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On a hyperbolic-parabolic chemotaxis model on networks for medical tissue engineering applications

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Chapter 1

Introduction

During last decades, mathematical analysis has become an effective tool to explore biological phenomena and to detect mechanisms that might be not evident to the experimenters. In the present work, a model of chemotaxis is proposed. Chemotaxis is the mechanism by which uni o multicellular organisms modify their motion in response to a variation of chemicals in the environment. In particular, this phenomenon influences the motion of fibroblasts, the stem cells in charge of dermal wound healing. When a trauma occurs, fibroblasts create a new extracellular matrix and then, driven by chemotaxis, migrate on it to fill the wound.

Wound healing is a complex and fragile process, factors such as diabetes, venous or arterial disease and infection can contribute to non-healing chronic wounds. In particular, diabetic patients can develop wounds that are slow to heal or might never heal, since high blood glucose levels prevents nutrients and oxygen from energizing cells, increases inflammation, decreases collagen deposition in the wound site and prevents the immune system from functioning efficiently. Such condition has a high risk of developing infections that can spread locally, to surrounding tissue and bone, or to further away areas of the body, eventually causing sepsis.

In order to improve wound repair and minimize scar formation, an interesting tissue engineering technique was developed, which consists in inserting artificial scaffolds within the wound. This way such structures provide fibroblasts a support to walk. A wide variety of artificial scaffolds made of both natural and synthetic polymers have been introduced to date. However, the development of optimal materials and structures for such scaffolds is still subject to research.

A new approach to describe such phenomenon consists in setting a one dimensional (1D) model on a network. Indeed, from a mathematical point of view, a scaffold can be described by an oriented network $\mathcal{N}$ composed of a finite number of oriented arcs. In this thesis the following hyperbolic-

parabolic model is considered

$$\begin{cases} u_t + v_x = 0 \\ v_t + \lambda^2 u_x = \phi_x u - v \\ \phi_t - D\phi_{xx} = au - b\phi \end{cases}$$

where unknowns are u, v, ϕ and they respectively represent density of cells, mean flux and density of chemoattractant. The parameters are: $D > 0$ the diffusion coefficient of chemoattractant, $a \geq 0$ and $b \geq 0$, which are, respectively, its production and degradation rate and finally $\lambda > 0$, the modulus of the constant velocity. The hyperbolic system describes the movement of the cells from a mesoscopic point of view. Moreover, as opposed to parabolic-type models, it implies a finite speed of propagation of the cells. Another feature of the model is that cells can move in two different oriented directions on the same arc.

The thesis is organised as follows: Chapter 2 briefly recalls some useful definitions, theorems and notations used throughout the thesis. Chapter 3 first introduces the biological background and some mathematical models for chemotaxis, then, a hyperbolic-parabolic model is derived and set on a network, with suitable nodes conditions. Finally, Chapter 4 describes the analytical results of the current problem.

Chapter 2

Preliminary results

The aim of this chapter is to briefly recall some definitions, theorems and notations that will be used later on in this work.

2.1 Some functional analysis tools

Here, some classical theorems of functional analysis are presented, these are necessary for the study of semilinear evolution equations. The proofs can be found in [6].

Theorem 2.1 (Banach Fixed Point Theorem)**.** *Let (E, d) be a complete metric space and let $f : E \to E$ be a mapping such that there $\exists k \in [0, 1)$ satisfying $d(f(x), f(y)) \leq kd(x, y)$ for every $(x, y) \in E \times E$. Then, there exists a unique point $x_0 \in E$ such that $f(x_0) = x_0$.*

Theorem 2.2 (Lax-Milgram Theorem)**.** *Let H be a Hilbert space and let $a : H \times H \to \mathbb{R}$ be a bilinear functional. Assume that there exist two constants $C < \infty$, $\alpha > 0$ such that:*

(i) $|a(u, v)| \leq C\|u\|\|v\|$ for all $(u, v) \in E \times E$ (continuity),

(ii) $a(u, u) \geq \alpha\|u\|^2$ for all $u \in H$ (coerciveness).

Then, for every $f \in H^\star$ (the dual space of H), there exists a unique $u \in H$ such that $a(u, v) = \langle f, v\rangle$ for all $v \in H$.

2.2 Sobolev spaces

It is important to recall Sobolev spaces since they often are the proper settings in which to apply functional analysis techniques in order to gain information about partial differential equations. To do so it is important to introduce the notion of weak derivative.

Notation 2.3. Let Ω be an open subset of $\mathbb{R}$, $C_c^\infty(\Omega)$ will denote the space of infinite differentiable functions with compact support Ω. A function ϕ belonging to $C_c^\infty(\Omega)$ is called a *test function*.

Definition 2.1. Set $u, v \in L^1_{loc}(\Omega)$ and α a multi-index, v is the α^{th} *weak partial derivative* of u, written $D^\alpha u = v$, if

$$\int_\Omega u D^\alpha \phi dx = (-1)^{|\alpha|} \int_\Omega v \phi dx \tag{2.1}$$

for every test function $\phi \in C_c^\infty(\Omega)$

Lemma 2.4. A *weak* α^{th} *partial derivative* of u, if it exists, is uniquely defined up to a set of measure zero.

Let Ω be open subset of $\mathbb{R}^n$, fix $1 \leq p \leq \infty$ and let k be a nonnegative integer.

Definition 2.2. The Sobolev Space is

$$W^{k,p} = \{f \in L^p(\Omega) : D^\alpha f \in L^p(\Omega) \text{ for all } \alpha \in \mathbb{N}^k s.t. |\alpha| \leq k\}. \tag{2.2}$$

Definition 2.3. If $f \in W^{k,p}$ its norm is defined as

$$\|f\|_{W^{k,p}} = (\sum_{|\alpha| \leq k} \|D^\alpha f\|_{L^p}) \tag{2.3}$$

Note that the Sobolev space $W^{k,p}$ equipped with this norm is a Banach Space.

Definition 2.4. $W_0^{k,p}(\Omega)$ denotes the closure of $C_c^\infty(\Omega)$ in $W^{k,p}(\Omega)$.

With $p = 2$ one sets $H^k(\Omega) := W^{k,2}(\Omega)$ and $H_0^k(\Omega) := W_0^{k,2}(\Omega)$. The letter H is used because it is an Hilbert space with scalar product

$$\langle u, v \rangle_{H^k} = \sum_{|\alpha| \leq k} \int_\Omega D^\alpha u D^\alpha v dx. \tag{2.4}$$

2.3 m-dissipative operators

Let X be a Banach space endowed with the norm $\|\cdot\|$.

Definition 2.5. A *linear unbounded operator* in X is a pair (D, A), where D is a linear subspace of X and A is a linear mapping $D \to X$. A is called *bounded* if there exists $c > 0$ such that

$$\|Au\| \leq c, \tag{2.5}$$

for all $u \in \{x \in D, \|x\| \leq 1\}$. Otherwise, A is not bounded.

Remark 2.5. Note that a linear unbounded operator can be either bounded or not bounded.

Definition 2.6. Let (D, A) be a linear operator in X, the *graph* $G(A)$ of A is defined by

$$G(A) = \{(u, f) \in X \times X; u \in D \quad and \quad f = Au\},$$

and the *range* $R(A)$ by

$$R(A) = A(D).$$

$G(A)$ is a linear subspace of $X \times X$ and $R(A)$ is a linear subspace of X.

Throughout this section a linear unbounded operator will be just called an operator where there is no risk of confusion. As usual, the pair (D, A) will be denoted by A with $D(A) = D$ meaning that the domain of A is D. Note that when defining an operator it is necessary to define its domain.

Definition 2.7. An operator A in X is *dissipative* if

$$\|u - \lambda Au\| \geq \|u\|,$$

for all $u \in D(A)$ and all $\lambda > 0$.

Definition 2.8. An operator is $m - dissipative$ if

(i) A is dissipative,

(ii) for all $\lambda > 0$ and all $f \in X$, there exists $u \in D(A)$ such that

$$u - \lambda Au = f. \tag{2.6}$$

Remark 2.6. If A is $m - dissipative$ in X it is clear that for all $f \in X$ and all $\lambda > 0$, there exists a unique solution u of the equation $u - \lambda Au = f$, moreover one has $\|u\| \leq \|f\|$.

Now some useful proposition regarding properties and characterization of m-dissipative operators are listed. The proofs are omitted and can be found in [6].

Proposition 2.7. Let A be a dissipative operator in X. The following are equivalent :

(i) A is m-dissipative in X;

(ii) there exists $\lambda_0 > 0$ such that for all $f \in X$ there exists a solution $u \in D(A)$ of $u - \lambda_0 Au = f$.

Proposition 2.8. If A is a m-dissipative operator, then $G(A)$ is closed in X.

Notation 2.9. From now on $\mathcal{L}(X,Y)$ will denote the space of linear, continuous mappings from X to Y and $\mathcal{L}(X)$ the space of linear, continuous mappings from X to X.

Corollary 2.10. *Let A be an m-dissipative operator. For every $u \in D(A)$, let $\|u\|_{D(A)} = \|u\| + \|Au\|$. Then $(D(A), \|\cdot\|_{D(A)})$ is a Banach space and $A \in \mathcal{L}(D(A), X)$.*

Remark 2.11. In what follows the Banach space $(D(A), \|\cdot\|_{D(A)})$ will be simply denoted with $D(A)$.

Now let X be a Hilbert Space with scalar product $\langle\cdot,\cdot\rangle$.

Proposition 2.12. *A is dissipative in X if and only if $\langle Au, u\rangle \leq 0$ for all $u \in D(A)$.*

Corollary 2.13. *If A is m-dissipative in X then $D(A)$ is dense in X.*

2.4 Contraction semigroups and Hille-Yosida Phillips Theorem

Let X be a Banach space and let A be an m-dissipative operator in X with dense domain. For $\lambda > 0$ set $A_\lambda = A(I - \lambda A)^{-1} f$ and $T_\lambda(t) = e^{tA_\lambda}$ for $t \geq 0$.

Theorem 2.14. *For all $x \in X$ the sequence $u_\lambda(t) = T_\lambda(t)x$ converges uniformly on bounded intervals of $[0,T]$ to a function $u \in C([0,\infty), X)$ as $\lambda \downarrow 0$. Set $T(t)x = u(t)$, for all $x \in X$ and $t \geq 0$. Then*

- *$T(t) \in \mathcal{L}(X)$ and $\|T(t)\| \leq 1$, $\forall t \geq 0$;*
- *$T(0) = I$;*
- *$T(t+s) = T(t)T(s), \forall s, t \geq 0$.*

Moreover, for all $x \in D(A)$, $u(t) = T(t)x$ is unique solution of the problem

$$\begin{cases} u \in C([0,\infty), D(A)) \cap C^1([0,\infty), X); \\ u'(t) = Au(t),\ \forall t \geq 0; \\ u(0) = x. \end{cases}$$

Finally

$$T(t)Ax = AT(t)x, \tag{2.7}$$

for all $x \in D(A)$ and $t \geq 0$.

Definition 2.9. A one parameter family $(T(t))_{t\geq 0} \subset \mathcal{L}(X)$ is a contraction semigroup in X if the following are satisfied :

(i) $\|T(t)\| \leq 1$ for all $t \geq 0$;

(ii) $T(0) = I$;

(iii) $T(t+s) = T(t)T(s)$ for all $s, t \geq 0$;

(iv) for all $x \in X$ the function $t \mapsto T(t)x$ belongs to $C([0,\infty), X)$.

Definition 2.10. The generator of $(T(t))_{t\geq 0}$ is the linear operator L defined by

$$D(L) = \{x \in X; \frac{T(t)x - x}{h} \text{ has a limit in X as h} \downarrow 0\}, \tag{2.8}$$

and

$$Lx = \lim_{h\to 0} \frac{T(t)x - x}{h} \tag{2.9}$$

for all $x \in D(L)$.

The following proposition justifies the introduction of m-dissipative operators in the previous section.

Proposition 2.15. Let $(T(t))_{t\geq 0}$ be a contraction semigroup in X and let L be its generator. Then L is m-dissipative and $D(L)$ is dense in X.

Proof. See [6] □

Theorem 2.16 (The Hille-Yosida-Phillips Theorem)**.** *A linear operator A is the generator of a contraction semigroup in X if and only if A is m-dissipative with dense domain.*

The following result shows the uniqueness of the semigroup generated by an m-dissipative operator with dense domain.

Proposition 2.17. Let A be an m-dissipative operator with dense domain and assume that A is the generator of a contraction semigroup $(S(t))_{t\geq 0}$. Then $(S(t))_{t\geq 0}$ is the semigroup corresponding to A given by theorem 2.14.

2.5 Inhomogeneous equations and abstract semilinear problems

Throughout this section X will be a Banach Space, A an m-dissipative operator with dense domain and $(T(t))_{t\geq 0}$ the contraction semigroup generated by A.

Let $T > 0$, given $x \in X$ and $f : [0,T] \mapsto X$ consider the following problem

$$\begin{cases} u \in C([0,T], D(A)) \cap C^1([0,T], X); \\ u'(t) = Au(t) + f(t),\ \forall t \in [0,T]; \\ u(0) = x. \end{cases}$$

Lemma 2.18 (Duhamel's formula)**.** Let $x \in D(A)$ and let $f \in C([0,T],X)$, consider a solution $u \in C([0,T],D(A)) \cap C^1([0,T],X)$ of the above problem. Then it satisfies :

$$u(t) = T(t)x + \int_0^t T(t-s)f(s)ds, \tag{2.10}$$

for all $t \in [0,T]$.

Corollary 2.19. *For all $x \in D(A)$ and $f \in C([0,T],X)$, the above problem has at most one solution.*

Remark 2.20. For all $x \in X$ and all $f \in C([0,T],X)$ the formula (Duhamel) defines a function $u \in C([0,T],X)$. The following proposition gives sufficient conditions for u to be the solution of the above problem.

Proposition 2.21. Let $x \in D(A)$ and $f \in C([0,T],X)$. Assume that at least one of the following conditions is satisfied :

- $f \in L^1((0,T),D(A))$;
- $f \in W^{1,1}((0,T),X)$; then u given by (Duhamel) is the solution of the above problem.

The following result is essential in the study of semilinear problems, not only for showing uniqueness but also for finding bounds on the solutions.

Lemma 2.22 (Gronwall's Lemma)**.** Let $T > 0$, $\lambda \in L^1(0,T)$, $\lambda \geq 0$ almost everywhere and $C_1, C_2 \geq 0$. Let $\phi \in L^1(0,T)$, $\phi \geq 0$ almost everywhere, be such that $\lambda\phi \in L^1(0,T)$ and

$$\phi(t) \leq C_1 + C_2 \int_0^t \lambda(s)\phi(s)ds, \tag{2.11}$$

for almost every $t \in (0,T)$. Then we have

$$\phi(t) \leq C_1 \exp(C_2 \int_0^t \lambda(s)ds), \tag{2.12}$$

for almost every $t \in (0,T)$.

Chapter 3

From biology to the model

Nowadays, mathematical analysis has become an effective tool to explore complex biological mechanisms. A mathematical model not only can detect mechanism that might be not evident to experiments, but can also foresee the evolution of very complex biological systems. For this reason, application of mathematics to medicine applications is a novel area of research of particular interest.

