISCs (d_{23}), the conservative rate of SRTCs after interaction with SAPCs (c_{21}) and the conservative rate of SRTCs after interaction with ISCs (c_{23}). On the other hand,

parameters

$$p_{12}, \quad p_{31} \quad \text{and} \quad d_{13} \tag{20}$$

have an indirect influence on the number density of SRTCs, because they represent the proliferative rate of SAPCs after interaction with SRTCs (p_{12}), the proliferative rate of ISCs after interaction with SAPCs (p_{31}) and the destructive rate of SAPCs after interaction with ISCs (d_{13}).

We underline that the influence of the conservation rates c_{21} and c_{23} on the number density of the SRTCs is quite recognizable, because we are dealing with a kinetic system which retains the conservative cellular interactions in the dynamics. On the other hand, the simulations show that the effect of the other conservation parameters, c_{12} and c_{13}, is not as recognizable in the evolution of the number density of the SRTCs because the related conservative interactions have an indirect impact on the evolution of SRTCs.

We consider different scenarios in view of illustrating the sensitivity of the solution when varying the parameters (19) and (20) that have biological significance in the present modelling of autoimmunity. More specifically, we have a first scenario describing the trend to illness and three other scenarios in which the autoimmune reaction is controlled to a certain extent.

(A) The scenario where there is *development of an autoimmune disease* corresponds to the situation in which the ISCs are unable to regulate the autoimmune reaction, resulting in a full autoimmune cascade and trending to illness. In this scenario, we consider

$$\begin{aligned} &w^\star = 1/30, \quad p_{21} = 19, \quad d_{23} = 0.025, \quad c_{21} = 10, \quad c_{23} = 0.01, \\ &p_{12} = 1, \quad p_{31} = 20, \quad d_{13} = 0.35, \end{aligned} \tag{21}$$

and the corresponding solution is depicted in Fig. 2. We can observe a considerable mass proliferation of very active SRTCs, of the order 10^4 of the

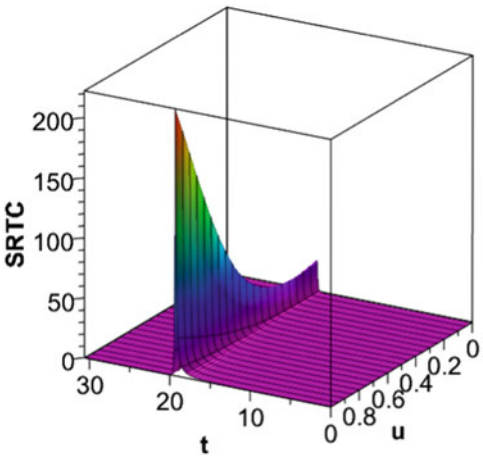

Fig. 2 *Scenario (A)—trend to illness.* The evolution of SRTCs is determined by the approximating solution to the kinetic system (2)–(4), when the parameters are given by (21). The figure shows a considerable mass proliferation of very active SRTCs

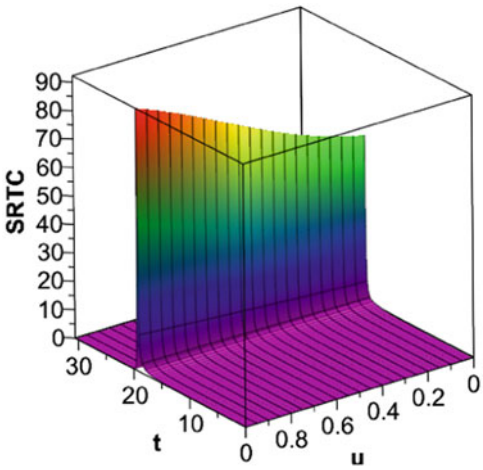

Fig. 3 *Scenario (B)—Immunotolerance.* Effect of increasing the parameter $w^\star$, as described in. The evolution of SRTCs is determined by the approximating solution to the kinetic system (2)–(4), when the parameters are given by (22), and in particular $w^\star = 29/30$

initial data, due to insufficient regulation by ISCs and low tolerance of SRTCs to SAPCs.

