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The role of chemotaxis in acute inflammation

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Ai miei genitori,
ai miei nonni.

Contents

Abstract

In this work, we investigate the role of chemotaxis in acute inflammation, with a particular focus on mathematical modeling approach. Starting from standard diffusion models in biomedical fields, we firstly discuss the classical Keller-Segel system and its recent modifications, incorporating reaction terms and logistic type in order to account for environmental constraints and also prevent the non-physiscal blow-up of solutions. As an immediate generalization, we present an attraction-repulsion chemotaxis model for Alzheimer's disease (AD) and investigate conditions leading to aggregation of microglia and formation of accumulations of chemical observed in (AD) senile plaques.
Next we investigate two recent reaction-diffusion-chemoltaxis systems that describe the immune response during an inflammatory attack.
We carry out a linear stability analysis of such reaction-diffusion type compartmental models, with multiple interacting species, in both parabolic and hyperbolic frameworks, for some medical applications, just ranging from AD to acute inflammations.
Besides a linear stability analysis, we also employ a generalized energy method to obtain decay bounds in the model. Additionally, stability analysis is performed using not only Fourier modes but also algebraic criteria such as the Gershgorin theory and the Routh-Hurwitz criterion. We then generalize these models to describe macrophage-driven inflammatory responses, introducing additional chemokine dynamics and studying the emergence of stationary and traveling wave solutions. The final part of this thesis explores the connection between chemotaxis and neurodegenerative processes, specifically Alzheimer's disease, where microglial activation follows chemotactic principles. We suggest modifications to existing models, incorporating memory effects (via the Cattaneo correction) and nonlocal interactions to better capture the complex interplay of cellular and chemical species. Our findings provide new insights into the mathematical structures underlying inflammation and neurodegeneration, with potential implications for therapeutic strategies.
Key words: Dynamical systems and reaction- diffusion models, chemotaxis, Alzheimer and inflammation models, stability analysis, energy arguments, spatial pattern forma-

tion, Turing and wave instability.

Introduction

Neurodegeneration refers to a range of neurological disorders characterized by the progressive degeneration of neurons, with devastating impacts on the central nervous system. Common neurodegenerative diseases include Alzheimer's, Parkinson's, Amyotrophic Lateral Sclerosis (ALS), frontotemporal dementia, and Huntington's disease. These conditions, despite having different pathogenic mechanisms, share a key feature: chronic neuroinflammation. Neurodegenerative diseases affect specific populations of neurons in particular areas of the brain, disrupting their function and leading to the progressive deterioration of cognitive, motor, and psychological abilities. A central aspect of neurodegeneration is the accumulation of abnormal proteins, such as amyloid-beta ($A\beta$) and tau, which play a key role in the pathology of many diseases, particularly Alzheimer's. Amyloid-beta is a protein that aggregates into plaques that interfere with neuronal communication, while tau forms tangles inside neurons, damaging cellular structures and promoting cell death. The presence of these two proteins is crucial for diagnosis and understanding the development of the disease. Alzheimer's, in particular, is characterized by the formation of extracellular $A\beta$ plaques and intracellular tau neurofibrillary tangles. The accumulation and aggregation of these proteins profoundly impact brain cell structure and function, causing irreversible damage over time. Another essential element of neurodegeneration is the inflammatory response associated with these diseases. Glial cells, which normally support and protect neurons in a healthy brain, become hyperactive in response to damage caused by abnormal proteins. Specifically, microglia and astrocytes are involved in the inflammation of the central nervous system. Microglia, the immune cells of the brain, become activated in response to foreign substances, such as $A\beta$ plaques, and attempt to remove them. However, in the presence of chronic $A\beta$ accumulation, microglia fail to effectively clear the plaques, becoming reactive and contributing to neuronal damage. Astrocytes, which typically regulate synaptic communication between neurons, proliferate as the disease progresses, further contributing to the inflammatory process. Inflammation plays a complex role in neurodegeneration. In the early stages of the disease, microglia activation may have a protective effect, aiding in the clearance

of Aβ plaques. However, as the disease advances, chronic inflammation and continuous microglia activation seem to contribute to worsening brain damage by increasing Aβ deposition and tau phosphorylation. This persistent inflammatory process is one of the primary mechanisms driving neurodegeneration.
In Alzheimer's disease specifically, the condition generally manifests after the age of 60, although in rare cases, it can occur earlier. The prevalence of the disease is rapidly increasing, with estimates predicting that by 2050, the number of affected individuals globally could rise to 131 million. This growing number of cases presents a significant public health challenge. The disease was first described over a century ago by Dr. Alois Alzheimer, who identified distinctive signs such as amyloid plaques and neurofibrillary tangles in the brain of a deceased patient.
Currently, research is focused on finding treatments to stop or slow down the progression of the disease. While several medical tools and technologies have been developed for the diagnosis and treatment of neurodegenerative diseases, many fundamental aspects of Alzheimer's pathogenesis remain unclear. Promising therapeutic strategies include anti-inflammatory drugs, such as non-steroidal anti-inflammatory drugs (NSAIDs), which in some studies have shown the ability to reduce the risk of developing Alzheimer's and limit Aβ deposition. However, more clinical and preclinical studies are needed to determine whether these treatments can effectively slow down or stop neurodegeneration.
Despite progress in research, neurodegeneration remains one of the primary challenges in medicine, with Alzheimer's continuing to be one of the leading causes of dementia worldwide. The increasing incidence of the disease and the aging population highlight the urgent need for more effective treatments, as well as a deeper understanding of the biological mechanisms behind neurodegeneration. Ongoing research is crucial for developing prevention strategies, early diagnostics, and targeted therapies to slow or stop the progression of the disease. Here we refer to *Inflammatory process in Alzheimer' s Disease* [12], *Role of neuroinflammation in neurodegeneration development* [13], *Neuroinflammation, Its Role in Alzheimer ' s Disease and Therapeutic Strategies* [14], *Nonlocal models in the analysis of brain neurodegenerative protein dynamics with application to Alzheimer's disease.* [26] and *Modeling Aggregation of Proliferating Microglia in Response to Amyloid-beta in Dementia*[4].
From a mathematical perspective, chemotaxis models provide an interpretative framework for describing cell migration induced by chemical signals. The Keller-Segel model [3], originally developed to describe bacterial behavior in response to attractants, has been widely applied in biomedicine to study the dynamics of immune cells in inflamed tissues. The generalization of this model, incorporating reactive terms and environmental regulation, allows for the analysis of more complex phenomena such as cellular aggregation and the propagation of inflammatory activation waves. In addition to the

Keller-Segel model, other mathematical approaches have been employed to describe brain inflammation and neurodegeneration. Reaction-diffusion models, for example, help to understand how immune cells and chemical mediators interact in space and time. Specifically, the introduction of memory terms and nonlocal interactions has improved the representation of the complexity of the inflammatory response and microglial activation dynamics in Alzheimer's disease. These models provide insights into how inflammatory processes spread spatially and how interventions can alter disease progression.
In the first chapter, after introducing preliminary concepts useful for understanding the paper, we have firstly focused on the analysis of the classical Keller-Segel model (1970), a model that concerns the diffusion of slime mold amoebas. This is a reaction- diffusion model consisting of a system of two partial differential equations (PDEs) that describe the evolution of cellular concentration and chemical concentration. The first equation is of the diffusion-transport type, including a term that represents the random movement of particles (diffusion) and a term modeling 'attractive' chemotactic movements, which occur in response to a positive gradient of the chemical. This term is also responsible for the nonlinearity of the model; a reaction term, such as a logistic-type reaction, may be included. The second equation, on the other hand, is of diffusion-reaction type, encompassing a diffusion term and terms that represent the chemical's production and degradation. We analyze the linear stability of the solutions, by applying the standard Fourier Method. This allows us to find sufficient conditions for the formation of chemotactic collapse. In the second part of this chapter we focus on a model for Alzheimer's disease developed by Luca et al. [7]; this model is very similar to the Keller-Segel model, but it is composed by a system of three PDEs, due to the presence of two interacting chemicals: the first one represents the chemoattraction and the second one the chemorepulsion. We analyze in detail the model, firstly in its one-dimensional version and determine, through the Routh-Hurwitz stability criterion, the conditions providing a critical threshold for stability, in order to guarantee no patterns formation. By an interesting comparison, we introduce an Energy type argument, to obtain decay estimates for the two-dimensional version of the model. We use also the Fourier method and we find conditions which avoid to have Hopf bifurcations. The second chapter focuses on developing mathematical models for acute inflammation, concerning in particular the interaction between macrophages and chemokines. The models, developed by Penner et al. [9] and by Giunta et al. [10], describe how macrophages respond to inflammatory signals and how different chemoattractants influence their movement. A detailed stability analysis for these models is performed using classical methods from linear algebra and perturbation theory. Special attention is given to the role of environmental constraints, modeled through logistic growth terms, and their impact on the formation of inflammatory clusters. The conditions for Turing instability are explored, providing insights into

how spatially heterogeneous inflammatory patterns emerge in biological tissues. From this analysis we have some useful information about the effects of therapeutic strategies. At the end in the third chapter we generalize the model presented in [5]. In fact, to modify the Alzheimer's model in light of the observations in Chapter 2 regarding acute inflammation, we could introduce several key changes, including additional logistic effects to the first PDE, introducing memory effects through the Cattaneo correction, and creating a hyperbolic "reaction-diffusion-drift" model. Furthermore, we could consider non-local behaviors and the division of attractive and repulsive chemicals into "healthy" and "toxic" cells.
The main objectives of this research are:

- Analyze mathematical models of chemotaxis with a focus on their application to inflammatory phenomena.
- To study the stability of reaction-diffusion models in biological contexts, evaluating the conditions for spatial pattern formation and traveling waves.
- To develop and generalize the Luca model for Alzheimer's disease by introducing memory effects and nonlocal interactions.
- To provide a mathematical perspective on brain inflammatory processes, with potential implications for the development of therapeutic strategies.

Chapter 1

Preliminaries

1.1 Basic Notions

In this subsection we introduce some basic notions useful for understanding the paper, having unified the notations to our needs. We refer to the following books: *Partial Differential Equations* of John [1] and *An Introduction to Partial Differential Equation* of Renardy and Rogers [2].

Definition 1.1.1. Given a smooth set $\Omega \subseteq \mathbb{R}^n$, a partial differential equation (PDE) for a function $u(x)$ of class $C^k(\Omega, \mathbb{R})$, with $k > 1$, is a differential equation with a finite number of partial derivatives of u presented as:

$$F(x, u(x), Du(x), ..., Du^k(x)) = 0 \tag{1.1}$$

where F is a given function of the indipendent variable $x \in \Omega$, of the "unknown" function $u(x)$ and of a finite number of partial of its partial derivatives until order k.
We call u the solution of (1.1), if substituting u and its partial derivatives, (1.1) is identically satisfied in a certain region Ω of the space.

Definition 1.1.2. We define *order* of a PDE the order of the highest derivative that occurs.
We define the *principal part* of a PDE the highest-order derivatives of the equation.
A PDE is said to be stationary if there are no temporal partial derivatives, in the other case evolutionary.

To simplify the notation we only consider only scalar PDEs whose classification depends on the coefficients.

Definition 1.1.3. A PDE is said to be *linear* if it is linear in the unknown functions and their derivatives, with coefficients depending on the indipendent variable and it has the form:

$$\sum_{|\alpha|=k} a_\alpha D^\alpha u = f(x),$$

where f and a_α are (at least) continuous functions.

Definition 1.1.4. A scalar PDE is said to be *semi-linear* if it is:

$$\sum_{|\alpha|=k} a_\alpha D^\alpha u + a_0(D^{k-1}, ..., Du, u, x) = 0$$

Definition 1.1.5. A scalar PDE of order k is said to be *quasi-linear* if it is linear in the derivatives of order k, whose coefficients depends on the indipendent variable and derivatives of order $< k$. The general form is:

$$\sum_{|\alpha|=k} a_\alpha(D^{k-1}, ..., Du, u, x) D^\alpha u + a_0(D^{k-1}, ..., Du, u, x) = 0$$

Definition 1.1.6. A scalar PDE is said to be *fully* non linear if it isn't *quasi-linear*.

Now we introduce I and II order PDEs, where we denote x and y two indipendent variables such that $(x, y) \in \Omega \subseteq \mathbb{R}^2$; we suppose $y > 0$, for its possible role of time towards evolutionary $1D$ models. We distinguish three different type of I order PDEs supposing that $u \in C^1(\Omega, \mathbb{R})$:

- A PDE is said *linear* if it is:

  $$a(x, y)u_x + b(x, y)u_y + c(x, y)u = d(x, y)$$

  Moreover it is also *homogeneous* if $d(x, y) = 0$;

- it is said *semi-linear* if it is:

  $$a(x, y)u_x + b(x, y)u_y = c(\cdot);$$

  where $(\cdot) = (x, y, u(x, y))$. So it is *homogeneous* if $c(\cdot) = 0$.

- it is said *quasi-linear* if it is:

  $$a(\cdot)u_x + b(\cdot)u_y = c(\cdot),$$

  where $(\cdot) = (x, y, u(x, y))$. In this case it is also *homogeneous* if $c(\cdot) = 0$ and $u = 0$ is a solution of this equation;

where $a, b, c \in C^1(\Omega^{''}, \mathbb{R})$, with $\Omega^{''} \subset \mathbb{R}$.

Definition 1.1.7. Given a scalar II order PDE, depending on the indipendent variables (x, y), considering:

$$a(\cdot)u_{xx}(x,y) + 2b(\cdot)u_{xy}(x,y) + c(\cdot)u_{yy}(x,y) = d(\cdot),$$

with $a, b, c, d \in C^1(\Omega^{''}, \mathbb{R})$ with $\Omega^{''} \subseteq \mathbb{R}^5$. It is said:

- *quasi-linear* if
$$(\cdot) = (x, y, u(x,y), u_x(x,y), u_y(x,y));$$
- *semi-linear* if
$$a = a(x,y),\ b = b(x,y),\ c = c(x,y),\ d = d(\cdot);$$
- *linear* if
$$(\cdot) = (x, y),$$
so in that case we can rewrite the PDE as:
$$a(\cdot)u_{xx}(x,y) + 2b(\cdot)u_{xy}(x,y) + c(\cdot)u_{yy}(x,y) = d(\cdot)u_x + e(\cdot)u_y + f(\cdot)u + g(\cdot).$$
Furthermore it is also homogeneous if and only if $g(\cdot) = 0$.

Definition 1.1.8. In presence of a nearly II order linear PDE, we can define a symmetric matrix 2×2 associated to the principal part, called the characteristic matrix of the model, denoted by A and defined as:

$$A = \begin{bmatrix} -a(\cdot) & -b(\cdot) \\ -b(\cdot) & -c(\cdot) \end{bmatrix}$$

whose determinant is $\det(A) = a(\cdot)c(\cdot) - b(\cdot)^2$.

A II order PDE is said:

- *elliptic* if $\det(A) > 0, \forall\ (x, y, u(x,y), u_x(x,y), u_y(x,y))$;
- *hyperbolic* if $\det(A) < 0, \forall\ (x, y, u(x,y), u_x(x,y), u_y(x,y))$;
- *parabolic* if $\det(A) = 0,\ \forall\ (x, y, u(x,y), u_x(x,y), u_y(x,y))$.

Remark 1.1.9. Elliptic models describe stationary models, while parabolic and hyperbolic models describe evolutionary models.

1.1.1 Fourier modes analysis

This method, which we will use in the next subsections, allows us to determine solutions to linearized models. Thinking of a single population diffusion-reaction model with $\rho = \rho(x,t)$ being the positive valued density of individuals, the method applies to the linearized version of the model around a stationary and homogeneous solution, denoted by ρ_0/ρ_c .
A Fourier mode solution has form:

$$\rho(x,t) = \rho_1 e^{i(kx-\omega t)} \text{ if } x \in \mathbb{R} \tag{1.2}$$

or

$$\rho(\vec{x},t) = \rho_1 e^{i(\vec{k}\cdot\vec{x}-\omega t)}, \text{ if } x \in \mathbb{R}^n \tag{1.3}$$

where:

- $\vec{k} \in \mathbb{R}^n$ is the real wave vector ($k^2 > 0$) and in the $1D$ case k is the wave number;
- ω is the frequency, real or complex, which depends on the wave number through the so-called dispersion equation;
- $V_f = \frac{\omega}{k}$ is the phase velocity;
- ρ_1 is the non null amplitude.

Then we define the so called growth rate parameter $\sigma = -i\omega$, which is important to analyze the behavior of the solution:

- if $\omega \in \mathbb{R}$, then $\sigma \in \mathbb{C}$ and the solution of (1.3) or (1.2) has an oscillatory behavior over time,
- if $\omega = Re(\omega) + i\ Im(\omega) \in \mathbb{C}$, with $Im(\omega) \neq 0$, then $\sigma = -i\omega = -iRe(\omega) + Im(\omega)$,

so in that case the sufficient condition for having exponential time growth is: $Im(\omega) > 0$. So, after a linearization of the model around the equilibrium solution $\rho_0 > 0$, we may seek a non null perturbation solution, in the scalar $1D$ case, defined as:

$$0 \neq \delta\rho = \rho_1 e^{i(kx-\omega t)}, \tag{1.4}$$

or in the vectorial $3D$ case:

$$0 \neq \delta\vec{\rho} = \vec{\rho_1} e^{i(\vec{k}\cdot\vec{x}-\omega t)}. \tag{1.5}$$

So we have the following identities:

1. $\frac{\delta}{\delta t}\delta\rho = -i\omega\rho$
2. $\frac{\delta}{\delta t}\delta\vec{\rho} = -i\omega\vec{\rho}$

Further, if we denote by $\vec{n} = \frac{\vec{k}}{k}$ the wave versor, the following identities hold:

$$\nabla\delta\rho = \delta\rho i\vec{k} = ik\ \delta\rho\ \vec{n} \tag{1.6}$$

$$\nabla\delta\vec{\rho} = \delta\vec{\rho}\ \otimes i\vec{k} = ik\ \delta\vec{\rho}\otimes\vec{n} \tag{1.7}$$

where we used the tensor product indicated with $\otimes$, which is linear and not invertible tensor defined as:

$$(\vec{u}\otimes\vec{v})\vec{w} = (\vec{v}\cdot\vec{w})\vec{u} \quad \forall\vec{u},\vec{v},\vec{w}\in\mathbb{R}^3.$$

For completeness, we add the identities:

$$\nabla\cdot\delta\vec{\rho} = \delta\vec{\rho}\cdot i\vec{k} = ik\ \delta\vec{\rho}\ \vec{n} \tag{1.8}$$

$$\nabla\ \times\ \delta\vec{\rho} = i\vec{k}\times\ \delta\vec{\rho} = k(i\vec{n}\times\ \delta\vec{\rho}) \tag{1.9}$$

$$\Delta\delta\rho = -k^2\delta\rho \tag{1.10}$$

$$\Delta\delta\vec{\rho} = -k^2\delta\vec{\rho} \tag{1.11}$$

In order to analyze the behavior of a homogeneous and stationary solution ρ_0, we choose a perturbation (1.4) and (1.5) and then we study the dispersion equation $\omega = \omega(k)$ using the stability parameter σ. For this reason, we have to apply the Ljapunov stability, closely related to the definition of stability and asymptotic stability in the sense of Ljapunov.

Definition 1.1.10. Given an equilibrium solution ρ_0, it is said to be stable in the sense of Ljapunov iff:

$$\forall\ \epsilon > 0\ \ \exists\delta_\epsilon > 0 : \forall\rho(x,0)\in B(\rho_0,\delta_\epsilon) \quad \parallel \rho(x,t) - \rho_0 \parallel < \epsilon\ \ \forall t > 0.$$

Moreover ρ_0 is said to be asymptotically stable if :

$$\lim_{t\to\infty}\rho(x,t) = \rho_0.$$

In short, we put into evidence the following special cases:

- if $\sigma \in \mathbb{R}^+$ there is instability
- if $\sigma \in \mathbb{R}^-$ there is asymptotic stability
- if $\sigma \in \mathbb{C}$ with $Re(\sigma) = 0$, there is only stability
- if $\sigma \in \mathbb{C}$ and $Re(\sigma) \neq 0$, stability / instability depends on the sign of $Re(\sigma)$.

1.1.2 Fick's law as the constitutive equations for reaction and diffusion models.

In this section, following [24] and [25], we have to consider the main characteristics of reaction-diffusion type models. First of all we assume that $\vec{x}(t) = \vec{x}(0)\ \forall\ t \geq 0$. We take $\Omega \subset \mathbb{R}^3$ a bounded (or unbounded) spatial domain, fixed in time, namely $\Omega(t) = \Omega(0)\ \forall t \geq 0$. Furthermore, it is required that the domain has a sufficiently smooth boundary $\delta\Omega$ to allow the application of Gauss Theorem. Finally the space time domain is indicated with $\Omega_t^+ := \Omega \times \{t > 0\}$. Let us consider, then, an evolutionary diffusion model for a generic species that spreads freely in space, described by the density $\rho = \rho(\vec{x}, t) \in C^2(\Omega_t^+, \mathbb{R}^+)$. The classical diffusion model, in its $3D$ version, will be described by the following second-order parabolic PDE:

$$\rho_t - D\Delta\rho = 0\ \forall(\vec{x}, t) \in \Omega_t^+ \tag{1.12}$$

which can be written in $1D$ dimension:

$$\rho_t - D\rho_{xx} = 0\ \forall(x, t) \in \Omega_t^+$$

where the constant D is called diffusive mobility and it is positive. In this model we can also introduce a supply term $r(\rho)$, which may depend (linearly/ non linearly) on the species density:

$$\rho_t = D\rho_{xx} + r(\rho)\ \forall(x, t) \in \Omega_t^+.$$

This reaction term accounts for any degradation or growth phenomena of the species; in order to reflect an environmental control we highlight the following logistic type form:

$$r(\rho) = a\rho(1 - \frac{\rho}{b})$$

where a and b are two positive constants, which represent the proliferation parameter and the carrying capacity respectively. In literature the diffusion models are known as the "flux-gradient" type models, since the constitutive equation for the flux vector J_ρ associated to the density ρ is the experimental Fick's law which, in its $3D$ formulation, is expressed as follows:

$$\vec{J_\rho}(\vec{x},t) = -D\nabla\rho(\vec{x},t)\ \forall(\vec{x},t) \in \Omega_t^+$$

It is worth to note that Fick's law, analogously to Fouries's law for heat diffusion is stationary and istantaneous. So the local balance equation for a reaction and diffusion model reads as:

$$\rho_t = -\nabla \cdot \vec{J_\rho} + r(\rho) \ \ \forall(\vec{x},t) \in \Omega_t^+. \tag{1.13}$$

The last two equations in $1D$ dimension, can be written $\forall(x,t) \in \Omega_t^+$ as:

$$\begin{cases} J_\rho(x,t) = -D\rho_x(x,t) \\ \rho_t = -(J_\rho)_x + r(\rho) \end{cases} \tag{1.14}$$

In this way it is evident the so called "flux-gradient" nature of such mathematical modeling. In particular in the $3D$ case, we have the following system:

$$\begin{cases} \rho_t = -\nabla \cdot \vec{J_\rho} + r(\rho) \\ \vec{J_\rho} = -D\nabla\rho \end{cases} \tag{1.15}$$

Since that D could be a function depending on ρ, from $(1.15)_1$ we can get a *quasi-linear* second order PDE, which in its $3D$ version is given by:

$$\rho_t = D(\rho)\Delta\rho + D'(\rho)\nabla\rho \cdot \nabla\rho + r(\rho) \ \ \forall(\vec{x},t) \in \Omega_t^+$$

and for the $1D$ case we have the following equation:

$$\rho_t = D_\rho\rho_{xx} + D^{'}(\rho)\rho_x^2 + r(\rho) \ \ \forall(x,t) \in \Omega_t^+$$

Given the static and instantaneous aspects of the classical Fick's law, which can lead to an experimental contradiction, the following subsections will examine key extensions that not only resolve this contradiction but also take into account potential interactions with other species involved in the phenomena being modeled mathematically.

