



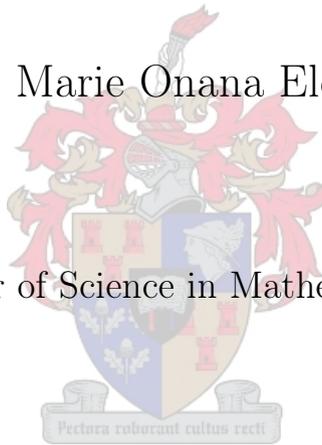
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Mathematical Modelling of the Stages of Solid Tumours Growth and the Nonlocal Interactions in Cancer Invasion.

by

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Abstract

For solid tumours to grow and metastasise, they need to pass through two distinct stages: the avascular growth phase in which the tumour remains in a limited diffusion size and the vascular growth phase where the invasion may take place. In order to accomplish the transition from the former to the latter growth phase, a solid tumour may secrete a substance known as tumour angiogenesis factor (TAF) into the surrounding tissues to stimulate its own blood vessels. Once the tumour has its own blood supply, it can invade other parts of the body destroying healthy tissues organs by secreting the matrix degrading enzymes (MDE). During the invasion, the adhesion both cell-cell and cell-matrix play an extremely important role.

In this work, we review some mathematical models dealing with various stages of development of solid tumours and the resulting reaction diffusion equations are solved using the Crank-Nicolson finite differences scheme. We also present a system of reaction-diffusion-taxis partial differential equations, with nonlocal (integral) terms describing the interactions between cancer cells and the host tissue. We then investigate the local and global existence of the solution of the previous model using the semigroup method and Sobolev embeddings.

OPSOMMING

Daar is twee afsonderlike fases nodig vir soliede kanker gewasse om te groei en kwaadaardig te word: die avaskulêre groeifase waarin die gewas tot 'n sekere diffusie grootte beperk word en die vaskulêre groei fase waar die indringing plaasvind. Ten einde die oorgang tussen die twee fases te bewerkstellig, skei die soliede gewas 'n stof in die omliggende weefsel af wat bekend staan as 'tumor angiogenese factor' (TAF). Dit stimuleer die vorming van die gewas se eie bloedvate. Wanneer die gewas sy eie bloedtoevoer het, kan dit ander dele van die liggaam indring en gesonde orgaanweefsel vernietig deur die afskeiding van die 'matrix degrading enzymes' (MDE). Gedurende hierdie proses speel die sel-sel en sel-matriks interaksies 'n belangrike rol. In hierdie werk het ons 'n paar wiskundige modelle vergelyk wat die verskillende stadiums van die ontwikkeling van soliede gewasse beskryf. Die gevolglike diffusiereaksie vergelykings is opgelos deur gebruik te maak van die 'Crank-Nicolson finite differences scheme'. Ons bied ook 'n stelsel van 'reaction-diffusion-taxis', met nie-lokale (integrale) terme wat die interaksies tussen kankerselle en die gasheerweefsel

ABSTRACT

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beskryf. Ons stel dan ondersoek in na die lokale en globale bestaan van die oplossing van die vorige model, met behulp van die semi-groep metode en die Sobolev ingebeddings.

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Chapter 1

Introduction

Every day, cancer nurses care for patients with life-threatening conditions, and they are responsible for the delivery of complex treatments to their patients. Before imposing them a medication, they have to understand how it works. To do so, they need to understand the process of tumour evolution which involves many different phenomena occurring at different scales. In fact, the phenomenological description depends on the enlargement used, this means, the microscopic, mesoscopic or macroscopic level.

Cancer is a term used for diseases that affect any organ in the body, in which abnormal cells divide in an uncontrolled manner and in some instances are able to invade other tissues. The abnormality in cancer is due to the imbalance between the proliferation and the death of cells, which is caused by the mutations of their genetic material. After the tumour's formation, cells require interactions with the extracellular matrix (ECM) components and these interactions are done via a family of transmembrane receptors, known as integrins. In addition to the fact that these receptors facilitate the adhesion of cells on the ECM, the receptors also regulate the signals of cells in processes such as proliferation, apoptosis and migration.

There are three different stages in the growth of a tumour and there is a lot of controversy over how exactly cancer is initiated. Researchers are concentrating their efforts on answering specific questions related to cancer development. A variety of mathematical models have been developed for various underlying aspects of cancer growth and attempts to give more biologically relevant models have been made by different people. Some focused on the first stage of tumour growth to find the origin of tumours, their internal structure, while others put their attention on the last two stages to study how a normal cell becomes a cancer cell and how a tumour invades other parts of the body. The next sections cover a review of literature relevant to this research.

1.1 Review of Previous Works on Tumour Growth Models

Various mathematical models of tumour growth by diffusion have been proposed. Some models are based on nutrients consumption and others on chemical inhibitors. We present models based on nutrients in the next two paragraphs.

The work by Tiina, Chapman and Maini in [39] provides a comprehensive list of existing models in the growth of avascular tumours. The authors discussed the models in great details. Casciari, Sotirchos and Sutherland in [12] presented a model of great experimental relevance as it includes a sufficient level of biochemical complexity. The model considered a spherical tumour interacting with oxygen, glucose, lactate, carbon dioxide, bicarbonate, chloride and hydrogen. The main focus of the paper was to estimate the pH level inside the tumour and to predict the oxygen and glucose concentration profile. It was found that the respective concentrations were much lower in the center of the spheroid than it was near the surface of the spheroid. Moreover, the pH at the center was lower than it was at the boundaries. Those findings were confirmed experimentally [12].

Anastasios, Chaplain and Vladimir in [31] examined a spatio-temporal mathematical model describing the growth of a solid tumour in the presence of an immune system response. They particularly focused their attention on the interaction of tumour cells with a special sub-population of T-cells, called tumour infiltrating cytotoxic lymphocytes (TICLS), in a relatively small multicellular tumour without central necrosis and at a stage prior to tumour-induced angiogenesis. Their numerical and bifurcation analysis of the spatio-temporal model of cytotoxic T-cell dynamics supported the idea that the TICLS play an important role in the control of cancer dormancy. Moreover the numerical simulations demonstrated the existence of dynamics that are quasi-stationary in time but heterogeneous in space. A linear stability analysis of the underlying spatial homogeneous ordinary differential equation (ODE) kinetics coupled with numerical investigation of the ODE system revealed the existence of a stable limit cycle.

While these models based on nutrients consumption were formulated, some works have also been done on models based on chemical inhibitors. John Adam in his paper [4] presented a one dimensional model of tumour growth in which the source of mitotic inhibition is nonuniformly distributed within the tissue. The purpose of the work was to examine the sensitivity of the results in the original schematic model of Glass [28] to nonuniform production in the central region. The results indicated that the model, though schematic, is very sensitive to the type of the source term assumed. John Adam and Maggelakis in [7] presented two mathematical models for the control of the growth of a tumour by diffusion of the mitotic inhibitors. They assumed the inhibitor production rate to be uniform in the necrotic core of the tumour for the first

model and nonuniform in the non-necrotic region for the second model. Comparisons of the results from the two models indicated a result that is similar to the one observed in [4], that the models are sensitive to the source distribution production.

In [4], a simplified one dimensional model of tumour growth was presented. The basic process involved was diffusion growth inhibitor which was produced in a nonuniform rate throughout the growing tissue. In [5], John Adam examined the properties of a mathematical model in one, two and three dimensions following the treatment of Shymko and Glass in [42] for uniform inhibitor production and he compared the two types of model. The analysis of the model represent a detailed study of the properties of highly non-uniform inhibition from which information on intermediate inhibition models can readily be deduced. A mathematical model for the control of growth by a diffusion mitotic inhibition is presented in [42]. The stability of growth was examined as a function of the values of the parameters describing the production, transport and decay of the mitotic inhibitor and also as a function of the geometry of the growing tissue. Shymko and Glass compared the patterns of mitosis mathematically and experimentally. Their results indicated that the cellular parameters, which closely reproduce patterns for growth as a sphere, lead to a self-limiting growth in three dimensions, but limitless growth in two dimensions. This means that the stability of growth can depend on the geometry of that growth. This observation is in agreement with earlier results from tissue culture [42]. In addition, they suggested some experimental approaches which can be used to study relative effects of vascularisation, nutrition, mitotic inhibition and growth geometry in normal and cancerous growth.

Based on the assumption that the growth inhibitory factor (GIF) diffuses within the spheroid in a nonlinear spatially dependent manner, Chaplain, Benson and Maini presented a mathematical model in [14] for the production of a growth inhibitory factor within the multicell spheroid. The results showed that the above assumption combined with a non linear source term can also account for the experimental observations. Hence they have shown that a nonuniform source function is not the only way to produce qualitatively correct GIF concentration profiles within multicell spheroids. They came with the conclusion that more experimental work on the precise mechanism governing cell cycle kinetic must be done to elucidate the underlying tissue heterogeneity.

1.2 Review of Previous Works on Cancer Invasion Models

One of the interesting mathematical model dealing with cancer invasion is the one presented by Gatenby and Gawlinski in [25] which describes the transition from benign to malignant growth using the acid mediated invasion hypothe-

sis. The model consists of coupled reaction-diffusion equations for cancer cells, normal cells and acidity. The model explores the hypothesis that, as a result of anaerobic metabolism (the creation of energy through the combustion of carbohydrates in the absence of oxygen), the cancer cells create an acidic environment which kills normal cells. This model predicts a variable interfacial structure, including a previously unrecognised hypocellular interstitial gap in some malignancies. It also predicts a strong correlation between the interfacial structure and the tumour growth velocity which can be readily tested.

Alexander and Chaplain in [38] proposed a hybrid discrete-continuum mathematical models for cancer invasion to study the early growth of solid tumours and their ability to degrade and migrate into the surrounding extracellular matrix. They considered cancer cells as discrete individual entities which interact with each other via a potential function. The extracellular matrix (ECM), the matrix degrading enzymes and the degrading stroma are governed by partial differential equations. The computational results they obtained are able to reproduce local invasion strategies of a small number of cancer cells.

Since the processes of chemotaxis (cellular locomotion directed in response to a concentration gradient of the diffusible matrix degrading enzymes (MDEs)) and haptotaxis (cellular locomotion directed in response to a concentration gradient of the non diffusible adhesive molecules within the extracellular matrix) are generally involved in tumour invasion, Christoph Walker and Glenn Webb in [48] modelled haptotaxis. They have investigated a system of non-linear partial differential equations modelling haptotaxis. They proved global existence and uniqueness of classical solutions. They interpreted the haptotaxis in tumour growth as the control of cell movement by the differential strengths of cell-cell adhesion gradients. Youshan Tao and Mingjun Wang in [47] combined the two processes of chemotaxis and haptotaxis to yield to a 3×3 chemotaxis-haptotaxis system modelling cancer invasion. The model consists of a parabolic chemotaxis-haptotaxis partial differential equation describing the evolution of tumour cell density, an elliptic partial differential equation governing the evolution of proteolytic enzyme concentration and an ordinary differential equation modelling the proteolysis of the ECM. The existence and uniqueness of the global classical solution is proved by the variation of a parameter. The central aim of the work was to develop new L^p -estimate techniques for a 3×3 chemotaxis-haptotaxis system.

Assuming that the haptotaxis process takes place during the invasion, Szymanska, Lachowicz, Chaplain and Wrzosek developed in [16] a mathematical model of cancer cells invasion of the tissue by incorporating cell-cell and cell-matrix adhesion. They also included an equation for the matrix degrading enzymes which are substances secreted by cancer cells to degrade the extracellular matrix. The results obtained showed that as the cell-matrix and cell-cell adhesions become stronger, cancer cells become more aggressive and they invade the tissue more quickly with the extracellular matrix being degraded by the enzymes.

Byrne and Chaplain focused on the physical aspect of cell-cell adhesion in the growth and development of carcinomas. They developed a mathematical model which assesses how changes in the relative importance of competing physical effects affect a tumour's potential invasion. It is important to note that here the tumour comprises proliferating cells only, and the growth rate is regulated by an external-supplied nutrient. The growth of the tumour depends on the balance between expansive forces (caused by cell proliferation) and cell-cell adhesion forces which exist to maintain the tumour's compactness. Cell-cell adhesion is incorporated into the model using the Gibb's theorem. The analysis of the model predicted that in the absence of cell-cell adhesion, all asymmetric models grow in time. The authors concluded that knowledge of the strength of cell-cell adhesion forces relative to the other forces acting within a tumour, could be clinically important in estimating a tumour's ability to invade its host environment.

In [26], Chaplain and Gerish formulated a novel continuum model of cancer cell invasion of tissue which explicitly accounts for the biological processes of cell-cell and cell-matrix adhesion. They used non-local terms in a system of partial differential equations with the assumption that cells use the so called "sensing radius" R to detect their environment. They concluded that the tumour microenvironment, the supply to the tumour, the biomechanical properties of the matrix and cell-cell and cell-matrix adhesion have a major impact on the invasion. In order to assess the invasiveness of HT1080 (primate malignant tumour), tumour cells migrating through a collagen gel, Perumpanani and Byrne developed a mathematical model in [37]. Analysis of the mathematical model suggested that the interactions between invasion and proliferation on collagen concentration. The result is consistent with experiments performed in the absence of externally imposed chemical gradients; which showed that HT1080 invasiveness was related in a biphasic manner to collagen (group of naturally occurring proteins) concentration [37]. Their work suggested that, in addition to the composition of ECM molecules, regional variations in their concentration may affect the propensity of the tumour to invade a particular tissue.

In this work we present a review of some mathematical models which attempt to describe the stages and processes involved in solid tumour growth and cancer invasion. Chaplain in [13], presented a mathematical model for the growth of an avascular tumour which focused on the role played by one or more growth inhibitory factors. Inspired by his model, we investigate a mathematical model showing the reaction of tumour cells to the diffusion of the growth inhibitory factor. However, the main aims of the research undertaken for this thesis is summarised as follows

- The development of a mathematical model of the interactions between growth inhibitory factors and tumour cells in the avascular stage.

- The development of a mathematical model of the interactions between the tumour angiogenesis factor and endothelial cells during the angiogenesis.
- The development of a mathematical model of the nonlocal interactions between the cells and the extracellular matrix during the cancer invasion.
- The local and global existence of the solutions.

The thesis consists of six chapters, of which this chapter is Chapter 1. In Chapter 2, we give a general view on how cancer is initiated from the microscopic to the macroscopic level. Chapter 3 is about the mathematical results that are going to be used. Mathematical models of the stages of solid tumours development are presented in Chapter 4. Then, in Chapter 5, a mathematical model of cancer invasion of the tissue is investigated. Chapter 6 concludes and a discussion of future research possibilities in this area is made.

Chapter 2

Biological Background

2.1 Preliminary Concepts

The human body is made up of about 10 trillion cells and the ability of each of these to produce exact replicas is an essential component of life. In order to understand what goes wrong with a normal cell to become a cancer cell, it is important to understand the normal cellular processes.

2.1.1 Control of the cell cycle

A cell is the basic unit of every living matter. Every cell is remarkable not only because it has the ability to carry out complex tasks, for example uptake of nutrients and conversion to energy, and the ability to replicate, but it also contains all the instructions to carry out these tasks [30]. There are two different types of cells, the prokaryotes and the eukaryotes. The fact that cancer is described as the uncontrolled proliferation and growth of cells into other tissues, leads us to explain the normal mechanisms that control the cell cycle. We begin by understanding how these controls may malfunction and cause cancer to develop.

- **Cyclins and Cyclin-Dependent Kinases**

There are many different proteins located within the cytoplasm which control the cell cycle; two of the main types are cyclins and cyclin-dependent kinases (CDKs). A cyclin joins with a CDK to form a complex cyclin-CDK. If a problem with the cell cycle is detected, then the activation of the cyclin-CDK complex is not completed. This leads to the activation of a transcription factor by the removal of a transcription factor inhibitor. The transcription factor activates transcription of the genes required for the next stage of the cell cycle, including the cyclin and CDKs genes. During the cell cycle, the levels of cyclins within the cell will rise and fall but the levels of CDKs will remain fairly constant. The activation of the CDKs is a central event in regulating the cell cycle and their activity is therefore regulated at many different levels [30].

- **Tumour Suppressor Genes**

Tumour suppressor genes prevent excessive growth of a cell; the well known ones are *P53* and retinoblastoma (Rb) gene. The latter one is involved in the G1 signal by binding to a family of transcription factors known as the E_{2F} family, thereby repressing their transcription of E_{2F} -responsive genes, such as thymidine kinase (TK), needed for DNA replication, and cyclin E and A, needed for cell cycle progression. Rb is activated when cyclin D forms a complex with *CDK4/6* (cyclin D/*CDK4/6*, hence making active) this in turn phosphorylates Rb, which allows E_{2F} to be released.

The *P53* protein is a tumour suppressor gene (TSG) essential for protecting us against cancer. More than half of human cancers have *P53* mutations and therefore no functioning *P53*. *P53* works by sensing DNA damage and halting the cell cycle. In response to a variety of stress signals, for example DNA damage, *P53* switches from an inactive state to an active one. This is essential because if the DNA is damaged but still replicated in the S-phase, it could eventually manifest in the form of a protein mutation. By halting the cell cycle at the G1 signal (check-point), this can be prevented. The *P53* protein is also involved at the G2 checkpoint in cases for example where DNA has been synthesized incorrectly. At this checkpoint, *P53* binds to E_{2F} and prevents it from triggering transcription of proto-oncogenes which are required for the mitosis. Proto-oncogenes are important promoters of normal cell growth and division. If they become mutated, they can have a detrimental effect. A single oncogene cannot cause cancer by itself but it can cause the cell cycle to lose its inhibitory controls thereby increasing the rate of mitosis. When a cell loses control over mitosis, it can be the beginning of the pathway leading to the development of cancer [30].

2.2 Behaviour of a Mutated Cell

According to [30], a review by Hanahan and Weinberg in 2000 summarized the changes that appear when a normal cell becomes malignant, as six alterations to cell physiology that collectively dictate malignant growth.

1. **Self-Sufficiency in Growth Signals**

For a normal cell to proliferate, it must wait for the growth signals, but cancer cells acquire the ability to produce their own growth signals, and they can synthesize growth factors to which they also respond. Briefly, the cell begins to operate as an independent entity.

2. **Insensitivity to Inhibitors**

Since cells are independent, they control their external environment and decide whether to proliferate or not. Many anti-proliferative signals func-

tion via the Rb protein therefore, if this is disrupted, the control of the cell cycle is lost and cell will proliferate.

3. Evasion of Apoptaxis

Research over the past decade has determined that the apoptotic programme is present in nearly all cells in the body in a latent form. It seems that resistance towards it is a characteristic of most and perhaps all cancers. One way in which apoptosis might be avoided is the loss or mutation of *P53*, which acts as a pro-apoptotic regulator by sensing DNA damage.

4. Limitless Replicative Potential

Research involving cells in culture have suggested that normal cells can only undergo 60-70 replications, after which time they stop growing and die. Cancer cells however have acquired the capability of endlessly replicating in many cases due to an enzyme known as telomerase.

5. Sustained Angiogenesis

Angiogenesis is the formation of the new blood vessels, which is an essential process that must be sustained if the cells in the tumour mass are to be supplied with oxygen and nutrients.