(B) The scenario where SRTCs *become more tolerant to* SAPCs corresponds to the situation in which SAPCs are less efficient in increasing the activity of SRTCs. In this scenario, we consider

$$w^\star = 29/30, \quad p_{21} = 19, \quad d_{23} = 0.025, \quad c_{21} = 10, \quad c_{23} = 0.01,$$
$$p_{12} = 1, \quad p_{31} = 20, \quad d_{13} = 0.35, \tag{22}$$

and the corresponding solution is illustrated in Fig. 3. We can observe that, in comparison with Fig. 2, a moderate decrease in the mass proliferation of very active SRTCs is observed, whereas a slight decrease in the mass proliferation of low active SRTCs is recognizable.

(C) The scenario where there is *immunosuppression of the autoimmune reaction* corresponds to the situation in which the biological system is able to abort the autoimmune reaction in an efficient manner, by controlling different proliferative or destructive rates.

In this scenario, we maintain all parameters of scenario (A) with exception of one that is varying once per time. In particular, we consider a lower value of p_{21} or p_{12}, or a greater value of p_{31}, d_{13} or d_{23}. The corresponding solutions are shown in diagrams (a)–(e) of Fig. 4. From the qualitative point of view, the behaviour represented in these diagrams is the same and all pictures exhibit a very low proliferation of active SRTCs.