1.1.3 Fick's law: the Cattaneo correction towards hyperbolic models

It has been observed experimentally that the instantaneous nature of Fick's law in its classical form, out of equilibrium, is an unrealistic approximation for diffusive phenomena. Therefore, it was deemed appropriate to introduce a kind of memory effect into the law in order to account for the so-called delayed response. Hence the Fick's law for the flux can be written as:

$$\vec{J}_\rho(\vec{x}, t+\tau) = -D\nabla\rho(\vec{x}, t) \quad \forall(\vec{x}, t)$$

and then the $1D$ case becomes:

$$J_\rho(x, t+\tau) = -D\rho_x(x, t) \quad \forall(x, t)$$

where the diffusive mobility D could be or not constant and $0 < \tau \ll 1$ represents a very short relaxation time. Hence we can consider a first order Taylor expansion, in order to find the following rate type constitutive equation:

$$\vec{J}_\rho(\vec{x}, t) + \tau(\vec{J}_\rho(\vec{x}, t))_t = -D\nabla\rho(\vec{x}, t) \quad \forall(\vec{x}, t), \tag{1.16}$$

which in the $1D$ version reads:

$$J_\rho(x, t) + \tau(J_\rho(x, t))_t = -D\rho_x(x, t) \quad \forall(x, t).$$

The general model for diffusion and reaction is now represented by the following system of two first-order PDEs, both evolutionary, in the $3D$ form:

$$\begin{cases} \rho_t = -\nabla \cdot \vec{J}_\rho + r(\rho) \\ \vec{J}_\rho + \tau(\vec{J}_\rho)_t = -D\nabla\rho \end{cases} \tag{1.17}$$

where the couple $(\rho(\vec{x}, t), \vec{J}(\vec{x}, t))$ is said the state of the model. In particular, when $\tau = 0$ we obtain (1.15). A *quasi-linear* or *semilinear* first-order evolutionary system is thus obtained, depending on whether $D = D(\rho)$ or not, with $r(\rho)$ potentially being non linear. In the $1D$ case, assuming for simplicity a constant diffusive mobility, deleting the flux dependence in equation (1.17) through simple steps, and under the appropriate regularity conditions, differentiating the first PDE with respect to t and the second with respect to x, namely:

$$\rho_{tt} = -(J_\rho)_{xt} + r(\rho)_t \tag{1.18}$$

and

$$\tau(J_\rho)_{xt} + (J_\rho)_x = -D\rho_{xx} \implies (J_\rho)_{t.x} = \frac{1}{\tau}(-D\rho_{xx} - (J_\rho)_x). \tag{1.19}$$

By requiring a C^2 regularity for both the species density ρ and the associated flux J_ρ, we can apply Schwarz theorem, which leads to the equality of mixed derivatives: $\rho_{xt} = \rho_{tx}$ and $(J_\rho)_{xt} = (J_\rho)_{tx}$. Substituting (1.19) in (1.18), we find:

$$\rho_{tt} = \frac{1}{\tau}(D\rho_{xx} + (J_\rho)_x) + r(\rho)_x \tag{1.20}$$

and using that $(J_\rho)_x = -\rho_t + r(\rho)$, we arrive at the desired equation:

$$\rho_{tt} = \frac{D\rho_{xx}}{\tau} - \frac{\rho_t}{\tau} + \frac{r(\rho)}{\tau} + r(\rho)_t. \tag{1.21}$$

We immediately notice that the main term of this equation is given by $\rho_{tt} - \frac{D\rho_{xx}}{\tau}$, so that, through the correction to the Maxwell-Cattaneo equation, we have moved from the second-order parabolic PDE (1.12) to the new second-order PDE (1.1.3), which is now classified as hyperbolic type. Thus, the nature of the diffusion and reaction model has been changed, transitioning from parabolic to hyperbolic. In fact, if we consider the model with $r(\rho) = 0$, the original diffusion model could be described by an hyperbolic system of two first order PDEs:

$$\begin{cases} \rho_t = -(J_\rho)_x \\ (J_\rho)_t = -\frac{D}{\tau}\rho_x - J_\rho \end{cases} \tag{1.22}$$

1.1.4 Another generalization of the Fick's law: the introduction of 'cross-diffusion' effects.

In the case where multiple interacting species coexist in a system, it often happens that a concentration gradient of one species can induce the flux of a second species. The diffusion of the second species will no longer be purely spatial and free, but instead will be 'chemotactically' driven by its interaction with the other species. This phenomenon is referred to as 'chemotaxis' , and it gives rise to the so-called 'cross-diffusion'. To mathematically account for this type of diffusion, 'drift' terms are introduced into the diffusion model. Let us now see how, starting from a completely general case, we can describe chemotaxis within a diffusion and also reaction model. Imagine we want to describe the dynamics of a species with density ρ_1 in the presence of an interacting

species with density ρ_2. In this case as well, we resort to a generalized Fick's law for the flux associated with the species with density ρ_1 which, in the $3D$ form, is given by:

$$\vec{J_{\rho_1}}(\vec{x},t) = -D\nabla(C(\rho_2)\rho_1),$$

where $D > 0$ might depend on both species, whereas $C = C(\rho_2) > 0$ is a function of class at least C^1. Expanding the expression above, it follows that the "effective" flux vector associated with ρ_1 can be written as the sum of two contributions: a "self-diffusive" one and a "chemotactic" one, due to the presence of the species with density ρ_2, as follows:

$$J_{\rho_1} = J_{\rho_1}^{\text{diff}} + J_{\rho_1}^{\text{chem}} \tag{1.23}$$

where:

$$J_{\rho_1}^{\text{diff}} := -DC(\rho_2)\nabla\rho_1 \tag{1.24}$$

and

$$J_{\rho_1}^{\text{chem}} =: -D\rho_1 C^{'}(\rho_2)\nabla\rho_2 \tag{1.25}$$

Now, defining all the parameters:

- $D_{\rho_1} := DC(\rho_2) > 0$, the classic diffusive mobility of the species with density ρ_1.
- $\chi_0 := -DC^{'}(\rho_2)$, the positive (or negative) chemosensitivity according as the species ρ_1 be attracted (or repelled) by the second species ρ_2.
- $D_{\rho_1\rho_2} := \chi_0\rho_1$, the drift mobility associated with the cross-diffusion of the species ρ_1 due to the chemotactic effect exerted by the species ρ_2.

The constitutive equation for the flux associated with the species of density ρ_1, in the presence of 'cross-diffusion' effects due to the species ρ_2, can be rewritten in $3D$ as follows:

$$\vec{J_{\rho_1}} = -D_{\rho_1}\nabla\rho_1 + D_{\rho_1\rho_2}\nabla\rho_2 \tag{1.26}$$

and, analogously in the $1D$ case:

$$J_{\rho_1} = -D\rho_1\rho_{1x} + D_{\rho_1\rho_2}\rho_{2x} \tag{1.27}$$

The equations (1.26) and (1.27) just written, therefore, represent the generalizations, in $3D$ and $1D$ versions respectively, of Fick's law in the case where the model in question needs to describe not only the simple spatial diffusion of species with density ρ_1 but also the 'cross-diffusion' effect due to the presence of a second species with density ρ_2, which is capable of exerting 'chemotaxis' on the first one. Finally, in the more general

case where the species with density ρ_1 interacts chemotactically with n other species, the constitutive equations for the flux can be generalized in the $3D$ case as follows:

$$J_{\rho_1} = -D_{\rho_1}\nabla\rho_1 + \sum_{m=2}^{n} D_{\rho_1\rho_m}\nabla\rho_m \tag{1.28}$$

and in $1D$ case:

$$J_{\rho_1} = -D_{\rho_1}\rho_{1x} + \sum_{m=2}^{n} D_{\rho_1\rho_m}\rho_{mx} \tag{1.29}$$

Returning for simplicity to the case with only two interacting species, the evolutionary equation for the species with density ρ_1 in the $3D$ diffusion model (assuming, as previously done, that the reaction term for this species is zero) will be given by:

$$\rho_{1t} = -\nabla\cdot\vec{J_{\rho_1}} = \nabla\cdot(D_{\rho_1}\nabla\rho_1) - \nabla\cdot(\chi_0\rho_1\rho_2) \tag{1.30}$$

It consists of a *quasi-linear* second-order parabolic PDE (due to the presence of the drift mobility) of the diffusion-drift type. Naturally, the mathematical model should be completed by adding a suitable PDE governing the evolutionary behavior of the second species, and both PDEs can also include interacting reaction effects.

1.2 The Keller-Segel model for chemotaxis and its consequences

The term chemotaxis frequently occurs in biology and refers to phenomena of chemically directed movements. A very much studied chemotaxis process in mathematical biology is that of the formation of *Amoebae* into a slime mold. Herein, we firstly describe the parabolic Keller-Segel theory developed by Keller-Segel in their pioneristic paper [3], and then we address a parabolic-elliptic Keller-Segel system, with a logistic source, recently proposed by Tanaka- Yokota [8]. The movement of the *Amoeba* si influenced by *Acrasin*, which works like the chemical signal that directs the aggregation process, just viewed as a disruption stability. For this reason our attention is mainly focused on stability analysis.

1.2.1 Formulation of the mathematical model

Let us denote by ρ and c the amoebae density and the concentration of the chemoattractant secreted by the amoebae, the so called cyclic-AMP (cAMP), respectively. Later for

mathematical reasons and for simplifications in the search of solutions we will restrict ourselves to two- dimensional space domains. From now on, we address a bounded/unbounded three-dimensional space domain Ω, fixed in time, where the notation $\vec{x} = (x_1, x_2, x_3)$ stands for the spatial point.
Henceforth the cell density $\rho = \rho(\vec{x}, t)$ and the chemical concentration $c = c(\vec{x}, t)$ are positive value functions of class at least C^2 in $\Omega_t^+ = \Omega \times \{t > 0\}$. In the phenomenon, Acrasina, the attractive chemical, and Acrasinase, the enzyme that breaks down Acrasina in an enzyme-substrate reaction, come into play. Acrasinase decays quickly, causing the disappearance of the chemical according to the reaction:

$$c + \eta \rightleftharpoons C \rightarrow \eta + \text{product}$$

where η represents the concentration of the enzyme and C is the concentration of the enzyme-substrate complex. Keeping in mind that our goal is to build a system of differential equations that describe the interaction and movement, we can neglect the chemical reaction and focus on a mean degradation function of the chemical, which we know is due to the enzymatic reaction. We will denote this function as $\Lambda(\rho, c)$. This allows us to examine only two equations, one for the amoeba and the other for the chemical, rather than four. We can assume the following:

1. Acrasina is produced by the amoeba according to a function $h(\rho, c)$ and is degraded according to a function $\Lambda(\rho, c)$, which is proportional to the substance itself. The functions $h(\rho, c)$ and $\Lambda(\rho, c)$ can be assumed to be constants, as will be the case in the following;

2. Birth and death of the amoeba can be neglected since they occur at times that are significantly shorter compared to those related to chemotactically driven movement;

3. Acrasina diffuses with a diffusion coefficient D_c;

4. The changes in the concentration of the amoeba are due to chemotactic movement in the direction of a positive Acrasina gradient, with random motion (which can be treated as diffusive motion with a diffusion coefficient D_ρ);

5. The interactions between the amoeba and the bacteria can be neglected.

The generalized Keller-Segel model is composed by a system of two PDEs $\forall(\vec{x}, t)$:

$$\begin{cases} \rho_t = \nabla \cdot (D_\rho(\rho, c)\nabla\rho) - \nabla \cdot (\chi_0 \rho \nabla c) + a\rho(1 - \frac{\rho}{b}) \\ c_t = \nabla \cdot (D_c(\rho, c)\nabla c) - \Lambda c + h\rho \end{cases} \tag{1.31}$$

where $(1.31)_2$ is a *quasi-linear* second order reaction and diffusion type parabolic PDE, when the chemical mobility $D_c = D_c(\rho, c)$ is a positive valued function; the Λ-term, $\Lambda > 0$, constant or not, is a degradation term whereas the h-term, $h > 0$, constant or not, represents a proliferation term.
The PDE for the chemical is a linear parabolic equation if D_c, Λ and h are positive constants; indeed if its RHS is null, with $D_c = 1$, we find the elliptic PDE investigated in [8]. In fact the chemical is produced by bacteria with a rate h and it is degraded with a rate $\Lambda > 0$.
$(1.31)_1$ is a reaction and diffusion-drift type parabolic equation, and it is always *quasi-linear*, even in the case of a constant bacterial mobility $D_\rho > 0$; the last term represents the reaction term of logistic type, with $a > 0$ and $b > 0$, playing the role of carrying capacity, as suggested in [8], but not present in the classical Keller-Segel model.

1.2.2 Linear stability analysis

Linear stability analysis follows some steps:

1. We firstly determine the equilibrium solutions ρ_c and c_c, which are stationary and homogeneous, so that they make null the reaction terms. In our model we impose the following conditions:
$$\begin{cases} a\rho(1 - \frac{\rho}{b}) = 0 \\ -\Lambda c + h\rho = 0 \end{cases} \tag{1.32}$$
from which we get two different cases:
   - $\vec{u}_c = (0, 0)$
   - $\vec{u}_c = (b, \frac{hb}{\Lambda})$

   Remark 1.2.1. The first one is not relevant from a biological point of view because it represents the null equilibrium state, where the concentrations of bacteria and chemicals are both null; the second one, biologically interesting, is a coexistence state, with $c_c = \frac{h\rho_c}{\Lambda}$ for $\rho_c = b$. It is worth to note that, in the absence of the logistic type reaction term, the system (1.32) reduces to the second algebraic relation and hence for any $\rho_c > 0$ one finds $c_c = \frac{h\rho_c}{\Lambda}$.
   Consequently $(1.31)_1$ is always satisfied when ρ and c are constants.

   Remark 1.2.2. We note that if $\Lambda = \Lambda(\rho, c)$ and $h = h(\rho.c)$ the equilibrium condition would become: $\Lambda(\rho_c, c_c)c_c + h(\rho_c, c_c)\rho_c = 0$

2. we introduce a small instantaneous perturbation denoted by $\delta s(\vec{x},t) = (\delta\rho(\vec{x},t), \delta c(\vec{x},t))$ and $\forall(\vec{x},t)$ we have:

$$\begin{cases} \rho(\vec{x},t) = \rho_c + \delta\rho(\vec{x},t) \\ c(\vec{x},t) = c_c + \delta c(\vec{x},t) \end{cases}$$

Replacing that in (1.31) we find the perturbed system:

$$\begin{cases} \delta\rho_t = \nabla\cdot(D_\rho(\rho_c+\delta\rho, c_c+\delta_c)\nabla\delta\rho) - \nabla\cdot(\chi_0(\rho_c+\delta\rho)\nabla\delta_c) + a(\rho_c+\delta\rho)(1-\frac{(\rho_c+\delta\rho)}{b}) \\ \delta_{c_t} = \nabla\cdot(D_c(\rho_c+\delta\rho, c_c+\delta c)\nabla\delta) - \Lambda(c_c+\delta c) + h(\rho_c+\delta\rho) \end{cases} \tag{1.33}$$

3. we linearize the model to apply Fourier method and to find the linearized version of the system we take the first-order truncated Taylor expansion for the mobility diffusions:

$$\begin{cases} D_\rho(\rho_c+\delta\rho, c_c+\delta_c) \simeq D_\rho(\rho_c, c_c) + \frac{\partial}{\partial\rho}D_\rho(\delta\rho+\rho_c, c_c+\delta c)_{|(\rho_c,c_c)} + \frac{\partial}{\partial c}D_\rho(\rho_c+\delta\rho, c_c+\delta_c)_{|(\rho_c,c_c)} \\ D_c(\rho_c+\delta\rho, c_c+\delta_c) \simeq D_c(\rho_c, c_c) + \frac{\partial}{\partial\rho}D_c(\delta\rho+\rho_c, c_c+\delta c)_{|(\rho_c,c_c)} + \frac{\partial}{\partial c}D_c(\rho_c+\delta\rho, c_c+\delta_c)_{|(\rho_c,c_c)} \end{cases}$$

where we have canceled higher order terms derivative. We define:

$$\begin{cases} D_\rho(0) := D_\rho(\rho_c, c_c) \\ D_c(0) := D_c(\rho_c, c_c) \end{cases}$$

Subsequently canceling all the quadratic terms, considering $(1.32)_2$ we obtain the linearized version of the perturbed system:

$$\begin{cases} \delta\rho_t = D_\rho(0)\Delta\delta\rho - \chi_0\rho_c\Delta\delta c - a\delta\rho \\ \delta c_t = D_c(0)\Delta\delta c - \Lambda\delta c + h\delta\rho \end{cases} \tag{1.34}$$

4. We search small perturbations $(\delta\rho(\vec{x},t)\ ,\delta c(\vec{x},t))$ of (1.34) made up of two homogeneous linear parabolic PDEs with constant coefficients in this form:

$$\begin{cases} 0 \neq \delta\rho(\vec{x},t) = \rho e^{i(\vec{k}\vec{x}-\omega t)} \\ 0 \neq \delta c(\vec{x},t) = c e^{i(\vec{k}\vec{x}-\omega t)} \end{cases} \tag{1.35}$$

Later substituting (1.35) in (1.34), deleting the exponential factor, we get the following homogeneous Cramer system:

$$\begin{cases} (\sigma + D_\rho(0)k^2 + a)\rho_1 - \chi_0\rho_c k^2 c_1 = 0 \\ -h\rho_1 + (\sigma + D_c(0)k^2 + \Lambda)c_1 = 0 \end{cases} \tag{1.36}$$

Using the Cramer theorem, the necessary and sufficient condition to have non trivial solutions is related to the following dispersion matrix D:

$$D = \begin{bmatrix} \sigma + D_\rho(0)k^2 + a & -\chi_0\rho_c k^2 \\ -h & \sigma + D_c(0)k^2 + \Lambda \end{bmatrix}$$

By imposing $\det(D) = 0$, we arrive at the desired dispersion equation for σ:

$$\sigma^2 + ((D_\rho(0) + D_c(0))k^2 + \Lambda + a)\sigma + (D_\rho(0)k^2 + a)(D_c(0)k^2 + \Lambda) - \chi_0\rho_c k^2 = 0$$

After, we discuss about the stability/ instability by analyzing the sign of its known term, since:

$$\begin{cases} \sigma_1 + \sigma_2 = -((D_\rho(0) + D_c(0))k^2 + \Lambda + a) \\ \sigma_1\sigma_2 = (D_\rho(0)k^2 + a)(D_c(0)k^2 + \Lambda) - \chi_0\rho_c h k^2 \end{cases} \tag{1.37}$$

The necessary and sufficient condition for asymptotic stability is given by:

$$(D_\rho(0)k^2 + a)(D_c(0)k^2 + \Lambda) - \chi_0\rho_0 h k^2 > 0$$

Now we analyze two different cases:

1. $a = 0$, corresponding to the classical Keller-Segel model.

   In this case we have to introduce two critical thresholds defined as:

   - $k^2_{KS} := \frac{h\rho_0\chi_0}{D_\rho(0)D_c(0)} > 0$
   - $k^2_{KS\Lambda} := k^2_{KS} - \frac{\Lambda}{D_c(0)} < k^2_{KS}$

   After, by experimental data, we have $D_c(0) >> D_\rho(0)$ and supposing that $k^2_{KS} - \frac{\Lambda}{D_c(0)} > 0$, then the sufficient condition to have chemotactic instability reads: $k^2 < k^2_{KS\Lambda}$.

   Remark 1.2.3. We underline the important role of Λ: in fact if $\Lambda > \frac{h\rho_0\chi_0}{D_\rho(0)}$ we wouldn't have instability.

   At the end we could observe that if $\Lambda = 0$, then the condition instability would become $k^2 < k^2_{KS}$. In conclusion thanks to Λ we recover stability in the range: $k^2_{KS\Lambda} < k^2 \leq k^2_{KS}$.

2. $a > 0$, corresponding to the generalized Keller-Segel model.

In this case the known term is:

$$D_\rho(0)D_c(0)k^4 + k^2(D_\rho(0)\Lambda + D_c(0)a - \chi\rho_c h) + a\Lambda$$

Then the necessary and sufficient condition to have asymptotic stability reads as follows:

$$k^4 - k^2(k_{KS}^2 - \frac{\Lambda}{D_c(0)} - \frac{a}{D_\rho(0)}) + \frac{a\Lambda}{D_\rho(0)D_c(0)} > 0 \tag{1.38}$$

from which, substituting $k_{KS\Lambda}^2$ into (1.38), we have:

$$k^4 - k^2(k_{KS\Lambda}^2 - \frac{a}{D_\rho(0)}) + \frac{a\Lambda}{D_\rho(0)D_c(0)} > 0.$$

Defining a new smaller critical threshold $k_{KS\Lambda a}^2 := k_{KS\Lambda}^2 - \frac{a}{D_\rho(0)} > 0$
$\Rightarrow k^4 - k^2 k_{KS\lambda a}^2 + \frac{a\Lambda}{D_\rho(0)D_c(0)} > 0.$
From these equations we get the following solutions:

- $k_+^2 = \frac{k_{KS\Lambda a}^2 + \sqrt{\Delta}}{2}$
- $k_-^2 = \frac{k_{KS\Lambda a}^2 - \sqrt{\Delta}}{2}$

where $\Delta = k_{KS\Lambda a}^2 - \frac{4a}{D_\rho(0)D_c(0)}$. Since that the solutions are positive $\Rightarrow k_-^2 < k_+^2 < k_{KS\Lambda a}^2$, so we recover more stability $\forall k$: $k^2 < k_-^2$ and in the range $k_+^2 < k^2 \leq k_{KS\Lambda}^2$.

1.2.3 Analysis of the model without diffusions

We consider the following dynamical system:

$$\begin{cases} \frac{d\rho}{dt} = a\rho(1 - \frac{\rho}{b}) \\ \frac{dc}{dt} = -\Lambda c + h\rho \end{cases} \tag{1.39}$$

from which we get the same equilibrium states found before and evaluating:

$$\begin{bmatrix} a - \frac{2a\rho}{b} & 0 \\ h & -\Lambda \end{bmatrix}$$

$\Rightarrow M(\vec{u}_c) = \begin{bmatrix} -a & 0 \\ h & -\Lambda \end{bmatrix} \Rightarrow \vec{u}_c$ is an equilibrium asymptotic equilibrium state. Then for the presence of the spatial diffusion we don't have stability $\forall\ k^2 < k_+^2$, $k_-^2 < k^2 < k_+^2$. Moreover thank to the presence of positive chemotaxis χ_0 the asymptotic stability gives the instability.

Definition 1.2.4. An equilibrium state $\vec{u}_c$ satisfies the Turing instability if it is asymptotic stable for the dynamic system without diffusion terms, but it will become for the presence of these terms.

If $a = 0 \Rightarrow$ we get:

$$\begin{cases} \rho_t = 0 \\ c_t = -\Lambda c + h\rho \end{cases}$$

$$\Rightarrow M(\vec{u}_c) = \begin{bmatrix} 0 & 0 \\ h & -\Lambda \end{bmatrix}$$

so the 2 eigenvalues are: $\lambda = 0$ and $\lambda = -\Lambda$; then the formation of chemotactic collapse leads to the formation of cellular aggregates.