One of the most important biological processes is *chemotaxis*. This neologism is composed of two greek words *chemeia* = *chemical* and *taxis* = *arrangement*, so it is the mechanism by which an organism modifies its motion in response of a chemical stimulus. For instance, bacteria swim towards the highest concentration of food molecules (glucose) in order to survive. Not only it is important for single-cell and unicellular organisms, but also for multicellular ones. Indeed chemotaxis is important in early stages of development (e.g., movement of sperm towards the egg during fertilization) as well as in normal function and health (e.g. the movement of immune cells, such as leukocytes, towards chemoattractants released at the region of infection). Moreover, it has been proven that mechanisms that govern chemotaxis in animals can be subverted during cancer metastasis.

In the last forty years the movement of bacteria, cells or other microorganisms under the effect of chemotaxis has been widely studied and many PDE's models have been proposed. The basic unknowns for such models are the density of individuals of a population and the concentration of chemoattractant. Modelling chemotactic movement of mobile species can be done from two different perspectives: either from the macroscopic or from the microscopic perspective. Both approaches have been used over the years and the derivation of the macroscopic equations from the microscopic is still a topic of particular interest.

A very important and famous model is the Patlak-Keller-Segel one proposed in 1970 [28], a diffusion model which arises from the study of the slime mold Dictyostelium Discoideum. This model consists in a parabolic equation

governing the evolution of the cell density and a parabolic or elliptic one for the evolution of the chemoattractant. There are a lot of variations of the original Patlak-Keller-Segel model (KS), the following is a one-dimensional version where u describes the evolution of the cell density, ϕ is the chemoattractant density and f, g are regular function to be specified.

$$\begin{cases} u_t - \lambda^2 u_{xx} + (g(\phi, \phi_x)u)_x = 0 \\ \phi_t - D\phi_{xx} = f(u, \phi) \end{cases} \tag{3.1}$$

A common choice for the function f, in the chemoattractant equation, is

$$f(u, \phi) = au - b\phi \tag{3.2}$$

where a and b are positive constants, which are respectively production and degradation rates for the chemoattractant. The behaviour of this (KS) system is well known: in the one-dimensional case the solution is always global in time [31, 22], but in bigger dimensions the solution can be global in time or blow up depending on the size of the initial data [24, 5]. The main reasons of the success of the (KS) model is its simplicity, analytical tractability, and its capacity to describe key behaviours of populations driven by chemotaxis (a.g auto-aggregation). On the other hand one, of the problems of diffusion models is that they lead to a fast dissipation or an explosive behaviour, implying an infinite speed of propagation of cell which is highly unrealistic. Moreover, this model is not able to reproduce a typical cells behaviour called *run* and *tumble*. For all these reasons, starting from [35, 13], models based on hyperbolic equations have been considered since they are characterized by a finite speed of propagation. In particular, the derivation of diffusive models from appropriate rescaled hyperbolic equations has been considered in many works, see for instance [32, 7, 23], showing that, heuristically, hyperbolic models can be interpreted as a description of chemotaxis phenomena at a mesoscopic scale.

3.1 Wound healing process

Skin is our largest organ and plays a fundamental role in protecting us against the external environment. It is composed of two primary layers: the *epidermis* (surface layer) which provides waterproofing and serves as a barrier to infection, and the *dermis* (deeper layer), which provides the physical strength as well as flexibility to skin and supports the extensive vasculature, lymphatic system, and nerve bundles. The epidermis mainly consists of layers of keratinocytes separated from the dermis by the basement membrane. The dermis is composed of the predominating Extracellular Matrix (ECM) and other cells, mainly fibroblasts and macrophages. ECM is a three-dimensional network made mainly of fibrous proteins, such

as collagen, and serves many functions: it provides support and anchorage for cells, it regulates cell's dynamic behaviour (proliferation and apoptosis) and provides directional information directly through the fibres along which cells tend to align (this process is called contact guidance).

Wound healing process is divided in four main processes: blood clotting (hemostasis), inflammation, tissue growth (proliferation) and tissue remodelling (maturation). In each of these phases, studying the interaction between cells and ECM is crucial. In the hemostatis phase, platelets in the blood activates and begin to stick to the injured site while releasing chemical signals to promote clotting. Once the blood clot has formed, during the inflammation phase, white blood cells invade the wound region moving on the ECM in order to clear out damaged areas along with bacteria and other pathogens or debris. Even before the inflammatory process has ended, fibroblasts begin to enter the wound site (proliferation), they grow and form a new, provisional extracellular matrix (ECM) by excreting collagen and driven by chemotaxis they migrate on it and fill the wound. The last phase of wound healing (maturation) is when collagen is remodelled from type III to type I and the wound fully closes, see Fig. 3.1.

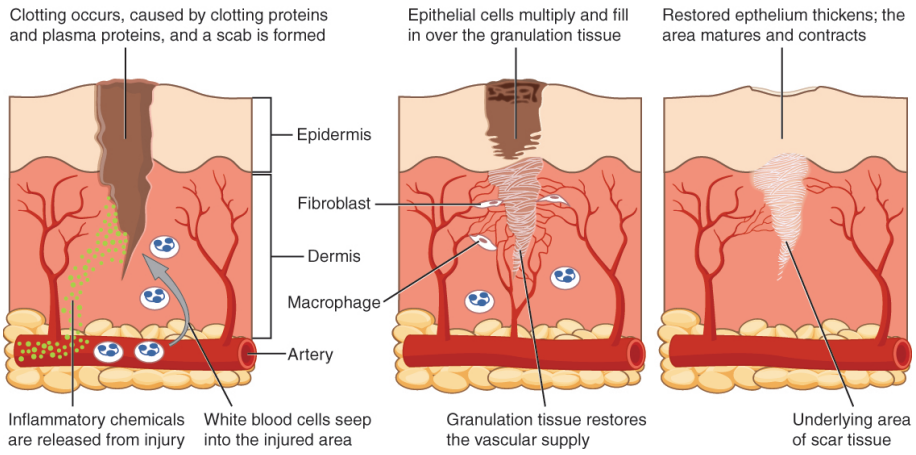

Figure 3.1: Tissue repair.

The type of ECM-cells interactions varies during the wound healing process and, although a lot of this interactions has been experimentally studied, several questions still need to be answered such as how the fibroblasts are stimulated to migrate into specific directions and how the reorganization of cells is induced.

Wound healing is a complex and fragile process, factors such as diabetes, venous or arterial disease and infection can contribute to non-healing chronic wounds. In particular, diabetic patients can develop wounds that are slow to heal or might never heal, since high blood glucose levels prevents nutrients and oxygen from energizing cells, increases inflammation, decrease collagen

deposition in the wound site and prevents immune system from functioning efficiently. Such condition has an high risk of developing an infections that can spread locally, to surrounding tissue and bone, or to further away areas of the body, eventually causing sepsis. Studies show that foot ulcers affect 15 percent of people with diabetes. These are painful sores can ultimately lead to foot amputation. The World Health Organisation (WHO) estimates that, annually, 6.5 million individuals suffer from chronic skin ulcers caused by prolonged pressure, venous stasis, or diabetes mellitus and over 300 000 deaths are attributable to fire-related burn injuries. In order to improve wound repair and minimize scar formation, artificial scaffolds can be inserted within the wound, since they provide a substitute ECM on which fibroblasts can attach and proliferate accelerating their reparation action, see Fig. 3.2. Both the structure and biochemical composition of the scaffold can affect cellular reorganization and activity. Not only material composition can affect cellular proliferation, but also pore sizing, pore orientation, fibre structure and fibre diameter of scaffolds [30].

In particular, considering the case of extensive burns or skin loss, skin grafting (i.e skin transplant) has always been a standard procedure. However, in case of very extensive trauma, autogenic transplants cannot be done considering the limited amount of donor material and allogenic transplants are often subject to rejection and pathogen transmission. Therefore, tissue-engineered solutions regarding the design and fabrication of appropriate scaffolds are urgently required.

A wide variety of artificial scaffolds made of both natural or synthetic polymers have been explored yet [33], but how to build proper material for such scaffolds is still subject for research. Biological polymers, such as collagen, keratin or gelatine could be considered as the first bio-degradable biomaterials used for this type of application, due to its biocompatibility, biodegradability and low cost. Thereafter, synthetic polymers were taken into consideration since their properties (e.g. porosity, degradation time etc) can be tailored for the specific applications.

Recent studies [26, 10] show how ECM-like scaffolds can be produced, with a high degree of complexity, using three-dimensional printing (3DP) technologies. The advantages of fabricating scaffolds using 3DP are numerous, including the ability to create complex geometries, porosities, and incorporate growth factors. For these reasons, three-dimensional printing has significant potential as a fabrication method in creating scaffolds in the field of regenerative medicine and tissue engineering.

3.2 Mathematical models of chemotaxis

Wound healing, angiogenesis and tumour invasion are all examples of cell invasion, lead by chemotaxis. As previously said, mathematical modelling

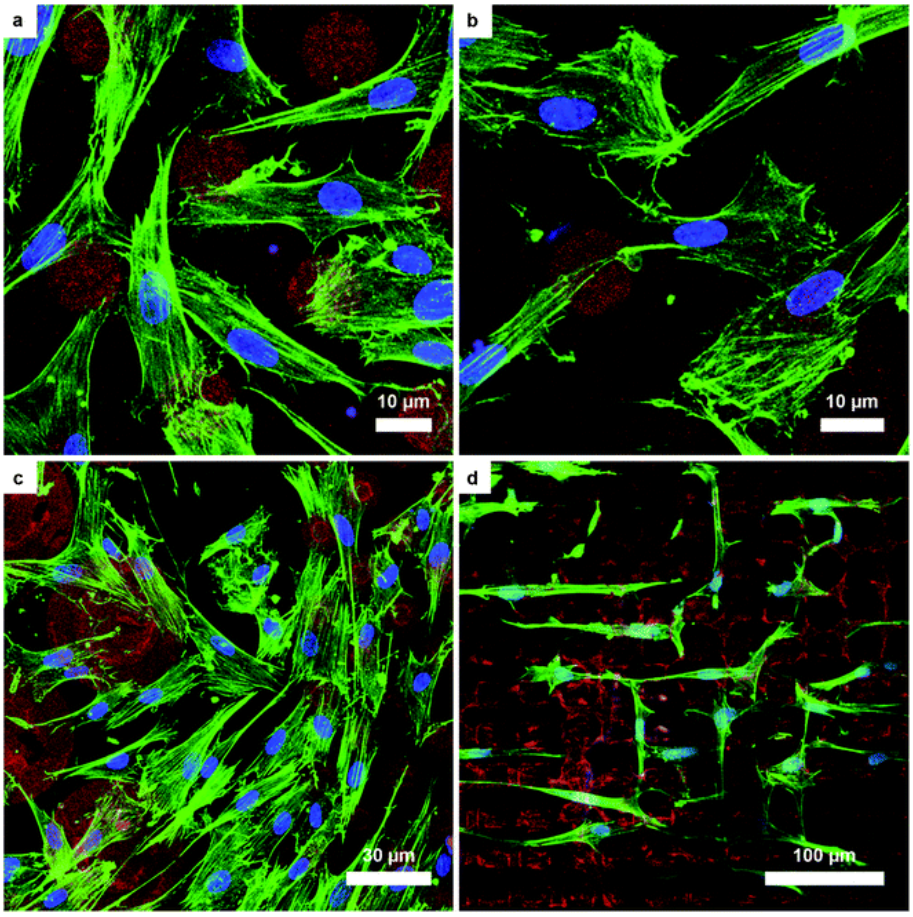

Figure 3.2: Confocal fluorescence images of human dermal fibroblasts (HDFb) cultured on scaffold [34]. The actin cytoskeleton of the HDFb was stained green, the cell nucleus was stained blue and the collagen was stained red.

is a powerful tool to describe such complex mechanisms and several models have been proposed to date. In particular, mathematical models describing wound healing process have thus far been directed towards the study of the proliferation and repair stage. For example, in [30], the interaction between ECM and fibroblasts is modelled using a multi-scale approach, in which extracellular materials are modelled as continua, while fibroblasts are considered as discrete units. These models assume a few well-known ECM-cells interactions properties. First of all, fibroblast movements are directed by the orientation of the extracellular matrix, a phenomenon known as *contact guidance*. Such mechanism was discovered in 1912, but it is with the recent development of tissue engineering that researchers focused increasing attention on it, seeing the potential of contact guidance in influencing the

reorganization of cells. Second, the extracellular matrix affects the speed of the fibroblasts. Third, the composition of the ECM alters the production of different proteins by the fibroblasts. Fourth, the ECM in the wound region contains a lot of different growth factors which influence fibroblast behaviour. Finally, it is assumed that fibroblasts produce fibres of ECM align with their direction of movement. Thus, not only do the fibroblasts affect the orientation of the matrix, but the matrix orientation also influences the movement of the fibroblasts. The starting point of the research presented in [30] is the so called orientation model, modelling the matrix collagen orientation, from which they derive a model for wound repair. The model is summarized as follows :

$$\begin{cases} \dot{f}^i(x,t) = s(||c(f^i(t),t)||, ||b(f^i(t),t)||)\frac{v^i(t)}{||v^i(t)||} \\ v^i(t) = (1-\rho)\frac{u^i(t)}{||u^i(t)||} + \rho\frac{\dot{f}^i(t-\tau)}{||\dot{f}^i(t-\tau)||} \\ u^i(t) = (1-\alpha)c(f^i(t),t) + \alpha b(f^i(t),t) \\ f(x,t) = \sum_{i=0}^{N} w^i(f^i(t)-x)\frac{\dot{f}^i(t-\tau)}{||\dot{f}^i(t-\tau)||} \end{cases} \tag{3.3}$$

Cell paths are denoted by $f^i(x,t)$, ρ is a polarization coefficient, τ is a time lag, $w^i(x,t)$ are weight functions and c, b represents the collagen and the fibrin, respectively. The last equation represents the total amount of extracellular matrix produced by N fibroblast, while the others govern the cell motion. In the last part of their work the model extended further in order to include a diffusible chemoattractant, mainly produced by leucocytes. In particular, they show that there is a trade-off between wound integrity and the degree of scarring. The former is found to be optimized under conditions of a large chemoattractant diffusion coefficient, while the latter can be minimized when repair takes place in the presence of a competitive inhibitor to chemoattractants.

3.2.1 Cattaneo Hillen Model

As previously observed, the Patlak-Keller-Segel model, and all its variations, are systems of parabolic equations. Such models are not sufficiently precise to describe the movement of cells for short times, since they lead to a fast dissipation. For this reason, hyperbolic models have been widely used to describe different biological phenomena such as population dynamics, forest fire models and combustion wavefronts. Such models imply a finite speed of propagation and allow a description of biological phenomena on intermediate spatial temporal scale.