6. Tissue Invasion and Metastasis

The majority of cancer deaths are caused by metastasis of primary tumour mass to other sites of the body. This begins with the rearrangement of the cells cytoskeletons (cellular skeleton), which allows them to attach to other cells and move over or around them. Once they hit a blockage, for example the basal lamina, the cancer cells secrete enzymes to break it down. Included in these enzymes are matrix metalloproteins (MMP) (proteins that contains metal ions), which act as "molecular scissor" and cut through proteins that might hinder the passage of the cancer cells. Once through the basal lamina, the cells can move into the bloodstream and circulate throughout the body until they find a suitable site to settle and regrow. A commonly observed alteration that leads to metastasis involves the cell-to-cell interaction molecule E-Cadherin. Coupling this molecule between cells results in transmission of antigrowth signals, acting as a suppressor of invasion and metastasis. It appears that E-Cadherin function is lost in the majority of epithelial cancers due to gene mutations [30].

2.2.1 Growth Factors and Cell-Extracellular Matrix Adhesion

During a tumour growth, there are many factors that are involved in the regulation of the mitosis. Although those factors remain poorly understood, three

major classes of active regulatory factors have been identified. We have nutrient and oxygen, growth stimulating factors and growth inhibitory factors (mitosis might be inhibited by products of cellular metabolism, such as carbon dioxide and lactic acid, or high concentration of regulatory molecules) [42].

For a tumour to become a cancer, it needs to pass through the angiogenesis which is the process of new blood vessel growth. The angiogenesis is induced by an angiogenetic factor called angiogenin, which is a protein provided by the ANG (angiogenin ribonuclease RNase A family 5) gene. In the process of angiogenesis, angiogenin helps stimulating the growth and division of endothelial cells, which line the inside surface of blood vessels to form new blood vessels. Besides its ribonucleolytic activity, the binding of the ANG gene with endothelial cells surface is also needed for its biological function. During an effort to identify the ANG receptor in endothelial cells, a 42-kDa cell surface protein was initially found as an ANG-binding molecule, and was later shown to be muscle type α -actin (protein). Upon binding of ANG to actin, some ANG-actin complex dissociate from the cell surface. Through the formation of its actin complex, the ANG promotes the degradation of the basement membrane and the ECM [24].

The acellular material around cells in the body is called the extracellular matrix (ECM). That mixture of nonliving material has the following functions

- Supports for cells and tissues.
- Integrates cells into tissues.
- Influences cells shape and cell movement.
- Influences cells development and differentiation.
- Coordinates cellular functions through signaling with cellular adhesion receptors.
- Saves as a reservoir the extracellular signaling molecules.

The ECM encompasses fibers (collagen and elastin, which provides strength and flexibility), proteoglycans (proteins-saccharide complexed, providing an ample matrix), adhesive glycoproteins (fibronectin and laminin, which glue cells and the ECM) [1].

Cells interact with the ECM via a family of transmembrane receptors, known as integrins. Integrins are receptors that mediate attachment between a cell and tissues (other cells or the ECM) surrounding it. They also play a role of cell signaling and thereby, regulate cellular shape, motility and cell cycle. Integrins work alongside other proteins such as cadherins, selectins and syndecans to mediate cell-cell and cell-matrix interaction and communication [21].

Chapter 3

Mathematical Preliminaries

In this chapter, we give a review of the results, definitions and theorems which will be used in our analysis. We will divide this chapter into four sections. In the first section we introduce the notations, in the second section we give useful definitions and theorems. An insight into what semigroups method is about is given in the third section. Finally, a general idea on the finite difference method of Crank-Nicolson is stated in section four.

3.1 Notation

In this section, we give a review of notation that will be used in the paper. We start by stating that $\partial_{x^k}^k$ will stand for the k -th partial derivative with respect to x . An n -tuple of non-negative integers $\alpha = (\alpha_1, \alpha_2, \dots, \alpha_n)$ is called a **multi-index** and we define

$$|\alpha| = \sum_{i=1}^n \alpha_i$$

and $x^\alpha = x_1^{\alpha_1} x_2^{\alpha_2} \dots x_n^{\alpha_n}$ for $x = (x_1, x_2, \dots, x_n)$. Denoting $D_k = \partial_{x_k}$ and $D = (D_1, D_2, \dots, D_n)$ we have

$$D^\alpha = D_1^{\alpha_1} D_2^{\alpha_2} \dots D_n^{\alpha_n} = \partial_{x_1^{\alpha_1}}^{\alpha_1} \partial_{x_2^{\alpha_2}}^{\alpha_2} \dots \partial_{x_n^{\alpha_n}}^{\alpha_n}.$$

If Ω is an open subset of \mathbb{R}^d , we denote by $L^p(\Omega)$, $p \in [1, \infty)$, the linear space of all measurable functions u in Ω such that the norm

$$\|u\|_p := \left(\int_{\Omega} |u(x)|^p dx \right)^{\frac{1}{p}}$$

is finite and by $L^\infty(\Omega)$, the linear space of all essentially bounded measurable functions u in Ω ; and its norm is defined by

$$\|u\|_\infty := \operatorname{ess\,sup}_{x \in \Omega} |u(x)|.$$

$L^p(\Omega)$ and $L^\infty(\Omega)$ are Banach spaces with respect to their norms. We define $W_p^{(l)}(\Omega), p \in [1, \infty)$ the Sobolev space

$$W_p^{(l)}(\Omega) = \{u \in L^p(\Omega) \mid D^\alpha u \in L^p(\Omega), |\alpha| \leq l\}.$$

$W_p^{(l)}(\Omega)$ is a Banach space with respect to the norm

$$\|u\|_p^{(l)} := \left(\sum_{|\alpha| \leq l} \|D^\alpha u\|_p^p \right)^{\frac{1}{p}}.$$

It is conventional to denote $W_2^{(k)}(\Omega)$ by $H^k(\Omega)$. By $\overset{\circ}{W}_p^{(l)}(\Omega)$ we denote the closure of $C_c^\infty(\Omega)$ in the norm of $W_p^{(l)}(\Omega)$ where by $C_c^\infty(\Omega)$ we denote the class of infinitely smooth functions in Ω with compact support. We denote by $L(X, Y)$ the space of continuous linear operators with domain X and range in Y , where X and Y are Banach spaces (when $X = Y$ we write $L(X)$). $\sigma(A)$ and $\rho(A)$ are the spectrum and the resolvent of the operator A , respectively .

3.2 Definitions and Theorems

Definition 3.2.1. Let X be a Banach space with the norm $\|\cdot\|_X$ and let u be an X -valued function of $t \in [0, \infty)$. **The strong derivative** $\frac{du(t)}{dt}$ of u at $t > 0$ is defined to be the element $\bar{u}(t)$ such that

$$\lim_{h \rightarrow 0} \|h^{-1}[u(t+h) - u(t)] - \bar{u}(t)\|_X = 0$$

provided that the limit exists ([33], Def 2.1.2).

Definition 3.2.2. A Banach space X is **of type L** if it consists of equivalence classes of numerically-valued functions defined on a set Ω and if it has the two following properties

1. If u is a continuous X -valued function defined on $I = [\alpha, \beta]$, then there exists a function ϕ measurable on the product $I \times \Omega$ such that $u(t) = \phi(t, \cdot)$ (equality in X) for each $t \in [\alpha, \beta]$.
2. If u is continuous on $I = [\alpha, \beta]$ and ϕ is any function that is measurable on $I \times \Omega$ and satisfies $u(t) = \phi(t, \cdot)$ for each $t \in [\alpha, \beta]$, then

$$\left[\int_\alpha^\beta u(t) dt \right] (\cdot) = \int_\alpha^\beta \phi(t, \cdot) dt.$$

The integral on the left hand side is the abstract Riemann integral and the one on the right hand side is the Lebesgue integral of numerically-valued function of type L ([33], Def 2.1.5).

Definition 3.2.3. Let Ω be a boundary domain in \mathbb{R}^n with a smooth boundary $\partial\Omega$. Consider the differential operator of order $2m$,

$$A(x, D) = \sum_{|\alpha| \leq 2m} a_\alpha(x) D^\alpha$$

where the coefficients are sufficiently smooth complex-valued functions of x in Ω . The operator $A(x, D)$ is **strongly elliptic** if there exists a constant $c > 0$ such that

$$A'(x, \xi) \geq c|\xi|^{2m}$$

for all $x \in \bar{\Omega}$ and $\xi \in \mathbb{R}^n$. Here,

$$A'(x, \xi) = \sum_{|\alpha|=2m} a_\alpha(x) \xi^\alpha$$

is the principal part of the operator $A(x, \xi)$ [36].

Definition 3.2.4. Let us consider the boundary value problem

$$\begin{cases} \frac{du}{dt} = Au, & t > t_0 \\ u(t_0) = u_0, \end{cases} \quad (3.1)$$

where A is a closed operator on a Banach space. A continuously differentiable function $u : [t_0, \infty) \rightarrow X$ is called a **classical solution** of the initial value problem (3.1), if $u(t) \in D(A)$ and u satisfies the initial value problem (3.1).

Definition 3.2.5. Let (X, d) be a complete metric space. A map $T : X \rightarrow X$ is a **contraction** if there exists a nonnegative number $\delta \leq 1$ such that

$$d(T(u), T(v)) \leq \delta d(u, v) \quad \text{for all } u, v \in X.$$

T is a **strict contraction** if $\delta < 1$.

A point $u \in X$ is called a **fixed point** of T if $T(u) = u$.

Theorem 3.2.6 (Banach's Contraction Mapping Theorem). Let (X, d) be a complete metric space and let $T : X \rightarrow X$ be a strict contraction. Then, there exists exactly one point $u \in X$ such that

$$T(u) = u.$$

Proof. See [2]. □

Theorem 3.2.7. Let a_{ij} , $(i, j = 1, 2, \dots, n)$ be functions independent of the time satisfying

$$a_{ij} \in L^\infty(\Omega), \quad \sum_{ij} a_{ij}(\Omega) \xi_i \xi_j \geq \alpha \sum_{i=1}^n \xi_i^2 \quad \text{a.e in } \Omega, \quad \alpha > 0.$$

For simplicity, we assume $a_{ij} = a_{ji}$, $i, j = 1, 2, \dots, n$. We set

$$a(u, v) = \sum_{ij} \left(a_{ij} \frac{\partial u}{\partial x_i}, \frac{\partial v}{\partial x_j} \right), \quad u, v \in H^1(\Omega), \quad (3.2)$$

where (\cdot, \cdot) is the scalar product in $L^2(\Omega)$. The semigroup $\{T(t)\}_{t \geq 0}$ generated by (3.2) subject to any boundary conditions independent of the time operates in $L^p(\Omega)$ for p such that $1 \leq p \leq +\infty$.

Proof. See [19], p.536-537. □

3.3 The Semigroup Method

Many phenomena in life are modelled in terms of differential or integro-partial differential equations. Actually those equations are in most cases evolution equations, that means they are built by balancing the change of the system in time against its spatial behaviour. Equations of applied sciences are usually formulated in such a way that all the operations such as differentiation and integration are understood in a classical sense and the equation is supposed to be satisfied for all values of the independent variables in the relevant domain. One would always like to be able to find the exact analytical solution to the equation. Although such cases exist, there are always some obstacles that appear to make things more interesting. Hence all the equations cannot be treated in the same way. However, the way forward is to determine whether or not the solution exist, whether the solution is unique and how the solution behaves for large values of time without trying to find it. Answering these questions serves at to validate the numerical analysis of the equation which eventually leads to answers needed by practitioners. Semigroup method is one of the particular way of looking at the evolution of a system in which the evolution is described by a family of operators parameterised by time.

Thus, what is it about? Let us consider the equation

$$\begin{cases} \partial_t u(t, x) &= Au(t, x), \\ u(0, x) &= u_0(x), \end{cases} \quad (3.3)$$

in an abstract space X which is partially chosen for the relevance to the problem and partially for mathematical convenience. Once the space is chosen, the right hand side of (3.3) might be interpreted as an operator

$$A : D(A) \longrightarrow X,$$

defined on some subset $D(A)$ of X . We have to note that $D(A)$, which is not uniquely defined, is not necessarily equal to X . The system (3.3) can then be written as an ordinary differential equation in X :

$$\begin{cases} \frac{du(t)}{dt} &= Au(t) \\ u(0) &= u_0. \end{cases} \quad (3.4)$$

Here the domain $D(A)$ is chosen in such a way that the solution originating from it could be differentiated and belong to $D(A)$ so that both sides of the equation make sense. On a heuristic level, the solution to this problem "ought" to be $u(t) = e^{tA}u_0$ like in the finite dimensional case. However, for a strict treatment, a meaning must be given to the exponential of tA if A is an operator. It is known from elementary calculus that e^{tA} can be written in the following three different ways

$$e^{tA} = \sum_{n=0}^{\infty} \frac{t^n A^n}{n!}, \quad (3.5)$$

$$e^{tA} = \lim_{n \rightarrow \infty} \left(1 + \frac{t}{n}A\right)^n, \quad (3.6)$$

and

$$e^{tA} = \lim_{n \rightarrow \infty} \left(1 - \frac{t}{n}A\right)^{-n} \quad (3.7)$$

if A is a scalar or an $n \times n$ matrix.

From [10], since the partial sums of the series defined by (3.5) converge with respect to the norm on the space of $n \times n$ matrices with complex entries $M_n(\mathbb{C})$ (when A is an $n \times n$ matrix), and the map $t \rightarrow e^{tA}$ is continuous satisfying the properties

$$\begin{aligned} e^{(t+s)A} &= e^{tA}e^{sA} \quad \text{for all } t, s \geq 0 \\ e^{0A} &= I, \end{aligned}$$

the family $\{e^{tA}\}_{t \geq 0}$ is a homomorphism of additive semigroup $[0, \infty)$ into a multiplicative semigroup of matrices M_n and forms what is termed a semigroup of matrices.

Now, if $A : X \rightarrow X$ is a **bounded** linear operator, the representation given by (3.5) can still be used for the solution $u(t) = e^{tA}u_0$ of (3.4) since the series remains convergent, this time with respect to the norm in $L(X)$.

What happens if the operator A is **not bounded** on the whole space X ? Generally in this case the domain of A is a proper subspace of X . Because (3.5) and (3.6) involve iterates of A , their common domain could shrink to the trivial subspace $\{0\}$; the solution will then be defined on the trivial space $\{0\}$. Thus in general (3.5) and (3.6) cannot be used to obtain the solution of the abstract Cauchy problem (3.4).

The representation of the solution $u(t) = e^{tA}u_0$ is meaningful with e^{tA} calculated according to (3.7) [10]. From [10] that limit exists and defines a **strongly continuous semigroup** $(S(t))_{t \geq 0}$, that is a family of bounded linear operators $S(t)$ satisfying

1. $S(t+s) = S(t)S(s)$ for all $t, s \geq 0$,
2. $S(0) = I$,

3. $\lim_{t \rightarrow 0^+} S(t)x = x$, $x \in X$, (strongly continuity)

if and only if A is a densely defined closed operator and there exist numbers $M > 0$, $\omega \in \mathbb{R}$ such that the resolvent set of A contains the half-line (ω, ∞) and the Hille–Yosida estimates

$$\|(\lambda I - A)^{-n}\| \leq \frac{M}{(\lambda - \omega)^n}, \quad \lambda > \omega \quad (3.8)$$

are satisfied [10].

Let us note that if 1, 2 and the property that the function $t \rightarrow T(t)x$ is real analytic on $0 < t < \infty$ for each $x \in X$, are fulfilled then, $\{T(t)\}_{t \geq 0}$ is an **analytic semigroup**. If in addition to 1, 2, 3, we have

$$\|T(t)\|_X \leq 1$$

for $t \geq 0$ (contraction property), then T is said to be a C_0 **semigroup of contractions**.

Definition 3.3.1. *The linear operator defined by*

$$D(A) = \left\{ x \in X : \lim_{t \rightarrow 0} \frac{T(t)x - x}{t} \text{ exists} \right\}$$

and

$$Ax = \lim_{t \rightarrow 0} \frac{T(t)x - x}{t} \quad \text{for } x \in D(A)$$

is called the **infinitesimal generator** of the semigroup T .

Definition 3.3.2. *Let X be a Banach space and A a linear operator in X . A is called a **sectorial operator** if it is a closed densely defined operator such that for some ϕ in $(\frac{\pi}{2}, \pi)$, $M \geq 1$ and a real \mathbf{a} , the sector*

$$S_{\mathbf{a}, \phi} = \{ \lambda, \quad |\arg(\lambda - \mathbf{a})| \leq \phi \quad \text{with } \lambda \neq \mathbf{a} \}$$

is in $\rho(L)$ and

$$\|(\lambda I - A)^{-1}\|_X \leq \frac{M}{|\lambda - \mathbf{a}|},$$

for all $\lambda \in S_{\mathbf{a}, \phi}$.

Theorem 3.3.3. *If A is a sectorial operator, then $-A$ is the infinitesimal generator of an analytic semigroup $\{e^{-At}\}_{t \geq 0}$ where*

$$e^{-At} = \frac{1}{2\pi i} \int_{\Gamma} (\lambda + A)^{-1} e^{\lambda t} d\lambda, \quad (3.9)$$

and Γ is a contour in $\rho(-A)$, with $\arg \lambda \pm \theta$, $|\lambda| \rightarrow \infty$ for some θ in $(\frac{\pi}{2}, \pi)$.

Definition 3.3.4. Suppose that A is a sectorial operator in a Banach space X and $\operatorname{Re}(\sigma(A)) > 0$. For any $\alpha > 0$ the **fractional power** of A is defined as follows

$$A^{-\alpha} = \frac{1}{\Gamma(\alpha)} \int_0^{\infty} t^{\alpha-1} e^{-At} dt,$$

with e^{-At} defined by (3.9).

Proof. See [29], p.21. □

Let us consider the nonlinear equation

$$\begin{cases} \frac{du}{dt} + Au = f(t, u), \\ u(t_0) = u_0, \quad t > 0, \end{cases} \quad (3.10)$$

where A is assumed to be a sectorial operator so that the fractional powers of $A_1 \equiv A + aI$ (a is a constant) are well defined, and the spaces $X^\alpha = D(A_1^\alpha)$ with the norm $\|u\|_{X^\alpha} = \|A_1^\alpha u\|_X$ are defined for $\alpha \geq 0$.

Lemma 3.3.5. If u is a classical solution of (3.10) on an interval (t_0, t_1) , then

$$u(t) = e^{-A(t-t_0)} u_0 + \int_{t_0}^t e^{-A(t-s)} f(s, u(s)) ds. \quad (3.11)$$

Conversely, if u is a continuous function from (t_0, t_1) into X^α and

$$\int_{t_0}^{t_0+\rho} \|f(s, u(s))\|_X ds < \infty$$

for some $\rho > 0$, and if (3.11) holds for $t_0 < t < t_1$, then u is a classical solution to the equation (3.10) on (t_0, t_1) .

Proof. See [29] p.53-54. □

Theorem 3.3.6. Let us assume that A is a sectorial operator, $0 \leq \alpha < 1$, and $f : U \rightarrow X$, U an open subset of $\mathbb{R} \times X^\alpha$, $f(t, u)$ is locally Hölder continuous in t and locally Lipschitzian in u . We also assume that for every closed bounded set $B \subset U$, the image $f(B)$ is bounded in X .

If u is the classical solution of (3.10) on (t_0, t_1) and t_1 is maximal, so that there is no classical solution of (3.10) on (t_0, t_2) if $t_2 > t_1$, then either $t_1 = +\infty$ or else there exists a sequence $t_n \rightarrow t_1^-$ as $n \rightarrow \infty$ such that $(t_n, u(t_n)) \rightarrow \partial U$. (If U is unbounded, the point at infinity is included in ∂U).

