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Kinetic models leading to pattern formation in the response of the immune system

Abstract. We consider a multicellular system with spatial structure described by the kinetic theory for active particles such that the microscopic state includes dependence on position and velocity, besides the biological activity of the considered populations. The changes in velocity are described by appropriate integral turning operators that include some effects like a velocity-jump process and a volume-filling effect for one population, and a random motion of particles leading to diffusion for another population. The model describes the migration of T-cells driven by cytokines and the possible lesion of particular tissues or organs resulting from inflammation in the response of the immune system within an autoimmune disease. We then derive the hydrodynamic limit of the kinetic system in a diffusive regime and obtain a diffusion-chemotaxis macroscopic model. The stability analysis of the macroscopic system without diffusion is developed, the Turing instability of the complete system and appearance of spatial patterns are investigated. Some numerical simulations are also performed in view of illustrating our theoretical results.

Keywords. Kinetic theory, multicellular systems, chemotaxis, Turing instability, pattern formation.

Mathematics Subject Classification: 82C40, 35C20, 35B36, 92C17.

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1 - Inroduction

The immune system plays a crucial role in protecting the body against infectious agents or anomalous cells, and by contributing to tissue repair and regeneration. Dysregulation of the immune system can lead to a variety of immunological diseases, including, among others, autoimmune disorders and immunodeficiency conditions. In particular, autoimmune diseases are a complex group of syndromes that arise due to an abnormal immune response against the body's own tissues. They are among the most severe and debilitating medical dysfunctions, the most diffused ones being inflammatory bowl disease, type 1 diabetes and multiple sclerosis. Health factors leading to the appearance of this surge are still under investigation, since the exact biological mechanisms underlying autoimmune responses are extremely complicated. See, for example, [**32**, **36**] and references cited therein.

In general terms, the core of autoimmune response is a process of activation and regulation based on interactions among cells. In view of building a mathematical model able to reproduce such a scenario, the kinetic theory approach is a particularly suitable choice, since it allows us to investigate cellular dynamics at a microscopic level and the global behaviour of the cellular populations at the macroscopic level. First kinetic approaches to the immune system interactions are the ones presented in [**6**] and developed in following works, describing tumor growth through interactions between tumor cells and the immune system. The kinetic modeling starts from a system of integro-differential equations representing interactions among cells and may lead, through proper integration, to a macroscopic description of biologically relevant quantities.

The application of kinetic models mimicking cellular interactions in autoimmune diseases has not yet been developed as in the case of tumour growth. However, there exist some contributions at this level, as those presented in the papers [**13**, **14**, **30**]. In particular, papers [**14**] and [**30**] provide the framework for the work developed in these proceedings. The model proposed in [**30**] describes rather satisfactorily an acute episode of autoimmunity, and populations of self-antigen presenting cells (SAPCs), self-reactive T cells (SRTCs) and immunosuppressive cells (ISCs) are endowed with a microscopic functional state (or activity variable) defining a specific biological function of each cellular population. The kinetic description of each population at the cellular level is performed by means of a distribution function depending on time and activity. Furthermore, the model that has been developed in [**14**] also includes the natural death of the cellular populations as well as a constant input of SAPCs caused by external environmental factors and unhealthy dietary habits. The model shows very rich dynamics and, in particular, it can reproduce the

recurrent patterns peculiar to many autoimmune diseases.

All the above cited papers about the kinetic description of autoimmune diseases do not consider the dependence on the space variable, since the focus is on interactions among cells and changes of the activity along time. Nevertheless a more realistic description of these clinical issues would also require a spatial component, in order to reproduce the migration of T-cells through the body and the possible lesion of particular tissues or organs resulting from inflammation. In fact, it is known from a medical point of view, that migration of Lymphocytes is driven by chemotaxis. The cytokines play the role of chemical attractors for T-cells which, in turn, detect the concentration gradient of cytokines and move towards the source. This phenomenon has been widely studied and reproduced through experiments [**32**, **36**]. Furthermore, chemotaxis is a crucial component of the immune response, and is a characteristic mechanism of motion for many other biological entities, like bacteria, sperm cells or cancer metastases.

Motivated by the biological context, the development of a model of partial differential equations including both diffusion and chemotaxis has always been of great interest to mathematicians and biologists. Some examples are the macroscopic models provided by Patlak [**27**] and then widely extended by Keller and Segel in order to study the behavior of *Dictyostelium discoideum* [**16**, **17**, **18**]. However, starting from a macroscopic description may lead to a loss of important information about cellular and chemical dynamics, since only global features are incorporated in the macroscopic equations. For this reason, a suitable procedure should be able to reproduce both the cellular dynamics at a microscopic level and the global behaviour of the populations at the macroscopic level. This can be obtained by starting from the kinetic model and applying asymptotic methods to reach a diffusive limit. Since this tool is common in the kinetic theory of various fields, as gas dynamics [**7**, **8**, **19**, **20**], it has also been applied to active particles [**5**], and, in particular, to bulks of cells [**2**, **3**]. This procedure allows, in particular, to express the transport and structural coefficients of the macroscopic equations in terms of cellular dynamics. As a result, it provides a more well-founded macroscopic system, coupled with a potential explanation of macroscopic phenomena based on microscopic features.

A further innovative idea is to include a bias coming from an external field in the kinetic equations, by means of a turning operator based on a velocity-jump process in order to reproduce the run and tumble movement of cells. This was introduced in [**1**] and then extended in various directions [**24**, **25**].

Most of the applications in the literature tend to be about the study of cancer cells [**4**] and, more particularly, brain tumors [**11**]. The aim of the present work is to adapt the procedure described above to the particular case of autoimmune diseases. Accordingly, we start from the kinetic model proposed

in [**14**], consider the new population of cytokines, add a spatial variable in the description and introduce a suitable turning operator in the kinetic dynamics. Then we introduce a time scaling and perform an asymptotic analysis to derive the corresponding macroscopic system.

The content of this work is part of a more extended and complete piece of research devoted to the passage from the kinetic to macroscopic model, investigation of Turing instability and pattern formation. The focus of the present study is on the derivation of the kinetic model and its capability to produce, in the diffusion limit, non-homogeneous spatial configurations.

After this introduction, the content of the paper is organized as follows. Section 2 presents the biological setting and the kinetic model, including the description of the microscopic dynamics, construction of the interaction operators with the study of their properties, and derivation of the kinetic equations. Section 3 deals with the derivation of the macroscopic reaction-diffusion system from the kinetic model in a diffusive regime, by performing an asymptotic analysis. Section 4 is devoted to the study of Turing instability of the reaction-diffusion system and the investigation of pattern formation. This section includes some numerical simulations illustrating the pattern formation when the diffusion contributions are added to the non-diffusive system in stable conditions. Section 5 contains our conclusions and a final discussion of the results obtained in this work.

2 - Biological setting and the kinetic model

Within immunological studies, what is definitely known is that, in healthy conditions, T-cells reacting against self-antigens are suppressed during the thymic maturation, through a process called negative selection. However, in an autoimmune condition, this self-tolerance mechanism becomes inefficient and self-reacting T-cells (SRTCs) can reproduce and enter peripheral lymphoid tissues. When SRTCs come across self-antigen presenting cells (SAPCs), naive T-cells become activated and may undergo proliferation, driven by cytokines, into effector memory T-cells. The effects of this stimulation is an uncontrolled autoimmune cascade, namely T-cells cause inflammation of target tissues and produce cytokines, that again activate and trigger proliferation of SRTCs. Since the presence of SRTCs in peripheral tissues may also occur in healthy subjects [**12**], the autoimmune response is generally regulated by specific cell populations of immunosuppressive cells (ISCs) like regulatory T lymphocytes (Tregs) [**10**, **31**] and natural killer cells [**28**, **33**], that are able to both inhibit or cause the death of SAPCs and SRTCs.

2.1 - *Kinetic modelling*

Starting from the biological setting explained above, we describe below the agents involved in the mathematical model, along with their associated distribution functions. The variables which these functions may depend on are time $t \in \mathbb{R}$, space $\mathbf{x} \in \Gamma$, with Γ being a bounded domain in $\mathbb{R}^n$, ($n = 1, 2, 3$ a general space dimension), velocity of SRTCs, $\mathbf{v} \in \mathfrak{D}_R = U\mathbb{B}^n$, with U being the maximal speed of cells and $\mathbb{B}^n$ the unit ball in $\mathbb{R}^n$, velocity of cytokines, $\mathbf{w} \in \mathfrak{D}_C = B\mathbb{B}^n$, with B being the maximal speed of the proteins, and the activity of cells $u \in [0, 1]$, which corresponds to a different task for each cellular population, as it will be specified in the following.