A fundamental model for chemosensitive movement was introduced by T. Hillen and, together with Y. Dolak, [11] he showed that the model was coherent with experimental observation on *Dicostyostelium discoideum* and *E.coli*.. They derived a model based on Cattaneos law, a modification of

Fouriers law of heat conduction that is used to describe heat propagation with finite speed. Let $\theta(t,x) \in \mathbb{R}$ denote the temperature of a homogenous medium $\Omega \subset \mathbb{R}^n$ and let $q(t,x)$ denote the heat flux, the Cattaneo law is

$$\tau q_t + q = -D\nabla\theta \tag{3.4}$$

with $\tau > 0$ a constant that describes the adaptation time of the heat flux q to the negative gradient of the temperature θ and $D > 0$ the diffusion constant. If the Cattaneo law is considered together with an equation for conservation of energy the so called "*Cattaneo system*" is obtained. Assuming $u(t,x) \in \mathbb{R}$ to be a particle density and $v(t,x) \in \mathbb{R}^n$ the particle flux, the Cattaneo model reads as

$$\begin{cases} u_t + \nabla v = 0 \\ \tau v_t + v = -D\nabla u \end{cases} \tag{3.5}$$

The main property of Cattaneo models is that the undesired feature of infinite fast propagation is omitted. In [11] a Cattaneo system has been derived from a moment closure approach of transport equations. In order to do this, Hillen considered a typical cells behaviour called *run and tumble*. They move towards a certain direction with almost constant speed (run) then they suddenly stop and choose a new direction (tumble) and restart the process. It is assumed that individuals choose any direction with bounded velocity. This type of movement can be modelled by a stochastic process called "*velocity jump process*". Since the tumbling intervals are short compared to the mean run times, the tumbling is assumed to be instantaneous. The model describing such process reads as the following linear transport equation

$$\partial_t u(x,t,v) + v\nabla u(x,t,v) = -\mu u(x,t,v) + \mu \int T(v,v')u(x,t,v')dv' \tag{3.6}$$

where $u(x,t,v)$ denotes the population density at spatial position $x \in \mathbb{R}^n$ at time $t \geq 0$ and with velocity v, μ indicates the *turning rate* or *turning frequency*, hence $\tau = \frac{1}{\mu}$ is the mean run time and $T(v,v')$ is the probability kernel for the new velocity v given the previous velocity was v'. The set $V \in \mathbb{R}^n$ is the set of possible velocities. In order to ensure particle conservation it has to satisfy

$$\int T(v,v')dv = 1. \tag{3.7}$$

Moreover, in order to derive Cattaneo System, it is assumed that the cells have no preferred turn angle, i.e $T(v,v') = |V|^{-1}$.

Although the most meaningful dimensions are $n = 1,2,3$, the theory describing such cell behaviour works for all $n \in \mathbb{N}$. Observe that *in vivo* motion corresponds $n = 3$ and planar motion on a substrate to $n = 2$. A common technique to understand the dynamic properties of reaction-transport equation, called *moment method*, consists in multiplying the previous linear

transport equation by powers of v and then integrating, an infinite sequence of equations for the moments of u is derived. Such sequence has a property, in the equation for the n-th moment the $(n+1)$-st moment appears, so an approximation of the $(n+1)$-moment is needed. One of the most important theories to close the moment equation is due to Hillen and is based on a minimization principle.

In this scenario the focus will be only in the first two equations. In order to do so, let introduce the velocity moments of u as

$$\begin{aligned} m_0(t,x) &:= \int_V u(t,x,v)dv \\ m_i(t,x) &:= \int_V v_i u(t,x,v)dv,\ i = 1,....,n \\ m_{i,j}(t,x) &:= \int_V v_i v_j u(t,x,v)dv\ i,j = 1,...n \end{aligned}$$

After multiplying the previous transport equation with 1 or v_i for $i = 1,....n$ and integrating along V the following system, for the first two moments is derived :

$$\begin{cases} m_{0,t} + \sum_{i=1}^n \partial_i m_i = 0 \\ m_{i,t} + \sum_{j=1}^n \partial_j m_{i,j} = -\mu m_i \end{cases} \tag{3.8}$$

In order to close the system the term that needs to be approximated is $m_{i,j}$. As thoroughly illustrated in Hillen [21] the above moment system can be closed by minimizing the $L^2(V) - norm$:

$$H(u) := \frac{1}{2}\int_\Omega u^2 dx \tag{3.9}$$

with constraints

$$\int u(t,x,v)dv = m_0(t,x) \tag{3.10}$$

and

$$\int v_i u(t,x,v)dv = m_i(t,x)\ i = 1,...,n. \tag{3.11}$$

The minimizer can be explicitly calculated as

$$u_{min}(t,x,v) = \frac{1}{|V|}(m_0(t,x) + \frac{n}{s^2}\sum v_i m_i(t,x)). \tag{3.12}$$

It is assumed that the second moment $m_{i,j}(u)$ of u is well approximated by the second moment of the minimizer u_{min}, i.e $m_{i,j}(u) \approx m_{i,j}(u_m in)$. Then the closed system reads

$$\begin{cases} M_{0,t} + \sum_{i=1}^n \partial_i M_i = 0 \\ M_{i,t} + \frac{s^2}{n}\partial_i m_{i,j} = -\mu M_i\ i = 1,...,n \end{cases} \tag{3.13}$$

Here the capital letters are used to distinguish moment of u from the solution (M_0, M_i) of this Cattaneo system.

There are two main advantages of choosing this type of model. First of all, this system is independent from $T(v, v')$ which is really difficult to measure for all possible cells velocities. Moreover, instead of the diffusive behaviour of a parabolic model, a good description of the first phase of the phenomenon is obtained, not only the asymptotic one. Now the corresponding Cattaneo model for chemosensitive movement can be derived in two different ways. Heuristically, the flux can be considered as

$$q = -D_u \nabla u + V(u, S)\nabla S \tag{3.14}$$

where $V(u, S)$ is a cross-diffusion coefficient chosen, for example, as $V(u, S) = u\beta(u)\chi(S)$, with $S(tx)$ the signal concentration, $\chi(S) \geq 0$ the *chemotatic sensitivity* and $\beta(u)$ the density control. Then the corresponding Cattaneo model reads as

$$\begin{cases} u_t + \nabla q = 0 \\ \tau q_t + q = -D_u \nabla u + V(u, S)\nabla S. \end{cases} \tag{3.15}$$

As shown by Hillen in [21] this model can also be derived from an associated transport model, where turning rate and $T(v, v')$ are chosen appropriately, using the moment closure procedure as down above.

It is important to highlight that in one space dimension, the Cattaneo system is equivalent to Goldstein-Kac model for a correlated random walk [20, 18]. In [21, 23] a one-dimensional version of Cattaneo-Hillen model is analysed, which reads as the following system

$$\begin{cases} \partial_t u^+ + \lambda \partial_x u^+ = -\mu^+(\phi, \partial_x \phi)u^+ + \mu^-(\phi, \partial_x \phi)u^- \\ \partial_t u^- - \lambda \partial_x u^- = \mu^+(\phi, \partial_x \phi)u^+ - \mu^-(\phi, \partial_x \phi)u^- \\ \partial_t \phi - D\partial_{xx}\phi = f(u^+ + u^-, \phi) \end{cases} \tag{3.16}$$

where $u^\pm$ denotes the density of the right/left moving part of the total population u, ϕ is the chemoattractant and f is linear function. Parameters λ, D are assumed to be strictly positive, they represent, respectively, the characteristic speed of propagation of $u^\pm$ and the diffusion coefficient for the chemoattractant. The terms $\mu^\pm$ are the turning rates and they control the probability of transition from u^+ to u^- and vice versa, i.e. the change of direction in the movement of a single individual. Experimental observations show that cells, in general, change their turning rate in response to external stimuli but they do not change their turn angle distribution. For this reason the turning rate should depend on the external signal ϕ and on its gradient $\partial_x \phi$.

The behaviour of such system is studied in [15] under very general assumptions on the coefficients. A general result of global stability of some constant states, for both the Cauchy problem on the whole real line and the Neumann problem on a bounded interval for small initial data, is proven using linearised operators and the accurate analysis of their non-linear perturbations.

3.2.2 Preziosi-Chauvière Cell Migration Model

As previously discussed, cell migration is an essential feature for both normal and pathological biological processes. Indeed, migration of cells plays a fundamental role in immune response and tissue homeostasis but also is the main process of metastasis dissemination and tumour invasion. The characteristics of migration can vary considerably depending on the properties of the cells and the external environment. For instance cell movement can be regulated by external factors that can be either diffusive chemicals (such as chemoattractant) or non-diffusive chemicals (like ligands bound to ECM). From recent experimental studies various cell migratory behaviours in the ECM have been identified. In particular cells can migrate interacting briefly with one another (*individual migration*) or they can form clusters (*collective migration*). Additionally, individual migration in ECM can be further split into *amoeboid* or *mesenchymal* types. In the mesenchymal type of migration, cells generate space to move by secreting ECM degrading enzymes. In the amoeboid case, cells migrate using the ECM as a scaffold, establishing brief contacts with fibres and frequently changing direction. The cell behaviour taken into consideration through the following thesis will be the amoeboid migration type.

In [9] A. Chauvière and L. Preziosi proposed an amoeboid cell migration model in ECM, under the effect of a chemical signal, that can be summarized as the following system

$$\begin{cases} \frac{\partial u}{\partial t}(x,t,v) + v\nabla u(x,t,v) = J_m^B(x,t,v) + J_c^B(x,t,v) \\ \frac{\partial \phi}{\partial t}(x,t) = K\Delta\phi + f(u,\phi) \end{cases} \tag{3.17}$$

where u is the density of the cell population, v is the velocity and ϕ is the chemical signal. The functions $J_m^B = J_m^B(x,t,v)$ and $J_c^B = J_c^B(x,t,v)$ represent, respectively, the interaction between ECM and chemical signal and the interaction between cells and chemical signal. Moreover, they have shown how macroscopic continuum models can be derived from mesoscopic transport equation. The hyperbolic-parabolic system that will be analysed throughout this thesis is a particular one-dimensional case of the previous model. For this reason here a particular attention is devoted towards A. Chauvière and L. Preziosi model. The relationship between the model taken into consideration in this thesis and the Preziosi-Chauvière one will be discussed in the next section.

In their work Preziosi-Chauvière considered a cell population moving in a domain $D \in \mathbb{R}^n$ described by the distribution function $u = u(t, x, v)$, depending on time $t > 0$, space position $x \in D$ and velocity v. Each of the cell moves with its own velocity $v \in V \subset \mathbb{R}^n$. It is assumed that the space V is radially symmetric and can be written as $V = |V|xS^{n-1}$, where $|V|$ denotes the range of possible speeds and S^{d-1} is the unit sphere in $\mathbb{R}^n$. The fibres of the extracellular matrix are described by the distribution function m. Since here the amoeboid cell motion is considered, the ECM distribution function is assumed to be time independent. Moreover the ECM fibres are symmetrical along their axis, meaning that both fibre directions are identical. These observation lead to write $m = m(x, n)$ where $n \in \mathbb{R}^{n-1}_+$ is a unit vector, representing the fibre orientation, defined over the half unit sphere S^{n-1}_+. Clearly such distribution can be extended to S^{n-1} as

$$m^e(x, n) = \begin{cases} m(x, n) \text{ for } n \in S^{n-1}_+ \\ m(x, -n) \text{ for } n \in S^{n-1}_- \end{cases} \tag{3.18}$$

The modelling framework is formulated as the following transport equation, deriving from velocity-jump processes, that reads as

$$\frac{\partial u}{\partial t}(t, x, v) + v\nabla u(x, t, v) = \mathcal{M}(x, t, v) \tag{3.19}$$

where $\mathcal{M}(x, t, v)$ is an integral operator describing peculiar cell motion with velocity-jump processes and ∇ denotes the spatial gradient. This transport equation approach uses a microscopic description of the cell movement, but it provides an output at the level of a cell population. For this reason such approach is commonly referred as *mesoscopic description*.

As previously mentioned the operator $\mathcal{M}$ models the characteristic properties of cell migration. Here some cases are taken into account.

Random Migration This case is the simplest model about cell migration and well describes the *run* and *tumble* motion, in which cells moves towards a direction and suddenly, interrupted at discrete times, they have an instantaneous random reorientation. In this kind of model, the source term of the above equation becomes

$$M(x, t, v) = -\mu u(x, t, v) + \mu \int_V T(v, v')u(x, t, v')dv', \tag{3.20}$$

where first term of the right-hand side describes how cells turn away from velocity v with a frequency μ that may depend on environmental factors. The second term calculates the rate at which cells reorient into velocity v given previous velocity v'. The function $T(v, v')$ defines a probability distribution for a cell with previous velocity v' to choose the new velocity v and so it satisfies

$$\int T(v, v')dv = 1. \tag{3.21}$$

Moreover, cell number conservation is needed, which yields

$$\int_V \mathcal{M}(x,t,v)dv = 0 \tag{3.22}$$

In [9] some examples of T choices are shown. For example T can be an uniform reorientation probability, this means that the re-orientation has no memory of the past.

It is important to highlight that this model was the starting point of the Hillen model derivation as seen in the previous paragraph.

Contact guidance Here a model of the cell movement on a given fibre network is considered. Contact guidance is a common biological process where the fibres of the matrix give a selection of preferred directions on which cells can move. In this case the general expression of the migration operator is

$$\mathcal{M}(x,t,v) = -\mathcal{L}(x,t,v) + \mathcal{G}(x,t,v) \tag{3.23}$$

where the term $\mathcal{L}$ is called *loss* term, that is the rate the rate at which cells turn away from velocity v , and the term $\mathcal{G}$ is called *gain* term, i.e the rate at which cells reorient into velocity v. Also in this case the total number of cells conservation is required. In order to describe such process, Preziosi and Chauvière assume that the realignment along the fibres of ECM does not appear at a turning frequency, but it is caused by interactions between cells and fibres with constant rate η_m. This means that a reasonable choice for the loss and gain terms of the migration operator is

$$\mathcal{L}(x,t,v) = u(x,t,v)\int_{S_+^{n-1}} \eta_m m(x,n')dn'$$

$$\mathcal{G}(x,t,v) = \int_{VxS_+^{n-1}} \eta_m \psi_m(v',v,n')u(x,t,v')m(x,n')dv'dn'$$

where the function $\psi_m(v',v,n')$ represent the probability, for a cell, to choose a new velocity v given the velocity v' when interacting with a fibre oriented toward n'. Clearly, since it is a probability distribution, it has to satisfy

$$\int_V \psi_m(v',v,n')dv = 1. \tag{3.24}$$

Assuming that η_m is constant and that the alignment process along a fibre is independent from the prior velocity v', the migration operator becomes

$$\mathcal{M}(x,t,v) = \eta_m M(x)\left(u(t,x)\psi(v)\frac{m^e(x,v)}{2M(x)} - u(x,t,v)\right) \tag{3.25}$$

where

$$M(x) = \int_{S_+^{n-1}} m(x,n)dn = \frac{1}{2}\int_{S^{n-1}} m^e(x,n)dn \tag{3.26}$$

is the fibre density of the matrix and

$$u(x,t) = \int_V u(x,t,v)dv \tag{3.27}$$

is the cell density.

Interaction between cells Following the previous approach a similar consideration can be done also for the cell-cell interaction. The interaction between cells is a complex phenomena, for this reasons is difficult to fully understand their behaviour. Here the focus is on the dynamical aspects of the cells interaction and only the orientational effect resulting from two moving cells is considered. Moreover it is assumed that realignment processes are dominated by fibre guidance. Under such assumptions the loss and gain terms become

$$\mathcal{L}(x,t,v) = u(x,t,v)\int_V \eta_c u(t,x,v')dv'$$
$$\mathcal{G}(x,t,v) = \int_{VxV} \eta_c \psi_c(v',v'_*,v)u(x,t,v')u(x,t,v'_*)dv'dv'_*$$

where the function $psi_c(v',v'_*,v)$ defines the probability, for a moving cell with given velocity v', to choose the new velocity v when interacting with a field cell, that is a surrounding cell with velocity v'_*. Since it is a probability distribution ψ_c satisfies

$$\int_V \psi_c(v',v'_*,v)dv = 1. \tag{3.28}$$

For coherence with the previous paragraph, it is assumed that the interaction between cells occur with rate c that is constant and the re-orientation caused by the collision has no memory of the past. Choosing ψ_c as an uniform transition probability it follows

$$\mathcal{M}(x,t,v) = \eta_c u(x,t)\left(u(x,t)\frac{\psi(v)}{\mathcal{V}_n} - u(x,t,v)\right) \tag{3.29}$$

where $\mathcal{V}_n$ represents the surface of the unit sphere in $\mathbb{R}^n$.