Proof. See [29], p.56. □

Theorem 3.3.7. Suppose $\Omega \subset \mathbb{R}^n$ is an open set having the C^m -extension property, $1 \leq p < \infty$, and A is a sectorial operator in $X = L^p(\Omega)$ with $D(A) = X^1 \subset W^{m,p}(\Omega)$ for some $m \geq 1$. Then for $0 \leq \alpha \leq 1$,

$$X^\alpha \hookrightarrow W^{k,p}(\Omega) \quad \text{when} \quad k - \frac{n}{q} < m\alpha - \frac{n}{p}, \quad p \geq p.$$

Proof. See [29], p.39-40. □

Theorem 3.3.8. *Assume A is sectorial, $f : U \rightarrow X$ is locally Lipschitzian on an open set $U \subset \mathbb{R} \times X^\alpha$, for some $0 \leq \alpha < 1$. Suppose u is a solution on $(t_0, t_1]$ of (3.10) and $(t_0, u_0) \in U$.*

Then if $\epsilon < 1$, $t \mapsto \frac{du(t)}{dt} \in X^\epsilon$ is locally Hölder continuous for $t_0 < t \leq t_1$, with

$$\left\| \frac{du}{dt} \right\|_{X^\epsilon} \leq C(t - t_0)^{\alpha - \epsilon - 1} \quad \text{for some constant } C.$$

Proof. See [29], p.71-72. □

Let us investigate the nonhomogeneous initial value problem.

$$\begin{cases} \frac{d}{dt}v(t) &= Av(t) + f(t) & t > 0 \\ v(0) &= z, \end{cases} \quad (3.12)$$

where $f : [0, \infty) \rightarrow X$ is locally L^1 . For the semigroups method associated with strongly elliptic differential operators in $L^p(\Omega)$, one generally chooses to work in $L^p(\Omega)$ rather than $L^2(\Omega)$ to obtain optimal regularity results.

Let $1 < p < \infty$ and let Ω be a bounded domain with smooth boundary $\partial\Omega$ in \mathbb{R}^n . Let

$$A(x, D) = \sum_{|\alpha| \leq 2m} a_\alpha(x) D^\alpha$$

be a strongly elliptic differential operator in Ω [36]. With that strongly elliptic operator, an unbounded linear operator A_p can be associated in $L^p(\Omega)$ as follows:

Definition 3.3.9. *Let $A = A(x, D)$ be a strongly elliptic operator of order $2m$ on a bounded domain Ω in \mathbb{R}^n and let $1 < p < \infty$. Set*

$$D(A_p) = W_p^{(2m)}(\Omega) \cap \overset{\circ}{W}_p^{(l)}(\Omega)$$

and

$$A_p u = A(x, D)u \quad \text{for } u \in D(A_p).$$

After defining the operator A_p the following theorem can be applied

Theorem 3.3.10. *Let $A(x, D)$ be a strongly elliptic operator of order $2m$ on a bounded domain Ω in \mathbb{R}^n and let $1 < p < \infty$. If A_p is the operator associated with A by definition (3.3.9) then $-A_p$ is the infinitesimal generator of an analytic semigroup on $L^p(\Omega)$.*

Proof. See [36], p.214. □

3.4 The Crank-Nicolson Numerical Scheme

Since our simulations are going to be done using the finite difference method of Crank-Nicolson it is important to explain how it works.

Let

$$\partial_t u = F(u, x, t, \partial_x u, \partial_{xx}^2 u) \quad (3.13)$$

be the equation we want to solve, subject to $u(0, x) = f(x)$ and other possible boundary conditions. We assume that the domain on which we are working is a rectangle with x (position) ranging from 0 to X and t (time) from 0 to T . We divide $[0, X]$ into N equally intervals of length Δx at x values indexed by $i = 0, \dots, N$ and $[0, T]$ into M equally intervals of length Δt at t values indexed by $j = 0, \dots, M$. We seek an approximation of the values of u at $(N + 1) \times (M + 1)$ gridpoints [3].

Letting $u_i^j = u(i\Delta x, j\Delta t)$ the approximation at the gridpoints, the Crank-Nicolson method is the average of the forward Euler method at j and the backward Euler method at $j + 1$ defined below

$$\begin{aligned} \frac{u_i^{j+1} - u_i^j}{\Delta t} &= F_i^j(u, x, t, \partial_x u, \partial_{xx}^2 u) \quad (\text{Forward}) \\ \frac{u_i^{j+1} - u_i^j}{\Delta t} &= F_i^{j+1}(u, x, t, \partial_x u, \partial_{xx}^2 u) \quad (\text{Backward}). \end{aligned}$$

This means that the Crank-Nicolson's method consists of discretizing equation (3.13) by using the following central difference method

$$\frac{u_i^{j+1} - u_i^j}{\Delta t} = \frac{1}{2} (F_i^{j+1}(u, x, t, \partial_x u, \partial_{xx}^2 u) + F_i^j(u, x, t, \partial_x u, \partial_{xx}^2 u)).$$

In general, there is an implicit and an explicit Crank-Nicolson scheme. Here we are interested in using the implicit one because it is known to be more stable (for a step Δx in position and Δt in time, the errors are of order $(\Delta x)^4$ and $(\Delta t)^2$ respectively). Therefore the implicit method (to get the "next" value of u in time, a system of algebraic equations must be solved) consists of approximating u , $\partial_x u$, $\partial_t u$ and $\partial_{xx}^2 u$ as follows

$$\begin{aligned} u &= \frac{u_i^{j+1} + u_i^j}{2} \\ \partial_t u &= \frac{u_i^{j+1} - u_i^j}{\Delta t} \\ \partial_x u &= \frac{u_{i+1}^{j+1} - u_{i-1}^{j+1} + u_{i+1}^j - u_{i-1}^j}{4(\Delta x)} \\ \partial_{xx}^2 u &= \frac{u_{i+1}^{j+1} - 2u_i^{j+1} + u_{i-1}^{j+1} + u_{i+1}^j - 2u_i^j + u_{i-1}^j}{2(\Delta x)^2}. \end{aligned}$$

Chapter 4

Mathematical Modelling of the Stages of Tumour Development

When modelling a new phenomenon, it is natural to focus initially on a simple and well defined system. Thus, before using the Navier-Stoke's equations to study turbulent fluid flow, one might first consider steady lamina flow. Looking through the mathematical literature on solid tumour growth, a similar pattern emerges: the earliest models focused on avascular tumour growth, then models of angiogenesis and vascular growth were developed, now models of cancer invasion and metastasis are starting to emerge. Given the large, and ever increasing number of mathematicians who are now studying different aspects of solid tumour growth, it would be impossible to review the entire modeling literature here. In this chapter we focus on mathematical models of avascular growth, angiogenesis and vascular growth.

Solid tumour growth is a complicated phenomenon involving many interrelated processes and as such presents the mathematical modeller with a correspondingly complex set of problems to solve. In this chapter we present a review of some recent mathematical models which attempt to describe the various stages and processes involved in solid tumour growth. In fact, solid tumours are known to develop into two distinct stages, avascular and vascular growth. In order to accomplish the transition from the former to the latter growth phase, the tumour passes through the stage called angiogenesis (the process in which new blood vessels are produced around the tumour for it to develop). In the avascular stage, the tumour mass is fed by the environment, thanks to the nutrients diffusing in the interstitial liquid (liquid found between the cells of the body that provides much of the liquid environment of the body). When the tumour mass has become so big (when the diameter has reached two millimeters) that this mechanism is no longer able to provide sufficient nutrients, the internal region forms a clump of dead cells called necrotic core. Just above the necrotic core, cells which have enough nutrients to survive (but cannot proliferate) form the quiescent layer. On the outside, a small rim with thickness of about three cells will have sufficient nutrients to proliferate. After reaching

its maximal size, the tumour stimulates the creation of a vascular structure, by secreting tumour angiogenesis factor (TAF) that diffuses into the surrounding tissue. When it reaches the neighbouring Endothelial Cells (EC) which are the cells forming blood vessels, the TAF stimulates the release of enzymes by endothelial cells which degrade their basement membrane. Once the degradation of the basement membrane has taken place, endothelial cells start to move in an orderly way towards the tumour. After the vascularisation is completed, the tumour can grow indefinitely and invade the other parts of the body.

We start our review in section 4.1, by presenting a simple but general model for the growth of an avascular tumour nodule, which focuses on the potential role played by one or more growth inhibitory factors (GIF) and the effect of the spatial distribution of this factor on cell mitosis. In the next model, studied in section 4.2, the growth and development of capillary sprout during tumour angiogenesis is investigated. The model focuses on the roles of endothelial cell proliferation and migration during angiogenesis. The chapter concludes with a summary of the preceding sections.

4.1 Avascular Tumour Growth: The Multicellular Spheroid Model

Assuming that the avascular growth can be studied in the laboratory by taking cancer cells in the form of a three dimensional multicell spheroid of radius R , in this section we present a mathematical model for the growth of a solid tumour at this stage. Since a realistic model of a spheroid growth should at least include certain nonuniformities in the central processes of inhibition of mitosis, consumption of nutrients, cell proliferation as well as the dependence of cell mitotic rate on growth inhibitor concentration, geometrical constraints and central necrosis, we will focus our attention on the diffusion of GIF within the spheroid and its possible effects on cell mitosis and proliferation.

4.1.1 Growth Inhibitory Factor Diffusion

Because of the associations (cell-cell junctions) in normal spheroid structure, intercellular permeability may not be constant between cells at different stages of the spheroid growth. In addition, it may happen that these associations are disrupted, and hence the possibility arises of normal intercellular signals being disrupted also. According to the above observations, we assume that the diffusion of the chemicals between cells may be non-constant and non-linear [13]. Here the chemicals we deal with are GIFs which are as in [13], assumed to control the mitosis by a discontinuous switch-like mechanism, such that if the concentration of the GIF is less than some threshold level α , say in any region within the tissue, mitosis occurs in the region, whereas if the concentration is greater than α , mitosis is completely inhibited. If $C = C(\mathbf{r}, t)$

is the concentration of GIF within the spheroid occupying the region Γ in \mathbb{R}^3 , its rate of increase is modelled as follows

$$\text{rate of increase of } C = \text{diffusion of GIF} - \text{decay of GIF} + \text{production of GIF}, \quad (4.1)$$

which mathematically is written as

$$\partial_t C = -\nabla \cdot J - \gamma C + \lambda S(\mathbf{r}), \quad (4.2)$$

where γ is the loss constant, λ the production rate, $S(\mathbf{r})$ the source function and J is the flux defined by

$$J = -D(\mathbf{r})\nabla C, \quad (4.3)$$

with $D(\mathbf{r})$ being the spatially dependent diffusion coefficient. Hence equation (4.2) becomes

$$\partial_t C = \nabla \cdot (D(\mathbf{r})\nabla C) - \gamma C + \lambda S(\mathbf{r}). \quad (4.4)$$

Previous papers make the assumption that the GIF is produced throughout the tissue by the individual cells modelled by a source $S(\mathbf{r})$ function, which has been used in various forms. According to [13], Shymko and Glass in their original model [42] assumed that the GIF is produced at a constant rate throughout the tissue and they defined the uniform function

$$S(\mathbf{r}) = \begin{cases} 1, & \mathbf{r} \text{ inside the tissue,} \\ 0, & \mathbf{r} \text{ outside the tissue.} \end{cases} \quad (4.5)$$

In order to more accurately model the heterogeneity of cells within the tumour, Adam in [4, 5, 6] considered a nonuniform source function of the form

$$S(r) = \begin{cases} 1 - \frac{r}{R}, & 0 \leq r \leq R, \\ 0, & r > R, \end{cases} \quad (4.6)$$

where r is the distance from the origin of the spheroid. However, Britton and Chaplain have shown in [11] that the above nonuniform source of Adam [4, 5, 6] is not realistic from the biological point of view since $S'(0)$ is not zero. Hence, they have suggested a smooth source function of the form

$$S(r) = \begin{cases} 1 - \frac{r^2}{R^2}, & 0 \leq r \leq R, \\ 0, & r > R. \end{cases} \quad (4.7)$$

In this work we intend to work with all three forms of the source functions to see their effects in the model.

In order to close the problem we have stated above, we need some appropriate boundary conditions. Therefore, because of the spherical symmetry of the

spheroid, we assume that at its center the flux of GIF is zero. Hence, we have the following equation

$$\partial_r C = 0 \quad \text{at } r = 0. \quad (4.8)$$

At equilibrium (at $r = R$), the concentration of GIF inside the tumour is equal to the one outside the tumour leading to

$$D(\mathbf{r})\partial_r C = -PC, \quad r = R, \quad (4.9)$$

where P is the permeability of the tissue. Thus, considering the spherical geometry [13], the problem under consideration is given by

$$\partial_t C = \frac{1}{r^2} \partial_r (r^2 D(r) \partial_r C) - \gamma C + \lambda S(r), \quad (4.10)$$

subject to

$$\begin{cases} \partial_r C = 0, & \text{at } r = 0, \\ D(r)\partial_r C - PC = 0, & \text{at } r = R, \end{cases} \quad (4.11)$$

with $S(r)$ taking the different forms mentioned above.

In order to reduce the number of parameters of the above system it is convenient to non dimensionalise, and hence (following [11]) we choose appropriate reference variables. Thus we define the new variables [15]

$$\bar{r} = \frac{r}{R}, \quad \bar{C} = \frac{C}{\alpha}, \quad \bar{t} = \frac{D_C t}{R^2}. \quad (4.12)$$

Considering the source function given by (4.5), dropping the bars for notational convenience and assuming that $D(r) = D_C d(r)$ where $d(r)$ is a monotonically increasing or decreasing function and D_C is a constant, the problem (4.10)-(4.11) becomes

$$\partial_t C = \frac{1}{r^2} \partial_r (r^2 d(r) \partial_r C) - L^2 C + aL^2, \quad (4.13)$$

with boundary conditions

$$\begin{cases} \partial_r C = 0, & \text{at } r = 0, \\ d(r)\partial_r C + \frac{L}{\eta} C = 0, & \text{at } r = 1, \end{cases} \quad (4.14)$$

where

$$L^2 = \frac{\gamma R^2}{D_C}, \quad a = \frac{\lambda}{\gamma \alpha}, \quad \eta = \frac{(\gamma D_C)^{\frac{1}{2}}}{P}. \quad (4.15)$$

Doing the same transformations for the source functions given by equations (4.6) and (4.7) we obtain the following problems, respectively,

$$\partial_t C = \frac{1}{r^2} \partial_r (r^2 d(r) \partial_r C) - L^2 C + aL^2(1 - r) \quad (4.16)$$

$$\partial_t C = \frac{1}{r^2} \partial_r (r^2 d(r) \partial_r C) - L^2 C + aL^2(1 - r^2), \quad (4.17)$$

both associated with the same boundary conditions given in (4.14).

How do tumour cells react to the diffusion of growth inhibitory factors? The answer to this question is the object of the next section.

4.1.2 Tumour Cells

Let us denote by T the density of tumour cells. We assume that tumour cells diffuse at a constant rate, proliferate and die. Considering the fact that the GIF will inhibit the proliferation of cells, we have the following conservation equation

rate of increase of T = diffusion of cells + proliferation of cells – death of cells
 (4.18)

which is mathematically written as

$$\partial_t T = \nabla \cdot J + f(T)g(C) - V(r), \quad (4.19)$$

where $J = D_T \nabla T$ is the cell flux, $f(T)$ is the proliferation term, $g(C)$ is the function modeling inhibition of proliferation by GIF on cells and $V(r)$ is the natural death of tumour cells. In addition, we suppose that tumour cells follow a logistic growth function as follows

$$f(T) = kT \left(1 - \frac{T}{T_0}\right), \quad (4.20)$$

where T_0 is the carrying capacity and k is the proliferation rate. Here we consider the function $g(C)$ to be as a switch off like mechanism,

$$g(C) = \begin{cases} 1, & C \leq \alpha, \\ 0, & C > \alpha, \end{cases} \quad (4.21)$$

where α is the critical GIF concentration discussed previously. By assuming the spherical geometry as for the previous model and substituting (4.20) in (4.19), we have the following equation

$$\partial_t T = D_T \frac{1}{r^2} \partial_r (r^2 \partial_r T) + kT \left(1 - \frac{T}{T_0}\right) g(C) - \beta T, \quad (4.22)$$

where β is the tumour cell death rate. We assume that at the center and at $r = R$ there is a zero flux of tumour cells. Thus we have

$$\begin{cases} \partial_r T = 0, & \text{at } r = 0, \\ \partial_r T = 0, & \text{at } r = R. \end{cases} \quad (4.23)$$

After the non dimensionalisation of equation (4.22) we will attempt to solve numerically the system

$$\begin{cases} \partial_t C &= \frac{1}{r^2} \partial_r (r^2 d(r) \partial_r C) - L^2 C + aL^2, \\ \partial_t T &= D \frac{1}{r^2} \partial_r (r^2 \partial_r T) + \delta T (1 - T) g(C) - \sigma T, \end{cases} \quad (4.24)$$

with boundary conditions

$$\begin{cases} \partial_r C = \partial_r T = 0, & \text{at } r = 0, \\ d(r)\partial_r C + \frac{L}{\eta}C = \partial_r T = 0, & \text{at } r = 1, \end{cases} \quad (4.25)$$

where

$$D = \frac{D_T}{D_C}, \quad \delta = \frac{kL^2}{\gamma}, \quad \sigma = \frac{\beta L^2}{\gamma}.$$

The same tumour cells density equation can also be coupled to the GIF concentration equation for different source functions, since the simulation results are the same. After non-dimensionalising the system, we observe that for a particular spheroid, the only parameter that cannot be fixed is the radius R since it varies. Thus we can analyse the system using different values for the spheroid radius R while holding constant the other parameters. Our goal here is to discover if a concentration profile of GIF inside the spheroid can be found corresponding to the observed pattern of necrosis. We also want to check if the tumour cells profile agrees with the GIF one. Since the analytical solution of the system of equations (4.24) subject to (4.25) cannot be easily found, the system is solved numerically using the finite difference method of Crank-Nicolson. Let us mention that both cases where the diffusion function is an increasing function ($d(r) = 0.8 + 0.2r^2$) and a decreasing function ($d(r) = 1 - 0.2r^2$) can be investigated (the variability in diffusion constants between spheroids grown from different cell lines has been verified experimentally in [23]). Let us consider R_{max} to be the maximal size that the tumour reaches at the avascular stage. Thus to effectively follow the development of the GIF concentration profile within the spheroid as it grows, we will vary R starting from $t = 0$ ($R(0)$) up to R_{max} . It is important to note that the non-dimensionalisation leads to the fact that in each case the critical threshold level occurs at $C = 1$.

4.1.3 Results and Comments

After discretizing the system of equations (4.24), we obtained the results which we are presented in this section. In order to compare our results with previous mathematical models of Chaplain and Britton in [15] and Shymko and Glass in [42], we choose the parameters following Chaplain in [13], $D = 5 \times 10^{-7} \text{cm}^2 \text{s}^{-1}$, $P = 10^{-4} \text{cm} \text{s}^{-1}$, $\gamma = 5 \times 10^{-5} \text{s}^{-1}$ and $\eta = 0.05$. Here the diffusion function is taken to be decreasing $d(r) = 1 - 0.2r^2$ and the source function is the one given by equation (4.7). The results are quite the same for the increasing function.