1.3 Luca model for Alzheimer disease

One of the most prevalent neurodegenerative disease of our time is Alzheimer disease, which causes a degeneration of neurons and eventually their death. This neurodegenerative disease is characterized by the presence of a large amount of (A β), amyloid-beta, which is a protein, whose aggregation, alters the cell makeup of the brain. Moreover dementia pathogenesis is marked by the presence of tau proteins undergo misfolding and detach from microtubules, resulting in the disintegration of the microtubules and ultimately causing cell death. In a healthy brain there are glial cells and neurons, but microglia and astrocytes are impacted during the degradation of neurons. Microglia cells are the immune response cells and they have a chemotatctic behavior as chemoattractant and chemorepellent. *The Luca et al.* model [7] presented below, emphasizes the presence of reactive microglia to gain a deeper understanding of the movement and its relationship with $A\beta$.
This model is a generalization of the previous one. Henceforth we refer to [7].
The $1D$ version (with $\Omega = (0, L)$) of the Luca model is described by the following system:

$$\begin{cases} \rho_t = (D_\rho \rho_x)_x - (\chi_1 \rho c_{1x} - \chi_2 \rho c_{2x})_x \\ c_{1t} = (D_{c1} c_{1x})_x - \Lambda_1 c_1 + h_1 \rho \\ c_{2t} = (D_{c2} c_{2x})_x - \Lambda_2 c_2 + h_2 \rho \end{cases} \tag{1.40}$$

The parameters used in (1.40) are found and commented in [4]:

Variable	Description	Value
D_ρ	Microglia random motility	33 μm^2 min^{-1}
χ_1	Chemoattraction	6-780 μm^2 $\text{nM}^{-1}\text{min}^{-1}$
χ_2	Chemorepulsion	Not provided
D_{c1}	IL-1 β diffusion	900 μm^2 min^{-1}
D_{c2}	TNF- α diffusion	900 μm^2 min^{-1}
h_1	IL- 1 β production rate	$6.25 * 10^{-6}$ pg min^{-1}
h_2	TNF- α production rate	$8.33 * 10^{-6}$ pg min^{-1}
Λ_1	IL-1 β decay rate	0.003-0.03 min^{-1}
Λ_2	TNF- α decay rate	0.002-0.03 min^{-1}
$\bar{\rho}$	Average cell density	$10^{-6} - 10^{-4}$ cells μm^{-3} min^{-1}

In these equations ρ , c_1, c_2 are the density of microglia, the concentration of the attractant interleukin-1 , IL-1β and the repellent (tumour necrosis factor- α), denoted by TNF- α, respectively. For the sake of simplicity, all the parameters in play are assumed positive constants.

Remark 1.3.1. We firstly note that $(1.40)_2$ and $(1.40)_3$ are two linear and homogeneous second order parabolic PDEs of reaction and diffusion type with decay rates Λ_i and production rates h_i, while $(1.40)_1$, is always a *quasi-linear* second order PDE due to the presence of the density of microglia ρ, within the two "drift terms".

Remark 1.3.2. Since the proliferation term is negligible in an adult brain, it is not present in $(1.40)_1$; indeed a generalization of the model might include a logistic type proliferation term, as previously introduced for the Keller-Segel model.

Now we rewrite the model in a dimensionless form, introducing the sizes $\bar{\rho}$ and $\frac{h_i\bar{\rho}}{\Lambda_i}$ respectively for microglia density and chemical concentrations. Furthermore we use the spatial scales for the attractant L_1 and repellent L_2 defined as $L_i = \sqrt{\frac{D_{ci}}{\Lambda_i}}$ for $i = 1, 2$, meaning the distance over which chemicals disperse during the characteristic decay time. We finally take $\tau = \frac{L_2^2}{D_\rho}$ as our time scale, which occurs for a cell to move over one unit. Let us introduce the dimensionless variables:

$$x^* = \frac{x}{\tilde{x}},\ t^* = \frac{t}{\tilde{t}},\ \rho^* = \frac{\rho}{\tilde{\rho}} \text{ and } c_i^* = \frac{c_i}{\tilde{c_i}}$$

where the scales are:

$$\tilde{t} = \tau\ ,\ \tilde{\rho} = \bar{\rho}\ ,\ \tilde{x} = L_2\ ,\ \tilde{c_i} = \frac{h_i\bar{\rho}}{\Lambda_i} \text{ for } i = 1, 2$$

Replacing all these quantities in (1.40) and dropping the stars for notational convenience, we obtain the following non dimensional system:

$$\begin{cases} \rho_t = \rho_{xx} - [(A_1 c_{1x} - A_2 c_{2x})\rho]_x \\ \epsilon_1 c_{1t} = c_{1xx} + a^2(\rho - c_1) \\ \epsilon_2 c_{2t} = c_{2xx} + \rho - c_2 \end{cases} \tag{1.41}$$

where the five non dimensional parameters are defined in this way:

$$A_1 = \frac{\chi_1 h_1 \bar{\rho}}{D_\rho \Lambda_1} \ , \ A_2 = \frac{\chi_2 h_2 \bar{\rho}}{D_\rho \Lambda_2}, \ a = \frac{L_2}{L_1} \text{ and } \epsilon_i = \frac{D_\rho}{D_{ci}} \text{ for } i = 1, 2$$

Remark 1.3.3. *a* represents the ratio between the spatial scales. In addition the parameter $A = \frac{\chi_1 h_1 D_{c2}}{\chi_2 h_2 D_{c1}}$ denotes the ratio of the effective strengths of attraction and repulsion, and it will be useful in a later discussion.

1.3.1 The spectral Fourier Method applied to AD

In this subsection we develop the linear stability of the model (1.41).

1. We have to determine the homogeneous steady state imposing:

$$\begin{cases} a^2(\rho - c_1) = 0 \\ \rho - c_2 = 0 \end{cases} \tag{1.42}$$

   From this system we obtain the critical solution $\vec{u}_c = (\rho, c_1, c_2)$ with $\rho = c_1 = c_2 = 1$, due to our dimensionless procedure, which represents the homogeneous steady-state distribution of cells and chemicals.

2. Hence,we consider the following perturbed densities, for any (x, t):

$$\begin{cases} \rho(x,t) = 1 + \delta\rho(x,t) \\ c_1(x,t) = 1 + \delta c_1(x,t) \\ c_2(x,t) = 1 + \delta c_2(x,t) \end{cases} \tag{1.43}$$

   Subsequently we replace the perturbed densities in (1.41) getting the perturbed system:

$$\begin{cases} \delta\rho_t = \delta\rho_{xx} - [(A_1 \delta c_{1x} - A_2 \delta c_{2x})(1 + \delta\rho)]_x \\ \epsilon_1 \delta c_{1t} = \delta c_{1xx} + a^2(1 + \delta\rho - 1 - \delta c_1) \\ \epsilon_2 \delta c_{2t} = \delta c_{2xx} + (1 + \delta\rho - 1 - \delta c_2) \end{cases} \tag{1.44}$$

3. After some simple simplifications we obtain the linear perturbation system:

$$\begin{cases} \delta\rho_t = \delta\rho_{xx} - [(A_1\delta c_{1x} - A_2\delta c_{2x})]_x \\ \epsilon_1\delta c_{1t} = \delta c_{1xx} + a^2(\delta\rho - \delta c_1) \\ \epsilon_2\delta c_{2t} = \delta c_{2xx} + (\delta\rho - \delta c_2) \end{cases} \tag{1.45}$$

4. We now use the Fourier method. In particular we search perturbations in this form:

$$\begin{cases} 0 \neq \delta\rho(x,t) = \rho^{'} e^{ikx+\sigma t} \\ 0 \neq \delta c_1(x,t) = c_1^{'} e^{ikx+\sigma t} \\ 0 \neq \delta c_2(x,t) = c_2^{'} e^{ikx+\sigma t} \end{cases}$$

where σ represents the growth rate parameter, $k = n\pi$ is the wavenumber of the perturbation with n a positive integer number and finally $\rho^{'}$ and $c_i^{'}$ are the non null amplitudes of the perturbations.
Replacing these equations in (1.45) ,deleting the exponential factor and rearranging all the terms we get the following Cramer system:

$$\begin{cases} \rho^{'}(\sigma + k^2) - A_1k^2c_1^{'} + A_2k^2c_2^{'} = 0 \\ a^2\rho^{'} - c_1^{'}(a^2 + \epsilon_1\sigma + k^2) = 0 \\ \rho^{'} - c_2^{'}(k^2 + \epsilon_2\sigma + 1) = 0 \end{cases} \tag{1.46}$$

Now we consider the dispersion matrix D in order to discuss the Cramer system:

$$D = \begin{bmatrix} \sigma + k^2 & -A_1k^2 & A_2k^2 \\ a^2 & -(a^2 + \epsilon_1\sigma + k^2) & 0 \\ 1 & 0 & -(k^2 + \epsilon_2\sigma + 1) \end{bmatrix}$$

Hence we compute the determinant of this matrix, in order to find a cubic equation for the "eigenvalues" σ, which is the dispersion equation of our model, by imposing $\det(D) = 0$; we have

$$\det(D) = (A_2k^2)(a^2 + \epsilon_1\sigma + k^2) + (k^2 + \epsilon_2\sigma + 1)[(\sigma + k^2)(a^2 + \epsilon_1\sigma + k^2) - A_1a^2k^2], \text{ namely}$$

$$\begin{aligned} \det(D) = {} & A_2a^2k^2 + A_2\epsilon_1\sigma k^2 + A_2k^4 + a^2k^2\sigma + \epsilon_1k^2\sigma^2 + \sigma k^4 + a^2k^4 + \epsilon_1\sigma k^4 - A_1a^2k^4 + \epsilon_2\sigma^2a^2 + \epsilon_1\epsilon_2\sigma^3 + \\ & + \epsilon_2\sigma^2k^2 + \epsilon_2\sigma^2k^2 + \epsilon_2\sigma a^2k^2 + \epsilon_1\epsilon_2\sigma^2k^2 + \epsilon_2\sigma k^4 - A_1\epsilon_2\sigma a^2k^2 + \sigma a^2 + \\ & + \epsilon_1\sigma^2 + \sigma k^2 + a^2k^2 + \epsilon_1\sigma k^4 + k^4 - A_1a^2k^2. \end{aligned}$$

Imposing $\det(D) = 0$, dividing for $\epsilon_1\epsilon_2$ and rearranging all the terms, we obtain the desired dispersion equation:

$$\sigma^3 + a_1\sigma^2 + a_2\sigma + a_3 = 0 \tag{1.47}$$

where:

- $a_1 = k^2 + (1+k^2)\frac{1}{\epsilon_2} + (a^2+k^2)\frac{1}{\epsilon_1}$
- $a_2 = [\frac{1}{\epsilon_1}(a^2+k^2) + \frac{A_2}{\epsilon_2} - \frac{a^2A_1}{\epsilon_1} + \frac{1}{\epsilon_2}(1+k^2)]k^2 + \frac{1}{\epsilon_1\epsilon_2}(a^2+k^2)(1+k^2)$
- $a_3 = \frac{k^2}{\epsilon_1\epsilon_2}[A_2(a^2+k^2) - A_1a^2(1+k^2) + (1+k^2)(a^2+k^2)]$

Necessary and sufficient conditions for the asymptotic stability of our equilibrium state, in view of the Routh-Hurwitz criterion, read as follows:

$$\begin{cases} a_i > 0 \quad \forall i = 1,2,3 \\ a_1a_2 > a_3 \end{cases}$$

Remark 1.3.4. We note easily that a_1 is always positive, while a_2, and a_3 are decreasing function of A_1 so the system above reads:

$$\begin{cases} [\frac{1}{\epsilon_1}(a^2+k^2) + \frac{A_2}{\epsilon_2} - \frac{a^2A_1}{\epsilon_1} + \frac{1}{\epsilon_2}(1+k^2)]k^2 + \frac{1}{\epsilon_1\epsilon_2}(a^2+k^2)(1+k^2) > 0 \\ \\ \frac{k^2}{\epsilon_1\epsilon_2}[A_2(a^2+k^2) - A_1a^2(1+k^2) + (1+k^2)(a^2+k^2)] > 0 \\ \\ k^2 + (1+k^2)\frac{1}{\epsilon_2} + (a^2+k^2)\frac{1}{\epsilon_1}([\frac{1}{\epsilon_1}(a^2+k^2) + \frac{A_2}{\epsilon_2} - \frac{a^2A_1}{\epsilon_1} + \frac{1}{\epsilon_2}(1+k^2)]k^2 + \frac{1}{\epsilon_1\epsilon_2}(a^2+k^2)(1+k^2)) > a_3 \end{cases}$$

Remark 1.3.5. Since that the cubic equations (1.47) has real coefficients, then we have at least one real solution; the other two can be real or complex conjugate.

Remark 1.3.6. If there aren't chemotactic interactions (meaning $A_1 = A_2 = 0$), then:

$$\begin{cases} R_1 := k^2 \\ R_2 := \frac{1}{\epsilon_1}(a^2+k^2) \\ R_3 := \frac{1}{\epsilon_2}(1+k^2) \end{cases}$$

So the equation (1.47) becomes:

$$\sigma^3 + (R_1+R_2+R_3)\sigma^2 + (R_1R_2 + R_1R_3 + R_2R_3)\sigma + R_1R_2R_3 = 0$$

So in that case the three solutions are: $\sigma_1 = -R_1$, $\sigma_2 = -R_2$, $\sigma_3 = -R_3$, hence the above conditions are easily satisfied, which means the asymptotic stability of the equilibrium state and, consequently no pattern formation.

Remark 1.3.7. If $A_1 = 0$, then the criterion is trivially satisfied too.

There are also two special cases:

- if one of the three real roots is zero and the other two are negative ($\sigma_1 = 0, \sigma_2 < 0, \sigma_3 < 0$) then $a_1 = -(\sigma_1 + \sigma_2) > 0$, $a_2 = \sigma_1\sigma_2 > 0$, $a_3 = 0$. This situation provides a bifurcation.

- if one root σ is a negative real solution and the other two are pure imaginary solutions, then we have a Hopf bifurcation.

Furthermore, we can underline that the expression $(a_1a_2 - a_3)$ plays an important role in the onset of bifurcations. In fact, if all roots σ_i have negative real part this implies that $(a_1a_2 - a_3) = -\sigma_1^2\sigma_2 - \sigma_1^2\sigma_3 - 2\sigma_1\sigma_2\sigma_3 - \sigma_1\sigma_2^2 - \sigma_3\sigma_2^2 - \sigma_1\sigma_3^2 - \sigma_2\sigma_3^2 > 0$. Conversely, if $a_3 > 0$ and also $(a_1a_2 - a_3 > 0)$, then all three roots have negative real parts, a result that follows from continuity and the above arguments about bifurcation behavior. At the end we have to consider two possible bifurcation scenarios:

- when $A_1 = \frac{(a^2+k^2)(1+k^2+A_1)}{a^2(1+k^2)}$, then $a_3 = 0$ and $a_2 > 0$. In that case a real root (1.47) must be equal to zero. At a greater value of A_1, this root becomes positive.

- At a critical value of A_1, then $a_3 > 0$, $a_2 > 0$ and $(a_1a_2 - a_3) = 0$. Hence in that case, a pair of imaginary conjugate roots of equation (1.47) exist. At a greater value of A_1, these complex roots will have a positive real part.

From this analysis the instability condition is obtained when $a_3 < 0$, that is:

$$\frac{k^2}{\epsilon_1\epsilon_2}[A_2(a^2+k^2) - A_1a^2(1+k^2) + (1+k^2)(a^2+k^2)] < 0$$
$$\Rightarrow A_1(1+k^2)a^2 - A_2(a^2+k^2) - (1+k^2)(a^2+k^2) > 0 \tag{1.48}$$

and noticing that:

$$\frac{\chi_1 h_1 \bar{\rho}}{D_\rho \Lambda_1}\frac{D_{c2}\Lambda_1}{D_{c1}\Lambda_2}(k^2+1) = \frac{\chi_2 h_2 \bar{\rho}}{D_\rho \Lambda_2}\frac{\chi_1 h_1 D_{c2}}{\chi_2 h_2 D_{c1}}(k^2+1) = AA_2(1+k^2) \tag{1.49}$$
$$\Rightarrow \frac{A}{(a^2+k^2)} - \frac{1}{(1+k^2)} > \frac{1}{A_2}$$

obtained replacing (1.49) in (1.48), and taking into account the previous definition of A. Since that the behavior of the system is determined by the left-hand side of (1.49), then we analyze the closely related function:

$$H(x) = \frac{A}{x+a^2} - \frac{1}{x+1}$$

where $x = k^2$. Since $H(x)$ depends on A and a we have a distinct stability behavior for different values of these two parameters. In particular using the following properties there are some regions where the instability occurs. In fact:

1. $H(x) \to 0$ as $x \to \infty$
2. if $A \neq 1$, then there is a critical point
$$x = \frac{a^2 - \sqrt{A}}{\sqrt{A} - 1}$$
3. $H(0) = \frac{A}{a^2} - 1$. Then $H(0) > 0$ when $a < \sqrt{A}$, $H(0) < 0$ when $a > \sqrt{A}$

1.3.2 Energy method

Here we analyze the fully non linear stability which allows us to find a critical threshold providing that aggregation of microglia will not occur. We follow *Decay bounds in a model for aggregation of microglia: application to Alzheimer disease senile plaques.*, [5] and *Decay for a Keller-Segel chemotaxis model.* [6].
We indicate with $< \cdot, \cdot >$ and $\| \cdot \|$ respectively the inner product and the norm in $L^2(\Omega)$, where $\Omega \subset \mathbb{R}^2$ is now a bounded and simply connected domain. We introduce the Energy defined as:

$$E(t) = \frac{1}{2} \| \rho \|^2 + \frac{\beta \epsilon_1}{2} \| \nabla c_1 \|^2 + \frac{\beta_2 \epsilon_2}{2} \| \nabla c_2 \|^2 \tag{1.50}$$

where β and β_2 represent two optimal positive constants.
First of all we rewrite the dimensionless perturbed system in two dimension (without using δ to simplify the notation):

$$\begin{cases} \rho_t = \Delta \rho - A_1 \Delta c_1 + A_2 \Delta c_2 - A_1 \nabla \cdot (\rho \nabla c_1) + A_2 \nabla \cdot (\rho \nabla c_2) \\ \epsilon_1 c_{1t} = \Delta c_1 + a^2(\rho - c_1) \\ \epsilon_2 c_{2t} = \Delta c_2 + \rho - c_2 \end{cases} \tag{1.51}$$

Remark 1.3.8. We denote with Γ the boundary of Ω and we assume homogeneous Neumann type boundary conditions:

$$\begin{cases} \nabla c_1 \cdot n = \frac{\partial c_1}{\partial n} = 0 \\ \nabla c_2 \cdot n = \frac{\partial c_2}{\partial n} = 0 \end{cases}$$

where n is the outward normal to Γ. In particular, having zero flux through Γ requires in $(1.41)_1$ that:

$$\frac{\partial \rho}{\partial n} - A_1 \rho \frac{\partial \rho}{\partial n} + A_2 \rho \frac{\partial \rho}{\partial n} = 0 \ \text{ on } \Gamma$$

and for the previous conditions we must have $\frac{\partial \rho}{\partial n} = 0$ on Γ.

Moreover equations (1.51) are to be solved under prescribed initial conditions for the functions ρ, c_1, c_2, corresponding to assigned initial perturbations and using some standard identities and then the Gauss Theorem, in view of homogeneous Neumann type boundary conditions, we obtain:

$$\frac{d}{dt}\frac{1}{2} \parallel \rho \parallel^2 = - \parallel \nabla \rho \parallel^2 + A_1 < \nabla c_1, \nabla \rho > - A_2 < \nabla c_2, \nabla \rho > + A_1 \int_\Omega \rho \nabla c_1 \cdot \nabla \rho \, dx$$

$$- A_2 \int_\Omega \rho \nabla c_2 \cdot \nabla \rho \, dx \tag{1.52}$$

After multiplying $(1.51)_2$ for $-\Delta c_1$ and $(1.51)_3$ for $-\Delta c_2$ and, like before, using the Neumann boundary conditions and integrating we find:

$$\frac{d}{dt}\frac{1}{2}\epsilon_1 \parallel \nabla c_1 \parallel^2 = - \parallel \Delta c_1 \parallel^2 + a^2 < \nabla \rho, \nabla c_1 > - a^2 \parallel \nabla c_1 \parallel^2 \tag{1.53}$$

$$\frac{d}{dt}\frac{1}{2}\epsilon_2 \parallel \nabla c_2 \parallel^2 = - \parallel \Delta c_2 \parallel^2 + < \nabla \rho, \nabla c_2 > - \parallel \nabla c_2 \parallel^2 \tag{1.54}$$

Now we choose $\beta_2 = A_2$ in (1.50) and we compute $\frac{d}{dt}E(t)$:

$$\frac{d}{dt}\frac{1}{2} \parallel \rho \parallel^2 + \frac{d}{dt}\frac{1}{2}\epsilon_1 \beta \parallel \nabla c_1 \parallel^2 + A_2 \frac{d}{dt}\frac{1}{2}\epsilon_2 \parallel \nabla c_2 \parallel^2 = - \parallel \nabla \rho \parallel^2 + A_1 < \nabla c_1, \nabla \rho > - A_2 < \nabla c_2, \nabla \rho >$$

$$+ A_1 \int_\Omega \rho \nabla c_1 \cdot \nabla \rho \, dx - A_2 \int_\Omega \rho \nabla c_2 \cdot \nabla \rho \, dx - \beta \parallel \Delta c_1 \parallel^2 + a^2 \beta < \nabla \rho, \nabla c_1 >$$

$$- \beta a^2 \parallel \nabla c_1 \parallel^2 - A_2 \parallel \nabla c_2 \parallel^2 + A_2 < \nabla \rho, \nabla c_2 > - A_2 \parallel \Delta c_2 \parallel^2$$

Remark 1.3.9. Since that $A_2 < \nabla \rho, \nabla c_2 >$ can be removed, then we won't gain the stability effect of the chemorepellent.

$$\Rightarrow \frac{d}{dt}E(t) = -(\| \nabla\rho \|^2 + \beta \| \Delta c_1 \|^2 + A_2 \| \Delta c_2 \|^2 + A_2 \| c_2 \|^2) - \beta a^2 \| \nabla c_1 \|^2 + (A_1 + a^2\beta) < \nabla\rho, \nabla c_1 >$$

$$+ A_1 < \rho\nabla\rho, \nabla c_1 > - A_2 < \rho\nabla\rho, \nabla c_2 > \tag{1.55}$$

In order to improve our estimation we have to use:

$$\begin{cases} (A_1 + \beta a^2) < \nabla c_1, \nabla\rho > \leq \frac{(A_1+\beta a^2)}{2\alpha} \| \nabla c_1 \|^2 + \frac{1}{2}\alpha(A_1 + \beta a^2) \| \nabla\rho \|^2 \\ \beta \| \Delta c_1 \|^2 = \beta\epsilon \| \Delta c_1 \|^2 + \beta(1-\epsilon) \| \Delta c_1 \|^2 \\ \| \Delta c_1 \|^2 \geq \beta_1 \| \nabla c_1 \|^2 \end{cases} \tag{1.56}$$

where:

- $(1.56)_1$ is the arithmetic-geometric mean inequality and the constant $\alpha > 0$ is determined in [4];
- $(1.56)_3$ is the Poincaré inequality, and $\beta_1 = \beta_1(\Omega)$ found in [6];
- in $(1.56)_2$ ϵ is a real number such that: $0 < \epsilon < 1$.