Influence of Environmental Factors In this paragraph a mathematical description of the cell response to environmental signals is briefly discussed. These signals can be of various natures, in particular, there are diffusible chemicals secreted into the environment that will trigger a chemotactic movement of the cell in response. Here chemotaxis is described using transport equations, introduced as a bias of the main movement, which is usually assumed to be a random motion. In order to do so, the starting point is the

description of cell migration in the ECM as a combination of random motion, contact guidance, and cellcell interaction as discussed in the previous paragraphs. Therefore, the idea is to integrate the influence of signalling as a bias of the main motion described by the operator

$$\mathcal{M}(x,t,v) = J_m(x,t,v) + J_c(x,t,v) \tag{3.30}$$

where J_m and J_c are function defined as in the previous paragraphs. This means that the source terms are extended respectively as

$$J_m(x,t,v) = \eta_m M(x)\left(u(x,t)\psi_v \frac{m^e(x,v)}{2M(x)}\left[1+\mathcal{B}(x,t,v)\right] - u(x,t,v)\right)$$
$$J_c(x,t,v) = \eta_c u(x,t)\left(u(x,t)\frac{\psi(v)}{\mathcal{V}_n}\left[1+\mathcal{B}(x,t,v)\right] - u(x,t,v)\right)$$

where the bias $\mathcal{B}$ accounts for an external stimulus that modifies the rate at which a cell reorients. The simplest expression of $\mathcal{B}$, proposed by Chauvière, is the following gradient-based bias

$$\mathcal{B}(x,t,v) = \pm\Gamma\frac{\nabla S(t,x)v}{\beta_s + S(x,t)} \tag{3.31}$$

where the Γ reflects the cell sensitivity to the signal, the $\pm$ sign represents the repellent (-) or attractive (+) effect in the direction of the gradient ∇S, the signal molecule density is S and $\beta_S > 0$ is a parameter introduced to avoid singularity when $S = 0$. Other, more complicated choices for $\mathcal{B}$ can be found in [9].

3.3 A hyperbolic-parabolic model on a network

In the previous section the Preziosi-Chauvière model was presented and the adaptation of such model to different biological cases were discussed. As already mentioned, the biological phenomena considered in this thesis is the process of dermal wound healing involving fibroblasts, the cells responsible for the reparation of dermal tissue. During the epidermic healing process, the fibroblasts create a new extracellular matrix, mainly made of collagen, and they move along it to fill the wound, driven by chemotaxis produced by themselves. At the end of this process, a new tissue, called scar tissue is formed. In order to accelerate this process, a common tissue engineering technique consists in inserting artificial scaffolds, made of a network of polymeric threads, within the wound. Indeed, in vitro experiments show that inserting such artificial scaffolds in damaged tissue accelerates the fibroblasts repairing action, since they provide a support to walk and they don't have to produce ECM fibres. Moreover if the scaffolds are enriched with growth factors, the process can be accelerated further. A classical approach

used to describe cell movements, under the effect of chemotaxis, is by considering the Patlak-Keller-Segel model (PKS). However, there are biological processes that cannot be well described by this kind of model. Indeed, the diffusive behaviour of (PKS) leads to a fast dissipation or an explosive behaviour, so it is not possible to observe intermediate organized structures for short times. For this reason the model considered in thesis is a hyperbolic-parabolic model. The parabolic equation for the population density u of the (PKS) model is now replaced with a hyperbolic system. On the contrary the equation governing the chemoattractant is parabolic, given its diffusive behaviour. Then the system, in one-dimension, reads as :

$$\begin{cases} u_t + v_x = 0 \\ v_t + \lambda^2 u_x = \phi_x u - v \\ \phi_t = D\phi_{xx} + au - b\phi \end{cases} \tag{3.32}$$

where u stands for the concentration of cells, v their flux, ϕ is the concentration of chemoattractant produced by cells themselves and $\phi_x u$ is a non-linear chemotactic term. The parameters are $D > 0$ that is the diffusion coefficient of chemoattractant, $a \geq 0$ and $b \geq 0$, which are, respectively, its production and degradation rate and finally $\lambda > 0$ represents the modulus of the constant velocity of each cell, that can move towards the right or left along the axis. A novel approach, recently introduced in [4], is to consider this one-dimensional model on a network. More precisely, a system like the above, is considered on each arc of the network, this means that a set of solutions (u, v, ϕ) is considered for each arc. Functions on different arcs will be coupled using suitable transmission conditions on each node of the network.

Now before setting the model on a network, the relationship between such model and those proposed in the last section is discussed.

Relationship with Preziosi Chauvière model

Referring to Preziosi Chauvière model

$$\frac{\partial u}{\partial t}(x,t,v) + v\nabla u(x,t,v) = J_m^B(x,t,v) + J_c^B(x,t,v) \tag{3.33}$$

now $J_c = 0$ since here, only the case of cell-fibre interaction in the presence of chemoattractant, is considered. An adaptation of such model on a oriented interval $I = [a,b]$ is here discussed. Let $u^{\pm}$ be the functions representing the densities of cells on the arc I, which move respectively from left to right and viceversa. Let $\pm\lambda$ the corresponding velocities, which are assumed to be constant, meaning that $+\lambda$ corresponds to positive orientation and $-\lambda$ to negative orientation. Now considering a Preziosi-Chauvière law for each of the cell density $u^{\pm}$, this leads to the following system:

$$\begin{cases} u_t^+ + \lambda u_x^+ = \mathcal{M}^+ \\ u_t^- - \lambda u_x^- = \mathcal{M}^- \end{cases} \tag{3.34}$$

where the general expression for the source term is

$$\mathcal{M}^{\pm}(x,t,v) = -L^{\pm}(x,t,v) + G^{\pm}(x,t,v). \tag{3.35}$$

with $L^{\pm}$ the rate of change of verse and velocity caused by the interaction with ECM and the presence of chemoattractant, while $G^{\pm}$ is the rate of random re-orienting. Since the cells move on the arc with constant velocities $\pm\lambda$, those function do not depend on the variable v, meaning that

$$L^{\pm}(x,t,v) = L^{\pm}(x,t) \tag{3.36}$$

and

$$G^{\pm}(x,t,v) = G^{\pm}(x,t,). \tag{3.37}$$

With refer to Preziosi Chauvière integral operator $\mathcal{M} = J_m$ let $\psi_{-,+}$ be the function that represent the probability to pass from velocity $-\lambda$ to $+\lambda$. Since it is a probability distribution, it is has to satisfy the following conditions

$$\begin{cases} \psi_{-,+} + \psi_{-,-} = 1 \\ \psi_{+,+} + \psi_{+,-} = 1. \end{cases} \tag{3.38}$$

Is not restrictive to assume that the probability to pass from velocity $-\lambda$ to $+\lambda$ is the same probability to stand in $-\lambda$, the same thing starting from the velocity $+\lambda$. This means that :

$$\psi_{-,+} + \psi_{-,-} = 1 \tag{3.39}$$

and

$$\psi_{+,+} + \psi_{+,-} = 1. \tag{3.40}$$

Following this choice, for each function of cell density, the source term have the form :

$$\mathcal{M}^{\pm}(x,t) = \eta m(x) \left[\frac{1}{2}(u^{+} + u^{-})(1 + \mathcal{B}^{\pm}(x,t)) - u^{\pm} \right] \tag{3.41}$$

where the function $\mathcal{B}^{\pm}(x,t)$ represent the external stimulus that modifies the rate at which a cell reorients, meaning that it is a function of the chemoattractant ϕ and the cell velocities $\pm\lambda$. It is important to highlight that the source terms $\mathcal{M}^{\pm}(x,t)$ do not depend on the velocity, since those are supposed to be constant. It is also assumed the total mass conservation, more precisely :

$$\begin{aligned} &\mathcal{M}^{+}(x,t) + \mathcal{M}^{-}(x,t) = \\ &= -L^{+}(x,t) + G^{+}(x,t) - L^{-}(x,t) + G^{-}(x,t) = 0. \end{aligned}$$

The terms $B^{\pm}(x,t)$ are chosen as $\mathcal{B}^{\pm}(x,t) = \frac{\phi_x}{\pm\lambda}$. This choice has a physical meaning. Indeed the cell reorientation is caused by the variation of chemoattractant, i.e its gradient. Moreover, the bigger is the velocity of a cell, less

effect can have the chemoattractant, released by itself, on the other cells, since it is moving away. Now, with this choice for $\mathcal{B}$ and setting $\eta m(x) = 1$ it follows

$$\begin{aligned} M^+ &= \left[\frac{1}{2}(u^+ + u^-)(1 + \frac{\phi_x}{\lambda}) - u^+\right] \\ &= \left[(\frac{1}{2}u^+ + \frac{1}{2}u^-)(1 + \frac{\phi_x}{\lambda}) - u^+\right] \\ &= \left[\frac{1}{2}u^+ + \frac{\phi_x}{2\lambda}u^+ + \frac{1}{2}u^- + \frac{\phi_x}{2\lambda}u^- - u^+\right] \\ &= \frac{1}{2}\left[(\frac{\phi_x}{\lambda} - 1)u^+ + (\frac{\phi_x}{\lambda} + 1)u^-\right] \\ &= \frac{1}{2\lambda}\left[(\phi_x - \lambda)u^+ + (\phi_x + \lambda)u^-\right], \end{aligned}$$

and,

$$\begin{aligned} M^- &= \left[\frac{1}{2}(u^+ + u^-)(1 - \frac{\phi_x}{\lambda}) - u^-\right] \\ &= \left[(\frac{1}{2}u^+ + \frac{1}{2}u^-)(1 - \frac{\phi_x}{\lambda}) - u^-\right] \\ &= \left[\frac{1}{2}u^+ - \frac{\phi_x}{2\lambda}u^+ + \frac{1}{2}u^- - \frac{\phi_x}{2\lambda}u^- - u^-\right] \\ &= \frac{1}{2}\left[(-\frac{\phi_x}{\lambda} + 1)u^+ - (\frac{\phi_x}{\lambda} + 1)u^-\right] \\ &= -\frac{1}{2\lambda}\left[(\phi_x - \lambda)u^+ + (\phi_x + \lambda)u^-\right]. \end{aligned}$$

The term ϕ, which is the concentration of chemoattractant produced by the cells themselves, satisfies the parabolic diffusion equation

$$\phi_t = D\phi_{xx} + f(u^+, u^-, \phi), \tag{3.42}$$

where D is a positive constant and f a function which influences the diffusion, depending on the cells density and the chemoattractant. The function is chosen as

$$f(u^+, u^-, \phi) = a(u^+ + u^-) - b\phi \tag{3.43}$$

where a and b are positive constants, which are respectively production and degradation rates for the chemoattractant. All this considerations yield at the following hyperbolic-parabolic system

$$\begin{cases} u_t^+ + \lambda u_x^+ = \frac{1}{2\lambda}\left((\phi_x - \lambda)u^+ + (\phi_x + \lambda)u^-\right), \\ u_t^- - \lambda u_x^- = -\frac{1}{2\lambda}\left((\phi_x - \lambda)u^+ + (\phi_x + \lambda)u^-\right), \\ \phi_t - D\phi_{xx} = a(u^+ - u^-) - b\phi. \end{cases} \tag{3.44}$$

Now recalling that the one-dimension Catteon-Hillen model is

$$\begin{cases} \partial_t u^+ + \lambda \partial_x u^+ = -\mu^+(\phi, \partial_x \phi)u^+ + \mu^-(\phi, \partial_x \phi)u^- \\ \partial_t u^- - \lambda \partial_x u^- = \mu^+(\phi, \partial_x \phi)u^+ - \mu^-(\phi, \partial_x \phi)u^- \\ \partial_t \phi - D\partial_{xx}\phi = a(u^+ + u^-) - b\phi \end{cases}, \tag{3.45}$$

the system obtained above is exactly an one-dimension Cattaneo-Hillen model with turning rates

$$\mu^+ = \frac{1}{2}(1 - \frac{\phi_x}{\lambda}), \tag{3.46}$$

and

$$\mu^- = \frac{1}{2}(1 + \frac{\phi_x}{\lambda}). \tag{3.47}$$

Now, the density of cells is chosen as

$$u := u^+ + u^- \tag{3.48}$$

and their average flux, that is the net rate at which the cells cross a unit square perpendicular to the x-axis, as

$$v := \lambda(u^+ - u^-). \tag{3.49}$$

With this in mind, the sum of the first two equations of the Cattaneo-Hillen model lead to

$$\partial_t(u^+ + u^-) + \lambda \partial_x(u^+ - u^-) = \partial_t u + \partial_x v = 0 \tag{3.50}$$

that is a standard conservation law. On the other hand, the subtraction of the first two equations of the Cattaneo-Hillen model yield

$$\begin{aligned} &\partial_t(u^+ - u-) + \lambda \partial_x(u^+ + u^-) = -2\mu^+ u^+ - 2\mu^- u^- \\ &\partial_t(\frac{v}{\lambda}) + \lambda \partial_x u = -[(\mu^+ + \mu^-)(u^+ - u^-) + (\mu^+ - \mu^-)(u^+ + u^-)] \\ &\partial_t(\frac{v}{\lambda}) + \lambda \partial_x u = -(\mu^+ + \mu^-)\frac{v}{\lambda} - (\mu^+ - \mu^-)u \\ &\partial_t v + \lambda^2 \partial_x u = -(\mu^+ + \mu^-)v - \lambda(\mu^+ - \mu^-)u, \end{aligned}$$

with the choice of turning rates provided above

$$\begin{aligned} \mu^+ + \mu^- &= 1 \\ \mu^+ - \mu^- &= -\frac{\phi_x}{\lambda} \end{aligned}$$

meaning that the equation becomes

$$\partial_t v + \lambda_x^2 u = \phi_x u - v. \tag{3.51}$$

Summing up all this results, the obtained system is

$$\begin{cases} u_t + v_x = 0 \\ v_t + \lambda^2 u_x = \phi_x u - v \\ \phi_t = D\phi_{xx} + au - b\phi. \end{cases} \tag{3.52}$$

3.4 Formalization of the model on a network

In previous sections the wound healing process and tissue engineering applications that accelerate this phenomenon were discussed. The healing process is a very complex biological phenomenon, here the focus is on the process of healing repair by fibroblasts.

In normal epidermic wound healing, the fibroblasts start wound healing process moving on the boundary of the damaged tissue and producing new extracellular matrix, essentially made of collagen, they move along it to fill the wound. During this process they are driven by chemotaxis, such chemoattractant is produced by themselves. At the end of the process a new tissue, called scar tissue, is formed. It is important to highlight that the cells move along the ECM fibres in both verses.

A common tissue engineer technique consists in inserting artificial scaffolds, within the wound, in order to provide a support to walk for fibroblasts. In this way their repairing action is accelerated. A novel approach, first proposed in [4], is to consider a one dimensional model on a network. More precisely, a system of the form

$$\begin{cases} u_t + v_x = 0 \\ v_t + \lambda^2 u_x = \phi_x u - v \\ \phi_t - D\phi_{xx} = au - b\phi \end{cases} \tag{3.53}$$

is considered, on each arc of the network. This means that a set of solutions (u, v, ϕ) is considered in each arc. This simple model of chemotaxis on a network is a good candidate for reproducing this configuration: the arcs of the network represent the fibres of the scaffold and the transport equations give the evolution of the density of fibroblasts on each fibre. Three reasons justify this kind of approach : cell dimension is of the same order of fibre section, so the choice of 1-D modelling is suitable, fibre width is much litter then its length, fibre density is much litter then ECM density.