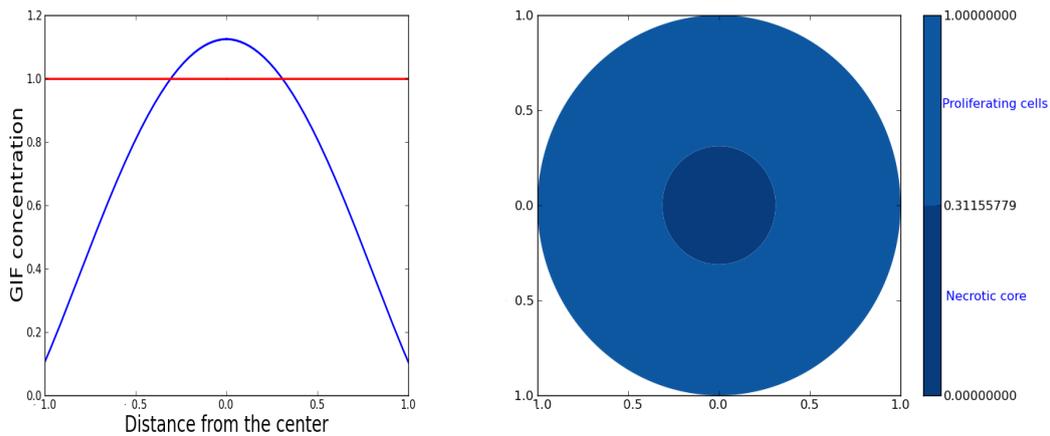


Figure 4.1: Plot of GIF concentration throughout multicell spheroid of size $R = 0.05 \text{ cm}$

Figure 4.1 shows the profile of GIF concentration throughout the multicell spheroid of size $R = 0.05 \text{ cm}$. Let us mention that in the code written, instead of making variable the value of R , the value of L is the one that varies. This is due to the fact that R is proportional to L . As can be seen on all the GIF concentration figures, there is a horizontal line drawn at $C = 1$, which represents the threshold value of GIF. When the concentration of GIF is less than 1, the proliferation takes place, but when it is greater than 1, the mitosis is inhibited giving rise to the necrotic core. The representation of these two layers can easily be seen on the contour (plot at the right) plot in figure 4.1. The necrotic core is the region where the blue color is darker which shows that GIF concentration is higher in comparison with the layer of proliferating cells. As the spheroid increases in size, the necrotic core becomes bigger leading to a narrow layer of proliferating cells which surrounds the necrotic core. This is due to the fact that, the bigger the tumour is, the more there are cells (tumour cells and healthy cells) but the GIF is diffused at the same rate. This is clearly shown in figure 4.2. These results are similar to those of Chaplain and Britton in [15]. The same results are obtained for the other source functions. A change is only observed in the shape of the plot. From this we can say that the source

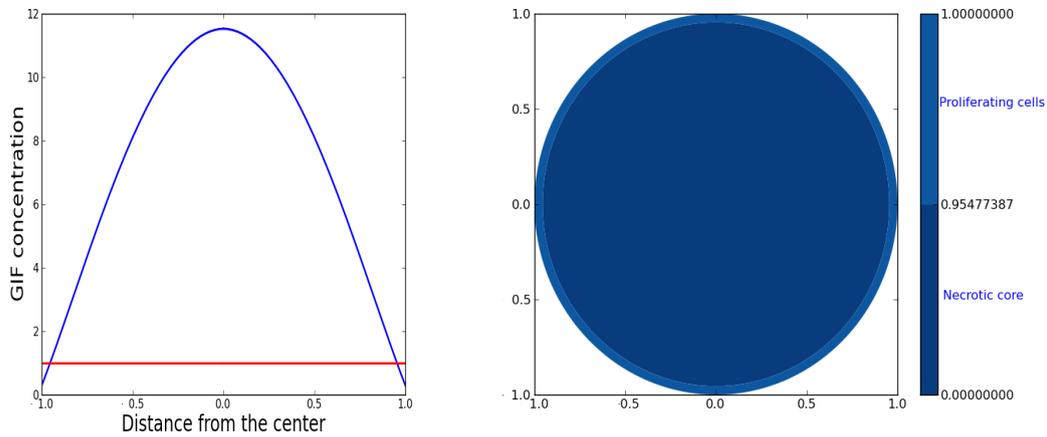


Figure 4.2: Plot of GIF concentration throughout multicell spheroid of size $R = 0.2 \text{ cm}$

function has a qualitatively effect on the spheroid. Let us have a look at what is happening with tumour cells density. Figure 4.3 shows us the profile of

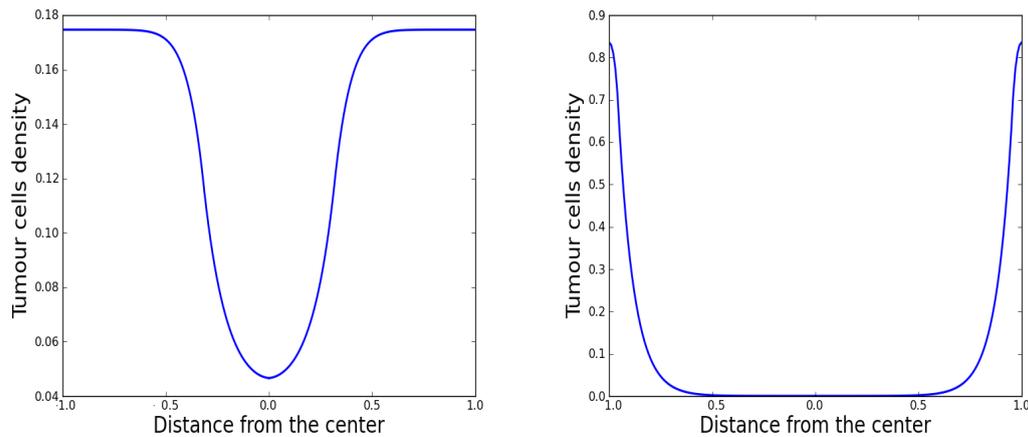


Figure 4.3: Plot of tumour cells density throughout multicell spheroid of size $R = 0.05 \text{ cm}$ and $R = 0.2 \text{ cm}$

tumour cells density throughout the multicell spheroid. We can see from the plot at the left ($R = 0.05 \text{ cm}$) of figure 4.3 that, the density of tumour cells around the center of the spheroid is very low and as we go further from the center, the density increases. When the radius increases ($R = 0.2 \text{ cm}$), there are completely no tumour cells in the surrounding of the center which explains the presence of the necrotic core. In this case, the density starts increasing when we go a bit further from the center and we end up with a narrow layer of proliferating cells. This is in good agreement with GIF concentration.

Now what happens when the tumour has reached its maximal size? In the

following section we present and model the two next stages of the tumour growth development.

4.2 Tumour Angiogenesis and Vascularisation

Tumour-induced angiogenesis is believed to occur when a small avascular tumour exceeds some critical diameter, above which normal tissue vasculature (network of capillary blood vessels) is no longer able to support its growth. At this stage, the tumour cells lack nutrients and oxygen and become hypoxic. This is assumed to trigger cellular release of tumour angiogenic factors (TAF), which start to diffuse into the surrounding tissue and approach the endothelial cells (cells lining all the blood vessels and arteries) of nearby blood vessels. Later on the TAF stimulates the release of enzymes by endothelial cells (EC) which degrade their own basal lamina. Once the degradation of the basement membrane has taken place, EC subsequently respond to the TAF concentration gradient by forming sprouts, migrating and proliferating toward the tumour. In fact, small capillary sprouts are formed by accumulation of EC which are recruited from the parent vessel. In this section the main events we model are the diffusion of TAF, the migration and proliferation of EC.

4.2.1 Tumour Angiogenesis Factors

Here we choose as in [13] to focus on the model of Gimbrone et al. [27] and Muthukkaruppan et al. [32]. They have implanted a fragment of tumour into the cornea of a test animal and have elicited an angiogenic response from blood vessels situated in the nearby limbus region of the cornea. It happens that once capillary sprouts are formed, mitosis is confined in a region at a short distance behind the sprouts tips. This is because cells at the tips of the sprouts act as sink for TAF [8]. The mathematical model presented here is a development and extension of that of Chaplain and Stuart in [18]. Following them, a sink term is incorporated in the model. Hence the conservation equation for the TAF is given by

$$\text{rate of increase of } A = \text{diffusion} - \text{loss due to cells} - \text{decay}, \quad (4.26)$$

where TAF have $A(x, t)$ as concentration. We are interested in the behaviour of EC from when they leave their basement membrane until they reach the tumour. Because of that reason and for simplification, we are working on the interval $[0, L]$, where L is the distance between the tumour and the limbus. Thus x is the distance from the tumour. If $E(x, t)$ is the density of Endothelial cells, equation (4.26) can be rewritten (assuming that the TAF is diffused at a constant rate) as

$$\partial_t A = D_A \nabla^2 A - f(A)g(E) - h(A). \quad (4.27)$$

D_A , $f(A)$, $g(E)$ and $h(A)$ are the TAF diffusion coefficient, the local rate of uptake TAF by EC, the function modelling the dependence of cells density during the consumption of TAF and obviously their decay, respectively. Since the Michaelis-Menten equation describes the rates of irreversible (which goes on until one of the reactant has disappeared) enzymatic reactions, we assume (following [18, 17]) that $f(A)$ is governed by a Michaelis-Menten kinetics law. In addition, it is observed by Ausprunk and Folkman in [8] that the greater the density of endothelial cells is, the more TAF will diminish because of cells acting as sink. Therefore, $g(E)$ is chosen to be a strictly increasing function. Thus we have

$$f(A) = \frac{QA}{K_{max} + A} \quad (4.28)$$

and

$$g(E) = \frac{E}{E_0}, \quad (4.29)$$

where Q is the maximum reaction rate and K_{max} is the Michaelis constant which is equivalent to the concentration of TAF required to achieve a reaction rate of $Q/2$ and E_0 is the carrying capacity. Let us note that, by [13], one can choose another form for $g(E)$, but it will not affect the model qualitatively. Following Sherratt and Murray in [40], we assume that $h(A)$ is governed by a first-order kinetics

$$h(A) = dA, \quad (4.30)$$

where d is the decay coefficient. The substitution of equation (4.28), (4.29), (4.30) in equation (4.27) leads to the following equation for the TAF in the external tissue

$$\partial_t A = D_A \nabla^2 A - \frac{QAE}{(K_{max} + A)E_0} - dA. \quad (4.31)$$

The initial condition is

$$A(x, 0) = A_0(x), \quad (4.32)$$

where A_0 is a function chosen by Chaplain and Stuart in [17] to describe qualitatively the profile of TAF in the external tissue when it reaches the limbal vessels. In the same paper, they assumed that the TAF has a constant value A_b on the boundary of the tumour. Since the boundary is allowed to move as TAF advances or recedes into the tissue, the concentration at the limbus is taken to be zero leading to

$$A(x, t) = \begin{cases} A_b, & x = 0, \\ 0, & x = L, \end{cases} \quad (4.33)$$

4.2.2 Endothelial Cells

Here we attempt to model the migration and the proliferation of endothelial cells during the process of angiogenesis. This is because all the events that take place during this process are essentially driven by Endothelial Cells (EC).

We will thus follow the way of EC from their origin in their parent vessels, their crossing of extracellular matrix and other material in the surrounding host tissue, to their destination within the tumour.

We then begin (following [18]) with a general conservation equation for the EC density $E(x, t)$ which is of the form

$$\text{rate of increase of } E = \text{cell migration} + \text{mitotic generation} - \text{cell loss.} \quad (4.34)$$

Following Chaplain and Stuart in [18], equation (4.34) leads to the partial differential equation

$$\partial_t E = -\nabla \cdot J + F(E)G(A) - H(E), \quad (4.35)$$

where J is the flux of cells, $F(E)$ and $H(E)$ stand for the growth term and loss term for EC respectively. We assume, like Sholley et al. in [41], that the mitosis is governed by a logistic growth and cell loss is a first order process. Hence

$$F(E) = \rho E \left(1 - \frac{E}{E_0}\right) \quad (4.36)$$

and

$$H(E) = \mu E, \quad (4.37)$$

where the unknown coefficients ρ and μ are a positive constant related to the maximum mitotic rate and the cell loss rate constant respectively. The fact that equation (4.36) contains a second order loss term while equation (4.37) is a first order loss term, has an explanation. In fact, Balding and McElwain in [9] assumed that the loss of cell is due to anastomosis (tip-tip and tip-branch) as a second order process. On the other hand, Stokes and Lauffenburger in [43] assumed that the loss is due to the budding. Moreover, they assumed that the probability of budding was uniform in all sprouts for all positions and times. This means that both terms can implicitly account for EC loss due to anastomosis and budding respectively.

For simplicity, Paweletz, Knierim and Paku in [35, 34] believed that it will be easy to assume that the EC proliferation is controlled in some way by the TAF, thus occurrence of $G(A)$ in equation (4.35). Since the response of EC to the TAF is first of all the migration and later on the proliferation (which is crucial but in the second position), we assume that there is a threshold concentration level of TAF A^* below which proliferation does not occur. Taking $G(A)$ to be a nondecreasing function, we choose (following Chaplain in [13]) it to be of the form

$$G(A) = \begin{cases} 0, & A \leq A^*, \\ \frac{A - A^*}{A_b}, & A^* < A, \end{cases} \quad (4.38)$$

where $A^* \leq A_b$. It is important to mention that the response of EC to TAF is a chemotactic one, [8, 43]. Thus we assume, following Chaplain in [13], that

the flux of EC consists two parts

$$J = J_{diffusion} + J_{chemotaxis}, \quad (4.39)$$

where

$$J_{diffusion} = -D_E \nabla E \quad (4.40)$$

and the well known chemotactic flux is of the form

$$J_{chemotaxis} = E\chi(A)\nabla A, \quad (4.41)$$

where D_E is the diffusion coefficient of EC, $\chi(A)$ represents the rate of increase of EC. Various forms of $\chi(A)$ have been proposed. For mathematical simplicity we take it to be constant

$$\chi(A) = C_0. \quad (4.42)$$

From the assumptions above, we end up with following diffusion-chemotaxis equation for EC

$$\partial_t E = D_E \nabla^2 E - C_0 \nabla \cdot (E \nabla A) + KE \left(1 - \frac{E}{E_0}\right) G(A) - \mu E, \quad (4.43)$$

where $G(A)$ is given by equation (4.38).

Equation (4.43) will be treated subject the assumptions that initially the EC density at the limbus is constant and zero anywhere else (as in [13]), giving the initial condition

$$E(x, 0) = \begin{cases} E_0, & x = L, \\ 0, & x < L \end{cases} \quad (4.44)$$

and for the boundary condition

$$E(L, t) = E_0. \quad (4.45)$$

That means the EC density remains the same at the limbus.

According to our aim, which is to monitor the progress of EC as they cross the ECM, we (as in [13]) assume that

$$E(0, t) = 0. \quad (4.46)$$

Actually once EC have reached the tumour and penetrated it, the assumptions of the present model no longer hold. The boundary conditions will remain valid up to the time when EC at the sprout tips first reach the tumour. Following Chaplain and Stuart [18, 17] we non dimensionalise equations (4.43), (4.44), (4.45) and (4.46) using the following reference variables

$$\tilde{A} = \frac{A}{A_b}, \quad \tilde{E} = \frac{E}{E_0}, \quad \tilde{x} = \frac{x}{L}, \quad \tilde{t} = \frac{t}{\phi}, \quad \text{where } \phi = \frac{L^2}{D_A}. \quad (4.47)$$

If we only consider a one dimensional problem and we drop the tildes, the equations become

$$\begin{cases} \partial_t A &= \partial_{x^2}^2 A - \frac{\theta EA}{\nu + A} - \sigma A \\ \partial_t E &= D\partial_{x^2}^2 E - \kappa\partial_x(E\partial_x A) + \tau E(1 - E)G(A) - \xi E, \end{cases} \quad (4.48)$$

where

$$\begin{aligned} \theta &= \frac{L^2 Q}{D_A A_b}, & \nu &= \frac{K_{max}}{A_b}, & \sigma &= \frac{L^2 d}{D_A}, \\ D &= \frac{D_E}{D_C}, & \kappa &= \frac{A_b C_0}{D_A}, & \tau &= \frac{L^2 K}{D_A}, & \xi &= \frac{L^2 \mu}{D_A} \end{aligned}$$

and the function $G(A)$ is given by

$$G(A) = \begin{cases} 0, & A \leq A^*, \\ A - A^*, & A^* < A. \end{cases} \quad (4.49)$$

The model is subject to the following initial and boundary conditions,

$$A(x, 0) = A_0(x), \quad (4.50)$$

$$A(x, t) = \begin{cases} 1, & x = 0, \\ 0, & x = 1 \end{cases} \quad (4.51)$$

and

$$E(x, 0) = \begin{cases} 1, & x = 1, \\ 0, & x < 1, \end{cases} \quad (4.52)$$

$$E(x, t) = \begin{cases} 0, & x = 0, \\ 1, & x = 1. \end{cases} \quad (4.53)$$

4.2.3 Estimation of Parameters

Whenever possible, parameter values are estimated from available experimental data. However, given the large number of parameters to be determined, it is perhaps not surprising that several are not quantified. When experimental data could not be found, parameter values were chosen to give the best qualitative numerical simulation results. This is in line with previous papers successfully simulating tumour growth.

- **Reference Diffusion Coefficient D**

Following Chaplain in [13], we choose $L = 2 \text{ mm}$ for the reference length between a tumour implant and the limbal vessel. According to Stokes, Lauffenburger, Balding and McElwain in [43] and [9], ϕ is taken to be 14 days (which is an average time for a vascularization to occur). From the formula $\phi = \frac{L^2}{D_A}$, we have $D_A = 3.3 \times 10^{-8} \text{ cm}^2 \cdot \text{s}^{-1}$.

In [40], Sherrat and Murray found $3.1 \times 10^{-7} \text{ cm}^2 \cdot \text{s}^{-1}$ and $5.9 \times 10^{-6} \text{ cm}^2 \cdot \text{s}^{-1}$ as estimates for diffusion coefficients of chemicals. Correspondingly, they estimated the diffusion coefficient D_E of EC under consideration in their model as $6.9 \times 10^{-11} \text{ cm}^2 \cdot \text{s}^{-1}$ and $3.5 \times 10^{-10} \text{ cm}^2 \cdot \text{s}^{-1}$. Using their values, it comes out that D belongs to the interval $[1.169 \times 10^{-5}, 1.129 \times 10^{-3}]$. In the light of these data, following Chaplain in [13], our choice for the diffusion of tumour cells density is 10^{-3} .

- **Concentration of TAF on the Boundary of the Tumour A_b**

Stokes et al. in [44] estimated the chemotaxis sensitivity of ECs migrating in a culture containing αFGF (α fibroblast growth factors) to be $2600 \text{ cm}^2 \cdot \text{s}^{-1} \cdot M^{-1}$. In the simulations carried out, the value for k varies between 0.3 and 1. From the value of D_A estimated above, $A_b \sim 10^{-11}$ which according to Chaplain in [13], is reasonable.

- **Reference Mitotic Rate τ**

Using the data based on epidermal wound healing [13], Sherrat and Murray in [40] estimated that $\varrho_{max} = 10\mu$ and based on in vitro experiments of EC proliferation in [13], Stokes and Lauffenburger in [43] estimated μ to be 0.056 h^{-1} under the assumption that all cells proliferate. But because cell mitosis in the sprouts is mainly confined to a region close to the tips and cells in the sprouts may proliferate, in most of their simulations they considered $\mu = 0.02 \text{ h}^{-1}$. Following Chaplain in [13], we assumed $\varrho_{max} \in [0.2 \text{ h}^{-1}, 0.56 \text{ h}^{-1}]$, thus $\tau = \frac{L^2 K}{D_A}$ belongs to $[70, 190]$.