Now using the integration by parts theorem and boundary conditions, for the cubic term, we have:

$$< \rho\nabla c_1, \nabla\rho > = \frac{1}{2}\int_\Omega 2\rho\, \nabla c_1 \cdot \nabla\rho \, dx = \frac{1}{2}\int_\Omega \nabla c_1 \cdot \nabla\rho^2 \, dx = -\frac{1}{2}\int_\Omega \Delta c_1 \rho^2 \, dx + \frac{1}{2}\int_\Gamma \frac{\partial c_1}{\partial n}\rho^2 \, d\sigma$$

$$= -\frac{1}{2} < \Delta c_1, \rho^2 >$$

and the same holds for the other term. Then:

$$\frac{dE}{dt} \leq -r \| \nabla\rho \|^2 - [\beta\epsilon\beta_1 + \beta a^2 - \frac{(A_1 + \beta a^2)}{2\alpha}] \| \nabla c_1 \|^2 - \beta(1-\epsilon) \| \Delta c_1 \|^2$$

$$- A_2(\| \Delta c_1 \|^2 + \| \Delta c_2 \|^2) - \frac{1}{2}A_1 < \Delta c_1, \rho^2) + \frac{1}{2}A_2 < \Delta c_2, \rho^2 > \tag{1.57}$$

$$\text{in which } r := 1 - \tfrac{1}{2}\alpha(A_1 + \beta a^2) > 0.$$

Subsequently calling $N := -\frac{1}{2}A_1 < \Delta c_1, \rho^2 > +\frac{1}{2}A_2 < \Delta c_2, \rho^2 >$ and using the Cauchy-Schwarz inequality we have:

$$N \leq \frac{1}{2}A_1 \parallel \Delta c_1 \parallel (\int_\Omega \rho^4 \ dx)^{\frac{1}{2}} + \frac{1}{2}A_2 \parallel \Delta c_2 \parallel (\int_\Omega \rho^4 \ dx)^{\frac{1}{2}}. \tag{1.58}$$

Furthermore we apply the Sobolev inequality:

$$\int_\Omega \rho^4 \ dx \leq C_1 \int_\Omega \rho^2 \ dx \int_\Omega \mid \nabla \rho \mid^2 \ dx$$

for a suitable positive constant C_1, depending on the geometry of the domain Ω, see [6] for its valuation. Later, using all the estimations above, we derive the value of $\frac{dE}{dt}$:

$$\frac{dE}{dt} = -D + \frac{A_1}{2}\sqrt{C_1} \parallel \Delta c_1 \parallel\parallel \rho \parallel\parallel \nabla \rho \parallel + \frac{A_2}{2}\sqrt{C_1} \parallel \rho \parallel\parallel \Delta c_2 \parallel\parallel \nabla \rho \parallel \tag{1.59}$$

where the dissipative D is defined as follows:

$$D = r \parallel \nabla \rho \parallel^2 + [\beta\epsilon\beta_1 + \beta a^2 - \frac{(A_1 + \beta a^2)}{2\alpha}] \parallel \nabla c_1 \parallel^2 + \beta(1-\epsilon) \parallel \Delta c_1 \parallel^2$$

$$+ A_2(\parallel \Delta c_2 \parallel^2 + \parallel \nabla c_2 \parallel^2)$$

Hence from (1.59), in view of the definitions of $E(t)$ and $D(t)$, we arrive at the final Energy inequality:

$$\frac{dE}{dt} \leq -D(1 - QE^{1/2}) \tag{1.60}$$

$$\text{where } Q := \frac{A_1\sqrt{C_1}}{2\sqrt{2\beta(1-\epsilon)r}} + \frac{\sqrt{A_2 C_1}}{2\sqrt{2r}}.$$

Remark 1.3.10. Now, in order to have an energy decay, we must require two conditions on (1.60), which guarantee that $\rho \to 0$, $\nabla c_1, \nabla c_2 \to 0$, that is microglia concentration returns to its steady state value, both the chemoattractant and the chemorepellent become constant:

- $D > 0$
- $E^{1/2}(0) < \frac{1}{Q}$

which means to require;

$$\begin{cases} (\frac{\|\rho(0)\|^2}{2} + \frac{\beta\epsilon_1\|\nabla c_1(0)\|^2}{2} + \frac{A_2\epsilon_2\|\nabla c_2\|^2}{2})^{1/2} < \frac{2\sqrt{2-\alpha(A_1+\beta a^2)}}{[A_1\sqrt{c_1}/\sqrt{\beta(1-\epsilon)}]+\sqrt{A_2c_1}} \\ \frac{\alpha(A_1+\beta a^2)}{2} < 1 \\ (\frac{A_1+\beta a^2}{2\alpha}) < \beta(\epsilon\beta_1 + a^2) \end{cases}$$

Hence the last two conditions imply that:

$$\begin{aligned} \frac{(A_1+\beta a^2)}{2\beta(\epsilon\beta_1+a^2)} < \alpha < \frac{2}{(A_1+\beta a^2)} \\ \Rightarrow (A_1+\beta a^2)^2 < 4\beta(\epsilon\beta_1+a^2) \\ \Rightarrow A_1 < 2\sqrt{\beta(\epsilon\beta_1+a^2)} - \beta a^2 := f(\beta) \end{aligned} \tag{1.61}$$

Hence $f(\beta)$ has its maximum value at $\beta = \frac{\epsilon\beta_1+a^2}{a^4}$, then replacing that in (1.61) we get $A_1 < 1 + \frac{\epsilon\beta_1}{a^2}$.
This computation provides the decay of $E(t)$, that is we have not microglia aggregation under these last two constraints. At the end if we substitute the optimal value β within the first inequality, we find:

$$\begin{aligned} (\frac{\| \rho(0) \|^2}{2} + \frac{\beta\epsilon_1 \| \nabla c_1(0) \|^2}{2} + \frac{A_2\epsilon_2 \| \nabla c_2(0) \|^2}{2})^{1/2} < \frac{2[2-\alpha\{A_1+(\epsilon\beta_1+a^2)/a^2\}]^{1/2}}{\sqrt{c_1A_2}+\sqrt{c_1}A_1a^2/[(1-\epsilon)\sqrt{\epsilon\beta_1+a^2}]} \\ < \frac{2\sqrt{1-A_1/[1+\epsilon\beta_1/a^2]}}{\sqrt{c_1A_2}+\sqrt{c_1}A_1a^2/[(1-\epsilon)\sqrt{\epsilon\beta_1+a^2}]} \end{aligned} \tag{1.62}$$

obtained choosing $\alpha = (1 + \frac{\beta\epsilon_1}{a^2})$ in accordance to the previous equation. Moreover we can see that $A_1 < 1 + \frac{\epsilon\beta_1}{a^2}$ is consistent with the previous equation and, since that in one dimension $\beta_1 = (\frac{\pi L_2}{L_1})^2$, then the condition on A_1 is : $A_1 < 1 + \epsilon(\frac{\pi L_1}{L_2})^2$. Replacing the original value of A_1 we obtain:

$$\frac{\chi_1 h_1 \bar{\rho}}{D_\rho \Lambda_1} < 1 + \epsilon(\frac{\pi L_1}{L_2})^2 \Rightarrow \bar{\rho} < \frac{D_\rho\Lambda_1}{\chi_1 h_1}[1 + \epsilon(\frac{\pi L_1}{L_2})^2].$$

This is the threshold below which the aggregation doesn't occur.
Looking for new mathematical models for Alzheimer's, in view of recent clinical studies, we can ask ourselves whether acute neuroinflammation is responsible for its onset and progression.
Alzheimer disease model could be seen as a more generalized model of acute cerebral inflammation?

Chapter 2

Chemotaxis modeling of Acute Inflammation

2.1 Introduction

In this chapter, we study the properties of a model describing Acute inflammations, in which, the first part of the essay, we refer to *Pattern formation in a model of acute inflammation.* [9], *Chemotaxis and cross-diffusion models in complex environments: Models and analytic problems toward a multiscale vision.*, [11], and in the second part *Pattern formation and transition to chaos in a chemotaxis model of acute inflammation.*,, [10], where we will see how logistical effects can affect the stability analysis and the other properties of the model. An immune system can be affected by an inflammation, which represents a biological response of the organism to an harmfuli stimuli. There exist some different types of disgregulation such as: trauma, obesity, atherosclerosis, asthma allergy, autoimmune disorders, cancer and also neurodegenerative disease (as Alzheimer disease seen in the previous chapter). Each inflammation is a result of multiple and complex interactions between cell types and molecules. In that chapter, we will see a simplified model: it consists on a fixed population of immune cells (as macrophages), and there are two molecules: the first one is denoted as inflammatory chemokine and the other is the anti-inflammatory cytokine. These two acts indifferently: chemokine are chemoattractant for immune cells, the other serve as inibithor. The author assume that macrophages produce these molucules, and the dynamics of anti- inflammatory cytokine is controlled by a fixed parameter τ which reduces the movement with respect to the other mulecules. In fact this choice is due, through a biological point of view, to the fact that immune cells produces anti-inflammatory cytokine with some delay to speed up the

immune response. Indeed,if higher concentrations of chemoacttractant engage more and more immune cells, so that there is an increased production of cytokines, on the other and, at the same time, anti-inflammatory cytokine inhibit the production.

2.1.1 Formulation of the model

The model of an acute inflammation is described through an interaction between three species of the inflammatory system represented as: inflammatory cells (macrophages), a chemokine and an anti-inflammatory cytokine denoted respectively by ρ, c_1, c_2. The authors assume that cytokine and chemokine are produced by macrophages with different dynamics: in fact the second one are slower than the first one, but they have the same kinetics. Last assumption is related to macrophages: attraction rate decreases as the concentration of c_1 increases, because the cell's signal receptors become saturated, preventing the macrophages from detecting the gradient. We denote the spatial domain $\Omega \subset \mathbb{R}^2$ which is simple connected and bounded, and we call respectively $\rho(\vec{x}, t)$, $c_1(\vec{x}, t)$, $c_2(\vec{x}, t)$ the concentration of macrophages, inflammatory chemokine and anti-inflammatory chetokine. Using these assumptions we get a three-variable PDE problem:

$$\begin{cases} \rho_t = \nabla \cdot \left(D_\rho \nabla \rho - \frac{\chi \rho}{(1+\alpha c_1)^2} \nabla c_1 \right) \\ c_{1t} = D_{c_1} \Delta c_1 - c_1 + \frac{\rho}{1+\beta c_2^\eta} \\ c_{2t} = \frac{1}{\tau}(D_{c_1} \Delta c_2 - c_2 + \frac{\rho}{1+\beta c_2^\eta}) \end{cases} \tag{2.1}$$

where χ represents the maximal chemotactic rate of the immune cells, D_ρ is the diffusive mobility for the macrophages, and D_{c1} is the diffusion for both chemokine and cytokine are constant. Let's assume $D_\rho < D_{c1}$. The quantity $1/(1+\alpha c_1)^2$ reflects the saturation of chemokine receptors, which leads to a reduction in chemoattraction as the concentration of c_1 rises. The other two parameters β and η are introduced to study the constraining effects of anty-inflammatory chemokine. As before the authors assume to have Neumann type homogeneous boundary conditions: $\nabla \rho \cdot n = \nabla c_1 \cdot n = \nabla c_2 \cdot n = 0$ on Γ, which is the boundary of Ω and n is the external normal unit vector to Γ.

Remark 2.1.1. When $\tau = 1$, this model can be reduced to Keller-Segel model, in which the two chemicals follows the same dynamics and receptors saturation doesn't provide any blow- up of the solutions. Infact, cytokines could blocks chemotactic effect, but this is not considered in the model.

Remark 2.1.2. In the second part of the chapter, studying traveling waves, it is also assumed that the density of macrophages is constant, that is: $M := \int_\Omega \rho(x, t) \ \ dx$.

Remark 2.1.3. Before proceeding with the analysis of the model, we underline some important aspects of the model. Starting from the equation $(2.1)_1$, this is a *quasi-linear* second order parabolic equation due to the presence of $\rho/(1+\alpha c_1)^2$ in the second term, whereas $(2.1)_{2,3}$ are also second-order parabolic PDEs, with the same proliferation term degraded by $h(c_2) := 1/(1+\beta c_2^\eta)$ which makes them *semi-linear*.

2.1.2 Stability analysis

As for the previous models we determine the nontrivial homogeneous steady solution $(\rho, c_1, c_2) = (\rho_c, c_{1c}, c_{2c})$ of (2.1), where ρ_c is exactly the total cells population M divided by the domain magnitude.

- Thus we impose:

$$\begin{cases} -c_1 + \frac{\rho}{(1+\beta c_2^\eta)} = 0 \\ \frac{1}{\tau}\big(- c_2 + \frac{\rho}{(1+\beta c_2^\eta)}\big) = 0 \end{cases} \tag{2.2}$$

  Hence $c_1 = c_2 = \frac{\rho}{1+\beta c_2^\eta} \Rightarrow (\rho_c, c_{1c}, c_{2c}) = (\rho_c, \frac{\rho_c}{(1+\beta c_{2c}^\eta)}, c_{2c})$, for any $\rho_c > 0$.

  Remark 2.1.4. It is shown that $(2.2)_2$ has a unique positive solution c_{2c}, in terms of ρ_c for all η and β, leading to a positive solution c_{2c} in view of $(2.2)_1$.

  As a special example, if we take $\eta = 1$, we find $c_{2c} = \frac{-1+\sqrt{(1+4\beta\rho_c)}}{2\beta}$, for all $\beta > 0$, which in turn leads to c_{1c}, via $(2.2)_1$.

- We now introduce the following perturbation $\forall(\vec{x}, t)$:

$$\begin{cases} \rho(\vec{x}, t) = \rho_c + \delta\rho(\vec{x}, t) \\ c_1(\vec{x}, t) = c_{1c} + \delta c_1(\vec{x}, t) \\ c_2(\vec{x}, t) = c_{2c} + \delta c_2(\vec{x}, t) \end{cases}$$

- Replacing these in (2.1) we obtain the perturbed system:

$$\begin{cases} \delta\rho_t = \nabla \cdot (D_\rho \nabla\delta\rho - \frac{\chi(\rho_c+\delta\rho)}{(1+\alpha(c_{1c}+\delta c_1))^2})\nabla\delta c_1 \\ \delta c_{1t} = D_{c1}\Delta\delta c_1 - c_{1c} - \delta c_1 + \frac{\rho_c+\delta_\rho}{(1+\beta(c_{2c}+\delta c_2)^\eta)} \\ \delta c_{1t} = \frac{1}{\tau}(D_{c1}\Delta\delta c_2 - c_{2c} - \delta c_2 + \frac{\rho_c+\delta_\rho}{(1+\beta(c_{2c}+\delta c_2)^\eta)}) \end{cases} \tag{2.3}$$

- Then we linearize the system (2.3), by neglecting $\delta\rho$ and δc_1 within the "drift mobility" in $(2.3)_1$ and δc_2 in the last term of $(2.3)_2$ and $(2.3)_3$; finally, taking into

account the equilibrium conditions (2.2), we find:

$$\begin{cases} \delta\rho_t = D_\rho \Delta\delta\rho - \frac{\chi\rho_c}{(1+\alpha c_{1c})^2}\Delta\delta c_1 \\ \delta c_{1t} = D_{c1}\Delta\delta c_1 - \delta c_1 + \frac{1}{(1+\beta c_{2c}^\eta)}\delta\rho \\ \delta c_{2t} = \frac{1}{\tau}(D_{c1}\Delta\delta c_2 - \delta c_2 + \frac{1}{(1+\beta c_{2c}^\eta)}\delta\rho) \end{cases} \tag{2.4}$$

- We now use the classical Fourier method and we seek perturbations with small amplitudes as follows:

$$\begin{cases} 0 \neq \delta\rho(\vec{x},t) = \bar{\rho}e^{i(\vec{k}\cdot\vec{x}-\omega t)} \\ 0 \neq \delta c_1(\vec{x},t) = \bar{c_1}e^{i(\vec{k}\cdot\vec{x}-\omega t)} \\ 0 \neq \delta c_2(\vec{x},t) = \bar{c_2}e^{i(\vec{k}\cdot\vec{x}-\omega t)} \end{cases}$$

where the vector $\vec{k}$, ω and $\sigma = -i\omega$ preserve the same meaning as previously seen. Replacing these in (2.4), canceling the exponential term, we finally recover the Cramer system for the amplitudes:

$$\begin{cases} \sigma\bar{\rho} = -D_\rho k^2\bar{\rho} + \frac{\chi\rho_c}{(1+\alpha c_{1c})^2}k^2\bar{c_1} \\ \sigma\bar{c_1} = -D_{c1}k^2\bar{c_1} - \bar{c_1} + \frac{1}{(1+\beta c_{2c}^\eta)}\bar{\rho} \\ \sigma\bar{c_2} = \frac{1}{\tau}(-D_{c1}k^2\bar{c_2} - \bar{c_2} + \frac{1}{(1+\beta c_{2c}^\eta)}\bar{\rho}) \end{cases} \tag{2.5}$$

namely:

$$\begin{cases} (\sigma + D_\rho k^2)\bar{\rho} - \frac{\chi\bar{\rho}}{(1+\alpha c_{1c})^2}k^2\bar{c_1} = 0 \\ (\sigma + k^2 D_{c1} + 1)\bar{c_1} - \frac{1}{(1+\beta c_{2c}^\eta)}\bar{\rho} = 0 \\ -\frac{1}{\tau(1+\beta c_{2c}^\eta)}\bar{\rho} + \bar{c_2}(\sigma + \frac{1}{\tau}(D_{c1}k^2 + 1)) = 0 \end{cases} \tag{2.6}$$

Remark 2.1.5. It is worth to note that in the $1D$ case, when Ω is an interval of length L, under no-flux boundary conditions, we work with a subclass of periodic perturbations in x of the following type $\cos kx$, with $k^2 = n^2\pi^2$. Hence we seek solutions of the form: $(\delta\rho, \delta c_1, \delta c_2)(x,t) = (\bar{\rho}e^{\sigma t}\cos(kx), \bar{c_1}e^{\sigma t}\cos(kx), \bar{c_2}e^{\sigma t}cos(kx))$. Hence the linear stability reads as the following eigenvalue problem:

$$\sigma \begin{bmatrix} \bar{\rho} \\ \bar{c_1} \\ \bar{c_2} \end{bmatrix} = \tilde{A}(k) \begin{bmatrix} \bar{\rho} \\ \bar{c_1} \\ \bar{c_2} \end{bmatrix} \tag{2.7}$$

where:

$$\tilde{A}(k) = \begin{bmatrix} -k^2 D_\rho & \frac{k^2 \chi c_{2c}(1+\beta c_{2c}^\eta)}{(1+\alpha c_{2c})^2} & 0 \\ \frac{1}{1+\beta c_{2c}^\eta} & -1 - k^2 D_{c1} & 0 \\ \frac{1}{\tau(1+\beta c_{2c}^\eta)} & 0 & -\frac{k^2 D_{c1}}{\tau} \end{bmatrix} \tag{2.8}$$

2.1.3 Gershgorin Theory

For the linear stability tool, the eigenvalue problem is related to the following "Dispersion matrix":

$$D(k^2) = \begin{bmatrix} \sigma + D_\rho k^2 & \frac{-\chi \rho_c k^2}{(1+\alpha c_{1c})^2} & 0 \\ -\frac{1}{(1+\beta c_{2c}^\eta)} & \sigma + D_{c1} k^2 + 1 & 0 \\ -\frac{1}{\tau(1+\beta c_{2c}^\eta)} & 0 & \sigma + \frac{(D_{c1} k^2 + 1)}{\tau} \end{bmatrix}$$

with σ playing the role of an eigenvalue.
Hence, by the standard Turing analysis, for a general reaction-diffusion system we have that, if the dispersion matrix has an eigenvalue $\sigma(k)$ with $Re(\sigma) > 0$ follows that there is a spatially periodic perturbation of the homogeneous steady state having wavelength $2\pi/k$ which has an exponential growth, which entails having an instability of the system. Otherwise if $Re(\sigma) < 0 \; \forall \sigma, k$ then the homogeneous steady state becomes asymptotically stable.
For this reason, in this subsection, we investigate better the role of the eigenvalues introducing the classical Gershgorin theory to make very fast deductions about their locations. This allows us to ensure to have a set of necessary conditions in order to determine the instability of the system. Hence, we determine the Gershgorin discs for the rows $i = 1, 2, 3$ of D:

$$i = 1 :\mid \sigma + D_\rho k^2 \mid \leq \frac{\chi k^2 \rho_c}{(1+\alpha c_{1c})^2},$$

$$i = 2 :\mid \sigma + k^2 D_{c1} + 1 \mid \leq \frac{1}{(1+\beta c_{2c}^\eta)},$$

$$i = 3 :\mid \sigma + \frac{(D_{c1} k^2 + 1)}{\tau} \mid \leq \frac{1}{\tau(1+\beta c_{2c}^\eta)}$$

We have to underline the role of each interval. In fact, the infimum of each interval ,in which the eigenvalue stays, (which is, respectively, $-D_\rho k^2$, $-k^2 D_{c1} - 1$ and $-\frac{(D_{c1} k^2 + 1)}{\tau}$) lies on the negative part of real axis. Therefore if 0 is inside of each disc, then D can

have some eigenvalues with positive real part, otherwise all the eigenvalues have negative real part. In particular, choosing $\eta = 1$, as before, we may have the condition in the discs i=2,3 becomes:

$$| \sigma + k^2 D_{c1} + 1 | \leq \frac{1}{1 + \beta c_{2c}};$$

$$| \sigma + \frac{(D_{c1} k^2 + 1)}{\tau} | \leq \frac{1}{\tau(1 + \beta c_{2c})}$$

$$\Rightarrow -\frac{1}{(1 + \beta c_{2c})} - k^2 D_{c1} - 1 \leq \sigma \leq \frac{1}{(1 + \beta c_{2c})} - k^2 D_{c1} - 1$$

Hence the second extreme is negative and 0 is not inside the discs for all the parameters fixed in the model. Considering the first Gershgorin disc we will find a condition guaranteeing that 0 is inside the interval:

$$\frac{\chi k^2 c_{2c}(1 + \beta c_{2c}^{\eta})}{(1 + \alpha c_{2c})^2} - D_\rho k^2 > 0 \Leftrightarrow \frac{\chi c_{2c}(1 + \beta c_{2c}^{\eta})}{(1 + \alpha c_{2c})^2} - D_\rho > 0 \Leftrightarrow \frac{\chi c_{2c}(1 + \beta c_{2c}^{\eta})}{D_\rho(1 + \alpha c_{2c})^2} - D_\rho > 1.$$

The condition above shows that if c_{2c} and consequently ρ_c are smaller and smaller, then 0 is not contained in the third disc, meaning that there are no pattern formation. At the same time the ratio $\frac{\chi}{D_\rho}$ plays an important role: in fact if it is small (that is the chemoattraction is weak) then there are also no pattern formation.
Finally, taking $\rho = 1$, the above inequality gives us a critical threshold to get the instability :

$$\frac{\chi}{D_\rho} > \frac{(1 + \alpha c_{2c})^2}{D_\rho(1 + \beta c_{2c})} \ \forall \ c_{2c} > 0$$

$$\Rightarrow \frac{\chi}{D_\rho} > \min_{a>0} \frac{(1 + \alpha a)^2}{D_\rho(1 + \beta a)} = \begin{cases} 4(\alpha - \beta) \text{ if } \alpha > \beta \\ \alpha^2/\beta \text{ if } \alpha \leq \beta \end{cases}$$

2.1.4 Routh-Hurwitz theory

In this subsection we analyze in detail the Routh-Hurwitz criterion to determine the stability of the system. Following [9], we firstly rewrite the dispersion matrix as:

$$D = \begin{bmatrix} \sigma + u & -p & 0 \\ -q & \sigma + r & 0 \\ -v & 0 & \sigma + \omega \end{bmatrix}$$

where we called $u := D_\rho k^2$, $p := \frac{\chi\rho_c k^2}{(1+\alpha c_{1c})^2}$, $q = \frac{1}{(1+\beta c_{2c}^\eta}$, $r := k^2 D_{c1} + 1$, $v = \frac{1}{\tau}(\frac{1}{(1+\beta c_{2c}^\eta)})$, $\omega = \frac{(D_{c1}k^2+1)}{\tau}$. Then we evaluate the determinant of D:

$$\det(D) = (\sigma+\omega)[(\sigma+r)(\sigma+u)-pq] = \sigma^3+\sigma^2 u+\sigma^2 r+\sigma ru-\sigma pq+\sigma^2\omega+\sigma u\omega+\sigma r\omega+\omega ru-\omega pq$$

$$= \sigma^3 + \sigma^2(u + r + \omega) + \sigma(ru + r\omega + u\omega - pq) + (\omega ru - \omega pq)$$

Defining now $N := u + r + \omega$, $P := (ru + r\omega + u\omega - pq)$, $Q = (\omega ru - \omega pq)$, we study the following dispersion equation:

$$\sigma^3 + N\sigma^2 + P\sigma + Q = 0 \tag{2.9}$$

As we have seen in Alzheimer disease model, the conditions that provide the stability of the equilibrium state are:

- $N > 0$;
- $Q > 0$;
- $R := NP - Q > 0$.