Other models for the same purpose have been proposed in literature, but the ECM matrix was always been considered as a continuum support. This approach provide a much detailed study of the wound healing process since the one-dimensional arcs of the network mimic the fibres of the scaffold.

Here the definition of a network is recalled.

Definition 3.1. A *one dimensional network* is a connected graph $G = (\mathcal{N}, \mathcal{A})$ formed by two finite sets, $\mathcal{N} = \{N_\nu : \nu \in \mathcal{P} = \{1, ..., n\}\}$ a set of n nodes (or vertices) and $\mathcal{A} = \{I_i : i \in \mathcal{M} = \{1, .., m\}\}$ a set of m arcs.

Here e_j with $j \in \mathcal{J} = \{1, ..., l\}$ indicates the external vertices of the graph. The internal nodes are indicated with N_ν with index $\nu \in \mathcal{P}$. Each arc is a closed and bounded interval of $\mathbb{R}$ and connects a pair of nodes. Arcs are indexed by $i \in \mathcal{M} = \{1, ..., m\}$.

Since arcs are bidirectional, the graph is non-oriented, but an "artificial" orientation is fixed in order to give a sign to the cell velocities. This means that every arc is parametrizes as an interval $I_i = [0, L_i]$ where 0 is the coordinate of the node at the beginning of the arc, and L_i is the coordinate of the ending node. Clearly L_i is also the length of the arc $\forall i \in \{1, ..., m\}$. Since an artificial orientation is set, there are incoming and outgoing arcs for each internal node $N_\nu \in \mathcal{P}$. The set of incoming arcs for an internal node N_ν is denoted as $\mathcal{A}^\nu_{in} = \{I_i : i \in \mathcal{I}^\nu\}$ and the set of outgoing ones as $\mathcal{A}^\nu_{out} = \{I_i : i \in \mathcal{O}^\nu\}$. This means that $\mathcal{M}^\nu = \mathcal{I}^\nu \cup \mathcal{O}^\nu$ is the set of all indexes of arcs that have an edge in N_ν.

Definition 3.2. A function defined on a network $(\mathcal{N}, \mathcal{A})$, represented as $f : \mathcal{A} \to \mathbb{R}$ is a m-tuple $f = (f_1, ..., f_m)$ with $f_i : I_i \to \mathbb{R}$ for all $i = 1, ..., m$.

Functional spaces on the network are defined in the same manner, meaning that L^2 is defined as

$$L^2(\mathcal{A}) := \prod_{i=1}^{m} L^2(I_i), \tag{3.54}$$

and both can be done for $C^0(\mathcal{A}), H^s(\mathcal{A})$.

Norms on such spaces are defined as

$$||f||_2 := \sum_{i \in \mathcal{M}} ||f_i||_2, \ ||f||_{H^s} := \sum_{i \in \mathcal{M}} ||f_i||_{H^s} \tag{3.55}$$

Remark 3.1. A continuous function on a network is a function that has continuous components on each arc, this means that it may not be continuous globally.

Setting the hyperbolic-parabolic model proposed above on each arc means

$$\begin{cases} u_{i,t} + v_{i,x} = 0 \\ v_{i,t} + \lambda_i^2 u_{i,x} = \phi_{i,x} u_i - v_i \quad x \in I, t \geq 0, i \in \mathcal{M} \\ \phi_{i,t} - D_i \phi_{i,xx} = a u_i - b \phi_i \end{cases} \tag{3.56}$$

where $\lambda_i, a \geq 0, b, D_i > 0$, u_i stands for the concentration of cells, v_i is their average flux and ϕ_i is the concentration of chemoattractant. The coefficients a and b could depend on the arc I_i but $\frac{a(i)}{b(i)}$ should be constant for $i \in \mathcal{M}$.

3.4.1 Discussing initial and boundary conditions

The system is coupled with initial conditions

$$u_i(x, 0) = u_{i0}(x), \ v_i(x, 0) = v_{i0}(x), \ \phi_i(x, 0) = \phi_{i0}(x), \tag{3.57}$$

with $x \in I_i$ and $i \in \mathcal{M}$. The regularity of such functions changes in view of the problem. For the local existence, that will be discussed in the next chapter, the following assumptions are made

$$u_{i0}, v_{i0} \in H^1(I_i),\ \phi_{i0} \in H^2(I_i) \text{ for } i \in \mathcal{M}. \tag{3.58}$$

The boundary conditions change in view of the phenomenon that needs to be modelled. For the hyperbolic part, the general Dirichlet boundary conditions are:

$$\begin{cases} u_i^+(0,t) = \alpha_i(t)u_i^-(0,t) + \beta_i(t), & \text{if } i \in I_{out} \\ u_i^-(L_i,t) = \alpha_i(t)u_i^+(L_i,t) + \beta_i(t), & \text{if } i \in O_{out} \end{cases} \tag{3.59}$$

where I_{out} and O_{out} are the set of arcs incoming and out-coming from the outer boundaries. Moreover

$$u^{\pm} := \frac{1}{2}\left(u \pm \frac{v}{\lambda}\right). \tag{3.60}$$

For the parabolic part Neumann boundary conditions are chosen.

Modelling fibroblasts chemotaxis in vitro Studying the movement of fibroblasts chemotaxis on a network in vitro, means that the system is isolated. This translates into null flux conditions, both for the cells and the chemoattractant, i.e

$$\begin{aligned} &v_i(e_j,t) = 0\ t > 0,\ i \in \mathcal{M},\ j \in \mathcal{J}, \\ &\phi_{ix}(e_j,t) = 0\ t > 0,\ i \in \mathcal{M},\ j \in \mathcal{J}. \end{aligned}$$

This means that $\alpha_i(t) = 1$ and $\beta_i(t) = 0$ from the above Dirichlet condition, more specifically

$$u_i^+(\cdot,t) = u_i^-(\cdot,t), \tag{3.61}$$

that is equivalent to

$$v(\cdot,t) = 0. \tag{3.62}$$

Modelling fibroblasts in the wound In order to improve fibroblasts repairing action, artificial scaffolds are inserted within the wound, providing them a support to walk. Clearly in this case the network, modelling such scaffold, is not isolated from the undamaged extracellular matrix. This means that the null flux condition is no longer suitable. Contrariwise is much more realistic that the fibroblasts enter the scaffold from some "external" nodes, i.e nodes which communicates with the undamaged ECM. Following these considerations let $\mathcal{C}^{ext} = \{a_k,\ k \in \mathcal{K}\}$ be a class of such external nodes, i.e a set of nodes which are connected with the original ECM. For each of them the boundary conditions will be

$$\sum_{i \in \mathcal{I}^j} \lambda_i v_i(a_j,t) - \sum_{i \in \mathcal{O}^j} \lambda_i v_i(a_j,t) = g(t),\ t > 0 \tag{3.63}$$

and

$$\phi_{ix}(a_j, t) = 0,\ t > 0 \tag{3.64}$$

where $\mathcal{I}^j, \mathcal{O}^j$ are the set of incoming and out-coming arcs from these nodes. In particular the first condition means that, for each time $t > 0$, there is an incoming flux of fibroblasts, from the ECM to the network, modelling the artificial scaffold. Since such flux can vary over time, the difference between the incoming and out-coming flux is expressed as a function of time. The function g is supposed to have enough regularity. In this case is not restrictive to assume there is a continuity of chemoattractant flux.

Improving wound healing As previously discussed, fibroblasts produce chemoattractant which influences their motion. When an extensive skin trauma occurs, artificial scaffolds are inserted within the wound. In order to further improve fibroblasts action, extra chemoattractant can be deposited on top of the scaffold. In this way more fibroblasts, driven by chemotaxis, will enter the scaffold starting from the surrounding undamaged ECM. This approach can be modelled as follows. Let $\mathcal{C}^{ext}$ a class of external nodes, i.e nodes that are on the top of the scaffolds. This means that in each arc that communicates with such node, a source term can be added to the chemoattractant parabolic equation, more specifically

$$\phi_{i,t} = D\phi_{i,xx} + au_i - b\phi_i + f_i(x,t)\ \forall i \in \mathcal{I}^{ext}$$

where $f_i(x,t) > 0$. The set $\mathcal{I}^{ext}$ indicates the set of all arcs which have one node in $\mathcal{C}^{ext}$.

This function can also be defined as a feedback $f_i = h_i(u_i(x,t))$, meaning that the amount of chemoattractant released, depends on the density of fibroblasts. Such hypothesis makes sense, there will be the higher concentration of external chemoattractant where there are less fibroblasts, since the aim is to attract them where there are not many cells yet. From a mathematical point of view, this means that h_i can be defined as a monotone decreasing function of u_i.

3.4.2 Transmission conditions at nodes

In the internal nodes more than a solution (u_i, v_i, ϕ_i) is defined. For this reason it is important to derive transmission conditions on such nodes.

Transmission conditions will couple solutions on contiguous intervals and will relate different densities. Not only transmission conditions determine how all the edges piece together but also they heavily condition the whole solution. Indeed, under these constraints it is possible to prove local existence for the system. Transmission conditions are chosen in order to guarantee two main properties of the model; first, the conservation of the flux (continuity) both for the density of cell and for the chemoattractant, second the energy

dissipation at the nodes. More precisely, the sum of the incoming fluxes balances the sum of outgoing ones, in this way the energy of the linearised homogeneous version of the system decays in time.

Transmission conditions at each node N_ν, for $\phi_i(N_\nu, t)$, reads as :

$$\begin{cases} D_i\phi_{ix}(N_\nu,t) = \sum_{j\in\mathcal{M}^\nu} \alpha_{ij}^\nu \left(\phi_j(N_\nu,t) - \phi_i(N_\nu,t)\right) \ i \in \mathcal{I}^\nu, \ t>0 \\ -D_i\phi_{ix}(N_\nu,t) = \sum_{j\in\mathcal{M}^\nu} \alpha_{ij}^\nu \left(\phi_j(N_\nu,t) - \phi_i(N_\nu,t)\right) \ i \in \mathcal{O}^\nu, \ t>0 \\ \alpha_{ij}^\nu \geq 0, \ \alpha ij^\nu = \alpha ji^\nu, \ \forall i,j \in \mathcal{M}^\nu \end{cases}$$

these conditions imply the continuity of the flux of chemoattractant at each node N_ν, for all $t > 0$, i.e

$$\sum_{i\in\mathcal{I}^\nu} D_i\phi_{ix}(N_\nu,t) = \sum_{i\in\mathcal{O}^\nu} D_i\phi_{ix}(N_\nu,t).$$

In a similar way, the conditions for the unknowns $v_i(N_\nu, t)$ and $u_i(N_\nu, t)$ are

$$\begin{cases} -\lambda_i v_i(N_\nu,t) = \sum_{j\in\mathcal{M}^\nu} K_{ij}^\nu \left(\lambda_j u_j(N_\nu,t) - \lambda_i u_i(N_\nu,t)\right) \ i \in \mathcal{I}^\nu, \ t>0 \\ \lambda_i v_i(N_\nu,t) = \sum_{j\in\mathcal{M}^\nu} K_{ij}^\nu \left(\lambda_j u_j(N_\nu,t) - \lambda_i u_i(N_\nu,t)\right) \ i \in \mathcal{O}^\nu, \ t>0 \\ K_{ij}^\nu \geq 0, \ Kij^\nu = Kji^\nu, \ \forall i,j \in \mathcal{M}^\nu \end{cases}$$

the above conditions ensure the conservation of the flux of the density of cells at each node N_ν, for $t > 0$, i.e

$$\sum_{i\in\mathcal{I}^\nu} \lambda_i v_i(N_\nu,t) = \sum_{i\in\mathcal{O}^\nu} \lambda_i v_i(N_\nu,t).$$

It is important to highlight that the previous equation corresponds to the conservations of the total mass, meaning that no death or birth of individuals occurs. Such physical property reads as

$$\sum_{i\in\mathcal{M}} \int_{I_i} u_i(x,t)dx = \sum_{i\in\mathcal{M}} \int_{I_i} u_{i0}(x,t)dx.$$

Now a full explanation of these transmission conditions is carried on, following [17].

Dissipative conditions

Here the attention is restricted to dissipative conditions. Consider a linear version of the hyperbolic system, namely :

$$\begin{cases} u_{i,t} + v_{i,x} = 0 \\ v_{i,t} + \lambda_i^2 u_{i,x} = -v_i \end{cases}$$

and consider the sum of the m energies of such system, i.e

$$E_1(t) = \sum_{i\in\mathcal{M}} \int_{I_i} \left(v_i^2(x,t) + \lambda_i^2 u_i^2(x,t)\right) dx. \tag{3.65}$$

With the same idea, consider the sum of the m energies of the homogeneous parabolic equation of the chemoattractant,

$$\phi_{i,t} = D_i \phi_{i,xx} - b\phi_i$$

that is

$$E_2(t) = \sum_{i\in\mathcal{M}} \int_{I_i} \phi_i^2(x,t) dx. \tag{3.66}$$

The following sufficient conditions at nodes ensure that the energies decay in time :

$$\Gamma_1^\nu(t) = \sum_{i\in\mathcal{I}^\nu} \lambda_i^2 v_i u_i(N_\nu,t) - \sum_{i\in\mathcal{O}^\nu} \lambda_i^2 v_i u_i(N_\nu,t) \geq 0,\ \nu\in\mathcal{P}$$
$$\Gamma_2^\nu(t) = \sum_{i\in\mathcal{I}^\nu} D_i\phi_i\phi_{ix}(N_\nu,t) - \sum_{i\in\mathcal{O}^\nu} D_i\phi_i\phi_{ix}(N_\nu,t) \leq 0,\ \nu\in\mathcal{P}$$

Moreover such conditions imply that the linear unbounded operators, appearing in the linearised equations above, are dissipative. This property is important in order to apply the theory of linear contraction semigroups that will be used to prove local existence in the next chapter.