- **Reference Cell Loss Rate ξ**

For the range of μ given above, $\xi = \frac{L^2 \mu}{D_A}$ lies between 3 and 18.

The concentration of TAF initially was taken to be $A_0(x) = 1 - x^2$ which matches with the shape of the TAF profile in the external tissue, that means 1 at the edge of the tumour and 0 at the limbus.

4.2.4 Results and Comments

The plot at the left of figure 4.4 shows the profile of the TAF concentration in the external host tissue at different times. As can be seen on the figure, the gradient profile of TAF decreases as time increases. According to the way in which the function $G(A)$ is defined, we can say that as EC approach the tumour they proliferate more since the concentration of TAF is very high in the tumour surroundings. The profile of EC is in good agreement with the

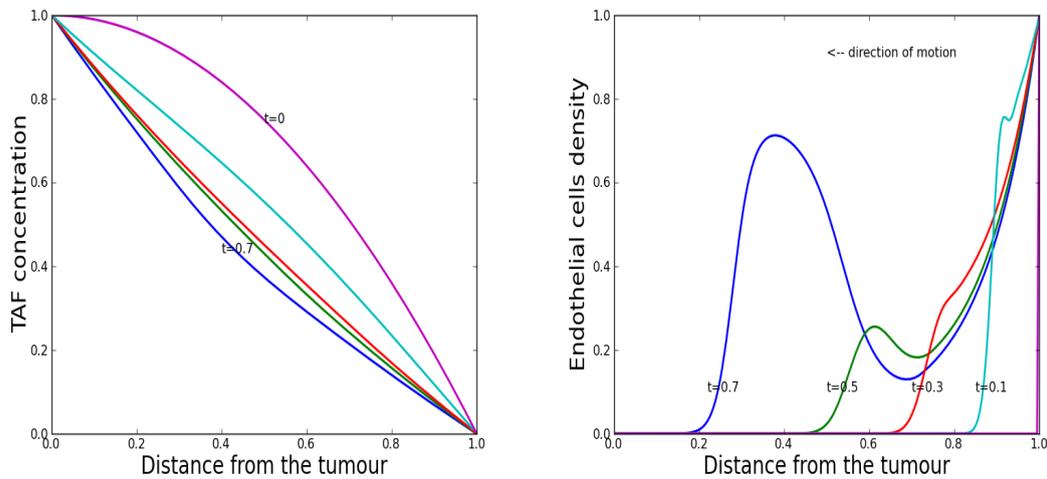


Figure 4.4: Plot of TAF concentration and EC density in the external host tissue at times $t = 0, 0.1, 0.3, 0.5, 0.7$.

one of the TAF concentration. From the plot at the right of figure 4.4, we can see how EC move towards the tumour as the time increases. From our simulations, we noticed that shortly after $t = 0.7$ the model loses its validity. Since at that time, EC are already in the tumour and they interact with tumour cells. Although these interactions are very important, it is no more a part of our model. In fact this stage is going to be studied in details in the next chapter.

Chapter 5

Mathematical Modelling of Cancer cell Invasion of the Tissue

Tumours are known to develop in two distinct stages: avascular and vascular stage. In the avascular stage, the tumour grows to a diffusion limited size of about two millimetres of diameter. After reaching its maximal size, the tumour starts secreting a substance known as tumour angiogenesis factor which is diffused into its surrounding tissues. This diffusion leads to the vascularisation, that is the tumour has developed its own blood vessels. During this stage, cells invade the tissue. In the invasion itself, adhesion both cell-cell and cell-matrix play an important role. In the following sections, we are going to develop a mathematical model of cancer cell invasion. Rather than taking into account all the complex details, the proposed model concentrates on modeling nonlocal interactions involved in the process. First, we are going to present the assumptions of the model, then write the mathematical model and analyse it using the tools presented before and we will conclude.

5.1 Assumptions and Mathematical Model

Rather than working in the vascular stage which can be complex to model because of the formation of blood vessels, we assume that this model is based on a generic tumour growth at avascular stage. We focus on the interactions between the cancer cells and the surrounding tissue which is the extracellular matrix (ECM). We develop a mathematical model consisting of two partial differential equations describing the evolution in time and space of the system of variables and including nonlocal (integral) terms. The model consists of the following two variables: cancer cell density u and ECM density v .

Let us now describe the way in which the cell density u and healthy cells density v are involved in the invasion process and derive partial differential equations governing the evolution of each of them.

5.1.1 Cancer Cells

During the invasion, the aim of cancer cells is to invade other parts of the tissue. For them to do so, they must find ways through which they can circulate. In vivo, to achieve this, cancer cells adhere to surrounding ECM molecules via specific receptors. After the adhesion, they produce and secrete several types of matrix degrading enzymes (MDEs), to degrade the ECM. Let us note that the ECM is formed of healthy cells which are grouped in different ways (different densities) by adhesive molecules. Once the MDEs are diffused, the ECM is degraded and there occurs death of normal cells, which provides space for the tumour cells. Cancer cells start to move into the created spaces and also set up tissue gradients, which cells exploit to move forward. We have to mention that cells move from regions of low concentrations to areas where adhesive molecules are highly concentrated. This tumour cells motility is called haptotaxis. From what is said above, we assume that the movement of tumour cells is governed by random motion and haptotaxis.

Within the tumour, it happens that cancer cells, under some conditions, are suppressed in their proliferation since they have to compete for nutrients, oxygen and space. For instance, cells in the interior of the tumour do not proliferate as quickly as the one on the surface. This phenomenon is taken into account by using a logistic growth term, since the proliferation of cells then depends on the cell and tissue density in a local neighbourhood. The immediate surrounding of a cell influences its ability to divide and therefore we include a non local term describing neighbourhood of a cell that inhibits its proliferation in the model.

Therefore, incorporating both the migration terms (random motility and haptotaxis) and the nonlocal proliferation terms, we adopt the following equation describing the spatio temporal dynamic of cancer cells

rate of increase of u = diffusion of cancer cells + proliferation of cancer cells
– cell-cell adhesion – cell-matrix adhesion,

which mathematically leads to

$$\begin{aligned} \partial_t u(x, t) = & -\nabla \cdot J + \mu_1 u(x, t) - \mu_1 u(x, t) \int_{\Omega} k_{1,1}(x, y) u(t, y) dy \\ & - \mu_1 u(x, t) \int_{\Omega} k_{1,2}(x, y) v(t, y) dy. \end{aligned} \quad (5.1)$$

As mentioned before, the flux of cancer cells consists of two parts, the random motion and the haptotactic motion of cells. Thus the flux J is given by

$$\begin{aligned} J = & J_{\text{diffusion}} + J_{\text{haptotactic}} \\ = & -D \nabla u(x, t) + \chi(v) u(x, t) \nabla v(x, t). \end{aligned} \quad (5.2)$$

By substituting equation (5.2) into equation (5.1), we have

$$\begin{aligned} \partial_t u(x, t) &= D\Delta u(x, t) - \nabla \cdot (\chi(v)u(x, t)\nabla v(x, t)) + \mu_1 u(x, t) \\ &\quad \left(1 - \int_{\Omega} k_{1,1}(x, y)u(t, y)dy - \int_{\Omega} k_{1,2}(x, y)v(t, y)dy\right), \end{aligned}$$

where Ω is a bounded domain in \mathbb{R}^d (here $d = 3$) with smooth boundary, D , μ_1 are the coefficient of diffusion of cancer cells and the proliferation rate of cells respectively. $\chi(v)$ is the haptotaxis sensitivity and $k_{1,1}$, $k_{1,2}$ are given spatial kernels that are used to describe the short-range cell-cell and cell-matrix interactions in a standard way. Let us note that the terms

$$u(x, t) \int_{\Omega} k_{1,1}(x, y)u(t, y)dy$$

and

$$u(x, t) \int_{\Omega} k_{1,2}(x, y)v(t, y)dy$$

describe the cell inhibition of cell proliferation caused by density of surrounding cancer cells and tissue respectively.

5.1.2 Extracellular Matrix

Because the extracellular matrix is static, any diffusion is neglected. As mentioned before, during the invasion process, the ECM is degraded by cancer cells. Since everything is happening in a certain domain Ω , we use an integral term to model the degradation of the ECM. We also assume that the ECM may be remodelled back to a normal, healthy level in a logistic manner in the absence of cancer cells and that it competes for the space with tumour cells. Using a modified mitotic growth with constant rate μ_2 to describe the ECM production we have the following conservative equation for the ECM

$$\begin{aligned} \text{rate of increase of } v &= \text{degradation of the ECM} + \text{proliferation} \\ &\quad - \text{cell-cell adhesion} - \text{cell-matrix adhesion.} \end{aligned}$$

This gives

$$\begin{aligned} \partial_t v(x, t) &= -\gamma v(x, t) \int_{\Omega} k(x, y)u(t, y)dy + \mu_2 v(x, t) \\ &\quad \left(1 - \int_{\Omega} k_{2,1}(x, y)u(t, y)dy - \int_{\Omega} k_{2,2}(x, y)v(t, y)dy\right), \end{aligned}$$

where γ is the ECM degradation rate, k , $k_{2,1}$ and $k_{2,2}$ are the kernels. Hence, the complete system describing the interaction between tumour cells

and extracellular matrix is,

$$\left\{ \begin{array}{l} \partial_t u(x, t) = D\Delta u(x, t) - \nabla(\chi(v)u(x, t)\nabla v(x, t)) + \mu_1 u(x, t) \\ \quad (1 - \int_{\Omega} k_{1,1}(x, y)u(t, y)dy - \int_{\Omega} k_{1,2}(x, y)v(t, y)dy), \\ \partial_t v(x, t) = -\gamma v(x, t) \int_{\Omega} k(x, y)u(t, y)dy + \mu_2 v(x, t) \\ \quad (1 - \int_{\Omega} k_{2,1}(x, y)u(t, y)dy - \int_{\Omega} k_{2,2}(x, y)v(t, y)dy). \end{array} \right. \quad (5.3)$$

Since we are working in a bounded domain, the range between cells and the ECM must be limited. Hence, $k, k_{i,j}, \chi$ are given functions which satisfy the following conditions.

$$\begin{aligned} k, k_{i,j} \in L^\infty(\Omega \times \Omega), \quad \nabla k, \nabla k_{2,j} \in (L^\infty(\Omega \times \Omega))^d \quad i, j = 1, 2, \\ k \geq 0 \quad k_{i,j} \geq 0 \quad i, j = 1, 2, \quad (5.4) \\ \chi \in C^2(\mathbb{R}), \chi \geq 0 \quad \text{and} \quad \chi, \chi' \quad \text{are globally lipschitz continuous.} \end{aligned}$$

It should be noted that these assumptions on the biological parameters are to simplify the mathematical analysis. Let us note that if we set

$$k \otimes u(x, t) = \int_{\Omega} k(x, y)u(y, t)dy,$$

then the system (5.3) can be rewritten as

$$\left\{ \begin{array}{l} \partial_t u(x, t) = D\Delta u - \nabla(\chi(v)u\nabla v) + \mu_1 u(1 - k_{1,1} \otimes u - k_{1,2} \otimes v), \\ \partial_t v(x, t) = -\gamma v k \otimes u + \mu_2 v(1 - k_{2,1} \otimes u - k_{2,2} \otimes v). \end{array} \right. \quad (5.5)$$

We can remark that if instead of Ω we consider \mathbb{R}^d , then it is natural to use the convolution $*$ instead of \otimes .

To close the system we need to impose boundary conditions and initial conditions. Guided by the in vitro experimental protocol in which invasion takes place within an isolated system, we assume that the cells migration which is governed by their random motility and the haptotaxis doesn't take place once cancer cells have reached the boundary of the isolated domain. Thus at the boundary, the flux of cancer cells is equal to the flux of ECM under the haptotaxis. From [45], we have

$$u\chi(v)\partial_\nu v - D\partial_\nu u = 0 \quad \text{on} \quad \partial\Omega \times (0, T), \quad (5.6)$$

where ν is the normal vector to $\partial\Omega$.

We note that the choice of the boundary conditions is rather mathematically than biologically motivated. Here we don't consider possible boundary effects

[46]. The boundary conditions, however, may be justified by the fact that the tumour is far from the boundary of the domain containing the tissue under consideration. We prescribe the initial data

$$(u(x, 0), v(x, 0)) = (u_0(x), v_0(x)) \quad (5.7)$$

In order to study the behaviour of the cancer and ECM density as time and space change we are going to prove the local and global solution of the solution.

5.2 Local Existence

In this section we are going to prove the local existence of solution of (5.3) using the semigroup theory. In order to use the Sobolev embeddings, we set

$$p > d.$$

For a fixed $T > 0$ let

$$\|u\|_p = \sup_{0 \leq t \leq T} \|u(t)\|_p, \quad \|u\|_p^{(l)} = \sup_{0 \leq t \leq T} \|u(t)\|_p^{(l)}.$$

For notational convenience and without loss of generality, we can (following [45]) assume

$$D = \gamma = \mu_1 = \mu_2 = 1.$$

We have to mention that although, we are taking those parameters to be equal to one for the proof of the local existence, their relative values are going to be taken for any other analysis of the model, like the computational simulations.

5.2.1 Transformation of the Model

To facilitate the analysis of the model, we simplify the boundary value problem by introducing the following transformation:

$$w(x, t) = \frac{u(x, t)}{z(x, t)}, \quad z(x, t) = \exp \left(\int_0^{v(x, t)} \chi(s) ds \right). \quad (5.8)$$

From (5.8) we have

$$\partial_t w(x, t) = \frac{1}{z} \partial_t u - \frac{u}{z^2} \partial_t z \quad (5.9)$$

From the first equation of (5.5) and (5.8), we have

$$\frac{1}{z} \partial_t u = \frac{1}{z} (\Delta(wz) - \nabla(wz\chi(v)\nabla v)) + wz(1 - k_{1,1} \otimes wz - k_{1,2} \otimes v). \quad (5.10)$$

But

$$\begin{aligned}
 \Delta(wz) &= \sum_{i=1}^d \partial_{x_i x_i}^2 (wz) \\
 &= z\Delta w + 2 \sum_{i=1}^d \partial_{x_i} w \partial_{x_i} z + w\Delta z \quad \text{and} \\
 \partial_{x_i} z &= z\chi(v)\partial_{x_i} v.
 \end{aligned} \tag{5.11}$$

Hence,

$$\Delta z = \chi(v) \sum_{i=1}^d \partial_{x_i} v \partial_{x_i} z + \Delta v \cdot z\chi(v) + z \sum_{i=1}^d \partial_{x_i} v \partial_{x_i} \chi(v). \tag{5.12}$$

Therefore,

$$\begin{aligned}
 \Delta(wz) &= z\Delta w + 2\chi(v)z \sum_{i=1}^d \partial_{x_i} w \partial_{x_i} v + w\chi(v) \sum_{i=1}^d \partial_{x_i} v \partial_{x_i} z \\
 &+ wz\chi(v)\Delta v + wz \sum_{i=1}^d \partial_{x_i} v \partial_{x_i} \chi(v).
 \end{aligned} \tag{5.13}$$

Moreover,

$$\begin{aligned}
 \nabla \cdot (wz\chi(v)\nabla v) &= \sum_{i=1}^d \partial_{x_i} (wz\chi(v)\partial_{x_i} v) \\
 &= \chi(v)w \sum_{i=1}^d \partial_{x_i} v \partial_{x_i} z + z\chi(v) \sum_{i=1}^d \partial_{x_i} v \partial_{x_i} w \\
 &+ wz\chi(v)\Delta v + wz \sum_{i=1}^d \partial_{x_i} v \partial_{x_i} \chi(v).
 \end{aligned} \tag{5.14}$$

Substituting equations (5.13) and (5.14) into (5.10) gives

$$\frac{1}{z} \partial_t u = \Delta w + \chi(v) \sum_{i=1}^d \partial_{x_i} w \partial_{x_i} v + w(1 - k_{1,1} \otimes wz - k_{1,2} \otimes v). \tag{5.15}$$

On the other hand, from the second equation of (5.5) we have

$$\begin{aligned}
 \frac{u}{z^2} \partial_t z &= \frac{u}{z^2} (\chi(v)z\partial_t v) \\
 &= -w\chi(v)vk \otimes wz + wv\chi(v)(1 - k_{2,1} \otimes wz - k_{2,2} \otimes v)
 \end{aligned} \tag{5.16}$$

Substituting equations (5.15) and (5.16) into (5.9) gives the first equation of the new system

$$\begin{aligned}
 \partial_t w &= \Delta w + \chi(v)\nabla w \cdot \nabla v + w(1 - k_{1,1} \otimes wz - k_{1,2} \otimes v) \\
 &+ \chi(v)wvk \otimes wz - \chi(v)wv(1 - k_{2,1} \otimes wz - k_{2,2} \otimes v).
 \end{aligned} \tag{5.17}$$

The second equation of (5.5) becomes

$$\partial_t v = -vk \otimes wz + v(1 - k_{2,1} \otimes wz - k_{2,2} \otimes v). \quad (5.18)$$

Using the same transformation, we obtain

$$\begin{aligned} \partial_\nu w &= \frac{1}{z} \partial_\nu u - \frac{u}{z^2} \partial_\nu z \\ &= \frac{1}{z} \partial_\nu u - \frac{u}{z^2} (z\chi(v) \partial_\nu v) \\ &= \frac{1}{z} (\partial_\nu u - u\chi(v) \partial_\nu v) \\ &= 0, \quad \text{from equation (5.6) with } D = 1. \end{aligned}$$

Therefore, in terms of the variables w and v , system (5.5) takes the form

$$\begin{cases} \partial_t w &= \Delta w + \chi(v) \nabla w \cdot \nabla v + w(1 - k_{1,1} \otimes wz - k_{1,2} \otimes v) \\ &+ \chi(v) wvk \otimes wz - \chi(v) wv(1 - k_{2,1} \otimes wz - k_{2,2} \otimes v), \\ \partial_t v &= -vk \otimes wz + v(1 - k_{2,1} \otimes wz - k_{2,2} \otimes v) \end{cases} \quad (5.19)$$

on $]0, T[\times \Omega$, subject to the linear boundary condition

$$\partial_\nu w = 0, \quad (t, x) \in]0, T[\times \partial\Omega \quad (5.20)$$

and the initial conditions

$$(w, v)(0, x) = (w_0, v_0)(x) \quad x \in \Omega. \quad (5.21)$$

5.2.2 Abstract Reformulation

The idea is to formulate the boundary problem (5.19) with the boundary condition (5.20), subject to the initial condition (5.21), as an abstract Cauchy problem in order to apply the theory of semigroups of linear and semilinear operators.

For each fixed $t \geq 0$, we introduce a function

$$\begin{aligned} (w_{(t)}, v_{(t)}) : \Omega &\longrightarrow \mathbb{R}^2 \\ x &\longmapsto (w_{(t)}(x), v_{(t)}(x)) = (w(x, t), v(x, t)). \end{aligned}$$

Hence we can define a vector-valued function

$$\begin{aligned} (\underline{w}, \underline{v}) : [0, \infty) &\longrightarrow L^p(\Omega) \times L^\infty(\Omega) \\ t &\longmapsto (\underline{w}(t), \underline{v}(t)) = (w_{(t)}, v_{(t)}). \end{aligned}$$

Note that, because $L^p(\Omega) \times L^\infty(\Omega)$ is a Banach space of type L , $(\partial_t w, \partial_t v)$ can be seen as the strong derivative $(\frac{d\underline{w}}{dt}, \frac{d\underline{v}}{dt})$ of the vector-valued function $(\underline{w}, \underline{v})$.