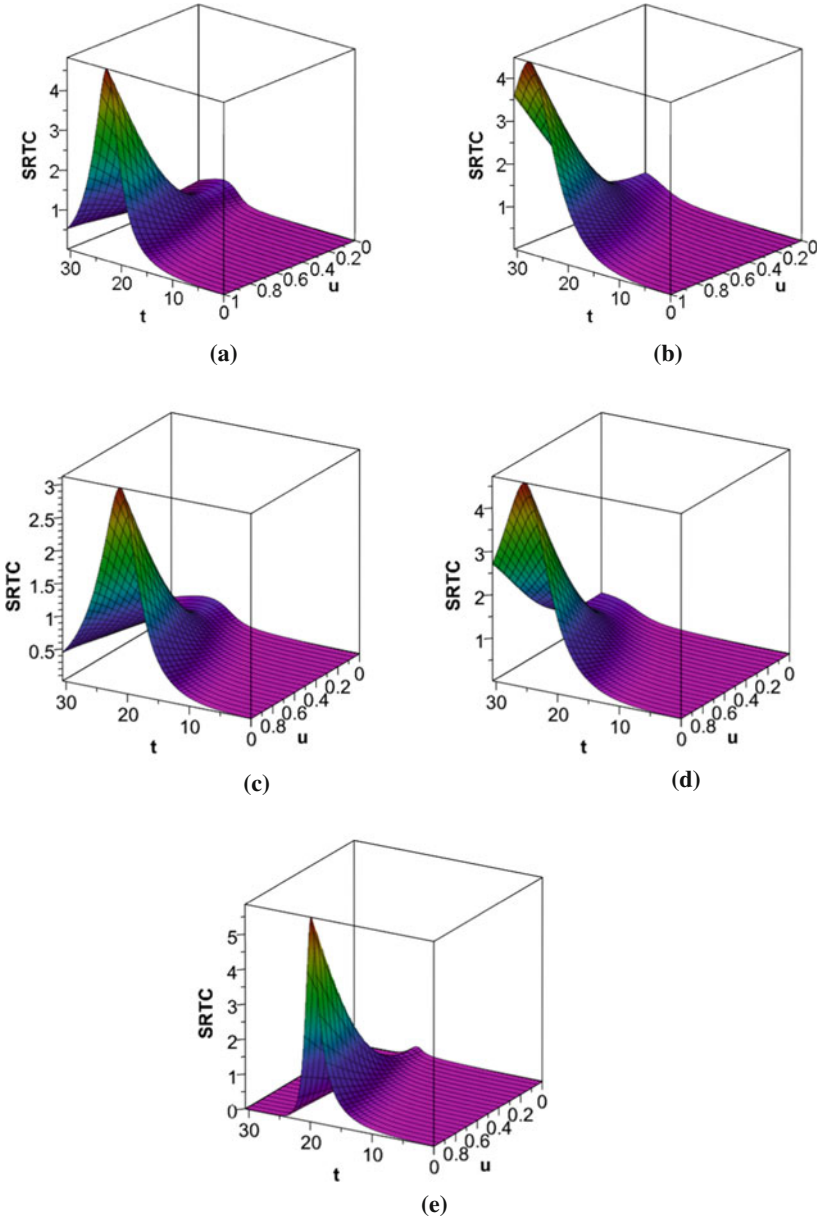

Fig. 4 *Scenario (C)—Immunosupression.* The evolution of SRTCs is determined by the approximating solution to the kinetic system (2)–(4), when the parameters are given by (21), with exception of one parameter. (**a**) Decreasing the proliferative rate p_{21} to $p_{21} = 17$. (**b**) Decreasing the proliferative rate p_{12} to $p_{12} = 0.5$. (**c**) Increasing the proliferative rate p_{31} to $p_{31} = 23$. (**d**) Increasing the destructive rate d_{13} to $d_{13} = 0.7$. (**e**) Increasing the destructive rate d_{23} to $d_{23} = 0.1$. Each diagram shows that, by varying one parameter with respect to the value considered in (21), the biological system is able to reduce considerably the mass proliferation of the SRTCs and therefore to abort the autoimmune reaction in an efficient manner

- In Fig. 4a, the reduction of SRTCs proliferative encounters with SAPCs (lower value of p_{21}) obviously implies a significant impact on the mass production of SRTCs capable of avoiding the trend to illness. The figure shows the effect of p_{21} on the suppression of the autoimmune reaction.
- In Fig. 4b, the reduction of SAPCs proliferative encounters with SRTCs (lower value of p_{12}) has an indirect impact on the mass production of SRTCs since the concentration of SAPCs decreases and the activation of SRTCs by SAPCs is weakened, so that the trend to illness is avoided. The figure illustrates the effect of p_{12} on the suppression of the autoimmune reaction.
- In Fig. 4c, the number of ISCs produced by the biological system is increased by proliferative interactions with SAPCs (greater value of p_{31}), the result being that the trend to illness is avoided in an efficient manner. The figure shows the effect of p_{31} on the suppression of the autoimmune reaction.
- In Fig. 4d, the results show that for the number of SAPCs destroyed as a consequence of their interaction with ISCs (greater value of d_{13}) will ultimately control the proliferation of SRTCs and therefore avoid illness. The figure shows the consequences of d_{13} on the suppression of the autoimmune reaction.
- In Fig. 4e, the results show that the number of SRTCs destroyed as a consequence of their interaction with ISCs (greater value of d_{23}) can definitively avoid a full blown autoimmune reaction. The figure shows the impact of d_{23} on the suppression of the autoimmune reaction.

(D) The scenario where there is *control of the disease* also corresponds to the situation in which the biological system is able to abort the autoimmune reaction in an efficient manner, due to a reduction of the activity of the SRTCs after conservative interactions with SAPCs or ISCs.

In this scenario, we maintain all parameters of scenario (A) with exception of one that is varying once per time. In particular, we consider lower values of c_{21} or greater values of c_{23}. The corresponding solutions are shown in diagrams (**a**)–(**d**) of Fig. 5.

The comparison between this scenario and scenario (A) shows that the total number of SRTCs for $u \in [0, 1]$ is exactly the same, because we only modify the rates of certain conservative encounters. As a consequence, the mass proliferation of SRTCs shows a moderate reduction and the aggressive nature of the autoimmnune reaction is only slightly weakened.

- Diagrams (**a**) and (**b**) of Fig. 5 show that the mass proliferation of very active SRTCs is slightly reduced when the conservative rate c_{21} is decreased. This is a consequence of a lower production of cytokines by SRTC since these encounters reduce the activity of SRTCs and, therefore, control the triggering of an inflammatory process and the development of an autoimmune disease to a certain extent.