The species involved in the dynamics are the following.

- A – Self-antigen presenting cells (SAPCs), distribution function $f_A(t, \mathbf{x}, u)$, the activity represents the ability to activate SRTCs.

- R – Self-reactive T cells (SRTCs), distribution function $f_R(t, \mathbf{x}, \mathbf{v}, u)$, the activity represents the production of cytokines.

- S – Immunosuppressive cells (ISCs)), distribution function $f_S(t, \mathbf{x}, u)$, the activity represents the ability to suppress SAPCs and SRTCs.

- C – Cytokines, distribution function $f_C(t, \mathbf{x}, \mathbf{w})$.

We also consider the population H of biological host environment and the interactions between A, R, and S cells with the cells of the H-population. We assume that the host population is constant in time and uniform in space.

Moreover, we use the indices $j = 1, 2, 3$ for the populations A, R and S, respectively. Since our ultimate scope is to study the time-space behavior of the cellular populations A, R, S and C, we consider macroscopic densities, defined as the integral of the distribution functions over the space of other variables, say activity, velocity or both. Thus, we introduce

$$A(t, \mathbf{x}) = \int_0^1 f_A(t, \mathbf{x}, u)\, du,$$

$$R(t, \mathbf{x}) = \int_0^1 \rho_R(t, \mathbf{x}, u)\, du, \quad \text{with} \quad \rho_R(t, \mathbf{x}, u) = \int_{\mathfrak{D}_R} f_R(t, \mathbf{x}, \mathbf{v}, u)\, d\mathbf{v},$$

$$S(t, \mathbf{x}) = \int_0^1 f_S(t, \mathbf{x}, u)\, du, \quad C(t, \mathbf{x}) = \int_{\mathfrak{D}_C} f_C(t, \mathbf{x}, \mathbf{w})\, d\mathbf{w}.$$

2.2 - *Cellular dynamics and interaction operators*

We will describe the admissible interactions among cells of different populations and define the corresponding kinetic operators. We will focus on the description of the novelties of the present model that do not appear in the original model developed in [**14**]. Each binary interaction between cells may be a conservative process that simply leads to a change of activity of the cells, or destructive or proliferative process that contributes to a change in the number of cells. Also, other proliferative and destructive dynamics coming from external sources or natural death are considered. Furthermore, we are also introducing other processes leading to a change in the velocity for both SRTCs and cytokines. The effects of all these interactive processes are described by means of suitable integral operators described as explained below. All the interaction rates will be considered constant, thus we will adopt the notation c_{ij}, $p_{ij}\, d_{ij}$ for conservative, proliferative and destructive encounter rates, respectively, while we shall denote by d_i the apoptosis and decay processes. We will use indices $i, j = 1, 2, 3, C$ corresponding to populations A, R, S, C, respectively.

As in [**14**], the SAPCs are involved in conservative interactions with SRTCs, in which the activity of each participating cell increases,

$$A + R \to A + R, \tag{2.1}$$

and with ISCs, in which the activity of each participating cell decreases,

$$A + S \to A + S. \tag{2.2}$$

The corresponding conservative operator for the species A is given by, see [**14**] for the details,

$$\begin{aligned}\mathcal{G}_A(\underline{\mathbf{f}}) = {} & 2c_{12}\int_0^u (u-u^*) f_A(t,\mathbf{x},u^*)du^* \int_{\mathfrak{D}_R}\int_0^1 f_R(t,\mathbf{x},\mathbf{v},u')du'\,d\mathbf{v} \\ & - c_{12}(u-1)^2 f_A(t,\mathbf{x},u)\int_{\mathfrak{D}_R}\int_0^1 f_R(t,\mathbf{x},\mathbf{v},u')du'\,d\mathbf{v} \\ & + 2c_{13}\int_u^1 (u^*-u) f_A(t,\mathbf{x},u^*)du^* \int_0^1 f_S(t,\mathbf{x},u')du' \\ & - c_{13}u^2 f_A(t,\mathbf{x},u)\int_0^1 f_S(t,\mathbf{x},u')du' \end{aligned} \tag{2.3}$$

where we have used the notation $\underline{\mathbf{f}} = (f_A, f_R, f_S, f_C)$.

The non-conservative processes involving SAPCs, instead, are given by a proliferative part represented by a constant input source α depending on external factors, proliferative interactions with SRTCs in which the newborn cells

have the same activity of their mother cells,

$$A + R \to A + A + R, \tag{2.4}$$

destructive interactions with ISCs,

$$S + A \to S + H, \tag{2.5}$$

and the natural decay of SAPCs. Putting all non-conservative effects together, the non-conservative operator can be written as

$$\begin{aligned}\mathcal{N}_A(\underline{\mathbf{f}}) = \alpha &+ p_{12} f_A(t,\mathbf{x},u)\int_0^1 f_R(t,\mathbf{x},\mathbf{v},u')du' \\ &- d_{13} f_A(t,\mathbf{x},u)\int_0^1 f_S(t,\mathbf{x},u')du' - d_1 f_A(t,\mathbf{x},u).\end{aligned} \tag{2.6}$$

For the SRTCs, we have again conservative interactions with SAPCs of type (2.1), along with conservative encounters with ISCs,

$$R + S \to R + S, \tag{2.7}$$

in which both the activity of ISCs and SRTCs decreases. The integral operator taking into account both conservative processes is

$$\begin{aligned}\mathcal{G}_R(\underline{\mathbf{f}}) = {} & 2c_{21}\int_{\mathfrak{D}_R}\int_0^u (u-u^*) f_R(t,\mathbf{x},\mathbf{v},u^*)du^*\int_0^1 f_A(t,\mathbf{x},u')du'\,d\mathbf{v} \\ & - c_{21}(u-1)^2 f_R(t,\mathbf{x},\mathbf{v},u)\int_0^1 f_A(t,\mathbf{x},u')du' \\ & + 2c_{23}\int_u^1 (u^*-u) f_R(t,\mathbf{x},\mathbf{v},u^*)du^*\int_0^1 f_S(t,\mathbf{x},u')du' \\ & - c_{23}u^2 f_R(t,\mathbf{x},\mathbf{v},u)\int_0^1 f_S(t,\mathbf{x},u')du'.\end{aligned} \tag{2.8}$$

Proliferation of SRTCs comes from interactions with SAPCs

$$A + R \to A + R + R, \tag{2.9}$$

as before, and newborn cells inherit the activity of mother cells. We recall that the reproduction of SRTCs is also stimulated by cytokines, but we do not consider here this effect, leaving its study to a future work. The destructive processes for SRTCs result from the interaction with ISCs,

$$S + R \to S + H, \tag{2.10}$$

and by natural apoptosis. The non-conservative operator for SRTCs is given by

$$\mathcal{N}_R(\underline{\mathbf{f}}) = p_{21} f_R(t,\mathbf{x},\mathbf{v},u)\int_0^1 f_A(t,\mathbf{x},u')du' - \tag{2.11}$$
$$d_{23} f_R(t,\mathbf{x},\mathbf{v},u)\int_0^1 f_S(t,\mathbf{x},u')du' - d_3 f_R(t,\mathbf{x},\mathbf{v},u).$$

Now, let us introduce the new kinetic operator representing the change in velocity and orientation of the SRTCs, caused by the chemical attraction of cytokines. Inspired by [**25**], we split this turning operator into two contributions, namely

$$\mathcal{L}_R[f_C](f_R)(\mathbf{v}) = \mathcal{L}_R^0(f_R)(\mathbf{v}) + \mathcal{L}_R^1[f_C](f_R)(\mathbf{v}). \tag{2.12}$$

Here, the operator $\mathcal{L}_R^0(f_R)$ takes into account the random movement of cells,

$$\mathcal{L}_R^0(f_R)(\mathbf{v}) = -\lambda f_R(\mathbf{v}) + \int_{\mathfrak{D}_R} \lambda T_0(\mathbf{v},\mathbf{v}') f_R(\mathbf{v}')d\mathbf{v}', \tag{2.13}$$

where the turning kernel T_0 represents the probability of the cells in changing their velocity from $\mathbf{v}'$ to $\mathbf{v}$, and it is taken as a uniform probability over the space of velocities, i.e.

$$T_0 = \frac{1}{\omega}, \tag{2.14}$$

with $\omega = |\mathfrak{D}_R|$ being the measure of the velocity space $\mathfrak{D}_R$, while the parameter $\lambda > 0$ is the turning rate. The operator $\mathcal{L}_R^1[f_C](f_R)$ in (2.12) accounts for the external biases represented by the chemotactic attraction of cytokines and reads as

$$\mathcal{L}_R^1[f_C](f_R)(\mathbf{v}) = \int_{\mathfrak{D}_R} \lambda T_1(\mathbf{v},\mathbf{v}',C) f_R(\mathbf{v}')d\mathbf{v}'. \tag{2.15}$$

We take the turning kernel analogous to the one presented in [**25**], in which the reciprocal orientation of the cytokines gradient and the incoming direction determines the new direction of the SRTCs. We also suppose that the SRTCs are more likely to move at higher speed. Moreover, we include a "volume filling" effect [**26**], i.e. we assume that the change in the velocity of a cell depends on the macroscopic population density. Thus, using the notation $\mathbf{v} = v\hat{\mathbf{v}}$, $|\hat{\mathbf{v}}| = 1$, we have

$$T_1(\mathbf{v},\mathbf{v}',C,R) = \gamma\psi(R)\frac{v}{U}\hat{\mathbf{v}}\cdot\hat{\mathbf{v}}'(\hat{\mathbf{v}}'\cdot\nabla C), \quad \psi(R) = \left(1-\frac{R}{R_M}\right)\mathbf{1}_{0\le R\le R_M}, \tag{2.16}$$

with $\gamma > 0$ being the microscopic chemotaxis parameter, R_M the maximal density of SRTCs that can be empirically computed from experimental data in relation to the biological setting considered, and $\mathbf{1}$ the indicator function.