As this will not cause any misunderstanding, we identify \underline{w} with w and \underline{v} with v .

The initial boundary value problem under consideration now may be formulated as an abstract semilinear Cauchy problem in $L^p(\Omega) \times L^\infty(\Omega)$ as follows

$$\begin{cases} \frac{d}{dt}(w, v) &= (- (A_p + I)w + N_1(w, v), N_2(w, v)) \\ (w(0), v(0)) &= (w_0, v_0), \end{cases} \quad (5.22)$$

where

$$\begin{aligned} N_1(w, v) &= \chi(v)\nabla v \cdot \nabla w + 2w - wk_{1,1} \otimes (wz) \\ &\quad - wk_{1,2} \otimes v + \chi(v)wv(k \otimes (wz) - 1 + k_{2,1} \otimes (wz) + k_{2,2} \otimes v), \\ N_2(w, v) &= -vk \otimes (wz) + v(1 - k_{2,1} \otimes (wz) - k_{2,2} \otimes v) \end{aligned}$$

and A_p is the sectorial operator defined by

$$A_p u = -\Delta u,$$

with

$$u \in D(A_p) = \{\xi \in W^{(2,p)}(\Omega) : \partial_\nu \xi = 0 \text{ on } \partial\Omega\}.$$

Since $A_p + I$ is a sectorial operator in $L^p(\Omega)$, from [29], $-(A_p + I)$ is an infinitesimal generator of an analytic semigroup $\{e^{-t(A_p+I)}\}_{t \geq 0}$.

For $u \in L^p(\Omega)$, we have

$$\begin{aligned} \|A^\beta e^{-tA} u\|_p &\leq \|A^\beta e^{-tA}\|_p \|u\|_p \\ &\leq C_\beta t^{-\beta} e^{-\delta t} \|u\|_p \text{ from [29]}, \end{aligned} \quad (5.23)$$

where $\delta \in (0, 1)$.

Let $p > d$ be fixed. Given $T > 0$, let

$$Y = C^0([0, T]; W_p^{(1)}(\Omega)) \text{ with the norm } \|\cdot\|_p^{(1)},$$

$$Y^{1,\infty} = C^0([0, T]; W_\infty^{(1)}(\Omega)) \text{ with the norm } \|\cdot\|_\infty^{(1)}.$$

We have the following theorem

Theorem 5.2.1. *Let the initial data defined by (5.21) be such that $(w_0, v_0) \in W_p^{(1)}(\Omega) \times W_\infty^{(1)}(\Omega)$. If assumptions (5.4) are satisfied, then there exists $T > 0$ such that the problem given by equation (5.19) has a unique solution $(w, v) \in Y \times Y^{1,\infty}$ and*

$$\begin{aligned} w &\in C^1((0, T); W_p^{(1)}(\Omega)) \cap C^0((0, T); W_p^{(2)}(\Omega)), \\ v &\in C^1((0, T); W_\infty^{(1)}(\Omega)). \end{aligned} \quad (5.24)$$

Moreover, if $w_0, v_0 \geq 0$ then

$$w(t) \geq 0, \quad v(t) \geq 0, \quad \text{for all } t \in [0, T]. \quad (5.25)$$

Proof. Considering the system (5.22), our first claim for the solution is immediate from Lemma 3.3.5. We define

$$\begin{aligned} J_1(w, v)(t) &= e^{-t(A_p+I)}w_0 + \int_0^t e^{-(t-s)(A_p+I)}N_1(w(s), v(s))ds \\ J_2(w, v)(t) &= v_0 + \int_0^t N_2(w(s), v(s))ds. \end{aligned} \quad (5.26)$$

With N_1 and N_2 defined as above. Let B_R , be the ball defined by

$$B_R = \{(w, v) \in Y \times Y^{1,\infty} : \|w\|_p^{(1)} + \|v\|_\infty^{(1)} \leq R\}$$

and

$$\begin{aligned} J : Y \times Y^{1,\infty} &\longrightarrow Y \times Y^{1,\infty} \\ (w, v) &\longmapsto J(w, v) = (J_1(w, v), J_2(w, v)). \end{aligned}$$

Our aim is to apply the Banach's contraction mapping theorem to derive the solution as a fixed point of a mapping in B_R .

Fix $R > K\|w_0\|_p^{(1)} + \|v_0\|_\infty^{(1)}$, where

$$K := \sup_{t \in [0, T]} \|e^{-t(A_p+I)}\|_{L(W_p^{(1)}(\Omega))}. \quad (5.27)$$

We have

$$\begin{aligned} \|J_1(w, v)(t)\|_p^{(1)} &\leq \|e^{-t(A_p+I)}w_0 + \int_0^t e^{-(t-s)(A_p+I)}N_1(w(s), v(s))ds\|_p^{(1)} \\ &\leq \|w_0\|_p^{(1)} \cdot \sup_{t \in [0, T]} \|e^{t(A_p+I)}\|_p^{(1)} \\ &\quad + \int_0^t \|e^{-(t-s)(A_p+I)}N_1(w(s), v(s))\|_p^{(1)} ds. \end{aligned} \quad (5.28)$$

$$(5.29)$$

However, for $\beta \in (\frac{1}{2}, 1)$ we have (from Theorem 3.3.7) the following embedding

$$X_p^\beta \hookrightarrow W_p^{(1)}(\Omega), \quad (5.30)$$

where $X_p^\beta = D((A_p + I)^\beta)$. From the embedding (5.30) we have

$$\begin{aligned} \|J_1(w, v)(t)\|_p^{(1)} &\leq K\|w_0\|_p^{(1)} + C_1 \int_0^t \|e^{-(t-s)(A_p+I)}N_1(w(s), v(s))\|_{X_p^\beta} ds \\ &\leq K\|w_0\|_p^{(1)} \\ &\quad + C_1 \int_0^t \|(A_p + I)^\beta e^{-(t-s)(A_p+I)}N_1(w(s), v(s))\|_p ds. \end{aligned}$$

From (5.23),

$$\|J_1(w, v)(t)\|_p^{(1)} \leq K\|w_0\|_p^{(1)} + C_1C_2 \int_0^t (t-s)^{-\beta} e^{-\delta(t-s)} \|N_1(w(s), v(s))\|_p ds. \quad (5.31)$$

$$\begin{aligned} \|N_1(w(s), v(s))\|_p &\leq \|\chi(v)\|_\infty \|\nabla v\|_\infty \|\nabla w\|_p + 2\|w\|_p \\ &\quad + \|w\|_p \|k_{1,1} \otimes (wz)\|_\infty + \|k_{1,2} \otimes v\|_\infty \\ &\quad + \|\chi(v)\|_\infty \|w\|_p \|v\|_\infty (\|k \otimes (wz)\|_\infty + 1) \\ &\quad + \|k_{2,1} \otimes (wz)\|_\infty + \|k_{2,2} \otimes v\|_\infty. \end{aligned} \quad (5.32)$$

Since we are working on the local existence, everything is happening inside the ball B_R . However,

$$\begin{aligned} (w, v) \in B_R &\implies \|w\|_p^{(1)} + \|v\|_\infty^{(1)} \leq R, \\ &\implies \|w\|_p^{(1)} \leq R \quad \text{and} \quad \|v\|_\infty^{(1)} \leq R. \end{aligned}$$

$$\begin{aligned} \|w\|_p^{(1)} \leq R &\implies \sup_{t \in [0, T]} \|w(t)\|_p^{(1)} \leq R, \\ &\implies \|w(t)\|_p^{(1)} \leq R, \quad \forall t \in [0, T]. \\ &\implies \int_\Omega \sum_{|\alpha| \leq 1} |\nabla^\alpha w(t)|^p dx \leq R^p, \quad \forall t \in [0, T], \\ &\implies \int_\Omega (|w(t)|^p + |\nabla w(t)|^p) dx \leq R^p, \quad \forall t \in [0, T], \\ &\implies \|w(t)\|_p^p + \|\nabla w(t)\|_p^p \leq R^p, \quad \forall t \in [0, T], \\ &\implies \|w(t)\|_p^p \leq R^p \quad \text{and} \quad \|\nabla w(t)\|_p^p \leq R^p, \quad \forall t \in [0, T]. \end{aligned}$$

That means,

$$\|w(t)\|_p \leq R \quad \text{and} \quad \|\nabla w(t)\|_p \leq R, \quad \forall t \in [0, T]. \quad (5.33)$$

In the same way we prove that

$$\|v(t)\|_\infty \leq R \quad \text{and} \quad \|\nabla v(t)\|_\infty \leq R, \quad \forall t \in [0, T]. \quad (5.34)$$

On the other hand, we have χ which is globally Lipschitz continuous, in particular, it is continuous at 0. That means there exists a constant C such that

$$|\chi(v) - \chi_0| \leq C|v| \implies \|\chi(v)\|_\infty \leq \chi_0 + CR, \quad (5.35)$$

where $\chi_0 = \chi(0)$.

Let us continue by computing the other terms of (5.32). We know that

$$\|k_{1,1} \otimes (wz)\|_\infty = \operatorname{ess\,sup}_{x \in \Omega} |k_{1,1} \otimes (wz)(x)|$$

and

$$\begin{aligned} |k_{1,1} \otimes (wz)(x)| &\leq \int_{\Omega} |k_{1,1}(x, y)| |w(y, t)| |z(y, t)| dy \\ &\leq \sup_{y \in \Omega} |k_{1,1}(y, t)| \int_{\Omega} |w(y, t)| |z(y, t)| dy. \end{aligned} \quad (5.36)$$

Moreover,

$$\log(|z(y, t)|) \leq \int_0^v \|\chi(s)\|_{\infty} ds \leq R(\chi_0 + CR).$$

Thus $|z(y, t)| \leq \exp(R(\chi_0 + CR))$ and equation (5.36) becomes

$$\begin{aligned} \|k_{1,1} \otimes (wz)(x)\|_{\infty} &\leq C_{11} \exp(R(\chi_0 + CR)) \int_{\Omega} |w(y, t)| dy \\ &\leq M_{11}, \quad \text{from Hölder's inequality,} \end{aligned} \quad (5.37)$$

where $M_{11} = C_{11} R (Mes(\Omega))^{\frac{1}{p}} \exp(R(\chi_0 + CR))$. In the same way, we have

$$\begin{aligned} \|k_{1,2} \otimes v\|_{\infty} &\leq M_{12}, \quad \|k \otimes (wz)\|_{\infty} \leq M_0, \\ \|k_{2,2} \otimes v\|_{\infty} &\leq M_{22}, \quad \|k_{2,1} \otimes (wz)\|_{\infty} \leq M_{21}, \end{aligned} \quad (5.38)$$

where

$$\begin{aligned} M_{12} &= C_{12} R Mes(\Omega), \quad M_0 = C_0 \exp(R(\chi_0 + CR)) (Mes(\Omega))^{\frac{1}{p}}, \\ M_{21} &= C_{21} \exp(R(\chi_0 + CR)) (Mes(\Omega))^{\frac{1}{p}}, \quad M_{22} = C_{22} R Mes(\Omega). \end{aligned}$$

By substituting (5.33), (5.34), (5.35), (5.37) and (5.38) in (5.32) we obtain

$$\|N_1(w(s), v(s))\|_p \leq Const(R), \quad (5.39)$$

where

$$Const(R) = 2R + RM_{11} + M_{12} + (\chi_0 + CR)R^2(2 + M_0 + M_{21} + M_{22}).$$

The substitution of equation (5.39) in (5.31) leads to

$$\|J_1(w, v)(t)\|_p^{(1)} \leq K \|w_0\|_p^{(1)} + C_1 C_2 Const(R) \int_0^t (t-s)^{-\beta} e^{-\delta(t-s)} ds. \quad (5.40)$$

Since $e^{-\delta(t-s)} < 1$ and

$$\begin{aligned} \int_0^t (t-s)^{-\beta} ds &= \frac{1}{1-\beta} t^{1-\beta} \\ &\leq \frac{1}{1-\beta} T^{1-\beta}, \end{aligned}$$

(5.40) becomes

$$\|J_1(w, v)(t)\|_p^{(1)} \leq K\|w_0\|_p^{(1)} + \frac{Const(R)}{1-\beta}T^{1-\beta}. \quad (5.41)$$

Proceeding as above, we have

$$\begin{aligned} \|J_2(w, v)(t)\|_\infty^{(1)} &\leq \|v_0\|_\infty^{(1)} + \int_0^t \|v\|_\infty \|k \otimes (wz)\|_\infty + \|v\|_\infty \\ &\quad (1 + \|k_{2,1} \otimes (wz)\|_\infty + \|k_{2,2} \otimes v\|_\infty) ds, \\ &\leq \|v_0\|_\infty^{(1)} + Const1(R) \int_0^t 1 ds, \end{aligned}$$

leading to

$$\|J_2(w, v)(t)\|_\infty^{(1)} \leq \|v_0\|_\infty^{(1)} + T \cdot Const1(R), \quad (5.42)$$

where

$$Const1(R) = RM_0 + R(1 + M_{21} + M_{22})$$

Now let us show that for T sufficiently small

$$J(B_R) \subset B_R. \quad (5.43)$$

In fact, let $(w, v) \in B_R$; from (5.41) and (5.42) we have

$$\begin{aligned} \|J_1(w, v)\|_p + \|J_2(w, v)\|_\infty^{(1)} &\leq K\|w_0\|_p^{(1)} + \|v_0\|_\infty^{(1)} \\ &\quad + \frac{Const(R)}{1-\beta}T^{1-\beta} + T \cdot Const1(R). \end{aligned}$$

However $R > K\|w_0\|_p^{(1)} + \|v_0\|_\infty^{(1)}$ and $\beta < 1$. Therefore,

$$1 - \beta > 0 \quad \text{and} \quad T^{1-\beta} \longrightarrow 0 \quad \text{as} \quad T \longrightarrow 0.$$

Thus, for T sufficiently small

$$\|J_1(w, v)\|_p + \|J_2(w, v)\|_\infty^{(1)} \leq R,$$

which means $J(w, v) \in B_R$. Thus (5.43). Now we want to show that for T small enough,

$$\begin{aligned} J : B_R &\longrightarrow B_R \\ (w, v) &\longmapsto (J_1(w, v), J_2(w, v)) \end{aligned}$$

is a contraction. That is, for (w_1, v_1) and (w_2, v_2) in B_R there exists a constant $L < 1$ such that

$$\|J(w_1, v_1) - J(w_2, v_2)\|_{B_R} \leq L\|(w_1, v_1) - (w_2, v_2)\|_{B_R}.$$

To be more explicit, we want to show that there exists $L < 1$ such that

$$\begin{aligned} \|\|J_1(w_1, v_1) - J_1(w_2, v_2)\|\|_p^{(1)} + \|\|J_2(w_1, v_1) - J_2(w_2, v_2)\|\|_\infty^{(1)} & \quad (5.44) \\ & \leq L(\|\|w_1 - w_2\|\|_p^{(1)} + \|\|v_1 - v_2\|\|_\infty^{(1)}). \end{aligned}$$

We have

$$\|\|J_1(w_1, v_1) - J_1(w_2, v_2)\|\|_p^{(1)} = \sup_{t \in [0, T]} \|\|J_1(w_1, v_1) - J_1(w_2, v_2)\|\|_p^{(1)}$$

and from (5.30) and (5.23)

$$\begin{aligned} & \|\|J_1(w_1, v_1) - J_1(w_2, v_2)\|\|_p^{(1)} \\ & \leq \int_0^t (t-s)^{-\beta} e^{-\delta(t-s)} (\|\|\chi(v_1)\nabla v_1 \cdot \nabla w_1 - \chi(v_2)\nabla v_2 \cdot \nabla w_2\|\|_p + 2\|w_1 - w_2\|_p \\ & \quad + \|\|w_1 k_{1,1} \otimes (w_1 z) - w_2 k_{1,1} \otimes (w_2 z)\|\|_p + \|\|w_1 k_{1,2} \otimes v_1 - w_2 k_{1,2} \otimes v_2\|\|_p \\ & \quad + \|\|\chi(v_1)w_1 v_1 - \chi(v_2)w_2 v_2\|\|_p \quad (5.45) \\ & \quad + \|\|\chi(v_1)w_1 v_1 k \otimes (w_1 z) - \chi(v_2)w_2 v_2 k \otimes (w_2 z)\|\|_p \\ & \quad + \|\|\chi(v_1)w_1 v_1 k_{2,1} \otimes (w_1 z) - \chi(v_2)w_2 v_2 k_{2,1} \otimes (w_2 z)\|\|_p \\ & \quad + \|\|\chi(v_1)w_1 v_1 k_{2,2} \otimes v_1 - \chi(v_2)w_2 v_2 k_{2,2} \otimes v_2\|\|_p) ds. \end{aligned}$$

Let us compute each term of (5.45). We have

$$\begin{aligned} & \|\|\chi(v_1)\nabla v_1 \cdot \nabla w_1 - \chi(v_2)\nabla v_2 \cdot \nabla w_2\|\|_p \\ & = \|\|\chi(v_1)\nabla v_1 \cdot \nabla w_1 - \chi(v_2)\nabla v_2 \cdot \nabla w_1 + \chi(v_2)\nabla v_2 \cdot \nabla w_1 - \chi(v_2)\nabla v_2 \cdot \nabla w_2\|\|_p \\ & \leq \|\|\nabla w_1\|\|_p \|\|\chi(v_1)\nabla v_1 - \chi(v_2)\nabla v_2\|\|_\infty + \|\|\chi(v_2)\|\|_\infty \|\|\nabla v_2\|\|_\infty \|\|\nabla w_1 - \nabla w_2\|\|_p \\ & \leq R \|\|\chi(v_1)\nabla v_1 - \chi(v_2)\nabla v_1 + \chi(v_2)\nabla v_1 - \chi(v_2)\nabla v_2\|\|_p \\ & \quad + (\chi_0 + CR) \|\|\nabla w_1 - \nabla w_2\|\|_p. \\ & \leq R(R \|\|\chi(v_1) - \chi(v_2)\|\|_\infty + (\chi_0 + CR) \|\|\nabla v_1 - \nabla v_2\|\|_\infty) \\ & \quad + (\chi_0 + CR) \|\|\nabla w_1 - \nabla w_2\|\|_p. \end{aligned}$$

Since χ is globally lipschitz continuous,

$$\|\|\nabla v_1 - \nabla v_2\|\|_\infty \leq \|\|v_1 - v_2\|\|_\infty^{(1)}$$

and

$$\|\|\nabla w_1 - \nabla w_2\|\|_p \leq \|\|w_1 - w_2\|\|_p^{(1)},$$

we have

$$\|\|\chi(v_1)\nabla v_1 \cdot \nabla w_1 - \chi(v_2)\nabla v_2 \cdot \nabla w_2\|\|_p \leq f_1(R) \|\|v_1 - v_2\|\|_\infty^{(1)} + f_2(R) \|\|w_1 - w_2\|\|_p^{(1)}, \quad (5.46)$$

where

$$\begin{aligned} f_1(R) & = R(K_1 R + \chi_0 + CR), \\ f_2(R) & = R(\chi_0 + CR). \end{aligned}$$