Remark 2.1.6. Let's note that $N = k^2(D_\rho + D_{c1}) + \frac{(D_{c1}k^2+1)}{\tau} + 1 > 0$ for all parameters chosen, but R, Q can be negative due to the presence of negative terms.

Remark 2.1.7. If $k = 0$, namely for the dynamical system, in the absence of self/cross spatial diffusion, then:

$$D = \begin{bmatrix} \sigma & 0 & 0 \\ -\frac{1}{(1+\beta c_{2c}^\eta)} & \sigma+1 & 0 \\ -\frac{1}{\tau(1+\beta c_{2c}^\eta)} & 0 & \sigma+\frac{1}{\tau} \end{bmatrix}$$

Since D is a lower triangular matrix, then $\det(D) = \sigma(\sigma+1)(\sigma+\frac{1}{\tau})$, which implies that one eigenvalue is 0, that corresponds to have a uniform steady state $\forall c_{2c}$.

Remark 2.1.8. Now we underline the importance of the following two special cases.

1. $Q = 0$ and $\sigma \neq 0$. This condition is verified when $ru = pq$ and implies that (2.9) can be written as: $\det(D) = \sigma^3 + N\sigma^2 + P\sigma = \sigma(\sigma^2 + N\sigma + P) = 0$; so that one eigenvalue must be 0, which means having a bifurcation into stationary spatial patterns.

2. When $R = 0$, that is $NP = Q$, then (2.9) becomes:

$$\sigma^3 + N\sigma^2 + P\sigma + NP = 0$$

$$\Rightarrow (\sigma + N)(\sigma^2 + P) = 0$$

Hence the eigenvalues are: $\sigma_1 = -N,\ \sigma_{2,3} = \pm i\sqrt{P}$. Since there are two complex conjugate eigenvalues, we have a bifurcation into spatial-temporal patterns (as the traveling waves which we study later).

We focus on finding conditions where nonzero values of k cause the second or third Routh-Hurwitz criterion to be violated, as we are interested in pattern-forming instabilities.
The following analysis, after fixing all the parameters, is based on the values of the maximum degree of chemotaxis χ and the time scale of the inflammatory cytokines τ, which vary since that there are no effect on the equilibrium steady state, but only on stability.
From now on, let us denote with $K =: k^2$ and we rewrite $Q(K)$ as product of three linear terms to make in evidence the importance of the wave number:

$$Q(K) = \frac{KD_\rho}{\tau}(D_{c1}K + 1)^2 - \frac{\chi c_{2c} K}{\tau}\frac{(KD_{c1} + 1)}{(1 + \alpha c_{2c})^2}$$

$$\Rightarrow Q(K) = \frac{K}{\tau}(KD_{c1} + 1)\Big[D_\rho(D_{c1}K + 1) - \frac{\chi c_{2c}}{(1 + \alpha c_{2c})^2}\Big]. \tag{2.10}$$

Imposing now $Q(K) = 0$ yields:

$$\Big[D_\rho(D_{c1}K + 1) - \frac{\chi c_{2c}}{(1 + \alpha c_{2c})^2}\Big] = 0$$

$$\Rightarrow K^* = \frac{\chi c_{2c}}{D_\rho D_{c1}(1 + \alpha c_{2c})^2} - \frac{1}{D_{c1}}.$$

Remark 2.1.9. We note that the first two linear terms of Q are positive $\forall K > 0$, hence Q is positive if and only if the root above is positive, that is:

$$\frac{\chi c_{2c}}{D_\rho D_{c1}(1 + \alpha c_{2c})^2} - \frac{1}{D_{c1}} > 0 \iff \chi > \chi_T := \frac{D_\rho(1 + \alpha c_{2c})^2}{c_{2c}};$$

then $Q(K) < 0\ \forall\ \chi > \chi_T,\ 0 < K < K^*$.
Moreover when $c_{2c} \to o$ then $\chi_T \to \infty$. Hence the instability occurs at a value of $\chi > \chi_T$. In particular χ_T is the smallest value for which there is a Turing bifurcation.

Now we have to consider the term $R(K)$. In terms of K it becomes:

$$R(K) = (D_\rho K)^2(KD_{c1}+1) + \frac{D_\rho K}{\tau}(KD_{c1}+1)^2 + \frac{(D_\rho K)^2}{\tau}(D_{c1}K+1) - \frac{\chi c_{2c}K^2 D_\rho}{(1+\alpha c_{2c})^2}$$
$$+K^2 D_{c1}D_\rho(KD_{c1}+1) + \frac{KD_{c1}}{\tau}(KD_{c1}+1)^2 + \frac{D_\rho D_{c1}(D_{c1}K+1)K^2}{\tau}$$
$$-\frac{\chi c_{2c}D_{c1}K^2}{(1+\alpha c_{2c})^2} + KD_\rho(KD_{c1}+1) + \frac{(KD_c+1)^2}{\tau} + \frac{D_\rho K(D_{c1}K+1)}{\tau} - \frac{\chi c_{2c}K}{(1+\alpha c_{2c})^2}$$
$$\frac{D_\rho K(KD_{c1}+1)^2}{\tau} + \frac{(KD_{c1}+1)^3}{\tau^2} + \frac{D_\rho K(KD_{c1}+1)^2}{\tau^2}$$
$$-\frac{\chi c_{2c}K^2(KD_c+1)}{\tau(1+\alpha c_{2c}^2)} - \frac{K}{\tau}(KD_{c1}+1)\Big[D_\rho(D_{c1}K+1) - \frac{\chi c_{2c}}{(1+\alpha c_{2c})^2}\Big].$$

Thus, collecting all the terms, we get $R(K) = a_0 + a_1K + a_2K^2 + a_3K^3$. Furthermore, all the coefficients b_j depend both on χ and τ, and b_0, b_3 are positive $\forall \chi, \tau$, so that, in order to obtain instability, we have to require b_1 and / or b_2 must be negative. According to Descartes' Rule of signs, there can be at most two positive roots, and if so, one or both of b_1, b_2 must be negative.
Following the authors, it is shown, by experimental data, that for each τ there exist $\chi_i(\tau)$ such that if $\chi > \chi_i(\tau)$:

$$\chi_1(\tau) = \frac{D_\rho(1+\alpha c_{2c})^2}{c_{2c}}\Big(\frac{\tau^2 + B_{11}\tau + B_{12}\tau}{\tau(\tau + B_{13})}\Big);$$

$$\chi_2(\tau) = \frac{D_\rho(1+\alpha c_{2c})^2(2D_{c1}+D_\rho)}{c_{2c}(D_\rho + D_{c1})} + \frac{B_{21}}{\tau} + \frac{B_{22}}{\tau^2};$$

where all the coefficients B_{ij} are strictly positive, which depends on all parameters and χ_i is a decreasing function of τ and $\chi_H(\tau) = \min(\chi_1(\tau), \chi_2(\tau))$. Moreover we can observe that when $\tau \to \infty$, $\chi_H \to \chi_1(\infty) := \frac{D_\rho(1+\alpha c_{2c})^2}{c_{2c}}$. As $\chi_T > \chi_1(\infty)$, for sufficiently slow dynamics of the inflammatory cytokine, there exist values of χ such that $Q(K) > 0$ for all $K > 0$, but $R(K) < 0$ for some K. Finally for $\tau \approx 0$, then $R(K) \approx \frac{B(K)}{\tau^2} + O(\frac{1}{\tau})$, where $B(K) = \frac{(KD_{c1}+1)^2}{\tau^2}[K(D_{c_1} + D_\rho) + 1]$. In that case we observe that both $B(K) > 0, R(K) > 0 \ \forall K$. We conclude that to have instability because of anti-inflammatory cytokine, we must require $\tau \to \infty$.
Following [9] fixed all the coefficients in terms of χ and τ, the authors has shown, numerically, that choosing:

$$[D_\rho \ \ D_{c1} \ \ \alpha \ \ \beta \ \ \rho_c \ \ \eta] = [0.45 \ \ 1 \ \ 0.5 \ \ 0.4 \ \ 10 \ \ 1]$$

for each value of τ:

1. if $\chi > \chi_T$, there are many wave numbers K, representing Turing instability;
2. if $\chi > \chi_H$ (where $\chi_H = \chi_1$ for the choice of parameters), then there are different values of K such that an oscillatory perturbation occurs with an exponential growth of the amplitude, which corresponds to have an Hopf bifurcation.

2.1.5 Stationary solutions

In this subsection we consider equilibrium solutions of the system (2.1) which are stationary, but not homogeneous; we suppose to work in a one-dimensional spatial domain of length L and, hereafter, we choose the parameter $\eta = 1$. As before, we consider either flux or periodic boundary conditions. The one-dimensional stationary version of (2.1) reads:

$$\begin{cases} 0 = \left(D_\rho \rho_x - \frac{\chi \rho c_{1x}}{(1+\alpha c_1)^2}\right)_x \\ 0 = D_{c1} c_{1xx} - c_1 + \frac{\rho}{(1+\beta c_2)} \\ 0 = D_{c1} c_{2xx} - c_2 + \frac{\rho}{(1+\beta c_2)}. \end{cases} \tag{2.11}$$

We focus on the equation $(2.11)_1$ and we integrate with respect to x to obtain:

$$k_0 = D_\rho \rho_x - \frac{\chi \rho c_{1x}}{(1+\alpha c_1)^2}. \tag{2.12}$$

Due to our hypothesis we have respectively that: under homogeneous Neumann boundary conditions, we set $k_0 = 0$; if we impose periodic boundary conditions, the homogeneity of the equations implies that, by a translation, the peaks in ρ_x and c_{1x} occur at 0, and again we can set $k_0 = 0$. Now, under the assumption that $\rho \neq 0$, we can integrate (2.12):

$$\int D_\rho \rho(x)_x \ \ dx = \int \frac{\chi \rho(x) c_1(x)_x}{(1+\alpha c_1(x))^2} \ \ dx$$

and using the method of separation of variables, it yields:

$$D_\rho \int \frac{d\rho}{\rho} \ = \chi \int \frac{dc_1}{(1+\alpha c_1)^2}$$

after defining $u(x) := (1+\alpha c_1(x))$, we use this substitution in the right-hand side to get:

$$\chi \int \frac{dc_1}{(1+\alpha c_1)^2} \ = \frac{\chi}{\alpha} \int \frac{1}{u^2} du$$

$$\Rightarrow D_\rho \log(\rho) = -\frac{\chi}{\alpha(1+\alpha c_1)} + C$$

$$\Rightarrow \rho = \rho(c_1) = k_1 \exp\Big(\frac{-\chi}{D_\rho \alpha(1+\alpha c_1)}\Big). \tag{2.13}$$

for a suitable positive constant k_1.
From this algebraic relation between ρ and c_1, we note that ρ is an increasing function of c_1, whose limit is k_1 when $c_1 \to \infty$. We emphasize that the constant k_1 is a parameter associated with the total number of macrophages in the spatial domain by integrating c_1 over the domain, but this can only be done once the function c_1 is known.
Now let's consider the equations $(2.11)_2$ and $(2.11)_3$. Subtracting from the third the second equation we get: $D_{c1}(c_1 - c_2)_{xx} = (c_1 - c_2)$. In view of no-flux boundary conditions, this second order ODE admits the unique solution $c_1 = c_2$. Thus, considering (2.13), substituting the value in $(2.11)_2$, setting $c_1 = C(x)$, we find:

$$D_{c1} C_{xx} = C - \frac{\rho(C)}{1+\beta C}$$

which can be written as an autonomous dynamical system in $\mathbb{R}^2$ of form:

$$\begin{cases} \frac{dC}{dx} = U, \\ D_{c1}\frac{dU}{dx} = C - \frac{\rho(C)}{1+\beta C}. \end{cases} \tag{2.14}$$

We can rescale space in $(2.14)_2$ and assume $D_{c1} = 1$, without any loss in generality. Furthermore our stationary solutions must satisfy the following boundary conditions: $C_x(0) = C_x(L) = 0$, i.e. $U(0) = U(L) = 0$. Periodic solutions must have at least one point in the domain such that C_x vanishes, so they can be translated to obey the same conditions.

2.1.6 Traveling Wave topic

In this subsection, we will study the behavior of Traveling Waves type solutions which depend on time. A traveling Wave may be defined as a periodic wave distribution that moves at a constant velocity along a specific direction, herein in the x direction, without changing its shape. By experimental data, it is seen that when τ is big, then the system (2.1) is well described by a signal representing traveling waves. First of all, we introduce the constant velocity V of a traveling wave, in order to look for solutions of this type: $(\rho(x,t), c_1(x,t), c_2(x,t)) = (M(z), C_1(z), C_2(z))$, where $z = x - Vt$. Using this assumption

within the one-dimensional version of (2.1), we find:

$$\begin{cases} -VM_z = D_\rho M_{zz} - \left(\frac{\chi M C_{1z}}{(1+\alpha C_1)^2}\right)_z, \\ -VC_{1z} = D_{c1}C_{1zz} - C_1 + \frac{M}{1+\beta C_2}, \\ -VC_{2z} = \frac{1}{\tau}\Big(D_{c1}C_{2zz} - C_2 + \frac{M}{1+\beta C_2}\Big). \end{cases} \tag{2.15}$$

A first integration of $(2.15)_1$, yields:

$$V(M - M_0) + D_\rho M_z = \frac{\chi M C_{1z}}{(1+\alpha C_1)^2}. \tag{2.16}$$

Let's note that the parameter M_0 represents the limit concentration of immune cells in solitary wave where $M_z, C_{1z} \to 0$ as $z \to \pm\infty$. Let's rewrite the system composed by (2.16) and $(2.15)_{2,3}$ as a five-dimensional first-order system choosing the variables (M, C_1, U, C_2, W):

$$\begin{cases} M_z = \frac{1}{D_\rho}\Big(- V(M - M_0) + \frac{\chi M U}{(1+\alpha C_1)^2}\Big), \\ C_{1z} = U, \\ U_z = \Big(- VU + C_1 - \frac{M}{(1+\beta C_2)}\Big)/D_{c1}, \\ C_{2z} = W, \\ W_z = \Big(- V\tau W + C_2 - \frac{M}{(1+\beta C_2)}\Big)/D_{c1} \end{cases} \tag{2.17}$$

Hence each solution of the above system must depend also on M_0 and the velocity V. This autonomous Dynamical system admits one constant solution, parametrized by the equilibrium value of C_2. The Jacobian of this system, evaluated at this equilibrium state reads:

$$J = \begin{bmatrix} -\frac{V}{D_\rho} & 0 & \frac{\chi C_{2c}(1+\beta C_{2c})}{D_\rho(1+\alpha C_{2c})^2} & 0 & 0 \\ 0 & 0 & 1 & 0 & 0 \\ -\frac{1}{D_{c1}(1+\beta C_{2c})} & \frac{1}{D_{c1}} & -\frac{V}{D_{c1}} & \frac{\beta C_{2c}}{D_{c1}(1+\beta C_{2c})} & 0 \\ 0 & 0 & 0 & 0 & 1 \\ -\frac{1}{D_{c1}(1+\beta C_{2c})} & 0 & 0 & \frac{1+2\beta C_{2c}}{D_{c1}(1+\beta C_{2c})} & -\frac{V\tau}{D_{c1}} \end{bmatrix}$$

In the case of $\tau = 1$, then C_1, C_2 follow the same dynamic. Hence the five- dimensional system (2.17) will be reduced to a three-dimensional system, whose solutions are traveling waves of a Keller-Segel type chemotaxis model:

$$\begin{cases} M_z = \frac{1}{D_\rho}\Big(V(M_0 - M + \frac{\chi M U}{(1+\alpha C_1)^2}\Big), \\ C_{1z} = U, \\ U_z = \frac{1}{D_{c1}}\Big(- VU + C_1 - \frac{M}{(1+\beta C_1)}\Big). \end{cases} \tag{2.18}$$

In this case the Jacobian will be:

$$J = \begin{bmatrix} -\frac{V}{D_\rho} & 0 & \frac{\chi C_{1c}(1+\beta C_{1c})}{D_\rho(1+\alpha C_{2c})^2} \\ 0 & 0 & 1 \\ -\frac{1}{D_{c1}(1+\beta C_{2c})} & \frac{1+2\beta C_{2c}}{D_{c1}(1+\beta C_{2c})} & -\frac{V}{D_{c1}} \end{bmatrix}$$

Computing the characteristic polynomial we get:

$$(-\frac{V}{D_\rho} - \sigma)\Big[-\sigma + \Big(-\frac{V}{D_{c1}} - \sigma\Big) - \frac{1+2\beta C_{2c}}{D_{c1}(1+\beta C_{2c})}\Big] - \frac{\chi C_{1c}(1+\beta C_{1c})\sigma}{D_\rho D_{c1}(1+\beta C_{2c})(1+\alpha C_{2c})^2} = 0$$

from which, rearranging all the terms, we find:

$$\sigma^3 + \sigma^2\Big(\frac{V}{D_{c1}} + \frac{V}{D_\rho}\Big) - \sigma\Big(\frac{\chi C_{1c}(1+\beta C_{1c})}{D_\rho D_{c1}(1+\beta C_{2c})(1+\alpha C_{2c})^2} + \frac{1+2\beta C_{2c}}{D_{c1}(1+\beta C_{2c})} + \frac{V^2}{D_{c1}D_\rho}\Big)$$
$$- \frac{V(1+2\beta C_{2c})}{D_\rho D_{c1}(1+\beta C_{2c})} = 0 \tag{2.19}$$

So, this equation has the form:

$$\sigma^3 + s_1\sigma^2 + \sigma s_2 + \sigma s_3 = 0$$

We assume $V > 0$, we reuse the Routh-Hurwitz criterion, in order to find the stability. We require that:

$$\begin{cases} s_1 > 0; \\ s_3 > 0; \\ r := s_1 s_2 - s_3 > 0. \end{cases}$$

We get that:

$$s_1 = \frac{V}{D_\rho} + \frac{V}{D_{c1}};$$
$$s_3 = -\frac{V(1+2\beta C_{2c})}{D_\rho D_{c1}(1+\beta C_{2c})};$$
$$r := V^2\Big(\frac{1}{(D_\rho)^2 D_{c1}} + \frac{1}{(D_{c1})^2 D_\rho}\Big) +$$
$$\Big(\frac{\chi C_{1c}(1+\beta C_{1c})}{D_{c1}(D_\rho)^2(1+\beta C_{1c})(1+\alpha C_{2c})^2} + \frac{\chi C_{1c}(1+\beta C_{1c})}{(D_{c1})^2(D_\rho)(1+\beta C_{1c})^2(1+\alpha C_{2c})} + \frac{(1+2\beta C_{2c})}{D_{c1}(1+\beta C_{2c})}\Big)$$

From this analysis, we note that r, s_1 are positive, but s_3 is negative. Then J has an eigenvalue with a positive real part and an eigenvalue with a negative real part, which means that the reduced system doesn't admit Hopf bifurcations.

2.2 A generalization of the model with a logistic term

In this section, to describe macrophages recruitment during the inflammatory response, we generalize the previous model, introducing a logistic term in the macrophages equation. There is, in fact, experimental evidence that, after the tissue- resident macrophages have initiated the inflammatory cascade, activation of the immune cells persists with the goal to amplify the inflammatory response. After recognition of the microbial challenge, resident macrophages also favored by the proinflammatory activity performed by the chemokines, drive the influx of monocyte- derived macrophages as a source of further inflammation. Thus, including the activation term in the model allows us to describe the early stages of the inflammatory response, namely, the cascade of both proinflammatory and anti-inflammatory species following the initial insult and their corresponding spatial dynamics. In particular, we get the possibility to investigate the effect of varying the strength of the activation rate on the system dynamics: since identification and regulation of the activation status of macrophages is believed to be useful diagnostic and therapeutic tool for various disease; in fact this analysis may provide valuable information about the effects of aberrant and impaired activation on inflammation and the effect of therapeutic strategies. The generalized model, recently investigated in [10], is described by the following system:

$$\begin{cases} \rho_t = \nabla \cdot (D_\rho \nabla \rho) - \nabla \cdot \left(\frac{\psi \rho \nabla c_1}{(1+\alpha c_1)^2} \right) + r \rho c_1 \left(1 - \frac{\rho}{\tilde{\rho}} \right); \\ c_{1t} = \nabla \cdot (D_{c1} \nabla c_1) + h_1 \frac{\rho}{(1+\beta c_2^\eta)} - \Lambda_1 c_1; \\ c_{2t} = \nabla \cdot (D_{c2} \nabla c_2) + h_2 \frac{\rho}{(1+\beta c_2^\eta)} - \Lambda_2 c_2. \end{cases} \tag{2.20}$$

where the values of parameters are:

Parameter	Description	Value	Source
D_ρ	Macrophages random motility	$800\ \frac{\mu m^2}{min}$	[15]
D_{c1}	Chemokine random motility	$900\ \frac{\mu m^2}{min}$	[7]
ψ	Chemoattraction	$[5 \times 10^9; 176 \times 10^9] \frac{pg}{min\ cells}$	[15]
α	Receptor-binding constant	$3 \times 10^6\ \frac{\mu m^3}{pg}$	[15]
r	Macrophages activation rate	$1.7 \times 10^5 \frac{\mu m^3}{pg\ min}$	[18]
$\tilde{\rho}$	Average resident macrophages density	$3 \times 10^{-5} \frac{cells}{\mu\ m^3}$	[16, 21]
Λ_1	Chemokine production rate	$[5.7 \times 10^{-6}; 1.96 \times 10^{-5}] \frac{pg}{min\ cells}$	[19, 20]
β	Inhibition rate	$3 \times 10^6 \frac{\mu m^3}{pg}$	Estimated
η	Inhibition rate	1	[17]
h_1	Chemokine decay rate	$[0.001; 0.03]\ min^{-1}$	[20]