We emphasize that, in the classical models proposed in [**24**, **25**], only the direction of the cell is assumed to change due to kinetics, whereas in our case, the speed of the cell can also vary. This choice results in a wider range of possibilities for the turning kernel, given that the cell is capable of increasing its speed, as modeled in equation (2.16). Additionally, at macroscopic level, as it will be shown in the next section, this new feature will lead to the dependence on maximal speed of chemotactic coefficient. The analytical properties of the turning kernels will be discussed in Subsection 2.3.

The ISCs are involved in conservative encounters as those described in (2.2) and (2.7), so the integral operator reads as

$$\begin{aligned}\mathcal{G}_S(\underline{\mathbf{f}}) = {} & 2c_{31}\int_u^1 (u^*-u) f_S(t,\mathbf{x},u^*)du^* \int_0^1 f_A(t,\mathbf{x},u')du' \\ & - c_{31}u^2 f_S(t,\mathbf{x},u)\int_0^1 f_A(t,\mathbf{x},u')du' \\ & + 2c_{32}\int_u^1 (u^*-u) f_S(t,\mathbf{x},u^*)du^* \int_{\mathfrak{D}_R}\int_0^1 f_R(t,\mathbf{x},\mathbf{v},u')du'\,d\mathbf{v} \\ & - c_{32}u^2 f_S(t,\mathbf{x},u)\int_{\mathfrak{D}_R}\int_0^1 f_R(t,\mathbf{x},\mathbf{v},u')du'\,d\mathbf{v}. \end{aligned} \tag{2.17}$$

Moreover, we may have proliferation of ISCs due to the interactions with SAPCs,

$$A + S \to A + S + S, \tag{2.18}$$

with, again, the newborn cells having the same activity of mother cells. We also consider the natural death of ISCs, and therefore the non-conservative operator can be written as

$$\mathcal{N}_S(\underline{\mathbf{f}}) = p_{31} f_S(t,\mathbf{x},u)\int_0^1 f_A(t,\mathbf{x},u')du' - d_3 f_S(t,\mathbf{x},u). \tag{2.19}$$

Finally, cytokines are produced by SRTCs when stimulated by SAPCs,

$$A + R \to A + R + C, \tag{2.20}$$

and are subject to natural decay. Therefore, the non-conservative operator may be written as

$$\mathcal{N}_C(\underline{\mathbf{f}}) = p_{C2}\int_{\mathfrak{D}_R}\int_0^1\int_0^1 f_A(t,\mathbf{x},u) f_R(t,\mathbf{x},\mathbf{v},u')du\,du'd\mathbf{v} - d_C f_C(t,\mathbf{x},\mathbf{w}). \tag{2.21}$$

Since the motion of cytokines is characterized by the diffusion through tissues, it would be sufficient to introduce a macroscopic diffusion coefficient D_C in the model equation. However, for the sake of coherence, we show how to rigorously derive this coefficient from the kinetic description of the microscopic dynamics. Accordingly, we write the turning operator in the more general form,

$$\mathcal{L}_C(f_C)(\mathbf{w}) = \int_{\mathfrak{D}_C} \left[T(\mathbf{w},\mathbf{w}')f_C(\mathbf{w}') - T(\mathbf{w}',\mathbf{w})f_C(\mathbf{w})\right] d\mathbf{w}', \tag{2.22}$$

and assume that the kernel depends only on the velocity of the cytokines after the interaction. Therefore,

$$T(\mathbf{w},\mathbf{w}') = \sigma M(\mathbf{w}), \tag{2.23}$$

$$M(\mathbf{w}) = \left[\gamma_i\left(\frac{n}{2},\frac{B^2}{2}\right) n\, B_n(\sqrt{2})^{n-2}\right]^{-1} \exp\left(-\frac{w^2}{2}\right), \tag{2.24}$$

where we choose the kernel giving the probability of a velocity jump from $\mathbf{w}'$ to $\mathbf{w}$. Moreover, B is the maximal speed of the cytokines introduced before, B_n is the volume of the unit ball, $\sigma > 0$ and γ_i the lower incomplete gamma function

$$\gamma_i(y,x) = \int_0^x t^{y-1}e^{-t}dt. \tag{2.25}$$

The spectral properties of $\mathcal{L}_C(f_C)$ leading to macroscopic diffusion will be analyzed in Subsection 2.3.

Our choice for the turning kernel is motivated by the models proposed in [**3**, **4**], where a more general form for the function $M(\mathbf{w})$ is considered, as long as it meets the required properties for deriving the macroscopic equations. In our case, we consider a relatively arbitrary Gaussian distribution of cytokines in the velocity space, as outlined in (2.24).

2.3 - *Spectral properties of the operators*

In this subsection, we state the analytical properties of the operators $\mathcal{L}_R[f_C]$ and $\mathcal{L}_C$, that will be used in Section 3 for the derivation of the macroscopic diffusion system. The spectral properties of the two operators ensure that it is possible to recover reaction-diffusion equations for the macroscopic densities, thanks to the results proved in [**25**] and [**3**] for operators $\mathcal{L}_R[f_C]$ and $\mathcal{L}_C$, respectively. In these papers, such results are presented for a more general case. Here, we provide the statements for our particular case, addressing the reader to the cited references for the proofs.

L e m m a 2.1. *Let $\mathcal{L}_R[f_C]$ be the turning operator given by* (2.12), (2.13), (2.15), *along with the turning kernels T_0 and T_1 defined in* (2.14) *and* (2.16), *respectively.*

(i) The turning kernel T_0 is constant and positive, and

$$\int_{\mathfrak{D}_R} T_0(\mathbf{v},\mathbf{v}')d\mathbf{v} = \int_{\mathfrak{D}_R} T_0(\mathbf{v},\mathbf{v}')d\mathbf{v}' = \int_{\mathfrak{D}_R}\int_{\mathfrak{D}_R} T_0^2(\mathbf{v},\mathbf{v}')d\mathbf{v}d\mathbf{v}' = 1. \tag{2.26}$$

Then, given the equation $\mathcal{L}_R^0(f) = g$, there exists a unique solution $f \in L^2(\mathfrak{D}_R)$ to this equation, provided that the following solvability condition holds,

$$\int_{\mathfrak{D}_R} f\, d\mathbf{v} = 0 \Leftrightarrow \int_{\mathfrak{D}_R} g\, d\mathbf{v} = 0. \tag{2.27}$$

The inverse of the operator $\mathcal{L}_R^0$ corresponds to the multiplication by $-\frac{1}{\lambda}$.

(ii) For any density C of cytokines, T_1, acting on the space $\mathfrak{D}_R \times \mathfrak{D}_R$, is an L^2 function, that is $T_1(\cdot,\cdot,C) \in L^2(\mathfrak{D}_R \times \mathfrak{D}_R)$, moreover

$$\int_{\mathfrak{D}_R} T_1(\mathbf{v},\mathbf{v}',C)d\mathbf{v} = 0. \tag{2.28}$$

L e m m a 2.2. *The kernel T defined in* (2.23)-(2.24) *is such that*

(i) $M(\mathbf{w})$ is bounded and strictly positive, and so it is $T(\mathbf{w},\mathbf{w}')$;

(ii) $\int_{\mathfrak{D}_C} M(\mathbf{w})\, d\mathbf{w} = 1$ *and* $\int_{\mathfrak{D}_C} \mathbf{w}\, M(\mathbf{w}) d\,\mathbf{w} = 0.$

Therefore, given the equation $\mathcal{L}_C(f) = g$, there exists a unique solution $f \in L^2\left(\mathfrak{D}_C, \frac{d\mathbf{w}}{M}\right)$ to this equation, provided that the following solvability condition holds

$$\int_{\mathfrak{D}_C} f\, d\mathbf{w} = 0 \Leftrightarrow \int_{\mathfrak{D}_C} g\, d\mathbf{w} = 0. \tag{2.29}$$

The inverse of the operator $\mathcal{L}_C$ corresponds to the multiplication by $-\frac{1}{\sigma}$.