Starting from $\Gamma_1^\nu(t)$, since the inequality holds for each node, it follows

$$\sum_{\nu\in\mathcal{P}} \left(\sum_{i\in\mathcal{I}^\nu} \lambda_i^2 v_i u_i(N_\nu,t) - \sum_{i\in\mathcal{O}^\nu} \lambda_i^2 v_i u_i(N_\nu,t) \right) \geq 0 \Leftrightarrow$$
$$\sum_{\nu\in\mathcal{P}} \left(-\sum_{i\in\mathcal{I}^\nu} \lambda_i^2 v_i u_i(L_i,t) + \sum_{i\in\mathcal{O}^\nu} \lambda_i^2 v_i u_i(0,t) \right) \leq 0$$

rearranging sums on the arcs

$$\sum_{i\in\mathcal{M}}[-\lambda_i^2 u_i v_i]_0^{L_i} \leq 0 \Leftrightarrow$$
$$\sum_{i\in\mathcal{M}}\int_{I_i}\frac{d}{dx_i}[-\lambda_i^2 u_i v_i]dx_i \leq 0 \Leftrightarrow$$
$$\sum_{i\in\mathcal{M}}\int_{I_i}[-\lambda_i^2 u_{i,x} v_i - \lambda_i^2 u_i v_{i,x}]dx_i \leq 0 \Rightarrow$$
$$\sum_{i\in\mathcal{M}}\int_{I_i}[-\lambda_i^2 u_{i,x} v_i - \lambda_i^2 u_i v_{i,x} - v_i^2]dx_i \leq 0 \Leftrightarrow$$
$$\sum_{i\in\mathcal{M}}\int_{I_i}[-\lambda_i^2 v_{i,x} u_i + v_i(-\lambda_i^2 u_{i,x} - v_i)]dx_i \leq 0 \Leftrightarrow$$
$$\sum_{i\in\mathcal{M}}\int_{I_i}2(\lambda_i^2 u_i u_{i,t} + v_i v_{i,t})dx_i \leq 0 \Leftrightarrow$$
$$\frac{d}{dt}E_1(t) \leq 0.$$

Now similar computations are done for $\Gamma_1^\nu(t)$. Starting from

$$\sum_{\nu\in\mathcal{P}}\left(\sum_{i\in\mathcal{I}^\nu} D_i\phi_i\phi_{i,x}(N_\nu,t) - \sum_{i\in\mathcal{O}^\nu} D_i\phi_i\phi_{i,x}\right) \leq 0 \Leftrightarrow$$
$$\sum_{\nu\in\mathcal{P}}\left(\sum_{i\in\mathcal{I}^\nu} D_i\phi_i\phi_{i,x}(L_i,t) - \sum_{i\in\mathcal{O}^\nu} D_i\phi_i\phi_{i,x}(0,t)\right) \leq 0$$
$$\sum_{i\in\mathcal{M}}[D_i\phi_i\phi_{i,x}]_0^{L_i} \leq 0 \Rightarrow$$
$$\sum_{i\in\mathcal{M}}[D_i\phi_i\phi_{i,x}]_0^{L_i} - \sum_{i\in\mathcal{M}}\int_{I_i} D_i\phi_{i,x}^2 dx_i \leq 0,$$

this last result is obtained integrating by parts on every arc the following expression

$$\sum_{i\in\mathcal{M}}\int_{I_i} D_i\phi_i\phi_{i,xx}dx_i \leq 0 \Rightarrow$$
$$\sum_{i\in\mathcal{M}}\int_{I_i} D_i\phi_i\phi_{i,xx} - b\phi_i^2 dx_i \leq 0 \Leftrightarrow$$
$$\sum_{i\in\mathcal{M}}\int_{I_i}\phi_i\left(D_i\phi_{i,xx} - b\phi_i\right)dx_i \leq 0 \Leftrightarrow$$
$$\sum_{i\in\mathcal{M}}\int_{I_i} 2\phi_i\phi_{i,t}dx_i \leq 0 \Leftrightarrow$$
$$\frac{d}{dt}E_2(t) \leq 0.$$

Transmission conditions for u and v

In order to derive the transmission conditions of u and v, first the simple case of two arcs with one node is considered. Let N_ν be the internal node and I_1, I_2 respectively the incoming and outcoming arcs. The conservation flux equation and the sufficient conditions for the energy dissipation leads to

$$\begin{aligned}&\lambda_1 v_1 = \lambda_2 v_2,\\ &\lambda_1^2 v_1 u_1 - \lambda_2^2 v_2 u_2 \geq 0,\end{aligned}$$

substituting the first equation in the second one, this leads to

$$\lambda_2 v_2(\lambda_1 u_1 - \lambda_2 u_2) \geq 0,$$

it is possible to make this condition true for $\forall t > 0$ choosing

$$\lambda_1 v_1 = \lambda_2 v_2 = k(\lambda_1 u_1 - \lambda_2 u_2),$$

with $k > 0$. In this way the following constraint is obtained

$$\lambda_1 v_1(\lambda_1 u_1 - \lambda_2 u_2)^2 = \lambda_2 v_2(\lambda_1 u_1 - \lambda_2 u_2)^2 \geq 0.$$

In the case of m arcs intersecting in N_ν, following the same method provides

$$-\sum_{i\in\mathcal{I}^\nu} \lambda_i v_i(\lambda_j u_j - \lambda_i u_i) + \sum_{i\in\mathcal{O}^\nu} \lambda_i v_i(\lambda_j u_j - \lambda_i u_i)$$

hence some relations among values v_i and $(\lambda_j u_j - \lambda_i u_i)$ are needed. Following the case of one node with two arcs, it is possible to assume that such relation is linear, meaning that

$$\begin{aligned}-\lambda_i v_i(N_\nu, t) &= \sum_{j\in\mathcal{M}^\nu} K_{ij}^\nu \left(\lambda_j u_j(N_\nu, t) - \lambda_i u_i(N_\nu, t)\right)\ i \in \mathcal{I}^\nu,\ t > 0,\\ \lambda_i v_i(N_\nu, t) &= \sum_{j\in\mathcal{M}^\nu} K_{ij}^\nu \left(\lambda_j u_j(N_\nu, t) - \lambda_i u_i(N_\nu, t)\right)\ i \in \mathcal{O}^\nu,\ t > 0.\end{aligned}$$

Now inserting the above relationship into the flux continuity

$$\begin{aligned}-\sum_{i\in\mathcal{I}^\nu}\sum_{i\in\mathcal{M}^\nu} k_{ij}^\nu(\lambda_j u_j - \lambda_i u_i) &= \sum_{i\in\mathcal{O}^\nu}\sum_{i\in\mathcal{M}^\nu} k_{ij}^\nu(\lambda_j u_j - \lambda_i u_i)\\ \sum_{i,j\in\mathcal{M}^\nu} k_{ij}^\nu(\lambda_j u_j - \lambda_i u_i) &= 0,\end{aligned}$$

summing the symmetrical terms

$$k_{ij}^\nu(\lambda_j u_j - \lambda_i u_i) + k_{ji}^\nu(\lambda_i u_i - \lambda_j u_j) = \lambda_i u_i(k_{ji}^\nu - k_{ij}^\nu) + \lambda_j u_j(k_{ij}^\nu - k_{ji}^\nu)$$

and so the sum can be written as

$$\sum_{i<j} \lambda_i u_i (k^\nu_{ji} - k^\nu_{ij}) + \lambda_j u_j (k^\nu_{ij} - k^\nu_{ji}) =$$
$$\sum_{i<j} (k^\nu_{ij} - k^\nu_{ji})(\lambda_j u_j - \lambda_i u_i)$$

now symmetry implies

$$\frac{1}{2} \sum_{i,j} (k^\nu_{ij} - k^\nu_{ji})(\lambda_j u_j - \lambda_i u_i) = 0 \Leftrightarrow$$
$$\frac{1}{2} \sum_j \lambda_j u_j [\sum_i (k^\nu_{ij} - k^\nu_{ji})] - \frac{1}{2} \sum_i \lambda_i u_i [\sum_j (k^\nu_{ij} - k^\nu_{ji})] = 0 \Leftrightarrow$$
$$\frac{1}{2} \sum_j \lambda_j u_j [\sum_i (k^\nu_{ij} - k^\nu_{ji})] + \frac{1}{2} \sum_j \lambda_j u_j [\sum_i (k^\nu_{ij} - k^\nu_{ji})] = 0 \Leftrightarrow$$
$$\sum_j \lambda_j u_j [\sum_i (k^\nu_{ij} - k^\nu_{ji})] = 0$$

this means that a sufficient condition is

$$\sum_{i \in \mathcal{M}} (k^\nu_{ij} - k^\nu_{ji}) = 0 \; \forall j \in \mathcal{M}^\nu.$$

Now, considering dissipation conditions, it follows

$$\sum_{i \in \mathcal{I}^\nu} \lambda_i u_i \left(- \sum_{j \in \mathcal{M}^\nu} k^\nu_{ij} (\lambda_j u_j - \lambda_i u_i) \right) - \sum_{i \in \mathcal{O}^\nu} \lambda_i u_i \left(\sum_{j \in \mathcal{M}^\nu} k^\nu_{ij} (\lambda_j u_j - \lambda_i u_i) \right) \geq 0 \Leftrightarrow$$
$$\sum_{i,j \in \mathcal{M}^\nu} k^\nu_{ij} \lambda_i (\lambda_i - \lambda_j) \geq 0,$$

sufficient conditions to make it true are

$$k^\nu_{ij} = k^\nu_{ji} \geq 0 \; \forall i, j \in \mathcal{M}^\nu.$$

Transmission conditions for ϕ

In order to derive the transmission conditions of ϕ, first the simple case of two arcs with one node is considered, as done for u, v

$$D_1 \phi_{1,x} = D_2 \phi_{2,x},$$
$$D_1 \phi_1 \phi_{1,x} - D_2 \phi_2 \phi_{2,x} \leq 0$$

replacing the first equation in the second, it follows

$$D_1 \phi_{1,x} (\phi_1 - \phi_2) = D_2 \phi_{2,x} (\phi_1 - \phi_2) \leq 0,$$

imposing transmission conditions

$$D_1\phi_{1,x} = \alpha(\phi_2 - \phi_1),\ -D_2\phi_{2,x} = \alpha(\phi_2 - \phi_1),$$

for every $\alpha \geq 0$ and $\forall t \geq 0$, the third inequality becomes

$$-D_1\alpha(\phi_2 - \phi_1)^2 = -D_2\alpha(\phi_2 - \phi_1)^2 \leq 0.$$

Now, for the general case of m arcs intersecting in N_ν, fix an index $j \in \mathcal{I}^\nu$, from the sufficient conditions for energy dissipation an the flux continuity it follows

$$\sum_{i\in\mathcal{I}^\nu} D_i\phi_i\phi_{i,x}(N_\nu,t) - \sum_{i\in\mathcal{O}^\nu} D_i\phi_i\phi_{i,x}(N_\nu,t) \leq 0 \Leftrightarrow$$

$$D_j\phi_j\phi_{j,x}(N_\nu,t) + \sum_{j\neq i\in\mathcal{I}^\nu} D_i\phi_i\phi_{i,x}(N_\nu,t) - \sum_{i\in\mathcal{O}^\nu} D_i\phi_i\phi_{i,x}(N_\nu,t) \leq 0 \Leftrightarrow$$

$$\sum_{j\neq i\in\mathcal{I}^\nu} D_i\phi_{i,x}(\phi_i - \phi_j)(N_\nu,t) - \sum_{i\in\mathcal{O}^\nu} D_i\phi_{i,x}(\phi_i - \phi_j)(N_\nu,t) \leq 0$$

$$\sum_{i\in\mathcal{I}^\nu} D_i\phi_{i,x}(\phi_j - \phi_i)(N_\nu,t) + \sum_{i\in\mathcal{O}^\nu} D_i\phi_{i,x}(\phi_j - \phi_i)(N_\nu,t) \leq 0$$

and the same is obtained with $j \in \mathcal{O}^\nu$. Following these computations the transmission conditions at nodes become

$$\begin{cases} D_i\phi_{ix}(N_\nu,t) = \sum_{j\in\mathcal{M}^\nu} \alpha_{ij}^\nu \left(\phi_j(N_\nu,t) - \phi_i(N_\nu,t)\right)\ i \in \mathcal{I}^\nu,\ t > 0 \\ -D_i\phi_{ix}(N_\nu,t) = \sum_{j\in\mathcal{M}^\nu} \alpha_{ij}^\nu \left(\phi_j(N_\nu,t) - \phi_i(N_\nu,t)\right)\ i \in \mathcal{O}^\nu,\ t > 0 \end{cases}$$

In order to obtain constraints for coefficients, the above conditions are inserted in the relations for flux conservation and energy dissipation. The computations are the same as done for u and v, with ϕ in role of u and ϕ_x in role of v. Substituting the previous conditions in the conservation of flux, it follows

$$\sum_{i\in\mathcal{I}^\nu}\sum_{j\in\mathcal{M}^\nu} \alpha_{ij}^\nu(\phi_j - \phi_i) = -\sum_{i\in\mathcal{O}^\nu}\sum_{j\in\mathcal{M}^\nu} \alpha_{ij}^\nu(\phi_j - \phi_i)$$

$$\sum_{i,j\in\mathcal{M}^\nu} \alpha_{ij}^\nu(\phi_j - \phi_i) = 0$$

ensured by the constraint

$$\sum_{i\in\mathcal{M}^\nu} (\alpha_{ij}^\nu - \alpha_{ji}^\nu) = 0\ \forall j \in \mathcal{M}^\nu.$$

Substituting in the dissipation conditions

$$\sum_{i\in\mathcal{I}^\nu} \phi_i \sum_{j\in\mathcal{M}^\nu} \alpha_{ij}^\nu(\phi_j - \phi_i) + \sum_{i\in\mathcal{O}^\nu} \phi_i \sum_{j\in\mathcal{M}^\nu} \alpha_{ij}^\nu(\phi_j - \phi_i) \leq 0$$

$$\sum_{i,j\in\mathcal{M}^\nu} \alpha_{ij}^\nu\phi_i(\phi_j - \phi_i) \leq 0.$$

with the constraint

$$\alpha_{ij}^{\nu} = \alpha_{ji}^{\nu} \; \forall i, j \in \mathcal{M}^{\nu}, \; \alpha_{ij}^{\nu} \geq 0.$$

it follows

$$\begin{aligned}
&\sum_{i,j \in \mathcal{M}^{\nu}} \alpha_{ij}^{\nu} \phi_i (\phi_j - \phi_i) \leq 0 \Leftrightarrow \\
&\sum_{i<j} \alpha_{ij}^{\nu} \phi_i (\phi_j - \phi_i) + \alpha_{ij}^{\nu} \phi_j (\phi_i - \phi_j) \leq 0 \Leftrightarrow \\
&\sum_{i<j} \alpha_{ij}^{\nu} \phi_i (\phi_j - \phi_i) - \alpha_{ji}^{\nu} \phi_j (\phi_j - \phi_i) \leq 0 \Leftrightarrow \\
&\sum_{i<j} \alpha_{ij}^{\nu} \phi_i (\phi_j - \phi_i)(-)(\phi_j - \phi_i) \leq 0 \Leftrightarrow \\
&- \sum_{i<j} \alpha_{ij}^{\nu} (\phi_j - \phi_i)^2 \leq 0.
\end{aligned}$$

Chapter 4

Analytical results

Here recalling [17], the following system is now analysed from an analytical point of view

$$\begin{cases} u_{i,t} + \lambda_i v_{i,x} = 0 \\ v_{i,t} + \lambda_i u_{i,x} = \phi_{i,x} u_i - v_i \quad x \in I, t \geq 0, i \in \mathcal{M} \\ \phi_{i,t} - D_i \phi_{i,xx} = a u_i - b\phi_i \end{cases} \tag{4.1}$$

with $\lambda_i, a \geq 0, b, D_i > 0$ and $\beta = 1$. The system is completed with initial conditions

$$u_{i0},\ v_{i0} \in H^1(I_i), \phi_{i0} \in H^2(I_i) \tag{4.2}$$

for $i \in \mathcal{M}$. On the outer points of the graph, a_i, null flux conditions are set, i.e

$$v_i(a_i, t) = 0\ i \in \mathcal{M},\ t > 0 \tag{4.3}$$

$$\phi_{i,x}(a_i, t) = 0\ i \in \mathcal{M},\ t > 0. \tag{4.4}$$

Moreover, at each node N_ν, transmission conditions for the unknowns u_i, v_i are

$$\begin{cases} -\lambda_i v_i(N_\nu, t) = \sum_{j \in \mathcal{M}^\nu} K_{ij}^\nu \left(u_j(N_\nu, t) - u_i(N_\nu, t)\right)\ i \in \mathcal{I}^\nu, \\ \lambda_i v_i(N_\nu, t) = \sum_{j \in \mathcal{M}^\nu} K_{ij}^\nu \left(u_j(N_\nu, t) - u_i(N_\nu, t)\right)\ i \in \mathcal{O}^\nu, \end{cases} \tag{4.5}$$

for $t > 0$, with $K_{ij}^\nu \geq 0$ and $K_{ij}^\nu = K_{ji}^\nu$, for all $i, j \in \mathcal{M}^\nu$. Similarly, the transmission conditions for ϕ_i are

$$\begin{cases} D_i \phi_{ix}(N_\nu, t) = \sum_{j \in \mathcal{M}^\nu} \alpha_{ij}^\nu \left(\phi_j(N_\nu, t) - \phi_i(N_\nu, t)\right)\ i \in \mathcal{I}^\nu, \\ -D_i \phi_{ix}(N_\nu, t) = \sum_{j \in \mathcal{M}^\nu} \alpha_{ij}^\nu \left(\phi_j(N_\nu, t) - \phi_i(N_\nu, t)\right)\ i \in \mathcal{O}^\nu, \end{cases} \tag{4.6}$$

for $t > 0$, where $\alpha_{ij}^\nu \geq 0$ and $\alpha_{ij}^\nu = \alpha_{ji}^\nu$, for all $i, j \in \mathcal{M}^\nu$.