Doing the same transformation as above, we have

$$\begin{aligned} \|w_1 k_{1,1} \otimes (w_1 z) - w_2 k_{1,1} \otimes (w_2 z)\|_p &\leq \|w_1\|_p \|k_{1,1} \otimes (w_1 z) - k_{1,1} \otimes (w_2 z)\|_\infty \\ &\quad + \|w_1 - w_2\|_p \|k_{1,1} \otimes (w_2 z)\|_\infty. \end{aligned}$$

$$\begin{aligned} |k_{1,1} \otimes (w_1 z) - k_{1,1} \otimes (w_2 z)| &\leq \int_{\Omega} |k_{1,1}| |w_1 - w_2| |z| dy, \\ &\leq M_{11} \exp(R(\chi_0 + CR)) \int_{\Omega} |w_1 - w_2| dy, \quad (5.47) \\ &\leq M_{11} \exp(R(\chi_0 + CR)) (Mes(\Omega))^{\frac{1}{p}} \|w_1 - w_2\|_p. \end{aligned}$$

$$\|w_1 k_{1,1} \otimes (w_1 z) - w_2 k_{1,1} \otimes (w_2 z)\|_p \leq f_3(R) \|w_1 - w_2\|_p^{(1)}, \quad (5.48)$$

where

$$f_3(R) = 2RM_{11} (Mes\Omega)^{\frac{1}{p}}.$$

Following the same procedure, we have

$$\|w_1 k_{1,2} \otimes v_1 - w_2 k_{1,2} \otimes v_2\|_p \leq f_4(R) \|v_1 - v_2\|_\infty^{(1)} + f_5(R) \|w_1 - w_2\|_p^{(1)}, \quad (5.49)$$

where

$$f_4(R) = M_{12} R Mes\Omega \exp(R(\chi_0 + CR))$$

and

$$f_5(R) = RM_{12} Mes\Omega.$$

$$\begin{aligned} &\|\chi(v_1) w_1 v_1 k \otimes (w_1 z) - \chi(v_2) w_2 v_2 k \otimes (w_2 z)\|_p \\ &\leq f_6(R) \|w_1 - w_2\|_p^{(1)} + f_7(R) \|v_1 - v_2\|_\infty^{(1)}, \quad (5.50) \end{aligned}$$

where

$$f_6(R) = 2M_0 R^2 (Mes(\Omega))^{\frac{1}{p}} (\chi_0 + CR) \exp(R(\chi_0 + CR))$$

and

$$f_7(R) = R^2 (Mes(\Omega))^{\frac{1}{p}} M_0 (\chi_0 + CR) (1 + K_1) \exp(R(\chi_0 + CR)).$$

$$\|\chi(v_1) w_1 v_1 - \chi(v_2) w_2 v_2\|_p \leq f_8(R) \|v_1 - v_2\|_\infty^{(1)} + f_9(R) \|w_1 - w_2\|. \quad (5.51)$$

$$f_8(R) = R(\chi_0 + CR) + K_1 R^2 \quad \text{and} \quad f_9(R) = R(\chi_0 + CR).$$

In the same way

$$\begin{aligned} &\|\chi(v_1) w_1 v_1 k_{2,1} \otimes (w_1 z) - \chi(v_2) w_2 v_2 k_{2,1} \otimes (w_2 z)\|_p \\ &\leq f_{10}(R) \|w_1 - w_2\|_p^{(1)} + f_{11}(R) \|v_1 - v_2\|_\infty^{(1)}, \quad (5.52) \end{aligned}$$

$$f_{10}(R) = 2M_{21} R^2 (Mes(\Omega))^{\frac{1}{p}} (\chi_0 + CR) \exp(R(\chi_0 + CR))$$

and

$$\begin{aligned}
 f_{11}(R) &= R^2(Mes(\Omega))^{\frac{1}{p}} M_{21}(\chi_0 + CR)(1 + K_1) \exp(R(\chi_0 + CR)). \\
 & \|\chi(v_1)w_1v_1k_{2,2} \otimes v_1 - \chi(v_2)w_2v_2k_{2,2} \otimes v_2\|_p \\
 & \leq f_{12}(R)\|w_1 - w_2\|_p + f_{13}(R)\|v_1 - v_2\|_{\infty}^{(1)}, \tag{5.53}
 \end{aligned}$$

where

$$f_{12}(R) = M_{22}R^2(\chi_0 + CR)Mes(\Omega)$$

and

$$f_{13}(R) = R^2M_{22}Mes(\Omega)(2(\chi_0 + CR) + K_1R).$$

The substitution of (5.46), (5.48), (5.49), (5.50), (5.51), (5.52) and (5.53) in (5.45) leads to

$$\begin{aligned}
 \|J_1(w_1, v_1) - J_1(w_2, v_2)\| & \leq \int_0^t (t-s)^{-\beta} e^{-\delta(t-s)} (F(R)\|w_1 - w_2\|_p^{(1)} \\
 & \quad + G(R)\|v_1 - v_2\|_{\infty}^{(1)}) ds \\
 & \leq Const2(R) (\|w_1 - w_2\|_p^{(1)} \\
 & \quad + \|v_1 - v_2\|_{\infty}^{(1)}) \int_0^t (t-s)^{-\beta} ds.
 \end{aligned}$$

Thus

$$\|J_1(w_1, v_1) - J_1(w_2, v_2)\|_p^{(1)} \leq \frac{Const2(R)}{1-\beta} T^{1-\beta} (\|w_1 - w_2\|_p^{(1)} + \|v_1 - v_2\|_{\infty}^{(1)}). \tag{5.54}$$

Here,

$$Const2(R) = \max(F(R), G(R)),$$

with

$$F(R) = f_2(R) + 2 + f_3(R) + f_5(R) + f_6(R) + f_9(R) + f_{10}(R) + f_{12}$$

and

$$G(R) = f_1(R) + f_4(R) + f_7(R) + f_8(R) + f_{11}(R) + f_{13}(R).$$

Using the same method for J_2 we have,

$$\begin{aligned}
 \|J_2(w_1, v_1) - J_2(w_2, v_2)\|_\infty^{(1)} &\leq \int_0^t (\|v_1 k \otimes (w_1 z) - v_2 k \otimes (w_2 z)\|_\infty^{(1)} \\
 &\quad + \|v_1 - v_2\|_\infty^{(1)} \\
 &\quad + \|v_1 k_{2,1} \otimes (w_1 z) - v_2 k_{2,1} \otimes (w_2 z)\|_\infty^{(1)} \\
 &\quad + \|v_1 k_{2,2} \otimes v_1 - v_2 k_{2,2} \otimes v_2\|_\infty^{(1)}) ds, \\
 &\leq \int_0^t (g_1(R)\|w_1 - w_2\|_p + g_2(R)\|v_1 - v_2\|_\infty^{(1)} \\
 &\quad + \|v_1 - v_2\|_\infty^{(1)} + g_3(R)\|w_1 - w_2\|_p \\
 &\quad + g_4(R)\|v_1 - v_2\|_\infty^{(1)} + g_5(R)\|v_1 - v_2\|_\infty^{(1)}) ds, \\
 &\leq \int_0^t (I(R)\|w_1 - w_2\|_p + J(R)\|v_1 - v_2\|_\infty^{(1)}) ds,
 \end{aligned}$$

where

$$I(R) = g_1(R) + g_3(R)$$

and

$$J(R) = g_2(R) + 1 + g_4(R) + g_5(R),$$

with

$$\begin{aligned}
 g_1(R) &= g_2(R) = M_0 R \exp(R(\chi_0 + CR))(Mes(\Omega))^{\frac{1}{p}}, \\
 g_3(R) &= g_4(R) = M_{21} R \exp(R(\chi_0 + CR))(Mes(\Omega))^{\frac{1}{p}} \\
 \text{and } g_5(R) &= 2M_{22} R \exp(R(\chi_0 + CR))Mes(\Omega).
 \end{aligned}$$

If we denote

$$Const3(R) = \max(I(R), J(R)),$$

then,

$$\|J_2(w_1, v_1) - J_2(w_2, v_2)\|_\infty^{(1)} \leq Const3(R).T(\|w_1 - w_2\|_p^{(1)} + \|v_1 - v_2\|_\infty^{(1)}). \quad (5.55)$$

From (5.54) and (5.55) we have

$$\begin{aligned}
 &\|J_1(w_1, v_1) - J_1(w_2, v_2)\|_p^{(1)} + \|J_2(w_1, v_1) - J_2(w_2, v_2)\|_\infty^{(1)} \\
 &\leq \frac{Const2(R)}{1 - \beta} T^{1-\beta} (\|w_1 - w_2\|_p^{(1)} + \|v_1 - v_2\|_\infty^{(1)}) \\
 &\quad + Const3(R).T(\|w_1 - w_2\|_p^{(1)} + \|v_1 - v_2\|_\infty^{(1)}),
 \end{aligned}$$

which means

$$\|J(w_1, v_1) - J(w_2, v_2)\|_{B_R} \leq L\|(w_1, v_1) - (w_2, v_2)\|_{B_R}, \quad (5.56)$$

where

$$L = \frac{Const2(R)}{1 - \beta} T^{1-\beta} + Const3(R).T.$$

Therefore, for T small enough $L < 1$ and J is a contraction on B_R which is a closed set in a Banach space $Y^{1,p} \times Y^{1,\infty}$. From Theorem 3.2.6, J has a unique fixed point in B_R . Thus local existence and uniqueness follow.

Let us proceed to the second part, (5.24), of Theorem 5.2.1. To show that $w \in C^1((0, T); W^{1,p}(\Omega))$, we have to show that for a fixed $t_0 \in (0, T)$,

$$\frac{d}{dt}w(t, \cdot)|_{t=t_0} \in W^{1,p}(\Omega). \quad (5.57)$$

Here we consider the following problem that involves w ,

$$\begin{cases} \frac{d}{dt}w &= -(A_p + I)w + N_1(w, v) \\ w(0) &= w_0 \end{cases} \quad (5.58)$$

where

$$\begin{aligned} N_1(w, v) &= \chi(v)\nabla v \cdot \nabla w + 2w - wk_{1,1} \otimes (wz) \\ &\quad - wk_{1,2} \otimes v + \chi(v)wv(k \otimes (wz) - 1 + k_{2,1} \otimes (wz) + k_{2,2} \otimes v). \end{aligned}$$

Our aim here is to apply Theorem 3.3.8. Thus we have to prove that the function $N_1(w, v)$ is locally Lipschitzian with respect to w on an open subset of $X_p^\beta = D((A_p + I)^\beta)$. Using the same arguments like previously, we have

$$\begin{aligned} & \|N_1(w_1, v) - N_1(w_2, v)\|_p \\ & \leq R^2 \|\nabla w_1 - \nabla w_2\|_p + 2\|w_1 - w_2\|_p + f_3(R)\|w_1 - w_2\|_p \\ & \quad + M_{12}R \text{Mes}(\Omega)\|w_1 - w_2\|_p + R^2 f'_3(R)\|w_1 - w_2\|_p + R^2\|w_1 - w_2\|_p \\ & \quad + R^2 f''_3(R)\|w_1 - w_2\|_p + M_{22}R^3 \text{Mes}(\Omega)\|w_1 - w_2\|_p. \end{aligned}$$

Hence we have

$$\|N_1(w_1, v) - N_1(w_2, v)\|_p \leq P(R)\|w_1 - w_2\|_p^{(1)}, \quad (5.59)$$

where

$$P(R) = 2R^2 + 2 + f_3(R) + (M_{12}R + M_{22}R^2)\text{Mes}(\Omega) + R^2 f'_3(R) + R^2 f''_3(R)$$

with

$$f'_3(R) = 2RM_0(\text{Mes}(\Omega))^{\frac{1}{p}}$$

and

$$f''_3(R) = 2RM_0(\text{Mes}(\Omega))^{\frac{1}{p}}.$$

Using $k = 1$, $p = q$ and $\beta \in (\frac{1}{2}, 1)$, we have

$$X_p^\beta \hookrightarrow W^{1,p}(\Omega).$$

This implies, from (5.59), that

$$\|N_1(w_1, v) - N_1(w_2, v)\|_p \leq Q(R)\|w_1 - w_2\|_{X_p^\beta}. \quad (5.60)$$

From Theorem 3.3.8,

$$\frac{d}{dt}w(t, \cdot)|_{t=t_0} \in X_p^\beta \hookrightarrow W_p^{(1)}(\Omega)$$

thus,

$$w \in C^1((0, T); W^{1,p}(\Omega)). \quad (5.61)$$

Now let us rewrite (5.17) in the nondivergence form

$$-\Delta w - b \cdot \nabla w + w = f - \partial_t w, \quad (5.62)$$

where $b = \chi(v)\nabla v$ and

$$f = w(2 - k_{1,1} \otimes (wz) - k_{1,2} \otimes v) + \chi(v)wv(k \otimes (wz) - 1 + k_{2,1} \otimes (wz) + k_{2,2} \otimes v).$$

But we have $b \in (L^\infty(\Omega))^d$ and, according to all the calculations done above, $f \in L^p(\Omega)$. From elliptic estimates, [22], $w(t_0) \in W_p^{(2)}(\Omega)$. Now, let us prove that for the same fixed $t_0 \in (0, T)$,

$$\frac{dv}{dt}(t, \cdot)|_{t=t_0} \in W_\infty^{(1)}(\Omega).$$

We consider the problem in v

$$\begin{cases} \frac{dv}{dt} &= v + N_2'(w, v) \\ v(0) &= v_0, \end{cases} \quad (5.63)$$

where $N_2'(w, v) = -vk \otimes (wz) + v(-k_{2,1} \otimes (wz) - k_{2,2} \otimes v)$.

Since the identity operator is a sectorial operator and $N_2'(w, v)$ is locally Lipschitzian with respect to v , we can again apply Theorem 3.3.8 and we have the result which ends the proof of (5.24).

Let us move to the proof of (5.25). We consider the problem

$$\begin{cases} \partial_t w &= \Delta w + b \nabla w + \varphi w, \\ \partial_\nu w &= 0 \quad \text{in } \partial\Omega, \end{cases} \quad (5.64)$$

with b and φ bounded in Ω .

Let λ be an arbitrary constant. By rescaling $\tilde{w} = e^{-\lambda t}w$, (5.64) becomes

$$\begin{cases} \partial_t \tilde{w} &= \Delta \tilde{w} + b \nabla \tilde{w} + \varphi \tilde{w} - \lambda \tilde{w}, \\ \partial_\nu \tilde{w} &= 0 \quad \text{in } \partial\Omega. \end{cases} \quad (5.65)$$

Since the problem given by (5.64) is equivalent to the one given by (5.65), the solution of (5.64) is non-negative if and only if the solution of (5.65) is non-negative.

For $\tilde{w} \in H^2(\Omega)$, (5.65) is equivalent to the variational problem below

$$\begin{cases} (\partial_t \tilde{w}, v) &= (\Delta \tilde{w}, v) + (b \nabla \tilde{w}, v) + (\varphi \tilde{w}, v) - (\lambda \tilde{w}, v), \\ (\partial_\nu \tilde{w}, v) &= 0 \quad \text{in } \partial\Omega, \end{cases} \quad (5.66)$$

for any $v \in H^1(\Omega)$. Applying the Green's formula to the first term on the right hand side of equation (5.66), we have

$$\begin{cases} (\partial_t \tilde{w}, v) &= -(\nabla \tilde{w}, \nabla v) + (b \nabla \tilde{w}, v) + (\varphi \tilde{w}, v) - (\lambda \tilde{w}, v), \\ (\partial_\nu \tilde{w}, v) &= 0 \quad \text{in } \partial\Omega, \end{cases} \quad (5.67)$$

for any $v \in H^1(\Omega)$.

From [20], $v \in H^1(\Omega)$ implies that $v^- \in H^1(\Omega)$, where $v = v^+ - v^-$. Since $\tilde{w} \in H^2(\Omega) \subset H^1(\Omega)$, $\tilde{w}^- \in H^1(\Omega)$. Thus, (5.67) is applicable for \tilde{w}^- and we have

$$(\partial_t \tilde{w}^-, \tilde{w}^-) = -(\nabla \tilde{w}^-, \nabla \tilde{w}^-) + (b \nabla \tilde{w}^-, \tilde{w}^-) + (\varphi \tilde{w}^-, \tilde{w}^-) - (\lambda \tilde{w}^-, \tilde{w}^-),$$

but

$$\begin{aligned} (\partial_t \tilde{w}^-, \tilde{w}^-) &= \int_{\Omega} \tilde{w}^- \partial_t \tilde{w}^- \, dx \\ &= \frac{1}{2} \int_{\Omega} \partial_t (\tilde{w}^-)^2 \, dx \\ &= \frac{1}{2} \frac{d}{dt} \int_{\Omega} (\tilde{w}^-)^2 \, dx = \frac{d}{2dt} \|\tilde{w}^-(t)\|_2^2. \end{aligned}$$

$$\frac{d}{2dt} \|\tilde{w}^-(t)\|_2^2 = -(\nabla \tilde{w}^-, \nabla \tilde{w}^-) + (b \nabla \tilde{w}^-, \tilde{w}^-) + (\varphi \tilde{w}^-, \tilde{w}^-) - (\lambda \tilde{w}^-, \tilde{w}^-). \quad (5.68)$$

We have

$$\begin{aligned} |(b \nabla \tilde{w}^-, \tilde{w}^-)| &\leq \max |b| (\sqrt{\epsilon} \|\nabla \tilde{w}^-\|_2, \frac{1}{\sqrt{\epsilon}} \|\tilde{w}^-\|_2), \\ &\leq \max |b| (\sqrt{\epsilon} \|\nabla \tilde{w}^-\|_2) (\frac{1}{\sqrt{\epsilon}} \|\tilde{w}^-\|_2) \quad \text{Cauchy-Schwarz inequality,} \\ &\leq \frac{\max |b|}{2} (\epsilon \|\nabla \tilde{w}^-\|_2^2 + \frac{1}{\epsilon} \|\tilde{w}^-\|_2^2) \quad ((A - B)^2 \geq 0). \end{aligned}$$

From (5.68) we have

$$\begin{aligned} \frac{d}{2dt} \|\tilde{w}^-(t)\|_2^2 &\leq -\|\nabla \tilde{w}^-\|_2^2 + \frac{\max |b|}{2} (\epsilon \|\nabla \tilde{w}^-\|_2^2 + \frac{1}{\epsilon} \|\tilde{w}^-\|_2^2) \\ &\quad + \max |\varphi| \|\tilde{w}^-\|_2^2 - \lambda \|\tilde{w}^-\|_2^2, \\ &\leq \|\nabla \tilde{w}^-\|_2^2 (-1 + \frac{\max |b|}{2} \epsilon) + \|\tilde{w}^-\|_2^2 (\frac{\max |b|}{2\epsilon} + \max |\varphi| - \lambda). \end{aligned}$$

If we take ϵ so small that

$$\epsilon \leq \frac{2}{\max |b|}$$

and λ so large that

$$\lambda \geq \frac{\max |b|}{2\epsilon} + \max |\varphi|,$$

then $\frac{d}{2dt} \|\tilde{w}^-(t)\|_2^2 \leq 0$ which implies that $\|\tilde{w}^-(t)\|_2$ is non-increasing.