The results presented in Lemmas 2.1 and 2.2 will be used in the next section.

2.4 - *Kinetic equations*

From the modelling aspects presented in Subsections 2.1 and 2.2, the evolution equations for the distribution functions f_A, f_S, f_R, and f_C is given by the following system of kinetic equations,

$$\frac{\partial f_A}{\partial t} = \mathcal{G}_A(\underline{\mathbf{f}}) + \mathcal{N}_A(\underline{\mathbf{f}}), \tag{2.30}$$

$$\frac{\partial f_R}{\partial t} + \mathbf{v}\cdot\nabla_{\mathbf{x}} f_R = \mathcal{L}_R[f_C](f_R) + \mathcal{G}_R(\underline{\mathbf{f}}) + \mathcal{N}_R(\underline{\mathbf{f}}), \tag{2.31}$$

$$\frac{\partial f_S}{\partial t} = \mathcal{G}_S(\underline{\mathbf{f}}) + \mathcal{N}_S(\underline{\mathbf{f}}), \tag{2.32}$$

$$\frac{\partial f_C}{\partial t} + \mathbf{w}\cdot\nabla_{\mathbf{x}} f_C = \mathcal{L}_C(f_C) + \mathcal{N}_C(\underline{\mathbf{f}}), \tag{2.33}$$

where the operators $\mathcal{L}_i$ for $i = R, C$, and $\mathcal{G}_i$ for $i = A, R, S$, and $\mathcal{N}_i$ for $i = A, R, S, C$ are those defined in equations (2.12), (2.22), and (2.3), (2.8) (2.17), and (2.6), (2.11), (2.19), (2.21), respectively.

3 - From the kinetic regime to macroscopic equations

In this section, starting from the kinetic equations (2.30)-(2.33), we derive the macroscopic system describing the evolution of the global densities of the populations involved in the dynamics, namely A, R, S and C. To this aim, we first perform a time scaling, assuming that the dominant processes are the movement of SRTCs and cytokines, whereas the conservative and non-conservative dynamics occur at lower time scale.

Choosing a small parameter ϵ, we write the system of integro-differential evolution equations for the distribution functions f_A, f_S, f_R, f_C as follows

$$\epsilon\,\frac{\partial f_A}{\partial t} = \epsilon\,\mathcal{G}_A(\underline{\mathbf{f}}) + \epsilon\,\mathcal{N}_A(\underline{\mathbf{f}}), \tag{3.1}$$

$$\epsilon\,\frac{\partial f_R}{\partial t} + \mathbf{v}\cdot\nabla_{\mathbf{x}} f_R = \frac{1}{\epsilon}\mathcal{L}_R[f_C](f_R) + \epsilon\mathcal{G}_R(\underline{\mathbf{f}}) + \epsilon\mathcal{N}_R(\underline{\mathbf{f}}), \tag{3.2}$$

$$\epsilon\,\frac{\partial f_S}{\partial t} = \epsilon\,\mathcal{G}_S(\underline{\mathbf{f}}) + \epsilon\,\mathcal{N}_S(\underline{\mathbf{f}}), \tag{3.3}$$

$$\epsilon\,\frac{\partial f_C}{\partial t} + \mathbf{w}\cdot\nabla_{\mathbf{x}} f_C = \frac{1}{\epsilon}\mathcal{L}_C(f_C) + \epsilon\,\mathcal{N}_{\mathcal{C}}(\underline{\mathbf{f}}), \tag{3.4}$$

where the operators $\mathcal{L}_i$ for $i = R, C$, and $\mathcal{G}_i$ for $i = A, R, S$, and $\mathcal{N}_i$ for $i = A, R, S, C$ are those defined in equations (2.12), (2.22), and (2.3), (2.8) (2.17), and (2.6), (2.11), (2.19), (2.21), respectively, of the previous section.

We also suppose that, for the evolution of f_R, the perturbation given by the cytokines gradient is of order ϵ, thus

$$\mathcal{L}_R[f_C](f_R)(\mathbf{v}) = \mathcal{L}_R^0(f_R)(\mathbf{v}) + \epsilon\,\mathcal{L}_R^1[f_C](f_R)(\mathbf{v}), \tag{3.5}$$

with $\mathcal{L}_R^0(f_R)$ and $\mathcal{L}_R^1[f_C](f_R)$ being given by (2.13)-(2.15), respectively.

The aforementioned decomposition is motivated by the one discussed in paper [**25**], where the considered perturbations, caused by external fields, exhibit varying magnitudes and affect both the turning rate λ and the turning kernel T of the unperturbed problem, and where the different effects on the parabolic limit are studied. However, in our analysis, we focus solely on the scenario regarding an order ϵ perturbation of the turning kernel.

3.1 - *Equations for A and S*

In order to derive the time and space evolution equations for the macroscopic densities $A(t,\mathbf{x})$ and $S(t,\mathbf{x})$, we formally integrate equations (3.1) and (3.3) in the activity variable u, obtaining

$$\frac{\partial A(t,\mathbf{x})}{\partial t} = \alpha + p_{12}A(t,\mathbf{x})R(t,\mathbf{x}) - d_{13}A(t,\mathbf{x})S(t,\mathbf{x}) - d_1A(t,\mathbf{x}), \tag{3.6}$$

$$\frac{\partial S(t,\mathbf{x})}{\partial t} = p_{31}S(t,\mathbf{x})A(t,\mathbf{x}) - d_3S(t,\mathbf{x}). \tag{3.7}$$

3.2 - *Equation for R*

For the time and space evolution equation of the density $R(t,\mathbf{x})$, we follow the procedure outlined in [**25**] for the case of an $O(\epsilon)$ perturbation of the turning kernel, namely $T_0 + \epsilon\,T_1$, with T_0 and T_1 defined in (2.14) and (2.16), respectively. We then use the properties of the operator $\mathcal{L}_0^R$ stated in Lemma 2.1, along with the property (2.28) of the perturbation kernel T_1 of Subsection 2.3.

We continue by writing f_R as a Hilbert expansion in ϵ,

$$f_R(t,\mathbf{x},\mathbf{v},u) = f_R^0(t,\mathbf{x},\mathbf{v},u) + \epsilon f_R^1(t,\mathbf{x},\mathbf{v},u) + \epsilon^2 f_R^2(t,\mathbf{x},\mathbf{v},u) + O(\epsilon^3), \tag{3.8}$$

and then we insert this expansion in equation (3.2). Equating the terms of same order in ϵ, we get the following set of equations at the ϵ^0, ϵ^1 and ϵ^2-

orders, respectively,

$$\mathcal{L}_R^0(f_R^0) = 0, \tag{3.9}$$

$$\mathbf{v}\cdot\nabla_{\mathbf{x}} f_R^0 = \mathcal{L}_R^0(f_R^1) + \mathcal{L}_R^1[f_C](f_R^0), \tag{3.10}$$

$$\begin{aligned}\frac{\partial f_R^0}{\partial t} &+ \mathbf{v}\cdot\nabla_{\mathbf{x}} f_R^1 \\ &= \mathcal{L}_R^0(f_R^2) + \mathcal{L}_R^1[f_C](f_R^1) + \mathcal{G}_R(f_A, f_R^0, f_S) + \mathcal{N}_R(f_A, f_R^0, f_S).\end{aligned} \tag{3.11}$$

Without loss of generality, we assume that the total density of the SRTCs is concentrated in f_R^0, and therefore

$$\int_{\mathfrak{D}_R} f_R^0(t,\mathbf{x},\mathbf{v},u)\,d\mathbf{v} = \rho_R(t,\mathbf{x},u), \quad \int_{\mathfrak{D}_R} f_R^i(t,\mathbf{x},\mathbf{v},u)d\mathbf{v} = 0, \quad i = 1,2. \tag{3.12}$$

Then, from (3.9) we get that f_R^0 does not depend on $\mathbf{v}$

$$f_R^0(t,\mathbf{x},\mathbf{v},u) = \frac{1}{\omega}\rho_R(t,\mathbf{x},u). \tag{3.13}$$