Here we analyze the main differences between this model and the previous one: starting from $(2.20)_1$, the second term models the chemoattraction of macrophages along the gradient of chemical signal. The sensivity $\chi_{c1} = \frac{\psi}{(1+\alpha c_1)^2}$ that describes the rate of attraction has been derived in the so-called receptor-binding model and displays saturation for increasing values of c_1 . The parameter ψ represents the maximal chemotactic rate ; α modulates the saturation of the chemokine receptors. In the third term, which represents the novelty term, the number of activated immune cells, imposed by the initial condition, was held fixed after activation. We want to consider the effects of macrophages activation driven by inflammation, which might concur to the settling of a recurrent or persistent inflammatory state. In fact, it is well known that, due to the presence of proinflammatory chemical species, macrophages release toxins, such as oxygen-free radicals. Such toxicants, on the one hand, could kill bacteria and destroy foreign bodies; on the other hand , they can also damage hosting tissue, inducing more inflammation with the consequent recruitment of more immune cells. Hence cytokines and macrophages act to amplify the inflammatory signal, promoting the activation of more immune cells. Here r and $\tilde{\rho}$ are, respectively, the growth rate coefficient and the carrying capacity of the acti-

vated macrophages. The carrying capacity $\tilde{\rho}$ has the meaning of the average density of the resting macrophages; the resting macrophages act as a cellular pool for the activated macrophages , so that, when $\rho = \tilde{\rho}$, all the resting immune cells have turned into their active state. As in the previous model, the initial insult that triggers the immune system is described by the initial conditions, assuming that the pathogen has already been eliminated, as a typical runaway inflammations. In $(2.20)_2$ and $(2.20)_3$ the parameters h_1 and h_2 represent the production rates per macrophages, while β and η control the inhibitory effects of the cytokines. Finally the last terms in both equations is the natural decay of both molecules. with decay rates Λ_1 and Λ_2, respectively. Since the production of anti- inflammatory mediators is relatively late compared to the production of proinflammatory chemicals, we shall set $D_{c2} = \frac{D_{c1}}{\tau}$, $h_2 = \frac{h_1}{\tau}$ and $\Lambda_2 = \frac{\Lambda_1}{\tau}$, where τ is a small parameter which regulates the slower time scale of the anti-inflammatory molecules.
First of all, let's introduce a set of dimensionless variables:

$$\rho^* = \frac{\rho}{\tilde{\rho}},\ c_1^* = \frac{\Lambda_1 c_1}{h_1 \tilde{\rho}},\ c_2^* = \frac{\Lambda_2 c_2}{h_2 \tilde{\rho}},\ D^* = \frac{D_\rho}{D_{c1}},\ t^* = \Lambda_1 t,$$

$$x^* = \sqrt{\frac{\Lambda_1}{D_{c1}}},\ r^* = \frac{\tilde{\rho} h_1 r}{\Lambda_1^2},\ \chi = \frac{\psi h_1 \tilde{\rho}}{\Lambda_1 D_{c1}},\ \alpha^* = \frac{\alpha \tilde{\rho} h_1}{\Lambda_1},\ \beta^* = \frac{\tilde{\rho} \beta h_2}{\Lambda_2}$$

With this non-dimensionalization, we have chosen the chemokines' average lifetime as the reference time scale and the average distance traveled by a proinflammatory molecule during its average lifetime as the reference spatial scale. The adimensional version of (2.20) reads as follows:

$$\begin{cases} \rho_t = D\Delta\rho - \nabla \cdot \left(\frac{\chi \rho \nabla c_1}{(1+\alpha c_1)^2} \right) + r\rho c_1 (1-\rho), \\ c_{1t} = \Delta c_1 + \frac{\rho}{(1+\beta c_2^\eta)} - c_1, \\ c_{2t} = \frac{1}{\tau}\Big(\Delta c_2 + \frac{\rho}{(1+\beta c_2^\eta)} - c_2 \Big). \end{cases} \tag{2.21}$$

2.2.1 Stability analysis

First of all we determine the homogeneous steady states, by imposing:

$$\begin{cases} r\rho c_1 (1-\rho) = 0 \\ \frac{\rho}{(1+\beta c_2^\eta)} - c_1 = 0 \\ \frac{\rho}{(1+\beta c_2^\eta)} - c_2 = 0 \end{cases} \tag{2.22}$$

from which we get the following equilibrium states:

1. $\vec{u}_c = (0,0,0)$ for $\rho = c_1 = 0$ from $(2.22)_1$;

2. $\vec{u}_c = (1, \frac{1}{(1+\beta c_2^{\eta})}, \frac{1}{(1+\beta c_2^{\eta})})$ for $\rho = 1$ from $(2.22)_1$.

Remark 2.2.1. If we limit our discussion to the case $\eta = 1$, from $(2.22)_3$ we find the constant value $c_2 = -\frac{-1+\sqrt{1+4\beta}}{2}$ which in turn yields the constant value c_1 via $(2.22)_2$.

As before we claim the perturbed densities:

$$\begin{cases} \rho(\vec{x},t) = 1 + \delta\rho(\vec{x},t); \\ c_1(\vec{x},t) = c_{1c} + \delta c_1(\vec{x},t); \\ c_2(\vec{x},t) = c_{2c} + \delta c_2(\vec{x},t). \end{cases}$$

Then we substitute these relations in (2.21) to recover the perturbed system:

$$\begin{cases} \delta\rho_t = D\ \Delta\delta\rho - \nabla \cdot \left(\frac{\chi(\rho_c+\delta\rho)\nabla\delta c_1}{(1+\alpha(c_{1c}+\delta c_1)^2} \right) + r(\rho_c+\delta\rho)(1-\rho_c-\delta\rho)(c_{1c}+\delta c_1); \\ \delta c_{1t} = \Delta\delta c_1 + \frac{(\rho_c+\delta\rho)}{(1+\beta(c_{2c}+\delta c_2)^{\eta})} - c_{1c} - \delta c_1; \\ \delta c_{2t} = \frac{\Delta\delta c_2}{\tau} + \frac{1}{\tau}\Big(\frac{(\rho_c+\delta\rho)}{(1+\beta(c_{2c}+\delta c_2)^{\eta}} - c_{2c} - \delta c_2 \Big). \end{cases} \tag{2.23}$$

Using that the reaction of the proinflammatory and anti- inflammatory chemicals are non zero, then in a neighborhood of an equilibrium point we have to consider the first order Taylor developments.

So the linearized perturbation system will become:

$$\frac{\partial}{\partial t}\begin{bmatrix} \delta\rho \\ \delta c_1 \\ \delta c_2 \end{bmatrix} = \begin{bmatrix} D & \frac{-\chi}{(1+\alpha c_{2c})^2} & 0 \\ 0 & 1 & 0 \\ 0 & 0 & \frac{1}{\tau} \end{bmatrix} \Delta \begin{bmatrix} \delta\rho \\ \delta c_1 \\ \delta c_2 \end{bmatrix} + \begin{bmatrix} -rc_{2c} & 0 & 0 \\ \frac{1}{1+\beta c_{2c}} & -1 & -\frac{\beta}{(1+\beta c_{2c})^2} \\ \frac{1}{\tau(1+\beta c_{2c})} & 0 & -\Big(\frac{1}{\tau} + \frac{\beta}{\tau(1+\beta c_{2c})^2}\Big) \end{bmatrix} \begin{bmatrix} \delta\rho \\ \delta c_1 \\ \delta c_2 \end{bmatrix} \tag{2.24}$$

$$= \hat{D}\Delta[\delta\rho, \delta c_1, \delta c_2]^T + K[\delta\rho, \delta c_1, \delta c_2]^T \tag{2.25}$$

where K represents the matrix of linearized kinetics and $\hat{D}$ is the diffusion matrix. We consider the one-dimensional version of the model, with $\Omega = (0, L)$ and we still search Fourier modes type solutions according to the subclass:

$$\begin{cases} \delta\rho(x,t) = \rho_1 e^{\sigma t}\phi_k(x) \\ \delta c_1(x,t) = c_1 e^{\sigma t}\phi_k(x) \\ \delta c_2(x,t) = c_2 e^{\sigma t}\phi_k(x) \end{cases}$$

where the functions $\phi_k(x) = \cos(kx)$ represent the eigenfunctions of the $1D$ Laplacian with Neumann homogeneous boundary conditions. So this problem is reduced to the eigenvalue problem:

$$\sigma \begin{bmatrix} \rho_1 \\ c_1 \\ c_2 \end{bmatrix} = A(k) \begin{bmatrix} \rho_1 \\ c_1 \\ c_2 \end{bmatrix} \tag{2.26}$$

in which:

$$A(k) = \begin{bmatrix} -k^2 D - r c_{2c} & \frac{k^2 \chi}{(1+\alpha c_{2c})^2} & 0 \\ \frac{1}{1+\beta c_{2c}} & -1 - k^2 & -\frac{\beta}{(1+\beta c_{2c})^2} \\ \frac{1}{\tau(1+\beta c_{2c})} & 0 & -\frac{k^2}{\tau} - \left(\frac{\beta}{\tau(1+\beta c_{2c})^2} + \frac{1}{\tau}\right) \end{bmatrix} = -k^2 \hat{D} + K \tag{2.27}$$

Remark 2.2.2. When $k = 0$, meaning that there are no self-cross spatial effects, we reduce to the stability matrix for the associated dynamical system:

$$A(0) = \begin{bmatrix} -r c_{2c} & 0 & 0 \\ \frac{1}{1+\beta c_{2c}} & -1 & -\frac{\beta}{(1+\beta c_{2c})^2} \\ \frac{1}{\tau(1+\beta c_{2c})} & 0 & -\left(\frac{\beta}{\tau(1+\beta c_{2c})^2} + \frac{1}{\tau}\right) \end{bmatrix}$$

Hence there are three negative eigenvalues: $\sigma_1 = -r c_{2c}$, $\sigma_2 = -1$, $\sigma_3 = -\left(\frac{\beta}{\tau(1+\beta c_{2c})^2} + \frac{1}{\tau}\right)$, which corresponds to have asymptotic stability for the homogeneous steady state, and this creates the basis for Turing type instability. Moreover, in case of $Im(\sigma) \neq 0$, there is a wave instability, instead when $Im(\sigma) = 0$, there is a Turing instability.

Now we study how the linear diffusion of chemotaxis influences the homogeneous steady state. There are some theorems that allows us to determine the instability of an equilibrium state. We refer to [22].

Definition 2.2.3. Given a real matrix $A = (a_{ij})$ of order n and $D = \text{diag}(d_1, d_2, ..d_n)$ a real diagonal matrix. Then A is said to be :

- strongly stable (strongly semistable) if $A - D$ is stable (semistable) $\forall\ D \geq 0$;
- D-stable or (D-semistable) if DA is stable (semistable) $\forall\ D > 0$;
- Volterra-Ljapunov stable if there exists $D > 0$ so that: $AD + DA^T < 0$.

Moreover if A is Volterra-Ljapunov stable, then it is D-stable and strongly stable.

Definition 2.2.4. For any subset of integers $1 \leq i_1 < i_2 < ... < i_j \leq n$ the principal submatrix $A_{i_1,...,i_j}$ is the matrix obtained canceling all rows and all columns except those with indices $i_1, i_2, ..i_j$. Moreover the corresponding principal minor $M_{i_1,...,i_j} = \det(A_{i_1,...,i_j})$. The minors M_{ii} are indicated by a_{ii}.

Definition 2.2.5. The signed principal minors of A are $(-1)^j M_{i_1,...,i_j}$. Moreover the characteristic polynomial of A can be written as:

$$\det(A - \sigma I) = \sigma^n + d_1\sigma^{n-1} + ... + d_{n-1}\sigma + d_n;$$

where $\forall j$:

$$d_j = \sum_{1 \leq i_1 < i_2 < ... i_j \leq n} (-1)^j M_{i_1,...,i_j}.$$

represents the sum of all signed principal minors of order j.

Definition 2.2.6. Let's denote with P the set of matrices whose signed principal minors are all positive and P_0^+ the set of matrices whose signed principal minors are all non-negative, with at least one of each order positive.

Theorem 2.2.7. *Given a real 3×3 matrix B, it is said:*

- *strongly stable if and only if B is stable and $B \in P_0^+$;*
- *D-stable if and only if $-\det(B)$ is dominated by $B \in P_0^+$ and $(-b_{11}, M_{23})$, $(-b_{22}, M_{13})$, $(-b_{33}, M_{12})$;*
- *Volterra-Lyapunov stable if and only if $B \in P$ and the following inequalities are satisfied at the same time:*

$$p_1(z) = (b_{31} + b_{13}z)^2 - 4z\ b_{11}b_{33} < 0;$$

$$p_2(z) = (a_2 + a_1 z)^2 - 4z\ M_{12}M_{13} < 0;$$

in which $a_1 = b_{12}b_{23} - b_{22}b_{13}$ and $a_2 = b_{21}b_{32} - b_{22}b_{31}$.

Definition 2.2.8. Three pairs of nonnegative real numbers (p_j, q_j), $j = 1, 2, 3$ are said to dominate a positive real number γ if:

$$\Big(\sum_{j=1}^{3} \sqrt{p_j q_j}\Big)^2 \geq \gamma$$

with equality implying that at least one of the pairs (p_j, q_j) has exactly one member equal to zero. .

Theorem 2.2.9. *If $\chi = 0$, then the homogeneous steady state is linearly stable.*

Proof.

We firstly note that the eigenvalues of the matrix K are: $-rc_{2c}, -1, -\Big(\frac{\beta}{\tau(1+\beta c_{2c})^2} + \frac{1}{\tau}\Big)$, so K is stable. Moreover, by definition 2.2.5 we have that all signed principal minors belong to P_0^+. Hence by the Theorem 2.2.7, K is a strongly stable matrix, meaning that by definition 2.2.3 $\forall\ \bar{D} = \mathrm{diag}(d_1, d_2, d_3)$, real diagonal and positive semidefinite matrix, the matrix $K - \bar{D}$ is stable. By assumption $\chi = 0$, so the matrix D defined in (2.24) is real, diagonal and positive semidefinite; hence for all k we have that: $K - k^2 D$ is stable. □

Remark 2.2.10. From this result, it follows that chemotaxis is the only potentially destabilizing mechanism, so that we will assume $\chi \neq 0$.

2.2.2 Wave instability

In this section, we will analyze the necessary and sufficient conditions for the occurrence of Turing instability for the system (2.21). We set $\tilde{K} := k^2$. Now, let $P(\sigma) := \sigma^3 + N(\tilde{K})\sigma^2 + P(\tilde{K})\sigma + Q(\tilde{K})$ the characteristic polynomial of $A(\tilde{K})$, where:

- $N(\tilde{K}) = \Big(D + 1 + \frac{1}{\tau}\Big)\tilde{K} + \Big(1 + \frac{\beta}{(1+\beta c_{2c})^2}\Big)\frac{1}{\tau} + rc_{2c} + 1;$
- $P(\tilde{K}) = \Big(\frac{D(\tau+1)+1}{\tau}\Big)\tilde{K}^2 + \Big(\frac{-\beta^2\chi}{(\alpha-\beta)^2(1+\beta c_{2c})} + \frac{\alpha\chi(c_{2c}\alpha\beta-\alpha+2\beta)}{(\alpha-\beta)^2(1+\alpha c_{2c})^2} + \frac{\beta(D+1)}{\tau(1+\beta c_{2c})^2} + \frac{(\tau+1)(c_{2c}r+D)+2}{\tau}\Big)\tilde{K} +$

$$\frac{c_{2c}(c_{2c}\beta(r(\tau+1)(\beta c_{2c}+2)+\beta) + 2\beta + r(\beta+\tau+1)) + \beta + 1}{\tau(1+\beta c_{2c})^2}$$

- $Q(\tilde{K}) = \frac{D}{\tau}\tilde{K}^3 + \frac{1}{\tau}\Big(- \frac{\chi}{(\alpha c_{2c}+1)^2(c_{2c}\beta+1)} + D\Big(\frac{\beta}{(\beta c_{2c}+1)^2} + 2\Big) + c_{2c}r\Big)\tilde{K}^2 +$

$$\Big(\frac{c_{2c}(c_{2c}(\alpha c_{2c}\beta(\alpha\beta D c_{2c} + 2D(\alpha+\beta) + \alpha r) + D(\alpha^2 + (\alpha+4)\alpha\beta + \beta^2) + 2\alpha\beta r))}{(\alpha c_{2c}+1)^2(c_{2c}\beta+1)^2} +$$

$$\frac{c_{2c}(2D(\alpha\beta+\alpha+\beta) + \beta(r-\chi) + \beta D + D - \chi}{(\alpha c_{2c}+1)^2(c_{2c}\beta+1)^2} + 2c_{2c}r\Big)\tilde{K} + \frac{c_{2c}r(c_{2c}\beta(c_{2c}\beta+2)+\beta+1)}{\tau(c_{2c}\beta+1)^2}.$$

Hence, referring to [23], we state and prove the following theorems:

Theorem 2.2.11 (**Conditions for Turing instability**). *There exists a critical value* $\chi_T > 0$ *such that, at* $\chi = \chi_T$*, the system* (2.24) *experiences a Turing bifurcation.*

Proof. By the Routh-Hurwitz criterion we know that all the roots have negative real part if and only if these conditions hold: $N(\tilde{K}) > 0$, $Q(\tilde{K}) > 0$ and $R(\tilde{K}) := N(\tilde{K})P(\tilde{K}) - Q(\tilde{K}) > 0$. The first condition is always satisfied, because $N(\tilde{K}) = -\mathrm{tr}(A(\tilde{K}))$ and $N(\tilde{K})$ is positive for all choices of the parameters and for all $\tilde{K}'$s. If $Q(\tilde{K}) > 0$, then the associated polynomial will either have no roots with a positive real part, or two roots with a positive real part. Consequently, to have just one root with positive real part, we must require thar $Q(\tilde{K}) < 0$. When $Q(\tilde{K}) > 0$, we have to exclude the case that two real roots changes simultaneously the sign. In fact, given that $Q(\tilde{K}) = -\sigma_1\sigma_2\sigma_3$ is the product of the three roots, then if $N(\tilde{K})P(\tilde{K}) - Q(\tilde{K})$ changes the sign, necessary would imply that two of the roots are complex. Hence Turing bifurcation occurs when $Q(\tilde{K})$ changes its sign, from positive to negative, indipendently from the sign of $N(\tilde{K})P(\tilde{K}) - Q(\tilde{K})$. Directly the only mechanism that can make $Q(\tilde{K}) < 0$ is the chemotactic term χ. Moreover, given that Q is a monotonously decreasing function of χ, there exists a unique value $\chi = \chi_T$, where $Q(\tilde{K})$ switches its sign, from positive to negative. □

Remark 2.2.12. From this result, it follows that given the polynomial $Q(\tilde{K})$ we can find a critical value χ_T such that for $\chi > \chi_T$ we have $Q(\tilde{K}) < 0$ in a compact interval $[\tilde{K_1}, \tilde{K_2}]$, with $\tilde{K_1} > 0$.

Remark 2.2.13. The violation of the third condition is not sufficient to ensure the presence of wave instability. In fact the conditions such that $N > 0$,$Q > 0$ and $R < 0$ ensure the existence of a couple of roots with positive real parts, but they can be complex. In order to have the wave instability we have to introduce the following result.

Definition 2.2.14. Let $f(z)$ a monic polynomial of order 3, namely $f(z) = z^3 + a_1z^2 + a_2z + a_3$. Its Bezoutiant matrix is defined as:

$$B = \begin{bmatrix} 3 & -a_1 & a_1^2 - 2a_2 \\ -a_1 & a_1^2 - 2a_2 & -a_1^3 - 3a_3 + 3a_1a_2 \\ a_1^2 - 2a_2 & -a_1^3 - 3a_3 + 3a_1a_2 & 4a_1a_3 - 4a_2a_1^2 + 2a_2^2 + a_1^4 \end{bmatrix}$$

Proposition 2.2.15. *Let* $f(z)$ *be a monic polynomial of degree 3 and* B *its Bezoutiant matrix. Then every real root of* f *corresponds to a positive eigenvalue of* B *and every pair of complex conjugates roots of* f *corresponds to a pair of eigenvalues of* B *with opposite sign.*

Remark 2.2.16. An immediate consequence of this result is that the Bezoutiant matrix of a monic polynomial of degree 3 can have signature $(3, 0)$ (corresponding to have all roots real), or $(2, 1)$, when only one root is real and two are complex conjugate

Theorem 2.2.17 (**Conditions for wave instability**). *System* (2.21) *admits a wave instability if and only if there exists* $\tilde{K} > 0$*, compatible with the boundary conditions, such that:*

1. $Q(\tilde{K}) > 0$*;*
2. $\det(B(\tilde{K})) < 0$*;*
3. $R(\tilde{K}) < 0$*;*

where $B(\tilde{K})$ *is the Bezoutiant matrix associated to the characteristic polynomial* $P(\sigma)$*.*

Proof. Since $N(\tilde{K})$ is always positive, the Routh-Hurwitz criterion guarantees that $P(\sigma)$ has at least one negative root. Therefore, to state necessary and sufficient condition for the occurrence of a wave bifurcation, we have to impose the remaining eigenvalues to be complex conjugate and with a positive real part. The first of the above requirements is satisfied by the second hypothesis, i.e. $\det(B) < 0$. In fact, this condition with the above remark, immediately gives us that the signature of the Bezoutiant is $(2, 1)$, corresponding to the occurrence of two complex conjugate roots of $P(\sigma)$. Hence, the Routh-Hurwitz criterion, together with the hypothesis (1) and (3), provides that the two complex roots have positive real part. □

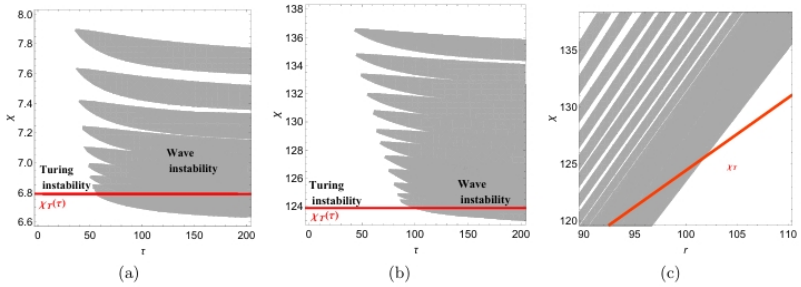

Figure 1. *Instability regions for system* (2.4)*. The red solid line* $\chi_T(\tau)$ *represents the bifurcation curve above which a Turing instability can be excited. The shaded areas represent the regions where a wave instability can occur. Parameters are fixed as follows:* $D = 0.9, \alpha = 0.01, \beta = 0.1$*.* (a)–(b) (τ, χ)*-plane for* $r = 2.4$ *and* $r = 100$*, respectively.* (c) (r, χ)*-plane for* $\tau = 100$*.*

In particular, in these figures, we will make in evidence the importance of these theorems. In fact, following the authors are focused on the emergence of Turing and wave instabilities in system (2.21), with particular emphasis on the variation of three key parameters: the macrophage activation rate r, the chemotactic coefficient χ, and the timescale of the cytokine dynamics τ, while keeping all other parameters constant. We

can see that in Figures 1(a) and 1(b) are fixed the value of r, (respectively $r = 2.4$, $r = 100$) and are plotted in the (τ, χ)-plane Turing bifurcation curve $\chi_T(\tau)$, represented by the red line above which system (2.21) displays a Turing instability, and wave instability regions, represented by the grey regions; in Figure 1(c) the instability regions are plotted in the (r, χ)-plane for a fixed value of $\tau = 100$. As it can be seen in Figures 1(a) and 1(b), the threshold value of the chemotaxis $\chi_T(\tau)$, which provides Turing patterns, is indipendent from τ: from a biological perspective, this suggests that if chemotaxis is strong enough, stationary clusters associated with sustained sites of inflammatory activity could form independently of the timescale of the anti-inflammatory response; instead for wave instability, that takes place following on the onset of structures whose local density oscillates in time, is significantly affected by the value of τ. In fact, the are more oscillations in corrispondence of high values of τ. Consequently, in the case of wave instability, if the anti-inflammatory mechanism is triggered with a delay long enough to allow the development of a full inflammatory response, a temporal resolution of the inflammation may occur. This situation aligns with the documented periodic occurrence of localized skin outbreaks, referred to as recurrent erythema multiforme , an acute, self-limiting inflammatory condition of unknown cause. An increased activation rate r results in an upward shift of both the Turing bifurcation threshold $\chi_T(\tau)$ and the regions of wave instability. This is consistent with the expectation that a higher activation rate promotes the stability of the homogeneous state, thereby necessitating a stronger chemotactic response for aggregation. The effect of r on the development of stationary and oscillatory localized inflammation is clearly observed in Figure 1(c): it is evident that, for a constant value of $\chi_T(\tau)$, the homogeneous steady state remains stable when r is high, but loses stability as r decreases.Figures 1(a) to 1(c) also illustrate which of the two competing instabilities emerges first as χ is increased, demonstrating that the order of occurrence of a Turing or wave instability is influenced by both τ and r. Specifically, from Figures 1(a) and 1(b), it can be seen that very small values of τ promote stationary structures, while higher values of τ favor the onset of a wave instability; the critical value of τ is dependent on r. In Figure 1(c), where τ is fixed, it is evident that increasing $r$favors the occurrence of Turing bifurcation over wave instability.