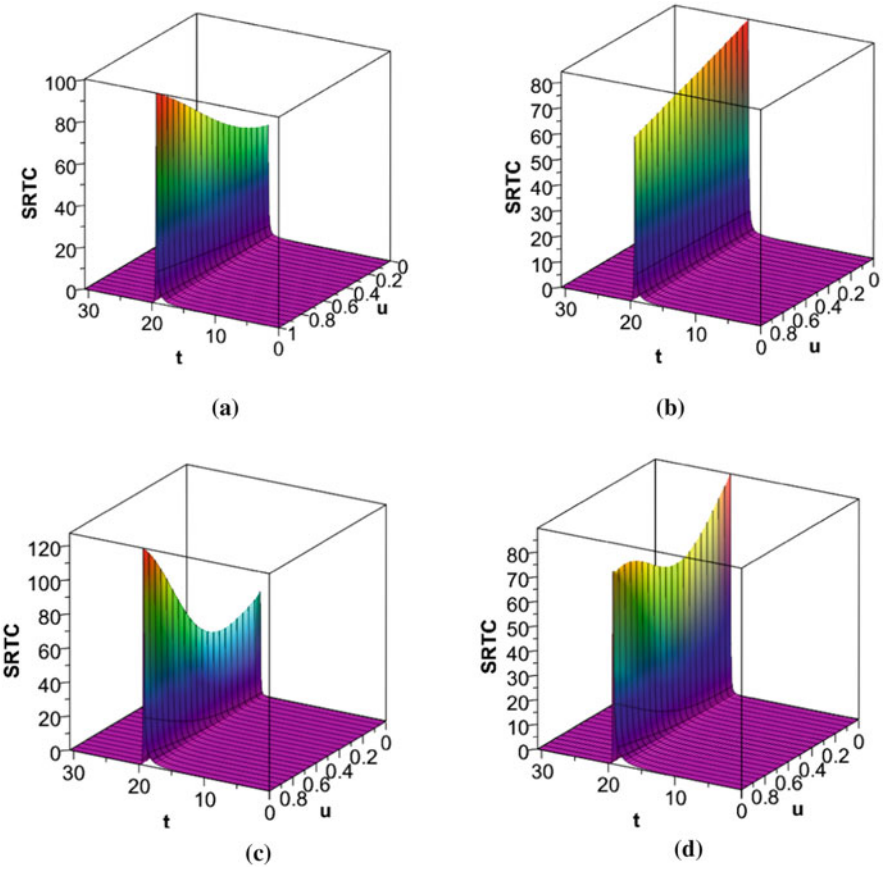

Fig. 5 *Immunosupression. The disease is controlled by decreasing the conservative rate* c_{21}*, diagrams* (***a***) *and* (***b***)*, or by increasing the conservative rate* c_{23}*, diagrams* (***c***) *and* (***d***)*, as described in scenario (D).* (**a**) $c_{21} = 2$. (**b**) $c_{21} = 0.5$. (**c**) $c_{23} = 0.03$. (**d**) $c_{23} = 0.05$. The evolution of SRTCs is determined by the approximating solution to the kinetic system (2)–(4), when the parameters are given by (21) with exception of c_{21} and c_{23}

- Diagrams (**c**) and (**d**) of Fig. 5 also show that the mass proliferation of very active SRTCs is slightly reduced when the conservative rate c_{23} is increased. This is a consequence of a lower production of cytokines by SRTC due to a greater inhibiting effect of ISCs on the SRTC function and, therefore moderating the autoimmune disease.

6 Conclusion and Perspectives

The mathematical model that has been proposed in [5], based on a kinetic theory approach, is here revisited. The mathematical analysis of the model, showing existence, uniqueness, positivity and boundedness of the solution, is also reviewed here.

Starting from the model proposed in [5], we develop here some numerical simulations in order to investigate the sensitivity of the model to certain parameters that are involved in the biological description. We consider different scenarios with the aim of describing different behaviors occurring in autoimmunity. In particular, we study the influence of certain parameters related to immunotolerance and immunosupression on the evolution of the variables characterizing this model for autoimmunity. The conclusion of this study is that increasing the parameters related to immunotolerance and immnunosupression is effective in reducing the production of highly active SRTCs and thefore controlling the progression of an autoimmune episode.

Therefore the numerical simulations developed here and the corresponding biological interpretation of the results constitute a valuable complement of the mathematical model proposed in [5].

Other extensions of the model proposed in [5] have been already considered and others are still open to further developments. We have extended our research work in view of introducing drug therapies on the dynamics and investigating optimal treatment strategies. The results have been submitted for publication, see [6, 7].

Another extension has been considered in order to introduce recurrence in the macroscopic model presented in [5] by considering a constant input by the host environment of self-antigen presenting cells (SAPCs) and the natural death of all cell populations involved. Such a model is able to study the chronic character of the autoimmune diseases. The results are presented in [16].

Other interesting problems that we plan to study is the introduction of delay terms in the equations in order to describe the delay in the reaction to cellular impulses. Memory terms may also be introduced with the aim of describing the ability of cells to retain information related to past experienced cell interactions.

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