A local solution is obtained by means of linear contraction semigroups theory, abstract theory of non-homogeneous and semilinear evolution problems. Transmission conditions at nodes are a key element here. Unknowns are proven to exist locally considering separately the hyperbolic and parabolic part of the whole system and then unified with a fixed point method.

Remark 4.1. It is important to highlight that the chemoattractant equation for (4.1) is the same as the one for (3.52). Moreover, choosing $u_i = \lambda_i w_i$ and replacing it in the hyperbolic part of (4.1), it follows

$$\begin{cases} \lambda_i w_{i,t} + \lambda_i v_{i,x} = 0 \\ v_{i,t} + \lambda_i^2 w_{i,x} = \lambda_i \phi_{i,x} w_i - v_i \\ \phi_{i,t} = D_i \phi_{i,xx} + \lambda_i a_i w_i - b\phi_i \end{cases}$$

then, rescaling the coefficient $\phi_{i,x}\lambda_i = \varphi_{i,x}$ of the non-linear part, the system reads as

$$\begin{cases} w_{i,t} + v_{i,x} = 0 \\ v_{i,t} + \lambda_i^2 w_{i,x} = \varphi_{i,x} w_i - v_i \\ \varphi_{i,t} = D\varphi_{i,xx} + a_i' w_i - b\varphi_i \end{cases}$$

which is exactly (3.52), the system obtained in the previous chapter. The same argument applies for the transmission conditions of (3.52). This means that the systems, coupled with their respective conditions at the nodes, are equivalent.

4.1 Local existence for ϕ

Let $X := L^2(\mathcal{A})$ be the space taken into consideration. An element here is a function defined on the whole set of oriented arcs by means of $\{\phi_i\}_{i=1,\dots,n}$ and such that $\phi_i \in L^2(I_i)$. Let $A_2 : D(A_2) \to X$ be a linear operator defined by

$$\begin{aligned} D(A_2) &= \{\phi \in H^2(\mathcal{A}) : (4.4), (4.6), \} \\ A_2(\phi) &= \{D\phi_{i,xx} - b\phi_i\}_{i\in\mathcal{M}} \end{aligned}$$

This space is endowed with the norm

$$|| \cdot ||_{H^1(\mathcal{A})} = || \cdot ||_{L^2(\mathcal{A})} + || \cdot_{,x} ||_{L^2(\mathcal{A})}$$

that adapted to a network reads as

$$||\phi||_{H^1(\mathcal{A})} = \sum_{i\in\mathcal{M}} ||\phi_i||_{L^2(I_i)} + \sum_{i\in\mathcal{M}} ||\phi_{i,x}||_{L^2(I_i)}.$$

In order to prove the local existence of the parabolic equation involving the chemoattractant, the following equivalent problem is considered

$$\begin{cases} \phi \in C([0,T]; D(A_2)) \cap C^1([0,T]; X) \\ \phi'(t) = A_2\phi(t) + g(t)\ t \in [0,T] \\ \phi(0) = \phi_0 \in D(A_2) \end{cases} \tag{4.7}$$

where $g(t) = au(t)$ and $T > 0$.

Local existence of such problem is proven following inhomogeneous evolution equations theory.

The proof here is given in the case of a graph composed of a single node N and m arcs I_i connecting that node to the external points e_i, $i \in \mathcal{M} = 1, 2, ..., m$. When integrating on internal arcs $I_i = (N_\nu, N_\mu)$, two transmission terms arise, each one corresponding to a node. In this case, the sum of all the transmission terms at each node of the graph can be treated separately, as in the case of a single node.

Proposition 4.2. Let $T < 1$, $g \in C([0,T]; H^1(\mathcal{A})) \cap C^1([0,T], L^2(\mathcal{A}))$, with $M > \sup_{[0,T]} ||g(t)||_{H^1}$, and $K > ||\phi_0||_{H^2} + 4M$, then there exists a unique solution to the problem (4.7) and

$$\sup_{t\in[0,T]} ||\phi(t)||_{H^2} \leq K.$$

Moreover, $\phi \in H^1((0,T); H^1(\mathcal{A}))$.

Proof. The first step consists in proving that A_2 generates a contraction semigroup in X. This is achieved by showing that A_2 is m-dissipative in X. A_2 is dissipative in X, i.e $(A_2\phi, \phi) \leq 0$ for every $\phi \in D(A_2)$:

$$(A_2\phi, \phi) = \sum_{i\in\mathcal{M}} \int_{I_i} (D_i\phi_{i,xx} - b\phi_i)\phi_i dx =$$
$$\sum_{i\in\mathcal{M}} \int_{I_i} (D_i\phi_{i,xx}\phi_i - b\phi_i^2) dx =$$

integrating by parts the left term in the integral and then using transmission conditions for ϕ it follows

$$= -\sum_{i\in\mathcal{M}} \int_{I_i} (D_i\phi_{i,x}^2 - b\phi_i\phi_i) dx + \sum_{i\in\mathcal{I}} D_i\phi_{i,x}(N,t)\phi_i(N,t)$$
$$-\sum_{i\in\mathcal{O}} D_i\phi_{i,x}(N,t)\phi_i(N,t)$$
$$= -\frac{1}{2}\sum_{i,j\in\mathcal{M}} \alpha_{ij}(\phi_j(N) - \phi_i(N))^2 - \sum_{i\in\mathcal{M}} \int_{I_i} (D_i\phi_{i,x}^2 - b\phi_i^2) dx \leq 0.$$

Since A_2 is dissipative, now is sufficient to show that for all $\varphi \in L^(\mathcal{A})$, there exists $\phi \in D(A_2)$ such that $\phi - A_2\phi = \varphi$. In order to prove this, the following bilinear form $a(\phi, \varphi) : (H^1(\mathcal{A}))^2 \to \mathbb{R}$ is introduced

$$a(\phi,\varphi) = \sum_{i\in\mathcal{M}} \int_{I_i} (D_i\phi_{i,x}\varphi_{i,x} + (1+b)\phi_i\varphi_i) dx$$
$$- \sum_{i,j\in\mathcal{M}} \alpha_{ij}(\phi_j(N) - \phi_i(N))^2\varphi_i(N).$$

This form is continuous, i.e $|a(\phi,\varphi)| \leq C||\phi||_{H^1}||\varphi||_{H^1}$, indeed :

$$\begin{aligned}
|a(\phi,\varphi)| &\leq \sum_i \int_{I_i} |D_i \phi_{i,x}\varphi_{i,x}|dx + \sum_i \int_{I_i} |(1+b)\phi_i\varphi_i|dx \\
&+ \sum_{i,j} \alpha_{ij}|\phi_j - \phi_i||\varphi_i|(N) \\
&\leq \sum_i D_i||\phi_{i,x}||_2||\varphi_{i,x}||_2 + \sum_i (1+b)||\phi_i||_2||\varphi_i||_2 \\
&+ \sum_{i,j} \alpha_{ij} \max\{||\phi_j||_1, ||\phi_i||_1\}||\varphi_i||_1 \\
&\leq C_1||\phi||_{H^1(\mathcal{A})}||\varphi||_{H^1(\mathcal{A})} + C_2||\phi||_{H^1(\mathcal{A})}||\varphi||_{H^1(\mathcal{A})} \\
&+ \sum_{i,j} \alpha_{ij} \max\{||\phi_j||_2, ||\phi_i||_2\}||\varphi_i||_2 \\
&\leq C||\phi||_{H^1(\mathcal{A})}||\varphi||_{H^1(\mathcal{A})}.
\end{aligned}$$

Moreover $a(\cdot,\cdot)$ is coercive, i.e $a(\cdot,\cdot) \geq C||\phi||^2_{H^1}$:

$$\begin{aligned}
a(\phi,\phi) &= \sum_i \int_{I_i} D_i(\phi_{i,x})^2 + (1+b)(\phi_i)^2 dx \\
&- \sum_{i,j\in\mathcal{M}} \alpha_{ij}(\phi_j - \phi_i)\phi_i(N) \\
&\geq \sum_{i\in\mathcal{M}} \int_{I_i} D_i(\phi_{i,x})^2 dx + \sum_{i\in\mathcal{M}} \int_{I_i} (1+b)(\phi_i)^2 dx \\
&\geq C||\phi||^2_{H^1}.
\end{aligned}$$

This means that all hypothesis of Lax-Milgram Theorem hold, that is $\forall \varphi \in L^2(\mathcal{A})$, there exists a unique $\phi \in H^1(\mathcal{A})$ such that, for all $\psi \in H^1(\mathcal{A})$, it holds that

$$a(\phi,\psi) = \sum_{i\in\mathcal{M}} \int_{I_i} \phi_i\psi_i dx,$$

taking $\psi_i \in H^1_0(I_i)$ for all $i \in \mathcal{M}$, it follows that $\phi_{i,x} \in H^1(I_i)$, then

$$\begin{aligned}
&\sum_i \int_{I_i} (-D_i\phi_{i,xx} + (1+b)\phi_i)\psi_i dx + \sum_{i\in\mathcal{I}} D_i(\phi_{i,x}(N)\psi_i(N) - \phi_{i,x}(e_i)\psi_i(e_i)) \\
&- \sum_{i\in\mathcal{O}} D_i(\phi_{i,x}(N)\psi_i(N) - \phi_{i,x}(e_i)\psi_i(e_i)) - \sum_{i,j\in\mathcal{M}} \alpha_{ij}(\phi_j - \phi_i)(N)\psi_i(N) \\
&= \sum_{i\in\mathcal{M}} \int_{I_i} \varphi_i\psi_i dx.
\end{aligned}$$

The above inequality hold for all $\psi_i \in C^\infty_0(I_i)$, then

$$-\phi_{i,xx} + (1+b)\phi_i = \varphi_i$$

almost everywhere for all $i \in \mathcal{M}$, moreover, with suitable choices of $\psi_i(N), \psi_i(a_i)$ ϕ satisfies the right boundary and transmission conditions to belong to $D(A_2)$. Since A_2 is m-dissipative it generates a contraction semigroup $\tau_2(t) \in X$. Since $g \in C^([0,T], L^2(\mathcal{A}))$, it is possible to apply the theory for non-homogeneous problems to conclude that there exists a unique solution to the problem (4.7). Such solution is given by

$$\phi(t) = \tau_2(t)\phi_0 + \int_0^t \tau_2(t-s)g(s)ds.$$

Posing

$$\mathcal{F}(t) := \int_0^t \tau_2(t-s)g(s)ds$$

it follows that $\mathcal{F} \in C^1([0,T]; L^2(\mathcal{A})) \cap C([0,T]; D(A_2))$ and, thanks to convolution properties,

$$\mathcal{F}'(t) = \int_0^t \tau_2(s)g'(t-s)ds + \tau_2(t)g(0).$$

Moreover $A_2\mathcal{F}(t) = \mathcal{F}'(t) - g(t)$. Now keeping in mind that $T < 1$ and the definitions of M, K it follows

$$\begin{aligned}
&||\phi(t)||_{D(A_2)} = ||\phi(t)||_X + ||A_2\phi(t)||_X \\
&\leq ||\phi_0||_{D(A_2)} + ||\mathcal{F}(t)||_X + ||A_2\mathcal{F}(t)||_X \\
&\leq ||\phi_0||_{D(A_2)} + \int_0^t ||g(s)||_X ds + ||\mathcal{F}'(t)||_X + ||g(t)||_X \\
&\leq ||\phi_0||_{D(A_2)} + ||g(0)||_X + ||g(t)||_X + T \sup_{t\in[0,T]} ||g(t)||_X + T \sup_{t\in[0,T]} ||g'(t)||_X \\
&\leq ||\phi_0||_{D(A_2)} + 2TM + 2M \\
&\leq ||\phi_0||_{D(A_2)} + 4M \leq K.
\end{aligned}$$

The inequality holds for any t, this means

$$\sup_{t\in[0,T]} ||\phi(t)||_{H^2} \leq K.$$

Now, in order to prove the last claim, i.e $\phi \in H^1((0,T); H^1(\mathcal{A}))$, it is sufficient to prove that there exists $C > 0$ such that, for all $0 < t_1 < t_2 < T$

$$\int_{t1}^{t2} ||\phi_x(t+h) - \phi_x(t)||_2^2 \leq C|h|^2.$$

for all $h \in \mathbb{R}$, with $|h| < \{t1, T - t2\}$. Let $\Delta^h\psi(t) := \psi(t+h) - \psi(t))$, using the equation it is possible to write

$$\int_{t1}^{t2} \int_{I_i} (\Delta^h\phi_{i,t}\Delta^h\phi_i - D_i\Delta^h\phi_{i,xx}\Delta^h\phi_i + \Delta^h g_i\Delta^h\phi_i - (\Delta^h\phi_i)^2)dxdt = 0,$$

then it follows

$$\sum_{i\in\mathcal{M}}\left(\int_{I_i}(\Delta^h\phi_i(t2))^2dx+\int_{t1}^{t2}\int_{I_i}(\Delta^h\phi_{i,x})^2dxdt\right)$$
$$\leq C\int_{t1}^{t2}\left(\sum_{i\in\mathcal{I}}D_i(\Delta^h\phi_{i,x})(\Delta^h\phi_i)(N,t)-\sum_{i\in\mathcal{O}}D_i(\Delta^h\phi_{i,x})(\Delta^h\phi_i)(N,t)\right)dt$$
$$+C\sum_{i\in\mathcal{M}}\left(\int_{I_i}(\Delta^h\phi_i(t1))^2dx+\int_{t1}^{t2}\int_{I_i}(\Delta^h g_i)^2dxdt\right),$$

hence the requested inequality follows thanks to the non-positivity of the first term on the right-hand side, since $\phi, g \in C^1((0,T);L^2(\mathcal{A}))$. □

Remark 4.3. In the previous chapter improving wound healing was discussed. This was modelled including a function f_i, depending on the space-time or as a function of the density of fibroblasts, in the chemoattractant equation as

$$\phi_{i,t} = D\phi_{i,xx} + au_i - b\phi_i + f_i \;\forall i \in \mathcal{I}^{ext}$$

where $f_i(x,t) > 0$ or $f_i = h_i(u_i(x,t))$, with $\mathcal{C}^{ext}$ a class of external nodes, i.e nodes that are on the top of the scaffolds and $\mathcal{I}^{ext}$ the set of all arcs which have one node in $\mathcal{C}^{ext}$.