Chapter 3

Future directions for Alzheimer's models

3.1 First generalization of AD model: introduction to a logistic term

In the first chapter, we analyzed the Alzheimer's model based on chemotaxis, emphasizing the importance of the interaction between microglia, cytokines, and neurodegenerative proteins. Now, in light of the observations from Chapter 2 on acute inflammations, we propose a structural modification of the model to better describe the neuroinflammatory dynamics associated with the disease. One of the most relevant aspects in the progression of Alzheimer's is the uncontrolled activation of microglia, which plays both a protective and detrimental role. To model this duality, we introduce a logistic term in the first equation of the model presented in [5] to account for the system's carrying capacity and the environmental constraints on microglial proliferation:

$$\rho_t = \nabla \cdot (D_\rho \nabla \rho) - \nabla \cdot (\chi_1 \rho \nabla c_1) + \nabla \cdot (\chi_2 \rho \nabla c_2) + n\rho\Big(1 - \frac{\rho}{b}\Big)$$

where n represents the microglia proliferation rate and b the carrying capacity of the environment. This modification allows us to study the effect of microglial population saturation in response to the presence of amyloid-beta and inflammatory cytokines. The introduction of the logistic term prevents unlimited microglial growth and enables us to observe emerging phenomena related to interactions with other system components, such as pro-inflammatory cytokine. Adding the logistic term not only enhances the realism of the model but also allows us to explore system stability conditions and threshold

phenomena, where the level of microglial activation determines disease progression. Previous studies have shown that microglia can assume different functional states depending on cytokine concentrations, and our model can be used to investigate such transitions. We have to consider the following system in $\mathbb{R}^3$, referring to [5]:

$$\begin{cases} \rho_t = \nabla \cdot (D_\rho \nabla \rho) - \nabla \cdot (\chi_1 \rho \nabla c_1) + \nabla \cdot (\chi_2 \rho \nabla c_2) + n\rho\Big(1 - \frac{\rho}{b}\Big) \\ c_{1t} = \nabla \cdot (D_{c1} \nabla c_1) - \Lambda_1 c_1 + h_1 \rho \\ c_{2t} = \nabla \cdot (D_{c2} \nabla c_2) - \Lambda_2 c_2 + h_2 \rho \end{cases} \tag{3.1}$$

For this system, we carry out the stability analysis:

- We determine the homogeneous steady state by imposing:

$$\begin{cases} n\rho\Big(1 - \frac{\rho}{b}\Big) = 0 \\ -\Lambda_1 c_1 + h_1 \rho = 0 \\ -\Lambda_2 c_2 + h_2 \rho = 0 \end{cases} \tag{3.2}$$

  From (3.2) we get the following steady states: $\vec{u}_c = (0, 0, 0)$ obtained when $\rho = 0$ from $(3.2)_1$ and this is the trivial steady state; the other one is $\vec{u}_c = (b, \frac{bh_1}{\Lambda_1}, \frac{bh_2}{\Lambda_2})$ for any $b > 0$. Hereafter we impose $b = 1$.

- We, now, consider the perturbed densities, for any $(\vec{x}, t)$:

$$\begin{cases} \rho(\vec{x}, t) = 1 + \delta\rho(\vec{x}, t) \\ c_1(\vec{x}, t) = c_{1c} + \delta c_1(\vec{x}, t) \\ c_2(\vec{x}, t) = c_{2c} + \delta c_2(\vec{x}, t) \end{cases} \tag{3.3}$$

  Next, we substitute the perturbed densities in (3.1), finding the perturbed system:

$$\begin{cases} \delta\rho_t = \nabla \cdot (D_\rho \nabla \delta\rho) - \nabla \cdot (\chi_1(1 + \delta\rho)\nabla \delta c_1) + \nabla \cdot (\chi_2(1 + \delta\rho)\nabla \delta c_2) + n(1 + \delta\rho)(1 - (1 + \delta\rho)) \\ \delta c_{1t} = \nabla \cdot (D_{c1} \nabla \delta c_1) - \Lambda_1(c_{1c} + \delta c_1) + h_1(1 + \delta\rho) \\ \delta c_{2t} = \nabla \cdot (D_{c2} \nabla \delta c_2) - \Lambda_2(c_{2c} + \delta c_2) + h_2(1 + \delta\rho) \end{cases} \tag{3.4}$$

- After some simple simplifications we obtain the following linearized system:

$$\begin{cases} \delta\rho_t = D_\rho \Delta \delta\rho - \chi_1 \Delta \delta c_1 + \chi_2 \Delta \delta c_2 - n\delta\rho \\ \delta c_{1t} = D_{c1} \Delta \delta c_1 + h_1 \delta\rho - \Lambda_1 \delta c_1 \\ \delta c_{2t} = D_{c2} \Delta \delta c_2 + h_2 \delta\rho - \Lambda_2 \delta c_2 \end{cases} \tag{3.5}$$

- Hence we address the following Fourier modes type perturbations $\forall(\vec{x},t)$:

$$\begin{cases} 0 \neq \delta\rho(\vec{x},t) = \rho_1 e^{i\vec{k}\cdot\vec{x}+\sigma t} \\ 0 \neq \delta c_1(\vec{x},t) = c_1 e^{i\vec{k}\cdot\vec{x}+\sigma t} \\ 0 \neq \delta c_2(\vec{x},t) = c_2 e^{i\vec{k}\cdot\vec{x}+\sigma t} \end{cases} \tag{3.6}$$

  Replacing (3.6) in (3.5), deleting the exponential factor and rearranging all the terms, we get the following Cramer system:

$$\begin{cases} \rho_1(\sigma + k^2 D_\rho + n) - \chi_1 c_1 k^2 + \chi_2 k^2 c_2 = 0 \\ c_1(\sigma + k^2 D_{c1} + \Lambda_1) - h_1\rho_1 = 0 \\ c_2(\sigma + k^2 D_{c2} + \Lambda_2) - h_2\rho_1 = 0 \end{cases} \tag{3.7}$$

Now we consider the dispersion matrix D in order to discuss the Cramer system:

$$D = \begin{bmatrix} \sigma+u & p & q \\ -h_1 & \sigma+r & 0 \\ -h_2 & 0 & \sigma+s \end{bmatrix}$$

where we have defined: $u := k^2 D_\rho + n$, $p := -\chi_1 k^2$, $q := \chi_2 k^2$, $r := k^2 D_{c1} + \Lambda_1$ and $s := k^2 D_{c2} + \Lambda_2$. Then we compute the determinant of D imposing:

$$\det(D) = h_2 q(\sigma + r) + (\sigma + s)[(\sigma + u)(\sigma + r) + p h_1]$$

from which, rearranging all the terms, we find the desired dispersion equation:

$$\sigma^3 + \sigma^2(u + r + s) + \sigma(h_2 q + ru + h_1 p + us + rs) + h_2 qr + rus + h_1 ps = 0 \tag{3.8}$$

Denoting with $\hat{N} := (u+r+s)$, $\hat{Q} := h_2 qr + rus + h_1 ps$ and $\hat{P} := h_2 q + ru + h_1 p + us + rs$, in view of the Routh-Hurwitz criterion, we have to require the following conditions providing asymptotic stability:

$$\begin{cases} \hat{N} > 0 \\ \hat{Q} > 0 \\ \hat{R} := \hat{N}\hat{P} - \hat{Q} > 0 \end{cases} \tag{3.9}$$

We see that $\hat{N} := k^2(D_\rho + D_{c1} + D_{c2}) + n + \Lambda_1 + \Lambda_2 > 0$ for all the parameters in play. With respect to $\hat{Q}$, we have to require:

$$-\chi_2 h_2 k^2(k^2 D_{c1} + \Lambda_1) + (k^2 D_\rho + n)(k^2 D_{c1} + \Lambda_1)(k^2 D_{c2} + \Lambda_2) - \chi_1 h_1 k^2(k^2 D_{c2} + \Lambda_2) > 0$$

from which we obtain the following stability condition:

$$\chi_2 < \frac{(k^2 D_{c2} + \Lambda_2)((k^2 D_\rho + n)(k^2 D_{c1} + \Lambda_1) - \chi_1 h_1 k^2)}{h_2 k^2} \tag{3.10}$$

Regarding on $\hat{R}$ we have to require:

$$(k^2 D_{c2} + \Lambda_2 + k^2 D_\rho + n)(h_2 \chi_2 k^2 + (k^2 D_{c1} + \Lambda_1)^2) + 2(k^2 D_\rho + n)(k^2 D_{c1} + \Lambda_1)(k^2 D_{c2} + \Lambda_2) +$$

$$(k^2 D_\rho + n)^2 (k^2 D_{c1} + \Lambda_1)(k^2 D_{c2} + \Lambda_2) > (k^2 (D_{c1} + D_\rho) + \Lambda_1 + n)((k^2 D_{c2} + \Lambda_2)^2 - \chi_1 h_1 k^2)$$

from which we obtain the following stability condition which allows us, as before, to find a threshold for χ_2, $\forall\ k^2$ such that:

$$\chi_2 > \frac{2(k^2 D_{c2} + \Lambda_2 + k^2 D_\rho + n)(k^2 D_{c1} + \Lambda_1) + 2(k^2 D_\rho + n)(k^2 D_{c1} + \Lambda_1)(k^2 D_{c2} + \Lambda_2) +}{(k^2 D_{c2} + \Lambda_2 + k^2 D_\rho + n) h_2 k^2}$$

$$\frac{(k^2 D_\rho + n)^2 (k^2 D_{c1} + \Lambda_1)(k^2 D_{c2} + \Lambda_2) + [(k^2 (D_{c1} + D_\rho) + \Lambda_1 + n)(k^2 D_{c2} + \Lambda_2)^2 -}{(k^2 D_{c2} + \Lambda_2 + k^2 D_\rho + n) h_2 k^2}$$

$$\frac{(k^2 (D_{c1} + D_\rho) + \Lambda_1 + n)\chi_1 h_1 k^2]}{(k^2 D_{c2} + \Lambda_2 + k^2 D_\rho + n) h_2 k^2} \tag{3.11}$$

Remark 3.1.1. We observe that if $k = 0$, then:

$$D(0) = \begin{bmatrix} \sigma + n & 0 & 0 \\ h_1 & \sigma + \Lambda_1 & 0 \\ h_2 & 0 & \sigma + \Lambda_2 \end{bmatrix}$$

This implies that the eigenvalues are: $\sigma_1 = -n$, $\sigma_2 = -\Lambda_1$, $\sigma_3 = -\Lambda_2$, hence there is asymptotic stability for the homogeneous steady state and, as in the model for acute inflammations and as in the Keller-Segel model with the logistic effect, this leads to having Turing instability. Moreover, considering a quick comparison with the model (2.20), the possibility of a logistic type reaction term for the microglia, including the chemoattractant chemical c_1, has to be evaluated. In fact in $D(0)$ instead of having n, we have nc_{1c} and as before, in the case of $Im(\sigma) \neq 0$, there is a wave instability.

3.1.1 Gershgorin theory applied to AD

Using the Gershgorin theory as in the previous chapter, we determine which are the conditions providing the stability.

$$i = 1: \ \mid \sigma + k^2 D_\rho + n \mid \leq (\chi_1 + \chi_2) k^2$$

$$i = 2: \ | \sigma + k^2 D_{c1} + \Lambda_1 | \leq h_1$$
$$i = 3: \ | \sigma + k^2 D_{c2} + \Lambda_2 | \leq h_2$$

From the condition in the first disc we get:

$$-(\chi_1 + \chi_2)k^2 - k^2 D_\rho - n \leq \sigma \leq (\chi_1 + \chi_2)k^2 - k^2 D_\rho - n$$

The infimum of this interval is negative, but the maximum can be positive or negative; henceforth to have stability we have to require the following:

$$(\chi_1 + \chi_2 - D_\rho)k^2 - n < 0 \Rightarrow k^2 < \frac{n}{(\chi_1 + \chi_2 - D_\rho)} \tag{3.12}$$

Assuming that: $\chi_1 + \chi_2 > D_\rho$ (otherwise (3.12) would never be satisfied) we make in evidence that we recover greater stability as the microglia growth rate n increases, with the denominator fixed.
From the conditions in the second and third discs we find respectively:

$$-k^2 D_{c1} - h_1 - \Lambda_1 \leq \sigma \leq h_1 - k^2 D_{c1} - \Lambda_1$$

$$-k^2 D_{c2} - h_2 - \Lambda_2 \leq \sigma \leq h_2 - k^2 D_{c2} - \Lambda_2$$

As before the infimum is negative, then in order to provide stability we require:

$$k^2 > \frac{h_1 - \Lambda_1}{D_{c1}}$$

$$k^2 > \frac{h_2 - \Lambda_2}{D_{c2}}$$

where we observe that after fixing $h_i - \Lambda_i > 0$ for $i = 1, 2$, the stability increases the smaller D_{c1} and D_{c2} are. At the end of this discussion the conditions satisfying the stability are:

$$\begin{cases} k^2 < \frac{n}{(\chi_1 + \chi_2 - D_\rho)} \\ k^2 > \frac{h_1 - \Lambda_1}{D_{c1}} \\ k^2 > \frac{h_2 - \Lambda_2}{D_{c2}} \end{cases}$$

3.1.2 Wave topic applied to AD

Here, following the same procedure as in the chapter 2, we will determine the conditions to have wave instability.
We can rewrite the linearized system (3.5) as follows:

$$\frac{\partial}{\partial t}\begin{bmatrix}\delta\rho\\ \delta c_1\\ \delta c_2\end{bmatrix} = \begin{bmatrix}D_\rho & -\chi_1 & \chi_2\\ 0 & D_{c1} & 0\\ 0 & 0 & D_{c2}\end{bmatrix}\Delta\begin{bmatrix}\delta\rho\\ \delta c_1\\ \delta c_2\end{bmatrix} + \begin{bmatrix}-n & 0 & 0\\ h_1 & -\Lambda_1 & 0\\ h_2 & 0 & -\Lambda_2\end{bmatrix}\begin{bmatrix}\delta\rho\\ \delta c_1\\ \delta c_2\end{bmatrix}$$

$$= \mathcal{D}\Delta[\delta\rho,\delta c_1,\delta c_2]^T + L[\delta\rho,\delta c_1,\delta c_2]^T \tag{3.13}$$

Now calling $A(k) := -k^2\mathcal{D} + L$ we have:

$$A(k) - \sigma\mathbb{I}_3 = \begin{bmatrix}-(k^2D_\rho + n + \sigma) & \chi_1k^2 & -\chi_2k^2\\ h_1 & -(\Lambda_1 + D_{c1}k^2 + \sigma) & 0\\ h_2 & 0 & -(\Lambda_2 + D_{c2}k^2 + \sigma)\end{bmatrix} \tag{3.14}$$

Now calling $\hat{K} := k^2$, we compute the characteristic polynomial of $A(k)$:

$$\det(A(k) - \sigma\mathbb{I}_3) = -h_2[\chi_2\hat{K}(D_{c1}\hat{K} + \Lambda_1 - \sigma)] -$$

$$(D_{c2}\hat{K} + \Lambda_2 + \sigma)[(\hat{K}D_\rho + n + \sigma)(D_{c1}\hat{K} + \Lambda_1 + \sigma) - \chi_1h_1\hat{K}] = 0 \tag{3.15}$$

from which, rearranging all the terms we finally get the desired cubic equation in σ:

$$\sigma^3 + \sigma^2(D_{c2}\hat{K} + n + \Lambda_1 + D_{c1}\hat{K} + \hat{K}D_\rho + \Lambda_2) + \sigma(D_{c1}\Lambda_2\hat{K} + \hat{K}\Lambda_2D_\rho + \Lambda_2n +$$

$$\Lambda_2\Lambda_1 + \hat{K}^2D_\rho D_{c2} + \hat{K}D_{c2}n + \Lambda_1\hat{K}D_{c2} + D_{c1}D_{c2}\hat{K}^2 + \hat{K}D_\rho\Lambda_1 + \hat{K}^2D_\rho D_{c1} + D_{c1}\hat{K}n -$$

$$\chi_1h_1\hat{K} + \chi_2\hat{K}h_2 + \Lambda_1n) + \hat{K}^2\Lambda_2D_\rho D_{c1} + \Lambda_2\hat{K}D_\rho\Lambda_1 + \Lambda_2\Lambda_1n + D_{c1}\hat{K}n\Lambda_2 -$$

$$\Lambda_2\chi_1h_1\hat{K} + D_{c2}D_\rho\Lambda_1\hat{K}^2 + D_{c2}D_\rho D_{c1}\hat{K}^3 + \Lambda_1nD_{c2}\hat{K} + D_{c1}D_{c2}n\hat{K}^2 - D_{c2}\chi_1h_1\hat{K}^2 +$$

$$\chi_2h_2\Lambda_1\hat{K} + \chi_2h_2D_{c1}\hat{K}^2 = 0 \tag{3.16}$$

Remark 3.1.2. Following the theorems 2.2.9 and 2.2.7 and definitions 2.2.5 and 2.2.3 and noticing that the three eigenvalues of the matrix L are: $-n, -\Lambda_1, -\Lambda_2$, then if $\chi_1, \chi_2 = 0$, then the homogeneous steady state is always linearly stable, as we expect in view of the stabilizing role of classica diffusion aspects.

Remark 3.1.3. If we rewrite (3.16) as:

$$\sigma^3 + \tilde{a}_1\sigma^2 + \tilde{a}_2 + \tilde{a}_3 = 0 \tag{3.17}$$

Then defining the Bezoutiant matrix associated to the characteristic polynomial we have:

$$\tilde{B} = \begin{bmatrix} 3 & -\tilde{a}_1 & \tilde{a}_1^2 - 2\tilde{a}_2 \\ -\tilde{a}_1 & \tilde{a}_1^2 - 2\tilde{a}_2 & -\tilde{a}_1^3 - 3\tilde{a}_3 + 3\tilde{a}_1\tilde{a}_2 \\ \tilde{a}_1^2 - 2 & -\tilde{a}_1^3 - 3\tilde{a}_3 + 3\tilde{a}_1\tilde{a}_2 & 4\tilde{a}_1\tilde{a}_3 - 4\tilde{a}_2\tilde{a}_1^2 + 2\tilde{a}_2^2 + \tilde{a}_1^4 \end{bmatrix}$$

then for the theorem 2.2.17 the conditions providing wave instability are:

$$\begin{cases} \tilde{a}_3 > 0 \\ \tilde{a}_1\tilde{a}_2 - \tilde{a}_3 < 0 \\ \det(\tilde{B}) < 0 \end{cases} \tag{3.18}$$

3.2 Introduction of memory effects via the Cattaneo correction

One of the main limitations of classical diffusion models is the assumption of instantaneous transport of information. To overcome this drawback, we apply the Cattaneo correction to Fick's law, leading to hyperbolic type systems, introducing $0 < \tau_\rho \ll 1$ on J_ρ, $0 < \tau_{c_1} \ll 1$ on J_{c_1} and $0 < \tau_{c_2} \ll 1$ on J_{c_2}, to obtain firstly the delayed Fick's laws, for any fixed x:

$$\begin{cases} J_\rho(t + \tau_\rho) = -D_\rho\rho_x + \chi_1\rho c_{1x} - \chi_2\rho c_{2x} \\ J_{c1}(t + \tau_{c1}) = -D_{c1}c_{1x} \\ J_{c2}(t + \tau_{c2}) = -D_{c2}c_{2x} \end{cases} \tag{3.19}$$

and then, by first order Taylor developments, we recover the new "rate type" constitutive equations:

$$\begin{cases} \tau_\rho(J_\rho)_t + J_\rho = -D_\rho\rho_x + \chi_1\rho c_{1x} - \chi_2\rho c_{2x} \\ \tau_{c1}(J_{c1})_t + J_{c1} = -D_{c1}c_{1x} \\ \tau_{c2}(J_{c2})_t + J_{c2} = -D_{c2}c_{2x}. \end{cases} \tag{3.20}$$

By inserting these equations into the parabolic model described in (1.40), we now arrive at a hyperbolic-type model which, in the $1D$ case, consists on the following six

first-order *quasi-linear* PDEs:

$$\begin{cases} \rho_t = -(J_\rho)_x + n\rho\Big(1 - \frac{\rho}{b}\Big) \\ (J_\rho)_t = -\frac{D_\rho}{\tau_\rho}\rho_x - \frac{J_\rho}{\tau_\rho} + \frac{\chi_1 \rho c_{1x}}{\tau_\rho} - \frac{\chi_2 \rho c_{2x}}{\tau_\rho} \\ c_{1t} = -(J_{c1})_x - \Lambda_1 c_1 + h_1 \rho \\ (J_{c1})_t = -\frac{D_{c1}}{\tau_{c1}} c_{1x} - \frac{J_{c1}}{\tau_{c1}} \\ c_{2t} = -(J_{c2})_x - \Lambda_2 c_2 + h_2 \rho \\ (J_{c2})_t = -\frac{D_{c2}}{\tau_{c2}} c_{2x} - \frac{J_{c2}}{\tau_{c2}} \end{cases} \tag{3.21}$$

In the $1D$ version, the model can be written in a compact form:

$$\vec{u}_t = A\vec{u}_x + \vec{R}(\vec{u})$$

where $\vec{u}(x,t)$ and $A(\vec{u}(x,t))$ and $R(\vec{u}(x,t)$, are respectively:

$$\vec{u}(x,t) = \begin{bmatrix} \rho(x,t) \\ J_\rho(x,t) \\ c_1(x,t) \\ J_{c_1}(x,t) \\ c_2(x,t) \\ J_{c2}(x,t) \end{bmatrix}$$

$$A(\vec{u}(x,t)) = \begin{bmatrix} 0 & -1 & 0 & 0 & 0 & 0 \\ -\frac{D_\rho}{\tau_\rho} & 0 & \frac{\chi_1 \rho}{\tau_\rho} & 0 & -\frac{\chi_2 \rho}{\tau_\rho} & 0 \\ 0 & 0 & 0 & -1 & 0 & 0 \\ 0 & 0 & -\frac{D_{c1}}{\tau_{c1}} & 0 & 0 & 0 \\ 0 & 0 & 0 & 0 & 0 & -1 \\ 0 & 0 & 0 & 0 & -\frac{D_{c2}}{\tau_{c2}} & 0 \end{bmatrix} \quad R(\vec{u}) = \begin{bmatrix} n\rho\Big(1 - \frac{\rho}{b}\Big) \\ -\frac{J_\rho}{\tau_\rho} \\ -\Lambda_1 c_1 + h_1 \rho \\ -\frac{J_{c1}}{\tau_{c1}} \\ -\Lambda_2 c_2 + h_2 \rho \\ -\frac{J_{c2}}{\tau_{c2}} \end{bmatrix}$$

The hyperbolicity test is therefore related to the eigenvalue problem for the characteristic matrix:

$$\det(A - \lambda \mathbb{I}_6) = 0 \iff \Big(\lambda^2 - \frac{D_\rho}{\tau_\rho}\Big)\Big(\lambda^2 - \frac{D_{c1}}{\tau_{c1}}\Big)\Big(\lambda^2 - \frac{D_{c2}}{\tau_{c2}}\Big) = 0$$

From this, six real and distinct eigenvalues are obtained, corresponding, according to the method of characteristic curves, to three pairs of progressive and regressive waves that propagate, in the simple 1D case we consider, with respective velocities:

$$\lambda_1^{\pm} = \pm\sqrt{\frac{D_\rho}{\tau_\rho}}, \quad \lambda_2^{\pm} = \pm\sqrt{\frac{D_{c1}}{\tau_{c1}}}, \quad \lambda_3^{\pm} = \pm\sqrt{\frac{D_{c2}}{\tau_{c2}}}.$$

The correction of the Fick's law towards Maxwell-Cattaneo type rate equations, applied to the initially parabolic diffusion-reaction model, allows us to obtain a strongly hyperbolic system or simply hyperbolic one, depending on whether the real eigenvalues obtained for the characteristic matrix A are all distinct or not.
This formulation allows for a more realistic description of microglial behavior in response to chemical signals, such as avoiding instantaneous diffusion and introducing memory effects.
From a biological perspective, memory in diffusion processes is crucial to representing the adaptive behavior of microglia. Experimental studies indicate that microglial cells can retain a "memory" of their previous activation, thus influencing future responses to inflammatory stimuli. "Memory" helps to represent how microglial responses can persist over time. Furthermore, the introduction of memory effects makes the model more suitable for analyzing instabilities and dynamic bifurcations. Indeed, hyperbolic models like the one derived from the Cattaneo correction exhibit wave propagation properties of information, which can be analyzed to better understand the spatial spread of neuroinflammatory reactions.