Consequently, the ϵ^1-order equation (3.10) becomes

$$\mathbf{v}\cdot\nabla_{\mathbf{x}}\frac{\rho_R}{\omega} - \mathcal{L}_R^1[f_C]\left(\frac{\rho_R}{\omega}\right) = \mathcal{L}_R^0(f_R^1). \tag{3.14}$$

Thanks to Lemma 2.1 and property (2.28), it is possible to invert equation (3.14) above, getting an explicit form for f_R^1

$$f_R^1(t,\mathbf{x},\mathbf{v},u) = -\frac{1}{\lambda}\mathbf{v}\cdot\nabla_{\mathbf{x}}\frac{\rho_R}{\omega} + \frac{\rho_R}{\omega}\int_{\mathfrak{D}_R} T_1(\mathbf{v},\mathbf{v}',C)d\mathbf{v}'. \tag{3.15}$$

Inserting now the expression of $f_R^1(t,\mathbf{x},\mathbf{v},u)$ into the ϵ^2-order equation (3.11), we obtain

$$\begin{aligned}\mathcal{L}_R^0[f_C](f_R^2) = {} & \frac{1}{\omega}\frac{\partial\rho_R}{\partial t} + \mathbf{v}\cdot\nabla_{\mathbf{x}}\left(-\frac{1}{\lambda}\mathbf{v}\cdot\nabla_{\mathbf{x}}\frac{\rho_R}{\omega} + \frac{\rho_R}{\omega}\int_{\mathfrak{D}_R} T_1(\mathbf{v},\mathbf{v}',C)d\mathbf{v}'\right) \\ & - \lambda\int_{\mathfrak{D}_R} T_1(\mathbf{v},\mathbf{v}',C)\left[-\frac{1}{\lambda}\mathbf{v}'\cdot\nabla_{\mathbf{x}}\frac{\rho_R}{\omega} + \frac{\rho_R}{\omega}\int_{\mathfrak{D}_R} T_1(\mathbf{v}',\mathbf{w},C)d\mathbf{w}\right]d\mathbf{v}' \\ & + \mathcal{G}_R(f_A,\rho_R,f_S) + \mathcal{N}_R(f_A,\rho_R,f_S).\end{aligned} \tag{3.16}$$

To derive explicitly the term f_R^2, we impose the solvability condition (2.27), and therefore the integral in $\mathbf{v}$ of the right-hand side term in the expression (3.16)

vanishes. This gives the following expression for ρ_R, in which we still have the dependence on u,

$$\frac{\partial \rho_R}{\partial t} - \nabla_{\mathbf{x}} \cdot \left(\int_{\mathfrak{D}_R} \frac{1}{\lambda} \mathbf{v} \otimes \mathbf{v} d\mathbf{v} \right) \cdot \nabla_{\mathbf{x}} \frac{\rho_R}{\omega} + \nabla_{\mathbf{x}} \cdot \left[\frac{\rho_R}{\omega} \int_{\mathfrak{D}_R} \int_{\mathfrak{D}_R} \mathbf{v} T_1(\mathbf{v}, \mathbf{v}', C) d\mathbf{v}' d\mathbf{v} \right]$$
$$= \left[\mathcal{G}_R(f_A, \rho_R, f_S) + \mathcal{N}_R(f_A, \rho_R, f_S) \right] \omega. \tag{3.17}$$

The first integral in the above equation (3.17) gives

$$\int_{\mathfrak{D}_R} \frac{1}{\lambda} \mathbf{v} \otimes \mathbf{v} \, d\mathbf{v} = \frac{U^2}{(n+2)\lambda} \omega \mathbb{I},$$

with $\mathbb{I}$ being the identical matrix of order n, whereas the second one can be written as

$$\int_{\mathfrak{D}_R} \int_{\mathfrak{D}_R} \mathbf{v} \, T_1(\mathbf{v}, \mathbf{v}', C) d\mathbf{v}' \, d\mathbf{v} = \gamma \, \psi(R) \int_{\mathfrak{D}_R} \mathbf{v} \otimes \hat{\mathbf{v}} \cdot \left(\int_{\mathfrak{D}_R} \frac{v}{U} \, \hat{\mathbf{v}}' \otimes \hat{\mathbf{v}}' d\mathbf{v}' \right) \nabla_{\mathbf{x}} C \, d\mathbf{v}$$

that, when computed, gives

$$\int_{\mathfrak{D}_R} \int_{\mathfrak{D}_R} \mathbf{v} \, T_1(\mathbf{v}, \mathbf{v}', C) d\mathbf{v}' \, d\mathbf{v} = \gamma \, \psi(R) \, \omega^2 \frac{U}{(n+1)^2} \nabla_{\mathbf{x}} C. \tag{3.18}$$

Defining the coefficient for SRTCs and the chemotaxis macroscopic parameter as

$$D_R = \frac{U^2}{(n+2)\lambda} \quad \text{and} \quad \chi = \gamma \omega \frac{U}{(n+1)^2}, \tag{3.19}$$

the partial differential equation (3.17) for ρ_R reads

$$\frac{\partial \rho_R}{\partial t} - \nabla_{\mathbf{x}} \cdot \left[D_R \nabla_{\mathbf{x}} \, \rho_R - \chi \, \psi(R) \, \rho_R \nabla_{\mathbf{x}} \, C \right]$$
$$= \mathcal{G}_R(f_A, \rho_R, f_S) + \mathcal{N}_R(f_A, \rho_R, f_S), \tag{3.20}$$

and if we integrate equation (3.20) above also in the variable u, we obtain

$$\frac{\partial R(t, \mathbf{x})}{\partial t} = \nabla_{\mathbf{x}} \cdot \left[D_R \nabla_{\mathbf{x}} \, R(t, \mathbf{x}) - \chi \, \psi(R(t, \mathbf{x})) \, R(t, \mathbf{x}) \nabla_{\mathbf{x}} \, C \right]$$
$$+ p_{21} R(t, \mathbf{x}) A(t) - d_{23} R(t, \mathbf{x}) S(t) - d_2 R(t, \mathbf{x}). \tag{3.21}$$

3.3 - *Equation for C*

The procedure proposed in [**3**] can be applied to derive the macroscopic equation for $C(t, \mathbf{x})$. The properties stated in Lemma 2.2 of Subsection 2.3. will be used in this derivation.

As done for the distribution of SRTCs, we also perform an expansion of f_C with respect to ϵ,

$$f_C(t, \mathbf{x}, \mathbf{w}) = f_C^0(t, \mathbf{x}, \mathbf{w}) + \epsilon f_C^1(t, \mathbf{x}, \mathbf{w}) + \epsilon^2 f_C^2(t, \mathbf{x}, \mathbf{w}) + O(\epsilon^3). \tag{3.22}$$

Inserting expansion (3.22) of f_C and expansion (3.8) of f_R into equation (3.4) and equating terms of the same order, we get the following equations at the ϵ^0, ϵ^1 and ϵ^2-orders, respectively,

$$\mathcal{L}_C(f_C^0) = 0, \tag{3.23}$$

$$\mathbf{w} \cdot \nabla_{\mathbf{x}} f_C^0 = \mathcal{L}_C(f_C^1), \tag{3.24}$$

$$\frac{\partial f_C^0}{\partial t} + \mathbf{w} \cdot \nabla_{\mathbf{x}} f_C^1 = \mathcal{N}_C(f_A, \rho_R, f_C^0) + \mathcal{L}_C(f_C^2). \tag{3.25}$$

From the order ϵ^0 equation (3.23), supposing also here that the mass is concentrated in the ϵ^0-order term of the expansion, we straightforwardly get

$$f_C^0(t, \mathbf{x}, \mathbf{w}) = M(\mathbf{w}) C(t, \mathbf{x}). \tag{3.26}$$

This allows us to write the ϵ^1-order equation (3.24) as

$$\mathbf{w} \cdot \nabla_{\mathbf{x}} M(\mathbf{w}) C = \mathcal{L}_C(f_C^1), \tag{3.27}$$

that provides

$$f_C^1(t, \mathbf{x}, \mathbf{w}) = -\frac{1}{\sigma} \mathbf{w} \cdot M(\mathbf{w}) \nabla_{\mathbf{x}} C. \tag{3.28}$$

We insert this expression into the ϵ^2-order equation (3.25), which then can be rewritten as

$$\mathcal{L}_C(f_C^2) = M(\mathbf{w}) \frac{\partial C}{\partial t} + \mathbf{w} \cdot \nabla_{\mathbf{x}} \left(-\frac{1}{\sigma} \mathbf{w} \cdot M(\mathbf{w}) \nabla_{\mathbf{x}} C \right) - \mathcal{N}_C[f_A, \rho_R, M(\mathbf{w}) C]. \tag{3.29}$$

According to the spectral properties of $\mathcal{L}_C$ stated in Lemma 2.2, equation (3.29) can be solved only if the integral in $\mathbf{w}$ of the term on its left-hand side is null. Then, the solvability condition (2.29) provides

$$\frac{\partial C(t, \mathbf{x})}{\partial t} = D_C \, \Delta_{\mathbf{x}} \, C(t, \mathbf{x}) + p_{C2} A(t, \mathbf{x}) R(t, \mathbf{x}) - d_C C(t, \mathbf{x}), \tag{3.30}$$

where the diffusion matrix for the cytokines is given by

$$\frac{1}{\sigma}\int_{\mathfrak{D}_C}\mathbf{w}\otimes\mathbf{w}M(\mathbf{w})\,d\mathbf{w}=\frac{1}{\sigma}\left[1-\frac{2}{n}\frac{\left(\frac{B}{\sqrt{2}}\right)^n\exp\left(-\frac{B^2}{2}\right)}{\gamma_i\left(\frac{n}{2},\frac{B^2}{2}\right)}\right]\mathbb{I}=:D_C\,\mathbb{I}, \tag{3.31}$$

being D_C the diffusion coefficient. As already mentioned, the dependence of D_C on the microscopic parameters n and B recognizable in (3.31) is not exploited later on.