In this case, the parabolic equation with homogenous boundary conditions 4.4 and transmission conditions 4.6 reads as the problem 4.7 with g function defined as $g = au + z$, where

$$z = (z_i)_{i\in\mathcal{M}}\begin{cases} f_i(x,t) > 0,\ i \in \mathcal{I}^{ext} \\ 0\ otherwise \end{cases}$$

where the set $\mathcal{I}^{ext}$ is the set of the arcs which communicates with a defined set $\mathcal{C}^{ext}$ of external nodes. In the case of a feedback $f_i = h_i(u_i(x,t))$ it follows

$$z = (z_i)_{i\in\mathcal{M}}\begin{cases} h_i(u_i(x,t)) > 0,\ i \in \mathcal{I}^{ext} \\ 0\ otherwise \end{cases}$$

In it important to highlight that transmission conditions 4.6 hold also in this case, since they were derived keeping in mind flux conservation and dissipation of m energies of the linearised problem $\phi_{i,t} = D_i\phi_{i,xx} - b\phi_i$, meaning that g does not play a role in the computation. In both cases f_i can be defined sufficiently regular such that $z \in C([0,T];H^1(\mathcal{A})) \cap C^1([0,T],L^2(\mathcal{A}))$ meaning that $g \in C([0,T];H^1(\mathcal{A})) \cap C^1([0,T],L^2(\mathcal{A}))$ and $M > \sup_{[0,T]}||g(t)||_{H^1}$, and so using proposition 4.2 local existence holds also in this case.

4.2 Local existence for (u,v)

Let $Y = \cup_{i\in\mathcal{M}}(L^2(I_i))^2$ be a functional space and $A_1 : D(A_1) \to Y$ be a linear operator with

$$\begin{aligned} D(A_1) &= \{U = (u, v) \in (H^1(\mathcal{A}))^2 : (4.3), (4.5)\} \\ A_1U &= (-\lambda_i v_{i,x}, -\lambda_i u_{i,x})_{i\in\mathcal{M}} \end{aligned}$$

and the hyperbolic problem

$$\begin{cases} U \in C([0,T]; D(A_1)) \cap C^1([0,T]; Y) \\ U'(t) = A_1U(t) + F(t, U(t)),\ t \in [0,T] \\ U(0) = (u_0, v_0) \in D(A_1) \end{cases} \tag{4.8}$$

where

$$F(t, U(t)) = \{(0, f_i(t)u_i(t) - v_i(t))\}_{i\in\mathcal{M}}$$

with the function f_i defined as

$$f_i(t) = \phi_{i,x}(t).$$

In order to prove local existence for (4.8), the following lemma is needed.

Lemma 4.4. Let $W = (w, z) \in \cup_{i\in\mathcal{M}}(C_0^\infty(I_i))^2$, there exists a unique $U = (u, v) \in D(A_1)$ such that $(I - A_1)U = W$.

Proof. Let $\delta_i = 1$ if $i \in \mathcal{I}$ and $\delta_i = -1$ if $i \in \mathcal{O}$. Consider the following elliptic problem

$$\begin{cases} -\lambda_i^2 u_{i,xx} + u_i = -\lambda_i z_{i,x} + w_i, \\ \delta_i \lambda_i^2 u_{i,x}(N) = \sum_{j\in\mathcal{M}} K_{ij}(u_j(N) - u_i(N)), \\ u_{i,x}(a_i) = 0. \end{cases}$$

In proposition 4.2, in the steps to obtain m-dissipativity of A_2, after applying Lax-Milgram theorem, the uniqueness of the solution for the same type of problem was shown. Moreover the components of the unique solution u, belongs to $C^\infty(I_i)$. Setting $v_i = z_i - \lambda_i u_{i,x}$, if follows that $v_i \in C^\infty(I_i)$ and

$$\begin{cases} \lambda_i v_{i,x} + u_i = w_i, \\ -\delta_i \lambda_i v_i(N) = \sum_{j\in\mathcal{M}} K_{ij}(u_j(N) - u_i(N)), \\ v_i(a_i) = 0. \end{cases}$$

□

It is important to highlight that if $f \in (C([0,T];H^1(\mathcal{A}))$, since in the previous section was shown that $||\phi(t)||_{H^2}$ is bounded, this means that $F(t,U(t)) = f(t)u(t) - \beta v(t)$ is a globally Lipschitz function, meaning that for any $K > 0$ there is a constant $L_F(K)$, such that for all $f \in C([0,T];H^1(\mathcal{A}))$ with $\sup_{[0,T]} ||f(t)||_{H^1(\mathcal{A})} \leq K$, it follows

$$\sup_{[0,T]} ||F(t,U_1(t)) - F(t,U_2(t))||_E \leq L_F(K) \sup_{[0,T]} ||U_1(t) - U_2(t)||_E$$

where $E = \cup_{i\in\mathcal{M}}(H^1(I_i))^2$.

Proposition 4.5. Let $f \in C([0,T_1];H^1(\mathcal{A}))\cap H^1((0,T_1);L^2(\mathcal{A}))$. Take $K > \sup_{[0,T_1]} ||f(t)||_{H^1}$ and $M > 2(||u_0||_{H^1}+||v_0||_{H^1})$. Fix $T < \min\{T_1, (2L_F(K))^{-1}\}$, then there exists a unique solution to the problem (4.8) on the interval $[0,T]$ and

$$\sup_{t\in[0,T]} ||U(t)||_E \leq M.$$

Proof. The first thing to prove is that A_1 is a m-dissipative operator in Y. Let $U \in D(A_1)$, using the transmission conditions at the nodes it follows

$$\begin{aligned}(A_1U,U) &= \sum_{i\in\mathcal{M}} \int_{I_i} (\lambda_i v_{i,x}u_i - \lambda_i u_{i,x}v_i) \\ &= -\left[\sum_{i\in\mathcal{I}} \lambda_i v_i(N)u_i(N) - \sum_{i\in\mathcal{I}} \lambda_i v_i(N)u_i(N)\right] \\ &= -\frac{1}{2}\sum_{i,j\in\mathcal{M}} K_{ij}(u_j(N) - u_i(N))^2 \leq 0.\end{aligned}$$

In order to complete the proof of the m-dissipativity of A_1, the following bilinear form $a : D(A_1)\times D(A_1) \to \mathbb{R}$ is introduced

$$a(U,\bar{U}) = \sum_{i\in\mathcal{M}} \int_{I_i} ((\lambda_i v_{i,x} + u_i)(\lambda_i \bar{v}_{i,x} + \bar{u}_i) + (\lambda_i u_{i,x} + v_i)(\lambda_i \bar{u}_{i,x} + \bar{v}_i))dx.$$

Such bilinear form is continuous and coercive, meaning that Lax-Milgram theorem applies, i.e for all $\Psi = (\psi_1,\psi_2) \in (L^2(\mathcal{A}))^2$, there exists a unique $U \in D(A_1)$ such that, for all $\bar{U} \in D(A_1)$, the following inequality holds:

$$a(U,\bar{U}) = \sum_{i\in\mathcal{M}} \int_{I_i} (\psi_1(\lambda_i \bar{v}_{i,x} + \bar{u}_i) + \psi_2(\lambda_i \bar{u}_{i,x} + \bar{v}_i)).$$

Then, following 4.4, $(I - A_1)U = \Psi$ almost everywhere. This means that A_1 is a m-dissipative operator, hence the generator of a contraction semigroup in Y, τ_1. Let introduce the following set

$$B_M = \{U \in C([0,T];E) : \sup_{t\leq T} ||U(t)||_E \leq M\}$$

equipped with the distance generated by the norm of $C([0,T];E)$. The solution to the problem (4.8) is the unique fixed point in B_M of the function

$$\Phi(U) = \Phi_U(t) = \tau_1(t)U_0 + \int_0^t \tau_1(t-s)F(s,U(s))ds$$

with $\Phi_U \in C([0,T];E)$. Now thanks to the Lipschitz continuity of F in E, for $U \in B_M$, it follows

$$||\Phi_U(t)||_E \leq ||U_0||_E + TL_F(K)M \leq M$$

and, for $V \in B_M$,

$$||\Phi_U(t) - \Phi_V(t)||_E \leq L_F(K)\int_0^t ||U(t) - V(t)||_E \leq \frac{1}{2}\sup_{[0,T]} ||U(t) - V(t)||_E.$$

Then it is possible to conclude and say that Φ is a contraction in B_M and it has a unique fixed point $U \in B_M$

$$U(t) = \tau_1(t)U_0 + \int_0^t \tau_1(t-s)F(s,U(s))ds.$$

Using the above expression, it is possible to deduce that, for $t \in [0, T-h]$, $h > 0$

$$||U(t+h) - U(t)||_Y \leq ||\tau_1(h)U_0 - U_0||_Y + \int_0^h ||F(s,U(s))||_Y ds$$
$$+ \int_0^t ((||f(s)||_{H^1} + 1)||U(s+h) - U(s)||_Y + ||U(s)||_E||f(s+h) - f(s)||_2)ds.$$

Since $f \in C([0,T];H^1(\mathcal{A})) \cap H^1((0,T);L^2(\mathcal{A}))$, using Gronwall's lemma

$$||U(t+h) - U(t)||_Y \leq C(M,K,T)h.$$

Using the above inequality and, again, the assumptions on f, it follows

$$||F(s+h,U(s+h)) - F(s,U(s))||_2 \leq C_1(K,M,T)h$$

and then U is the solution to the problem (4.8) since $U_0 \in D(A_1)$. □

4.3 Local existence for the whole system

In the previous sections local existence for the unknowns (u,v), ϕ was discussed, considering separately the hyperbolic and parabolic part of the system (4.1). Now the local existence for the whole system is obtained combining the local solutions of the two disjointed problems with the fixed point technique.

Remark 4.6. The solutions of the disjoint systems verify

$$\sup_{[0,T]} ||u_t(t)||_2,\ \sup_{[0,T]} ||v_t(t)||_2,\ \sup_{[0,T]} ||\phi_t(t)||_2 \leq Q(K,M),$$

where the quantity Q depends only on a, b, λ_i, D_i besides M and K.

Theorem 4.7. *(Local existence) There exists a unique local solution (u, v, ϕ) to the hyperbolic-parabolic system*

$$(u,v) \in (C([0,T]; H^1(\mathcal{A}) \cap C^1([0,T]; L^2(\mathcal{A})))^2,$$
$$\phi \in C([0,T]; H^2(\mathcal{A}) \cap C^1([0,T]; L^2(\mathcal{A})).$$

Moreover, $\phi \in H^1((0,T); H^1(\mathcal{A}))$.

Proof. Let $M > 2(||u_0||_{H^1}+||v_0||_{H^1})$, $K > ||\phi_0||_{H^2}+4M$, $T \leq \min\{(2L_F(K))^{-1}, 1\}$ and

$$\begin{aligned} B_{MK} =&\{(u,v,\phi) \in (C([0,T]; H^1(\mathcal{A})))^2 \times C([0,T]; H^2(\mathcal{A})) : \\ &\sup_{[0,T]} ||u(t), v(t)||_E \leq M,\ \sup_{[0,T]} ||\phi(t)||_{H^2} \leq K, \\ &u, \phi \in C^1([0,T]; L^2(\mathcal{A})),\ \sup_{[0,T]} ||u(t)||_2,\ \sup_{[0,T]} ||\phi_t(t)||_2 \leq Q(K,M)\}. \end{aligned}$$

Then consider the function G defined in B_{MK} as:

$$\begin{aligned} &(u^0, v^0, \phi^0) \in B_{MK}, \\ &G(u^0, v^0, \phi^0) = (u^1, v^1, \phi^1), \end{aligned}$$

where $U^1 = (u^1, v^1)$ is the solution to (4.8) with $f = \phi^0_x$ and ϕ^1 is the solution to problem (4.7) with $g = au^1$. Moreover the previous proposition ensures that G is well defined from B_{MK} to itself. Now let

$$\begin{aligned} &(\hat{u}^0, \hat{v}^0, \hat{\phi}^0),\ (\bar{u}^0, \bar{v}^0, \bar{\phi}^0) \in B_{MK}, \\ &(\bar{u}^1, \bar{v}^1, \bar{\phi}^1) = G(\bar{u}^0, \bar{v}^0, \bar{\phi}^0), \\ &(\hat{u}^1, \hat{v}^1, \hat{\phi}^1) = G(\hat{u}^0, \hat{v}^0, \hat{\phi}^0), \\ &\bar{F} = (0, \bar{\phi}^0_x \bar{u}^1 - \bar{v}^1), \\ &\hat{F} = (0, \hat{\phi}^0_x \hat{u}^1 - \hat{v}^1); \end{aligned}$$

$C(M,K)$ constants depending only on the quantities K, M and $\gamma(t)$ functions of t which go to zero when t goes to zero. Then estimates follows

$$\begin{aligned} ||\bar{U}^1(t) - \hat{U}^1(t)||_E &= \sup_{[0,T]} || \int_0^t \tau_1(t-s)(\bar{F}(s) - \hat{F}(s))ds||_E \\ &\leq C(K,M) \int_0^T \left(||\bar{U}^1(t) - \hat{U}^1(t)||_E + ||\bar{\phi}^0(t) - \hat{\phi}^0(t)||_{H^2} \right) dt, \end{aligned}$$

from which

$$\sup_{[0,T]} ||\bar{U}^1(t) - \hat{U}^1(t)||_E \leq \gamma(T)C(M,K) \sup_{[0,T]} ||\bar{\phi}^0(t) - \hat{\phi}^0(t)||_{H^2}.$$

Moreover, using the equations and the above inequality, it follows

$$\sup_{[0,T]} ||\bar{u}_t^1(t) - \hat{u}_t^1(t)||_2 \leq C(M,K)\gamma(T) \sup_{[0,T]} ||\bar{\phi}^0(t) - \hat{\phi}^0(t)||_{H^2}.$$

Finally using, again, the previous inequalities

$$\sup_{[0,T]} ||\bar{\phi}_t^1(t) - \hat{\phi}_t^1(t)||_2 \leq \gamma(T)C(M,K) \sup_{[0,T]} ||\bar{\phi}^0(t) - \hat{\phi}^0(t)||_{H^2}.$$

If T is sufficiently small, then G is a contraction function in B_{MK} and let $(U,\phi) = (u,v,\phi)$ be its unique fixed point :

$$U(t) = \tau_1 U_0 + \int_0^t \tau_1(t-s)F(s,U(s))ds,$$
$$\phi(t) = \tau_2\phi_0 + a\int_0^t \tau_2(t-s)u(s)ds.$$

Now $u \in C^1([0,T];L^2(\mathcal{A}))$, $\phi \in H^1((0,T);H^1(\mathcal{A})$ and $u \in C^1([0,T];L^2(\mathcal{A}))$, therefore $(U,\phi) = (u,v,\phi)$ is the claimed solution. □

Chapter 5

Conclusion and future work

The study of partial differential equations defined on a network has been developed in recent years but is still a novel area of research. In this work a one-dimensional model on a network for modelling wound healing process was proposed. Starting from the biological background and some mathematical models, the hyperbolic-parabolic system was derived and set on a network, with suitable nodes conditions. Finally, some analytical results for the boundary homogenous case where presented.

Lots of questions now arise from modelling the wound healing process as a hyperbolic-parabolic system on networks. For instance it would be interesting to model a suitable feedback, in the chemoattractant equation, in order to reach a target stationary state, where fibroblasts are spread all over the network. This could have a direct application in the field of regenerative medicine, because it would allow to understand how to distribute the chemoattractant in the scaffold, in order to lead to an optimal reconstruction of the tissue. Moreover is interesting to explore new suitable conditions at nodes and to rediscuss local existence. Indeed, during dermal wound healing the scaffold is not isolated, meaning that null flux boundary conditions are not suitable. Last but not least, numerical simulations could be carried on, since they provide a preliminary tool to explore the analytical properties of the model.

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