3.3 Nonlocal models in the analysis of brain neurodegenerative protein dynamics applied to AD

In this subsection, we present a multiscale approach to examine how the concentrations of tau and amyloid-beta spread across the brain's connectome. In particular, we apply a modified heterodimer model to understand protein-protein interactions. High toxic levels of amyloid-beta and tau proteins result in brain cell destruction. We have to analyze the spread of these concentrations in both primary and secondary tauopathies, as well as in their mixed forms. The damage to brain cells is modeled by considering the nonlocal effects of these toxic substances within the cells. Through detailed analysis, we evaluate the stability of the stationary points related to the homogeneous system. When we incorporate brain connectome data into the model, we find that although the patterns of toxic concentration spread are similar throughout the brain, their levels differ across various regions. Furthermore, the time it takes for the damage to spread varies in each part of the brain connectome.
First of all, let $\Omega \subset \mathbb{R}^3$ a given spatial domain. Now, for $\vec{x} \in \Omega$ and time $t \in \mathbb{R}^+$, we denote with u and $\tilde{u}$, respectively, the healthy and toxic $A\beta$ protein, while v and $\tilde{v}$ represent the health and toxic tau- protein. From now on, we will refer to the following very recent articles: *Protein-protein interactions in neurodegenerative diseases: A conspiracy*

theory [27], *A comparison of modeling approaches for the spread of prion diseases in the brain* [28], *Pathology dynamics in healthy-toxic protein interaction and the multiscale analysis of neurodegenerative diseases* [29] and *Nonlocal multiscale interactions in brain neurodegenerative protein dynamics and coupled proteopathic processes* [30]. Hence we address a non local model described by the following set of coupled integro-differential equations:

$$\begin{cases} u_t = \nabla \cdot (D_u \nabla u) + a_0 - a_1 u - \frac{a_2 u}{1+c_u u}\phi \ * \tilde{u} \\ \tilde{u_t} = \nabla \cdot (D_{\tilde{u}} \nabla \tilde{u}) - \tilde{a_1}\tilde{u} + a_2 \tilde{u} \ \phi \ * \left(\frac{u}{1+c_u u}\right) \\ v_t = \nabla \cdot (D_v \nabla v) + b_0 - b_1 v - b_3 \tilde{u} v \tilde{v} - \frac{b_2 v}{1+c_v v}\phi \ * \tilde{v} \\ \tilde{v_t} = \nabla \cdot (D_{\tilde{v}} \nabla \tilde{v}) - \tilde{b_1}\tilde{v} + b_3 \tilde{u} v \tilde{v} + b_2 \tilde{v}\phi \ * \left(\frac{v}{1+c_v v}\right) \end{cases} \tag{3.22}$$

where the first two equations represent the healthy and toxic variants of the protein $A\beta$ and the last two play the same role for tau protein. Moreover b_0 and a_0 are the mean production rates of healthy proteins, while $a_1, b_1, \tilde{a_1}, \tilde{b_1}$ are the mean clearance rates of healthy and toxic proteins, and a_2, b_2 represent the mean conversion rates of healthy to toxic proteins. The parameter b_3 is the coupling between the two proteins and it is considered due to the fact that the amyloide enhances the seeding of new toxic tau concentration. Like previous models, the parameters $D_u, D_{\tilde{u}}, D_v, D_{\tilde{v}}$ characterize the spreading of each proteins. The coefficients c_u, c_v have units of the reciprocal concentrations of healthy proteins of amyloide and tau. For simplicity sake, all the parameters in play are considered positive constants.

Remark 3.3.1. For any fixed time t, the convolution term $\phi \ * \tilde{u}$ at the spatial point $\vec{x} = (x_1, x_2, x_3)$ is given by:

$$(\phi \ * \tilde{u})(\vec{x}, t) := \int_\Omega \phi(\vec{x} - \vec{z})\tilde{u}(\vec{z}, t)dz$$

ϕ represents the kernel function and it describes the conversion efficiencies between the points $\vec{x}$, $\vec{z}$. We assume that the kernel is a non - negative and even function and it has compact support in $\mathbb{R}^3$. Moreover ϕ satisfy the following condition:

$$\int_\Omega \phi(\vec{x})dx = 1$$

In analogous manner we define the other convolutions within (3.22).

Following *In vivo rate-determining steps of tau seed accumulation in Alzheimer's*

disease [31] we can modify the model by introducing logistic type reactions as follows:

$$\begin{cases} u_t = \nabla \cdot (D_u \nabla u) + u(a_0 - a_1 u) - \frac{a_2 u}{1+c_u u}\phi * \tilde{u} \\ \tilde{u}_t = \nabla \cdot (D_{\tilde{u}} \nabla \tilde{u}) - \tilde{a_1}\tilde{u} + a_2 \tilde{u} * \left(\frac{u}{1+c_u u}\right) \\ v_t = \nabla \cdot (D_v \nabla v) + v(b_0 - b_1 v) - b_3 \tilde{u} v \tilde{v} - \frac{b_2 v}{1+c_v v}\phi * \tilde{v} \\ \tilde{v}_t = \nabla \cdot (D_{\tilde{v}} \nabla \tilde{v}) - \tilde{b_1}\tilde{v} + b_3 \tilde{u} v \tilde{v} + b_2 \tilde{v}\phi * \left(\frac{v}{1+c_v v}\right) \end{cases} \tag{3.23}$$

with appropriate initial and no-flux boundary conditions for all the components.
The system described above governs the distribution of two variants of the proteins (one healthy and the other toxic) across the domain Ω. The rise in the density of toxic proteins at a specific spatial point $\vec{x}$ disrupts the extracellular environment around $\vec{x}$ and triggers intracellular activities. The full extent of the effects of these toxic variants remains unclear. However, Thompson et al. [27] identified a correlation and introduced a general measure of regional neuronal damage, represented by the function $f(\vec{x}, t) \in [0, 1]$ at a spatial point x and a time t. In particular we impose that:

$$\begin{cases} f(\vec{x}, t) = 0 & \text{if the neuron is healthy} \\ f(\vec{x}, t) = 1 & \text{otherwise} \end{cases}$$

Hence we can describe the evolution of the damage through the following equation:

$$f_t = (h_1 \tilde{u} + h_2 \tilde{v} + h_3 \tilde{u}\tilde{v} + h_4 \psi * q)(1 - q)$$

in which the initial condition is $f(\vec{x}, 0) = 0$, while:

- h_1 represents the damage effect due to toxic $A\beta$;
- h_2 represents the same effect of h_1 due to toxic τ protein;
- h_3 represents the damage due to the combined presence of both toxic loads;
- h_4 is the rate of transneuronal damage propagation. In particular, it reflects aggregate neuronal damage from regional neighbors.

We also assume that all h_i's are non negative functions.

3.3.1 Analysis of the continuous model

For simplicity sake, in this subsection we focus only on the temporal dynamics of the model (3.23). Firstly we have to ignore all the spacial dependencies; hence the diffusion terms will become 0 and the convolution term $\phi * n = n$ for any $n > 0$. Thus the model, with these assumptions will be represented as a dynamical system:

$$\begin{cases} u_t = u(a_0 - a_1 u) - \frac{a_2 u}{1+c_u u}\tilde{u} \\ \tilde{u}_t = -\tilde{a_1}\tilde{u} + \frac{a_2 u}{1+c_u u}\tilde{u} \\ v_t = v(b_0 - b_1 v) - b_3 \tilde{u} v \tilde{v} - \frac{b_2 v}{1+c_v v}\tilde{v} \\ \tilde{v}_t = -\tilde{b_1}\tilde{v} + b_3 \tilde{u} v \tilde{v} + \frac{b_2 v}{1+c_v v}\tilde{v} \end{cases} \tag{3.24}$$

In order to find all the equilibrium points, we have to impose:

$$\begin{cases} u(a_0 - a_1 u) - \frac{a_2 u}{1+c_u u}\tilde{u} = 0 \\ -\tilde{a_1}\tilde{u} + \frac{a_2 u}{1+c_u u}\tilde{u} = 0 \\ v(b_0 - b_1 v) - b_3 \tilde{u} v \tilde{v} - \frac{b_2 v}{1+c_v v}\tilde{v} = 0 \\ -\tilde{b_1}\tilde{v} + b_3 \tilde{u} v \tilde{v} + \frac{b_2 v}{1+c_v v}\tilde{v} = 0 \end{cases} \tag{3.25}$$

After some straightforward algebraic calculations, we find:

- $E_1 = (0, 0, 0, 0)$
- $E_2 = \left(\frac{a_0}{a_1}, 0, 0, 0\right)$
- $E_3 = \left(0, 0, \frac{b_0}{b_1}, 0\right)$
- $E_4 = \left(\frac{a_0}{a_1}, 0, \frac{b_0}{b_1}, 0\right)$
- $E_5 = \left(\frac{\tilde{a_1}}{a_2 - c_u \tilde{a_1}}, \frac{a_0(a_2 - c_u \tilde{a_1}) - \tilde{a}_1 a_1}{(a_2 - c_u \tilde{a}_1)^2}, 0, 0\right)$
- $E_6 = \left(0, 0, \frac{\tilde{b_1}}{b_2 - c_v \tilde{b}_1}, \frac{b_0(b_2 - c_v \tilde{b}_1) - b_1 \tilde{b}_1}{(b_2 - c_v \tilde{b}_1)^2}\right)$
- $E_7 = \left(\frac{\tilde{a}_1}{a_2 - c_u \tilde{a}_1}, \frac{a_0(a_2 - c_u \tilde{a}_1) - a_1 \tilde{a}_1}{(a_2 - c_u \tilde{a}_1)^2}, \frac{b_0}{b_1}, 0\right)$
- $E_8 = \left(\frac{a_0}{a_1}, 0, \frac{\tilde{b}_1}{b_{2 - c_v \tilde{b_1}}}, \frac{b_0(b_2 - c_v \tilde{b}_1) - b_1 \tilde{b}_1}{(b_2 - c_v \tilde{b}_1)^2}\right)$

These equilibrium states can be free from the toxic substances or from the healthy ones of the two chemicals.

Remark 3.3.2. E_1 is the trivial equilibrium point. In fact, generally, it doesn't occur in the living brain cell, but only in the dead brain cell. All the other equilibrium points depend on all parameters, where at least one component is zero. The concentration in each of the component can't be negative, and this creates threshold effects. Moreover for the existence of the equilibrium points E_5 and E_8 we have to require that the following conditions must hold:

$$\begin{cases} a_2 > c_u\tilde{a}_1 \\ \frac{a_0}{a_1} \geq \frac{\tilde{a_1}}{(a_2 - c_u\tilde{a}_1)}. \end{cases}$$

Similarly for the feasibility of the equilibrium points E_6 and E_7 we must have:

$$\begin{cases} b_2 > c_v\tilde{b}_1 \\ \frac{b_0}{b_1} \geq \frac{b_1}{(b_2 - c_v\tilde{b}_1)}. \end{cases}$$

Remark 3.3.3. We denote a stationary state healthy $A\beta$ (healthy τ) if the second (fourth) component of the equilibrium point is zero; otherwise it is toxic. We easily note that E_2 and E_3 contain either healthy $A\beta$ or healthy τ concentrations and these are healthy $A\beta$ and healthy τ , respectively, stationary states. Moreover we call the equilibrium point E_4 the disease-free stationary state, since it does not have any of the toxic loads $A\beta$ or τ. All the other equilibrium points are brain disease states since these brain states have either amyloid plaques or neurofibrillary tau tangles.

Now we want to find an equilibrium point where both toxic loads are present. If we denote by $E_* = (u_*, \tilde{u}_*, v_*, \tilde{v}_*)$ a positive equilibrium point, then we have that:

1. $u_* = \frac{\tilde{a}_1}{(a_2 - c_u\tilde{a}_1)}$
2. $\tilde{u}_* = \frac{(a_0a_2 - a_1\tilde{a}_1 - c_ua_0\tilde{a}_1)}{(a_2 - c_u\tilde{a}_1)^2}$
3. $\tilde{v}_* = \frac{(b_0 - b_1v_*)(c_vv_* + 1)}{(b_3c_v\tilde{u}_*v_* + b_3\tilde{u} + b_2)}$

where v_* satisfy the following quadratic equation:

$$b_3c_v\tilde{u}^*v_*^2 + (b_2 - b_3\tilde{u}_* - \tilde{b}_1c_v)v_* - \tilde{b}_1 = 0 \tag{3.26}$$

For the feasibility conditions we must require:

$$\begin{cases} a_2 > c_u\tilde{a}_1 \\ \frac{a_0}{a_1} > \frac{\tilde{a}_1}{(a_2 - c_u\tilde{a}_1)} \\ b_0 > b_1v_* \end{cases}$$

where v_* is the positive solution of (3.26). In this case the equilibrium point E_* becomes "toxic A β- toxic τ" stationary state since it contains both amyloid plaques and neurofibrillary tau tangles. Now we will analyze the stability of the equilibrium points of the system (3.24). In particular,as for the previous models, the stability behavior depends on the eigenvalues of the Jacobian matrix, evaluated in correspondence of the equilibrium point in study. Given a fixed equilibrium point, if all the real parts of the eigenvalues of the Jacobian matrix are negative, the equilibrium point is stable; otherwise it is unstable. We denote the equilibrium point $P = (u_c, \tilde{u}_c, v_c, \tilde{v}_c)$, then the Jacobian is:

$$J = \begin{bmatrix} J_{11} & J_{12} & 0 & 0 \\ J_{21} & J_{22} & 0 & 0 \\ 0 & J_{32} & J_{33} & J_{34} \\ 0 & J_{42} & J_{43} & J_{44} \end{bmatrix}$$

where we have called: $J_{11} := a_0 - 2a_1u_c - \frac{a_2\tilde{u}_c}{(1+c_uu_c)^2}$, $J_{12} := -\frac{a_2u_c}{(1+c_uu_c)}$, $J_{21} := \frac{a_2\tilde{u}_c}{(1+c_uu_c)^2}$,
$J_{22} := -\tilde{a}_1 + \frac{a_2u_c}{(1+c_uu_c)}$, $J_{32} := -b_3v_c\tilde{v}_c$, $J_{33} := -b_0 - 2b_1v_c - b_3\tilde{u}_c\tilde{v}_c - \frac{b_2\tilde{v}_c}{(1+c_vv_c)^2}$,
$J_{34} := -\frac{b_2v_c}{(1+c_vv_c} - b_3\tilde{u}_cv_c$, $J_{42} := b_3v_c\tilde{v}_c$, $J_{43} := b_3\tilde{u}_c\tilde{v}_c + \frac{b_2\tilde{v}_c}{(1+c_vv_c)^2}$,
$J_{44} := -b_1 + b_3\tilde{u}_cv_c + \frac{b_2v_c}{(1+c_vv_c}$. Thus, computing the characteristic polynomial we get:

$$(J_{11}-\sigma)(J_{22}-\sigma)[(J_{33}-\sigma)(J_{44}-\sigma)-J_{34}J_{43}]-J_{12}J_{21}[(J_{33}-\sigma)(J_{44}-\sigma)-J_{34}J_{43}] = 0 \quad (3.27)$$

from which collecting all the terms:

$$[(J_{11}-\sigma)(J_{22}-\sigma) - J_{12}J_{21}][J_{33}J_{44} - J_{33}\sigma - J_{44}\sigma + \sigma^2 - J_{34}J_{43}] = 0 \quad (3.28)$$

Now, calling $T := -(J_{11} + J_{22})$, $D := J_{11}J_{22} - J_{12}J_{21}$, $\widehat{T} := -(J_{33} + J_{44})$,
$\widehat{D} := J_{33}J_{44} - J_{34}J_{43}$ then equation (3.28) reduces to the splitting form:

$$(\sigma^2 + \sigma\widehat{T} + \widehat{D})(\sigma^2 + \sigma T + D) = 0$$

which yields:

$$\sigma^4 + \sigma^3(T + \widehat{T}) + \sigma^2(\widehat{D} + D + \widehat{T}T) + \sigma D\widehat{T} + D\widehat{D} = 0$$

Therefore the eigenvalues of the matrix J are: $\sigma_{1,2} = -(T \pm \sqrt{T^2 - 4D})/2$ and $\sigma_{3,4} = -(\widehat{T} \pm \sqrt{\widehat{T} - 4\widehat{D}})/2$. Depending on the parameters the stability of stationary points is different. The stability/ instability analysis of the stationary points is particularly intriguing and leads to very different topological classifications.

The nonlocal extension of the model introduces notable mathematical challenges, particularly in the treatment of spatial diffusion. Replacing local differential operators with integral terms complicates both the analytical and numerical analysis, affecting stability assessment and solution characterization. In particular, long-range interactions can lead to emergent behaviors that are not present in the local framework, requiring advanced mathematical techniques for a rigorous understanding. More research is needed to explore the full implications of these non-local effects on the dynamics of the system.

Conclusions

The study presented in this thesis has extensively explored the intricate role of chemotaxis in acute inflammations, drawing from mathematical models and their applications in biological and medical contexts. A key component of our work has involved the study of partial differential equations (PDEs) to model the spatial and temporal dynamics of inflammatory responses. By delving into fundamental diffusion laws, such as Fick's law and its generalizations, we have demonstrated the necessity of incorporating nonlocal and memory effects to refine classical models. These modifications are particularly crucial in neurodegenerative conditions, where spatial and temporal delays significantly influence disease progression.

The first chapter has provided a rigorous introduction to mathematical modeling with PDEs, focusing on reaction-diffusion equations and stability analysis. A significant part of this chapter has been dedicated to the Keller-Segel model, which serves as a foundation for many subsequent chemotaxis-driven mathematical models. Originally formulated to describe bacterial aggregation, the pionieristic Keller-Segel model has been widely applied to various biological systems, including inflammatory and neurodegenerative processes. This model consists of coupled PDEs that describe the temporal evolution of cellular concentration and chemical concentration through self-diffusion and chemotactic interactions. By employing linear/ non linear stability analysis, via Fourier mode technique and Energy type methods, we have characterized the stability conditions governing cellular aggregations and pattern formation. Furthermore, the Keller-Segel model has provided the basis for the Luca model for Alzheimer disease, which introduces additional complexities by incorporating chemoattractive and chemorepulsive interactions. In turn, the Luca model may be generalized by incorporating suitable logistic type reaction terms, memory effects via the Cattaneo correction of the Fick's law, accounting for cross-diffusion aspects and also non local properties, better encapsulating the complexities inherent to inflammatory responses.

Then we have applied our mathematical tools to acute inflammation models, incorporating macrophages, inflammatory cytokines, and anti-inflammatory responses. Using

PDEs-based models consisting of coupled reaction-diffusion equations, we have analyzed the role of chemotactic coefficients and activation rates in determining the stability of inflammatory sites to model Alzheimer's disease. The application of Gershgorin's theory and Turing instability analysis have allowed us to have conditions under which inflammation can persist, oscillate, or resolve. Notably, we have demonstrated that wave instability and traveling wave solutions play a crucial role in understanding the spread of inflammatory signals within biological tissues. A significant advancement in our research has been the adaptation of these mathematical frameworks to model Alzheimer 's disease. Building upon the Luca model discussed in Chapter 1, we further have modified it by incorporating logistic effects, memory-driven diffusion terms, which lead to hyperbolic reaction-diffusion equations. These extensions have allowed us to explore how environmental factors and external regulatory mechanisms influence cellular behavior in inflammatory and neurodegenerative contexts. Through the application of the Routh-Hurwitz criterion and Fourier analysis, we have identified critical thresholds for stability and the onset of oscillatory behaviors, offering new insights into potential strategies for mitigating the effects of chronic neuroinflammation. A particularly compelling result of our research has been the determination of critical thresholds where small variations in chemotactic parameters significantly affect inflammatory outcomes. We have demonstrated how targeted modulation of chemotactic factors could potentially serve as a viable strategy for controlling inflammation and slowing disease progression. These insights are particularly relevant for the development of novel therapeutic approaches aimed at mitigating the effects of chronic neuroinflammation in conditions such as Alzheimer's disease. Our findings suggest that the integration of multi-scale modeling approaches, bridging molecular-level interactions with macroscopic inflammatory patterns, could significantly enhance our understanding of these complex systems. The inclusion of fractional-order PDEs and nonlocal interactions could also provide new insights into long-range effects in chemotactic responses. In conclusion, this thesis has demonstrated that mathematical modeling, particularly through the use of PDE-based approaches, serves as a powerful tool for unraveling the mechanisms of chemotaxis-driven inflammation. By refining and extending existing frameworks, we have contributed to the broader understanding of inflammatory processes in both acute and chronic settings. Our findings pave the way for future interdisciplinary research combining mathematics, biology, and medical sciences to develop innovative strategies for managing inflammation-related diseases. Ultimately, these insights hold significant potential for improving therapeutic interventions and patient outcomes, emphasizing the need for a continued synergy between theoretical modeling and experimental validation. The implications of this research extend beyond the immediate applications in neuroinflammation and acute inflammatory responses. The mathematical tools and techniques developed here can be applied to a wide range

of biomedical problems. Chemotactic mechanisms are fundamental to many physiological and pathological processes, and a deeper understanding of these dynamics could lead to breakthroughs in multiple areas of medical science. Furthermore, this research underscores the necessity of a multidisciplinary approach to tackling complex biological problems. The intersection of mathematics, computational modeling, and biomedical research represents a rapidly evolving field with immense potential. As computational power continues to increase and experimental techniques become more refined, the integration of these disciplines will likely yield even more precise and predictive models of inflammatory and neurodegenerative diseases. Ultimately, the work presented in this thesis lays the foundation for continued exploration of chemotaxis-driven inflammation and its implications for human health. Through ongoing collaboration between mathematicians, biologists, and medical researchers, we can further refine these models and translate theoretical insights into tangible medical advancements. By embracing this interdisciplinary approach, we can contribute to the development of more effective treatments for inflammatory diseases, ultimately improving the quality of life for worldwide patients.

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