3.4 - *Reaction-diffusion system*

We first collect the macroscopic equations (3.6), (3.7), (3.21), and (3.30) derived in the previous subsections, giving the evolution of the global densities of the populations involved in the dynamics. The macroscopic system is then given by

$$\frac{\partial A(t,\mathbf{x})}{\partial t}=\alpha+p_{12}A(t,\mathbf{x})R(t,\mathbf{x})-d_{13}A(t,\mathbf{x})S(t,\mathbf{x})-d_1A(t,\mathbf{x}), \tag{3.32}$$

$$\frac{\partial S(t,\mathbf{x})}{\partial t}=p_{31}S(t,\mathbf{x})A(t,\mathbf{x})-d_3S(t,\mathbf{x}), \tag{3.33}$$

$$\begin{aligned}\frac{\partial R(t,\mathbf{x})}{\partial t}&=\nabla_{\mathbf{x}}\cdot\left[D_R\,\nabla_{\mathbf{x}}\,R(t,\mathbf{x})-\chi\,\psi(R(t,\mathbf{x}))\,R(t,\mathbf{x})\,\nabla_{\mathbf{x}}C\right]\\&\quad+p_{21}R(t,\mathbf{x})A(t,\mathbf{x})-d_{23}R(t,\mathbf{x})S(t,\mathbf{x})-d_2R(t,\mathbf{x}),\end{aligned} \tag{3.34}$$

$$\frac{\partial C(t,\mathbf{x})}{\partial t}=D_C\,\Delta_{\mathbf{x}}C(t,\mathbf{x})+p_{C2}A(t,\mathbf{x})R(t,\mathbf{x})-d_CC(t,\mathbf{x}). \tag{3.35}$$

Then, we perform the change of variables

$$\widetilde{t}=\Lambda t,\qquad\widetilde{\mathbf{x}}=\sqrt{\frac{\Lambda}{D_R}}\,\mathbf{x}, \tag{3.36}$$

where the parameter Λ is given by

$$\Lambda:=\frac{d_3p_{21}}{p_{31}}+\frac{d_{23}\,(d_1d_3-p_{31}\alpha)}{d_{13}d_3}-d_2, \tag{3.37}$$

with parameters being chosen in such a way that Λ is positive.

Then we define non-dimensional macroscopic densities,

$$\widetilde{A}=\frac{A\Lambda}{\alpha},\quad\widetilde{S}=\frac{Sd_{13}}{\Lambda},\quad\widetilde{R}=\frac{R}{R_M},\quad\widetilde{C}=\frac{C\Lambda^2}{p_{C2}\alpha\,R_M}, \tag{3.38}$$

and define the new coefficients

$$\beta = \frac{R_M\, p_{12}}{\Lambda}, \quad \zeta = \frac{d_1}{\Lambda}, \quad \mu = \frac{p_{31}\alpha}{\Lambda^2}, \quad \nu = \frac{d_3}{\Lambda}, \quad \delta = \frac{D_C}{D_R},$$

$$\tau = \frac{d_C}{\Lambda}, \quad \xi = \chi\,\frac{p_{C2}\alpha\, R_M}{D_R\Lambda^2}, \quad \eta = \frac{p_{21}\alpha}{\Lambda^2}, \quad \phi = \frac{d_{23}}{d_{13}}, \quad \theta = \frac{d_2}{\Lambda},$$

and the function

$$\Psi(y) = (1-y)\,\mathbf{1}_{0\le y\le 1}.$$

Referring equations (3.32)-(3.35) to the non-dimensional densities (3.38), we obtain the following system,

$$\frac{\partial A}{\partial t} = 1 + \beta A\, R - A\, S - \zeta A, \tag{3.39}$$

$$\frac{\partial S}{\partial t} = \mu\, A\, S - \nu\, S, \tag{3.40}$$

$$\frac{\partial R}{\partial t} = \nabla_{\mathbf{x}} \cdot (\nabla_{\mathbf{x}} R - \xi\, \Psi(R) R\, \nabla_{\mathbf{x}} C) + \eta\, A\, R - \phi\, R\, S - \theta\, R, \tag{3.41}$$

$$\frac{\partial C}{\partial t} = \delta \Delta_{\mathbf{x}} C + A\, R - \tau\, C, \tag{3.42}$$

where, for convenience, we have renamed the tilde-labeled densities and parameters by removing the tilde, and omit the dependence of the macroscopic densities on time and space.

Equations (3.39)-(3.42) constitute our reaction-diffusion system that will be analysed in the next section in terms of pattern formation. They describe the behaviour of the global densities of the populations, exhibiting the diffusion of both the SRTCs and the Cytokines.

4 - Turing instability

Reaction-diffusion systems may exhibit Turing instability when a spatially homogeneous steady state exists such that it is stable in absence of diffusion and may become unstable by adding the diffusive terms, see [**34**]. This condition may lead to the formation of spatial patterns that have been widely used in literature to describe phenomena in biology, [**15**, **21**, **22**], in particular in the study of autoimmune pathologies like multiple sclerosis [**23**], and phenomena in chemistry [**9**, **29**]. In the case of chemotaxis, a more general discussion may be found e.g. in [**35**] along with an analytical proof of global existence of solution.

Thus, in view of studying the Turing instability for system (3.39)-(3.42), we first characterize its steady states when the diffusion terms are absent, and

study their stability. Then we investigate conditions that lead to the formation of patterns for the complete system with diffusion (3.39)-(3.42).

4.1 - *Existence and stability of equilibria*

The steady states of system (3.39)-(3.42) without the diffusive terms are given by $E_k := (A_k, S_k, R_k, C_k)$, $k = 1, \dots, 4$, with

$$E_1 = \left(\frac{\nu}{\mu}, \frac{-\theta\,\mu + \eta\,\nu}{\mu\,\phi}, \frac{-\theta\,\mu\,\nu + \eta\,\nu^2 - \mu^2\,\phi + \zeta\,\mu\,\nu\,\phi}{\beta\,\mu\,\nu\,\phi}, \frac{\nu}{\mu\tau}\,R_1 \right), \tag{4.1}$$

$$E_2 = \left(\frac{1}{\zeta}, 0, 0, 0 \right), \tag{4.2}$$

$$E_3 = \left(\frac{\nu}{\mu}, \frac{\mu - \zeta\,\nu}{\nu}, 0, 0 \right), \tag{4.3}$$

$$E_4 = \left(\frac{\theta}{\eta}, 0, \frac{-\eta + \zeta\,\theta}{\theta}, \frac{\nu}{\mu\tau}\,R_4 \right). \tag{4.4}$$

We want to focus on equilibria that would be biologically relevant, i.e. the ones that belong to the set

$$\mathcal{A} = \Big\{ A(t,\mathbf{x}) \geq 0,\, S(t,\mathbf{x}) \geq 0,\, 0 \leq R(t,\mathbf{x}) \leq 1,\, C(t,\mathbf{x}) \geq 0 \Big\}. \tag{4.5}$$

For this reason, we consider equilibrium E_1, that belongs to $\mathcal{A}$ if the following conditions are satisfied

$$-\theta\,\mu + \eta\,\nu > 0, \qquad \beta\,\mu\,\nu\,\phi > -\theta\,\mu\,\nu + \eta\,\nu^2 - \mu^2\,\phi + \zeta\,\mu\,\nu\,\phi > 0. \tag{4.6}$$

Written in terms of the microscopic parameters of the model before the adimensionalization, the conditions above become

$$\Sigma := d_3 p_{21} - d_2 p_{31} > 0, \tag{4.7}$$

$$\alpha < \alpha^*, \quad \text{with} \quad \alpha^* := \frac{d_1 d_3}{p_{31}} + \frac{d_{13} d_3 (d_3 p_{21} - d_2 p_{31})}{d_{23} p_{31}^2}. \tag{4.8}$$

We observe that the results above are analogous to those obtained in [**14**], but in this case we have the additional condition

$$\bar{\alpha} < \alpha, \quad \bar{\alpha} := \alpha^* - \frac{d_3\,p_{12}\,R_M}{p_{31}}. \tag{4.9}$$

Concerning the asymptotical stability of the equilibrium E_1, we first linearize system (3.32)-(3.35) around E_1, resulting in

$$\frac{\partial \mathbf{W}}{\partial t} = \mathbb{A}\mathbf{W}, \qquad \text{for} \quad \mathbf{W} = \begin{pmatrix} A - A_1 \\ S - S_1 \\ R - R_1 \\ C - C_1 \end{pmatrix}, \tag{4.10}$$

where the Jacobian matrix $\mathbb{A}$ is given by

$$\mathbb{A} = \begin{pmatrix} & \mathbb{J} & & 0 \\ & & & 0 \\ & & & 0 \\ 0 & 0 & 1 & -\tau \end{pmatrix}, \quad \text{with} \quad \mathbb{J} = \begin{pmatrix} -\dfrac{\mu}{\nu} & -\dfrac{\nu}{\mu} & \dfrac{\beta\nu}{\mu} \\ \dfrac{-\theta\mu + \eta\nu}{\phi} & 0 & 0 \\ \dfrac{\eta}{\beta\,\phi} & -\dfrac{1}{\beta} & 0 \end{pmatrix}. \tag{4.11}$$

Since the eigenvalues of the matrix $\mathbb{A}$ are $-\tau$ and those of the matrix $\mathbb{J}$, it is immediate that the stability of the equilibrium state E_1 is determined by the eigenvalues of the matrix $\mathbb{J}$, so that we study its characteristic polynomial, say $P_{\mathbb{J}}(\lambda) = -P(\lambda)$, with

$$P(\lambda) = \lambda^3 + \frac{\mu}{\nu}\lambda^2 - \left(\frac{\eta\nu}{\phi\,\mu} + \frac{\nu}{\phi\mu}(\theta\mu - \eta\nu)\right)\lambda + \frac{\nu}{\mu\,\phi}\,(\eta\nu - \theta\mu)\,.$$

The coefficients of $P(\lambda)$ may be written in the form

$$\frac{\mu}{\nu} = \frac{p_{31}\alpha}{d_3\Lambda}\ ,$$

$$-\left(\frac{\eta\nu}{\phi\,\mu} + \frac{\nu}{\phi\mu}(\theta\mu - \eta\nu)\right) = \frac{d_3 d_{13}\Sigma}{p_{31}d_{23}\Lambda^2} - \frac{p_{21}(\alpha^* - \alpha)}{\Lambda^2}\ ,$$

$$\frac{\nu}{\mu\,\phi}\,(\eta\nu - \theta\mu) = \frac{\Sigma(\alpha^* - \alpha)}{\Lambda^3}\ ,$$

where the parameter Λ can be written as

$$\Lambda = \frac{d_{23}p_{31}}{d_{13}d_3}\,(\alpha^* - \alpha)\,,$$

thanks to (3.37) and (4.8). Thus, for $\alpha < \alpha^*$, we recover the stability condition obtained in [**14**], that is

$$\alpha > \alpha^H, \tag{4.12}$$

with α^H the unique positive zero of function

$$h(\alpha) = d_{23}p_{21}p_{31}\alpha^2 + (d_3\Sigma(d_{13}+d_{23}) - d_{23}p_{21}p_{31}\alpha^*)\,\alpha - d_3d_{23}\Sigma\alpha^*. \tag{4.13}$$

We then conclude that linear asymptotic stability of equilibrium E_1 is obtained for

$$\max\left(\alpha^H, \bar{\alpha}\right) < \alpha < \alpha^*. \tag{4.14}$$

Therefore, the condition that determines the linear asymptotic stability of the equilibrium state E_1 is

$$\max\left(\alpha^H, \bar{\alpha}\right) < \alpha < \alpha^*. \tag{4.15}$$

4.2 - *Pattern formation*

To investigate Turing instability for system (3.39)-(3.42) , we consider now the linearized system (4.10) with the diffusion terms added, imposing no-flux conditions on the boundary $\partial\Gamma$ of the spatial evolution domain Γ. Therefore, the system of interest is

$$\begin{cases} \dfrac{\partial \mathbf{W}}{\partial t} = \mathbb{D}\Delta_{\mathbf{x}}\mathbf{W} + \mathbb{A}\mathbf{W} & \text{on } (0,\infty)\times\Gamma \\ \widehat{\mathbf{n}}\cdot\nabla_{\mathbf{x}}\mathbf{W} = 0 & \text{on } (0,\infty)\times\partial\Gamma \end{cases} \tag{4.16}$$

where $\widehat{n}$ is the external unit normal to $\partial\Gamma$, and $\mathbb{D}$ is the diffusion matrix,

$$\mathbb{D} = \begin{pmatrix} 0 & 0 & 0 & 0 \\ 0 & 0 & 0 & 0 \\ 0 & 0 & 1 & -\xi\Psi(R_1)R_1 \\ 0 & 0 & 0 & \delta \end{pmatrix}. \tag{4.17}$$

We have formation of patterns for the system (4.16), whenever the matrix $\mathbb{A} - k^2\mathbb{D}$ has at least one eigenvalue with positive real part for some value of k, and this is equivalent to require that $\det(\mathbb{A} - k^2\mathbb{D}) < 0$ for some value of k. The determinant of $\mathbb{A} - k^2\mathbb{D}$, as function of k, reads as

$$\det(\mathbb{A} - k^2\mathbb{D}) = \frac{\nu\,(-\theta\,\mu + \eta\,\nu)}{\mu\,\phi}\,\left(k^4\delta + k^2\,(\delta + \tau - \xi\,\Psi(R_1)\,R_1) + \tau\right). \tag{4.18}$$

Defining

$$h(k^2) := k^4\delta + k^2\,(\delta + \tau - \xi\,\Psi(R_1)\,R_1) + \tau, \tag{4.19}$$

and holding the existence conditions (4.6), necessary and sufficient conditions to have $det(\mathbb{A} - k^2\mathbb{D}) < 0$ are

$$\delta + \tau - \xi\,\Psi(R_1)\,R_1 < 0, \tag{4.20}$$

$$h_{min} > 0, \quad h_{min} = (\delta + \tau - \xi\,\Psi(R_1)\,R_1)^2 - 4\,\delta\,\tau, \tag{4.21}$$

which lead to

$$\xi - \frac{2\sqrt{\delta\tau} + \delta + \tau}{\Psi(R_1)\,R_1} > 0. \tag{4.22}$$

Therefore, we have formation of patterns for the system (3.39)-(3.42) whenever condition (4.22) holds.

4.3 - *Parameters discussion*

In this subsection, we discuss conditions in the parameter space leading to Turing instability, in light of the conditions (4.15) and (4.22) previously obtained. We set our analysis on the kinetic parameters of the model, namely destructive rates d_{ij}, proliferative rates p_{ij}, death rates d_i, constant input of SAPCs α, turning rate λ, and microscopic chemotactic parameter γ, and put the focus on α, λ, and γ. Having this in mind, equation (4.22) is rewritten as

$$\xi(\alpha,\lambda,\gamma) - \frac{2\sqrt{\delta(\lambda)\tau(\lambda)} + \delta(\lambda) + \tau(\alpha)}{\Psi(R_1(\alpha))R_1(\alpha)} > 0, \tag{4.23}$$

where

$$\begin{gathered} R_1(\alpha) = \frac{p_{31}(\alpha^* - \alpha)}{d_3\,p_{12}\,R_M}, \quad \tau(\alpha) = \frac{d_{13}\,d_3\,d_C}{d_{23}p_{31}(\alpha^* - \alpha)}, \\ \delta(\lambda) = \frac{D_C(2+n)\lambda}{U^2}, \quad \xi(\alpha,\lambda,\gamma) = \frac{\alpha\,\lambda\,\gamma\,d_{13}^2\,d_3^2\,(2+n)\omega p_{C2}R_M}{d_{23}^2(1+n)^2p_{31}^2(\alpha^* - \alpha)^2}. \end{gathered} \tag{4.24}$$

As stated in Subsection 3.3, we are going to neglect the dependence of D_C on microscopic quantities n and B carried out in (3.31).

Then for some fixed values of parameters d_{ij}, p_{ij}, and d_i, we choose a value of α compatible with the stability condition (4.15) and then discuss the range of parameters λ and γ in agreement with pattern formation condition (4.22). Accordingly, we define the reference function

$$G(\lambda,\gamma) := \xi(\lambda,\gamma) - \frac{2\sqrt{\delta(\lambda)\tau(\lambda)} + \delta(\lambda) + \tau}{\Psi(R_1)R_1}, \tag{4.25}$$

with the dependence of ξ, R_1, δ, τ on the microscopic parameters given by in (4.24), and look for parameters λ and γ such that

$$G(\lambda, \gamma) > 0. \tag{4.26}$$

Following the above described strategy, we develop some numerical simulations in the next subsection.

4.4 - *Numerical results*

Here, we perform numerical simulations to reproduce pattern formation in the 1-dimensional domain $\Gamma = [0, 25]$, imposing zero-flux at the boundary and starting from a random perturbation of equilibria. Our main objective is to show that it is possible to single out certain values for α, λ, γ leading to pattern formation as a consequence of diffusion of SRTCs and cytokines. The numerical tests developed are merely illustrative, and therefore, the choice of parameters was not based on real data. We consider

$$\begin{gathered} D_C = 90, \quad U = 0.5 \quad p_{C2} = 100, \quad d_C = 0.5, \quad R_M = 10, \\ p_{12} = 0.1, \quad p_{21} = 9, \quad p_{31} = 4, \\ d_{13} = 1, \quad d_{23} = 9 \quad d_1 = 9, \quad d_2 = 0.14, \quad d_3 = 20, \end{gathered} \tag{4.27}$$

meaning that the autoimmune dynamics is reflected in a rather high death rate of ISCs, specifically $d_3 = 20$, along with a low death rate of SRTCs, namely $d_2 = 0.14$. Moreover, we then obtain the critical values

$$\bar{\alpha} = 64.92, \quad \alpha^H = 65.53, \quad \alpha^* = 69.92, \tag{4.28}$$

and consider $\alpha \in (\alpha^H, \alpha^*)$. Function G is continuous and, since $\dfrac{\partial G}{\partial \gamma} > 0$ for any fixed value of $\lambda = \bar{\lambda}$, function G is also positive for γ sufficiently large. Figure 1 shows the plot of G in the $\lambda\gamma$-plane, for $\alpha = 68.7$ and the other parameters given as in (4.27). We can identify a critical threshold curve in the $\lambda\gamma$-plane where function G becomes positive.

Taking again $\alpha = 68.7$, we choose λ and γ in the region in which condition (4.26) for function G being positive is satisfied, visible in Figure 1, more precisely we choose $\lambda = 3.5 \times 10^{-4}$ and $\gamma = 5.5$. Then we run a finite-difference method for system (3.39)-(3.42), taking as initial data a random perturbation of spatially homogeneous equilibrium E_1 given in (4.1).

Figure 2, panel (a), shows the time-space plot of SRTCs density, namely $R(t, \mathbf{x})$, in the spatial domain Γ and a window of time $[0, 350]$, exhibiting the

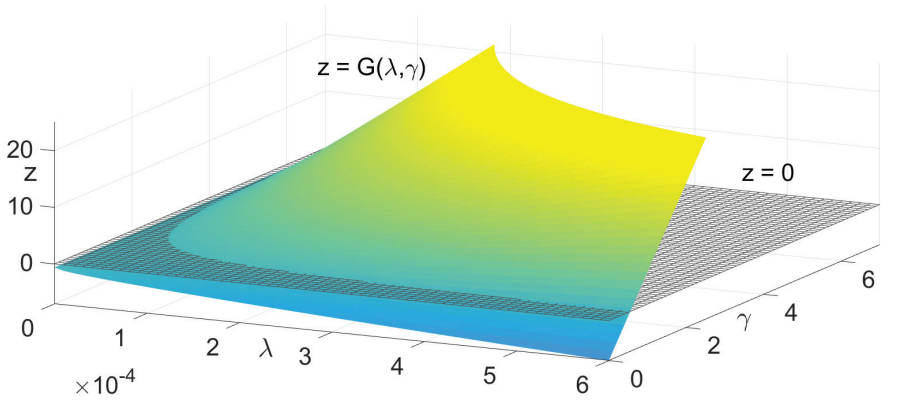

Fig. 1. Representation in the $\lambda\gamma$-plane of function G defined in (4.25), with microscopic parameters taken as in (4.27), and $\alpha = 68.7$.

pattern formation generated by the diffusion processes. Panel (b) shows the spatial non-homogeneous representation of SRTCs density for the final time $t = 350$ (solid line), compared with the spatial homogeneous equilibrium without diffusion (dashed line).

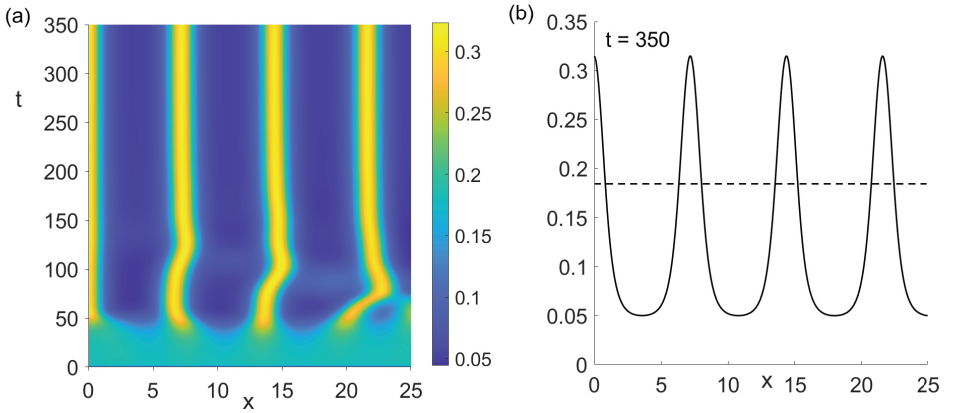

Fig. 2. Evolution of SRTCs density $R(x,t)$ with microscopic parameters taken as in (4.27), and $\alpha = 68.7$, $\lambda = 3.5 \times 10^{-4}$, $\gamma = 5.5$. *Panel (a)* – time-space plot. *Panel (b)* – spatial representation for the final time $t = 350$, showing the non-homogeneous distribution (solid line) compared with the homogeneous equilibrium distribution without diffusion (dashed line).

5 - Conclusions

In this work, we have proposed a kinetic model to be adopted for the study of the dynamics of cells involved in autoimmune diseases. Starting from the model presented in [**14**], in which the behavior of antigen presenting cells (SAPCs), self reactive T-cells (SRTCs) and immunosuppressive cells (ISCs) was studied only with respect to time, we have here included a spatial component. Moreover, we have also considered the chemotactic motion of T-cells driven by cytokines, in order to get diffusion-chemotaxis terms in the macroscopic model.

We have written the kinetic equations for the distribution functions of populations cited above. The integral terms taking into account the conservative and non-conservative encounters among cells are analogous to those derived in [**30**], along with the constant input of SAPCs and natural decay of cells introduced in [**14**]. We have, then, considered an additional term in the equation of SRTCs for the changes in the velocity. More precisely, we took an integral turning operator inspired by the one proposed in [**25**], based on a velocity-jump process, including a volume-filling effect and a dependence on the cell speed in the turning kernel. In addition, we have built up the kinetic equation for the cytokines, considering their production coming from encounters between SAPCs and SRTCs and natural decay. A turning operator has been considered in this case as well, but it has been chosen in a more general form, like the ones proposed in [**3**], considering only a random motion of particles leading to diffusion.

A time scaling has been performed in order to derive macroscopic equations. In particular, we supposed that the processes involving the velocity are the dominant ones, while all the conservative and non-conservative ones are happening at a lower time scale. This has allowed us to obtain a system of four macroscopic equations for the densities, in which the diffusion and the chemotaxis terms appear in the equations for SRTCs and cytokines.

We have outlined the stability analysis of the system without diffusion, setting our discussion on the parameter representing the constant input of SAPCs and then, after a reduction to a system involving only the diffusive species, we have performed Turing instability analysis. We have been able to find conditions on the macroscopic parameters involved in diffusive and chemotaxis constants leading to the appearance of spatial patterns, confirming our findings through numerical simulations.

The aim of this work has been to enrich the kinetic models describing autoimmune diseases present in literature, as the procedure here adopted has many advantages. Above all, it allows us to obtain a macroscopic model in which the coefficients depend on the microscopic features of the agents involved

and provides a more consistent mathematical tool to be applied and adapted to more specific cases of pathological conditions.

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