However, $\tilde{w}^-(0) = 0$ (because $\tilde{w}^-(0) = \sup(-\tilde{w}(0), 0)$ and $\tilde{w}(0) \geq 0$). Thus, for any positive t , we have

$$\begin{aligned} \|\tilde{w}^-(t)\|_2 \leq \|\tilde{w}^-(0)\|_2 = 0 &\implies \tilde{w}^-(t) = 0 \quad \forall t > 0, \\ &\implies \tilde{w}(t) \geq 0 \quad \forall t > 0, \\ &\implies w(t) \geq 0 \quad \forall t > 0. \end{aligned}$$

Here, the solution is positive in $L^2(\Omega)$, this implies the positivity of the semigroup in $L^2(\Omega)$. But from (3.2), the semigroup operates in $L^p(\Omega)$ for $1 \leq p \leq +\infty$. Since the positivity in $L^2(\Omega)$ means that, in particular, solutions starting from $C_c^\infty(\Omega)$ initial conditions are positive.

However, if a solution $w(t) = w_0 T(t) \in L^p(\Omega)$ then, $w(t) \in L^2(\Omega)$ and $w_0 \in L^p(\Omega) = \overline{C_c^\infty(\Omega)}$ means there exists a serie $w_n(t) \in C_c^\infty(\Omega)$ such that $w_n(t) \rightarrow w_0$. Therefore, for any positive t

$$w(t) = T(t) \lim_{n \rightarrow \infty} w_n(t) = \lim_{n \rightarrow \infty} w_n(t) T(t) > 0.$$

The equation involving v can be rewritten as $\partial_t v = vg(x, t)$, where $g(x, t) = k \otimes wz + 1 - k_{2,1} \otimes wz - k_{2,2} \otimes v$. Thus we have

$$v(x, t) = v_0(x) e^{\int_0^t g(x,s) ds} \geq 0.$$

Therefore, we conclude the non-negativity of w and v . □

According to [45], by the prolongation arguments given by Theorem 3.3.6 we have the following corollary.

Corollary 5.2.2. *Let T_{max} be the maximal existence time. If there is a continuous function $\omega : (0, \infty) \rightarrow (0, \infty)$ such that, for each $\tau > 0$,*

$$\|w(t)\|_p^{(1)} \leq \omega(\tau), \quad \|v(t)\|_\infty^{(1)} \leq \omega(\tau) \quad \text{for } 0 < t < \min\{\tau, T_{max}\}, \quad (5.69)$$

then

$$T_{max} = +\infty.$$

Returning to the change of variable $u = wz$, we have the following.

Corollary 5.2.3. *Let $(u_0, v_0) \in W_p^{(1)}(\Omega) \times W_\infty^{(1)}(\Omega)$. Assume (5.4) are satisfied, then there exists $T > 0$ such that the problem given by (5.5) has a unique solution*

$$\begin{aligned} u &\in C^0([0, T]; W_p^{(1)}(\Omega)) \cap C^1((0, T); W_p^{(1)}(\Omega)) \cap C^0((0, T), W_\infty^{(1)}(\Omega)), \\ v &\in C^0([0, T]; W_\infty^{(1)}(\Omega)) \cap C^1((0, T); W_\infty^{(1)}(\Omega)). \end{aligned} \quad (5.70)$$

Proof. Since $u_0 \in W_p^{(1)}(\Omega)$, definitely $w_0 \in W_p^{(1)}(\Omega)$. In addition, $v_0 \in W_\infty^{(1)}(\Omega)$, therefore the application of Theorem 5.2.1 leads to the existence of $T > 0$ such that the problem (5.19) has a unique solution $(w, v) \in Y \times Y^{1, \infty}$ and

$$\begin{aligned} w &\in C^1((0, T); W_p^{(1)}(\Omega)) \cap C^0((0, T); W_p^{(2)}(\Omega)), \\ v &\in C^1((0, T); W_\infty^{(1)}(\Omega)). \end{aligned} \quad (5.71)$$

Taking (5.71) into account and that $u = wz$, the proof of (5.70) follows. \square

5.3 Global Existence

In various systems describing cell motions and chemotaxis, the solutions may blow up in finite time. Here we prove that the solutions to the system of nonlocal equations (5.3) exist globally in space dimension without imposing any kind of smallness conditions on the initial conditions.

In order to prove the global existence of the solution, we assume that (u, v) is a non-negative solution to system of equations (5.3), (5.6), (5.7) on the time interval $[0, T]$, with $T > 0$. To begin we are going to prove some simple lemmas to provide priori estimates.

Lemma 5.3.1.

$$v(t, x) \leq v_0(x)e^T \quad t \in [0, T], \quad x \in \Omega. \quad (5.72)$$

Proof. We have

$$\begin{aligned} \partial_t v(t, x) &= \mu_2 v(t, x) - \left(\gamma v(t, x) \int_\Omega k(x, y) u(t, y) dy \right. \\ &\quad \left. + \mu_2 v(t, x) \left(\int_\Omega k_{2,1}(x, y) u(t, y) dy + \int_\Omega k_{2,2}(x, y) v(t, y) dy \right) \right). \end{aligned}$$

If we set

$$\begin{aligned} f(t, x) &= \gamma v(t, x) \int_\Omega k(x, y) u(t, y) dy + \mu_2 v(t, x) \left(\int_\Omega k_{2,1}(x, y) u(t, y) dy \right. \\ &\quad \left. + \int_\Omega k_{2,2}(x, y) v(t, y) dy \right), \end{aligned}$$

then the function $f(t, x)$ is positive for any $(t, x) \in [0, T] \times \Omega$, since $(u, v) \geq 0$ and $\gamma > 0$, $k \geq 0$, $k_{i,j} \geq 0$ from (5.4). Thus,

$$\partial_t v(t, x) \leq v(t, x), \quad (5.73)$$

since $\mu_2 = 1$. Integrating both sides of (5.73) over $[0, T]$, we have

$$v(t, x) \leq v_0(x) + \int_0^t v(s, x) ds.$$

But $v_0 \geq 0$, so we can apply the Gronwall's lemma and then we have the result (5.72). \square

Lemma 5.3.2.

$$\|u\|_1 \leq \|u_0\|_1 e^T, \quad \|v\|_1 \leq \|v_0\|_1 e^T. \quad (5.74)$$

Proof. We have

$$\begin{aligned} \partial_t u(t, x) &= \nabla \cdot (\nabla u(t, x) - \chi(v)u(t, x)\nabla v(t, x)) + u(t, x) \\ &\quad \left(1 - \int_{\Omega} k_{1,1}(x, y)u(t, y)dy - \int_{\Omega} k_{1,2}(x, y)v(t, y)dy\right). \end{aligned} \quad (5.75)$$

By integrating both sides of (5.75) in $[0, t]$, for any $0 \leq t \leq T$, we obtain

$$\begin{aligned} u(t, x) &= u_0(x) + \int_0^t u(s, x) ds + \int_0^t \nabla \cdot (\nabla u(t, s) - \chi(v)u(s, x)\nabla v(s, x)) ds \\ &\quad - \int_0^t u(s, x) \left(\int_{\Omega} k_{1,1}(x, y)u(s, y)dy + \int_{\Omega} k_{1,2}(x, y)v(s, y)dy \right) ds \\ &\leq u_0(x) + \int_0^t u(s, x) ds + \int_0^t \nabla \cdot (\nabla u(t, s) - \chi(v)u(s, x)\nabla v(s, x)) ds, \end{aligned}$$

because of the positivity of (u, v) and $k_{i,j}$ ($i, j = 1, 2$). Let us integrate over Ω on both sides

$$\begin{aligned} \int_{\Omega} u(s, x) dx &\leq \int_{\Omega} u_0(x) dx + \int_{\Omega} \int_0^t u(s, x) ds dx \\ &\quad + \int_{\Omega} \int_0^t \nabla \cdot (\nabla u(t, s) - \chi(v)u(s, x)\nabla v(s, x)) ds dx, \\ &\leq \int_{\Omega} u_0(x) dx + \int_0^t \int_{\Omega} u(s, x) dx ds \\ &\quad + \int_0^t \int_{\Omega} \nabla \cdot (\nabla u(t, s) - \chi(v)u(s, x)\nabla v(s, x)) dx ds, \end{aligned}$$

from Fubini's Theorem. But

$$\begin{aligned}
 & \int_{\Omega} \nabla \cdot (\nabla u(t, s) - \chi(v)u(s, x)\nabla v(s, x)) dx \\
 &= \int_{\Omega} \operatorname{div}(\nabla u(t, s) - \chi(v)u(s, x)\nabla v(s, x)) dx \\
 &= \int_{\partial\Omega} (\nabla u(t, s) - \chi(v)u(s, x)\nabla v(s, x)) \nu d(\partial\Omega), \\
 &= 0
 \end{aligned}$$

from the divergence formula and the boundary condition (no flux of the cancer cells on the boundary domain). Here ν is the outward normal vector to $\partial\Omega$. Therefore

$$\begin{aligned}
 \int_{\Omega} u(s, x) dx &\leq \int_{\Omega} u_0(x) dx + \int_0^t \int_{\Omega} u(s, x) dx ds \\
 &\leq \|u_0\|_1 + \int_0^t \|u(s)\|_1 ds.
 \end{aligned}$$

From Gronwall's lemma, since $u \geq 0$ we have

$$\|u(t)\|_1 \leq \|u_0\|_1 e^t. \quad (5.76)$$

Taking the supremum in both sides of (5.76) on $[0, T]$ we have the first result of (5.74).

Knowing that $z^{-1} \leq 1$, we can write

$$\begin{aligned}
 \|w\|_1 &= \|uz^{-1}\|_1 \leq \|u\|_1 \\
 &\leq \|u_0\|_1 e^T.
 \end{aligned}$$

Hence, we end the proof. \square

Lemma 5.3.3.

$$\|v\|_{\infty}^{(1)} \leq C_1(\|v_0\|_{\infty}^{(1)} + C_2), \quad (5.77)$$

where the constants C_1 and C_2 depend on T , $\|u_0\|_1$ and $\|v_0\|_{\infty}$.

Proof. From the second equation of the system (5.19), we have

$$\begin{aligned}
 \nabla(\partial_t v) &= \partial_t \nabla v \\
 &= -v \nabla(k \otimes u) - k \otimes \nabla v \\
 &\quad + v \nabla(1 - k_{2,1} \otimes u - k_{2,2} \otimes v) + (1 - k_{2,1} \otimes u - k_{2,2} \otimes v) \nabla v,
 \end{aligned}$$

but

$$\begin{aligned}
 \nabla(k \otimes u(t, x)) &= \nabla \int_{\Omega} k(x, y) u(t, y) dy \\
 &= \int_{\Omega} \nabla_1 k(x, y) u(t, y) dy = \nabla_1 k \otimes u(t, x),
 \end{aligned}$$

where ∇_1 stands for the gradient with respect to the first variable x . Thus we have

$$\begin{aligned} \partial_t \nabla v &= -v \nabla_1 k \otimes u - k \otimes u \nabla v \\ &\quad -v(\nabla_1 k_{2,1} \otimes u + \nabla_1 k_{2,2} \otimes v) + \nabla v(1 - k_{2,1} \otimes u - k_{2,2} \otimes v). \end{aligned}$$

Taking the absolute value and integrating on $[0, t]$ we obtain

$$\begin{aligned} |\nabla v(t, x)| &\leq |\nabla v_0(x)| + \int_0^t v(\nabla_1 k \otimes u + \nabla_1 k_{2,1} \otimes u + \nabla_1 k_{2,2} \otimes v) |ds \\ &\quad + \int_0^t |\nabla v(s, x)| (1 + k \otimes u + k_{2,1} \otimes u + k_{2,2} \otimes v) |ds. \end{aligned}$$

We have

$$\begin{aligned} |\nabla_1 k \otimes u(t, x)| &\leq \int_{\Omega} |\nabla_1 k(x, y)| u(t, y) dy, \\ &\leq \operatorname{ess\,sup}_{(x,y) \in \Omega \times \Omega} |\nabla_1 k(x, y)| \int_{\Omega} u(t, y) dy, \\ &\leq \operatorname{ess\,sup}_{(x,y) \in \Omega \times \Omega} |\nabla k(x, y)| \int_{\Omega} u(t, y) dy, \\ &\leq c_1 \|u(t)\|_1, \quad \text{from (5.4)}. \end{aligned}$$

In the same way

$$\begin{aligned} |\nabla_1 k_{2,2} \otimes v(t, x)| &\leq \operatorname{ess\,sup}_{(x,y) \in \Omega \times \Omega} |\nabla_1 k_{2,2}(x, y)| \operatorname{ess\,sup}_{y \in \Omega} |v(t, y)| \int_{\Omega} 1 dy, \\ &\leq c_2 \|v(t)\|_{\infty}. \end{aligned}$$

We thus have

$$\begin{aligned} |\nabla v(t, x)| &\leq |\nabla v_0(x)| + \int_0^t \|v(s)\|_{\infty} (2c_1 \|u(s)\|_1 + c_2 \|v(s)\|_{\infty}) ds \\ &\quad + \int_0^t |\nabla v(s, x)| (1 + 2c_1 \|u(s)\|_1 + c_2 \|v(s)\|_{\infty}) ds. \end{aligned}$$

Let us set

$$K_1 = \max(2c_1, c_2) \quad \text{and} \quad K_2 = \max(1, c_1, c_2).$$

Then we have the following inequality

$$\begin{aligned} |\nabla v(t, x)| &\leq |\nabla v_0(x)| + K_1 \int_0^t \|v(s)\|_{\infty} (\|u(s)\|_1 + \|v(s)\|_{\infty}) ds \\ &\quad + K_2 \int_0^t |\nabla v(s, x)| (1 + \|u(s)\|_1 + \|v(s)\|_{\infty}) ds, \\ &\leq |\nabla v_0(x)| + K_1 \int_0^t \|v\|_{\infty} (\|u\|_1 + \|v\|_{\infty}) ds \\ &\quad + K_2 \int_0^t |\nabla v(s, x)| (1 + \|u\|_1 + \|v\|_{\infty}) ds. \end{aligned}$$

From Lemma 5.72 and Lemma 5.74 we have

$$\begin{aligned}
 |\nabla v(t, x)| &\leq |\nabla v_0(x)| + K_1 e^{2T} \int_0^t \|v_0\|_\infty (\|u_0\|_1 + \|v_0\|_\infty) ds \\
 &\quad + K_2 e^T \int_0^t |\nabla v(s, x)| (1 + \|u_0\|_1 + \|v_0\|_\infty) ds, \\
 &\leq |\nabla v_0(x)| + K_1 T e^T \|v_0\|_\infty (\|u_0\|_1 + \|v_0\|_\infty) \\
 &\quad + K_2 e^T (1 + \|u_0\|_1 + \|v_0\|_\infty) \int_0^t |\nabla v(s, x)| ds,
 \end{aligned}$$

therefore from Gronwall's lemma we obtain

$$\begin{aligned}
 |\nabla v(t, x)| &\leq (|\nabla v_0(x)| + K_1 T e^T \|v_0\|_\infty (\|u_0\|_1 + \|v_0\|_\infty)) \\
 &\quad \times \exp(K_2 T e^T (1 + \|u_0\|_1 + \|v_0\|_\infty)).
 \end{aligned} \tag{5.78}$$

On the other hand we have

$$\begin{aligned}
 \|v\|_\infty^{(1)} &= \sum_{|\alpha| \leq 1} \text{ess sup}_{x \in \Omega} |D^\alpha v(t, x)| \\
 &\leq \|v(t)\|_\infty + \|\nabla v(t)\|_\infty
 \end{aligned}$$

Inequalities (5.72) and (5.78) lead to

$$\begin{aligned}
 \|v\|_\infty^{(1)} &\leq \|\nabla v(t)\|_\infty + \|v(t)\|_\infty \\
 &\leq (\|\nabla v_0\|_\infty + K_1 T e^T \|v_0\|_\infty (\|u_0\|_1 + \|v_0\|_\infty)) \\
 &\quad \times \exp(K_2 T e^T (1 + \|u_0\|_1 + \|v_0\|_\infty)) + \|v_0\|_\infty e^T.
 \end{aligned}$$

Since

$$\|v_0\|_\infty e^T \leq \|v_0\|_\infty \exp(K_2 T e^T (1 + \|u_0\|_1 + \|v_0\|_\infty)),$$

the following inequality holds

$$\begin{aligned}
 \|v\|_\infty^{(1)} &\leq (\|v_0\|_\infty + \|\nabla v_0\|_\infty + K_1 T e^T \|v_0\|_\infty (\|u_0\|_1 + \|v_0\|_\infty)) \\
 &\quad \times \exp(K_2 T e^T (1 + \|u_0\|_1 + \|v_0\|_\infty)).
 \end{aligned}$$

By setting

$$C_1 = K_2 T e^T (1 + \|u_0\|_1 + \|v_0\|_\infty) \quad \text{and} \quad C_2 = K_1 T e^T \|v_0\|_\infty (\|u_0\|_1 + \|v_0\|_\infty),$$

we complete the proof. \square

Lemma 5.3.4. *We have*

$$\|w\|_p^{(1)} \leq C_3 \|w_0\|_p^{(1)}, \tag{5.79}$$

where the constant C_3 depends on T , $\|u_0\|_1$ and $\|v_0\|_\infty$.

Proof. From the local existence and Lemma 3.3.5, w has the following form

$$\begin{aligned} w(t) = & e^{-t(A_p+I)}w_0 + \int_0^t e^{-(t-s)(A_p+I)}(\chi(v)\nabla v \cdot \nabla w + 2w \\ & - wk_{1,1} \otimes u - wk_{1,2} \otimes v + \chi(v)wvk \otimes u \\ & - \chi(v)wv(1 - k_{2,1} \otimes u - k_{2,2} \otimes v))ds. \end{aligned} \quad (5.80)$$

Considering the facts that

$$\|\nabla w\|_p \leq \|w\|_p^{(1)}, \quad \|w\|_p \leq \|w\|_p^{(1)},$$

in addition to (5.30) and (5.23), we have

$$\begin{aligned} \|w(t)\|_p^{(1)} \leq & \text{const.}t^{-\beta}e^{-\delta t}\|w_0\|_p \\ & + \text{const.} \int_0^t (t-s)^{-\beta}e^{-\delta(t-s)}\|w\|_p^{(1)}(\|\chi(v)\|_\infty\|\nabla v\|_\infty \\ & + 1 + \|k_{1,1} \otimes u\|_\infty + \|k_{1,2} \otimes v\|_\infty + \|\chi(v)\|_\infty\|v\|_\infty(\|k \otimes u\|_\infty \\ & + 1 + \|k_{2,1} \otimes u\|_\infty + \|k_{2,2} \otimes v\|_\infty))ds. \end{aligned}$$

From (5.35) and knowing that $k, k_{i,j} \in L^\infty(\Omega \times \Omega)$,

$$\begin{aligned} \|w(t)\|_p^{(1)} \leq & \|w_0\|_p^{(1)}\text{const.}t^{-\beta} + \text{const.} \int_0^t (t-s)^{-\beta}\|w(s)\|_p^{(1)} \\ & \times (1 + (\|v(s)\|_\infty^{(1)} + \chi_0)\|v(s)\|_\infty^{(1)} + \|u(s)\|_1 + \|v(s)\|_\infty \\ & + (\|v(s)\|_\infty + \chi_0)\|v(s)\|_\infty(\|u(s)\|_1 + 1 + \|v(s)\|_\infty))ds. \end{aligned}$$

According to [45], from [29] (Theorem 7.1.1), (5.72), (5.74) and (5.77) we have

$$\|w\|_p^{(1)} \leq \|w_0\|_p^{(1)}\text{const.}t^{-\beta} \quad \forall t \in (0, T]. \quad (5.81)$$

Let us show by contradiction that there exists a constant r such that

$$\|w\|_1^{(p)} \leq r, \quad (5.82)$$

where r is a constant.

Assume that for all r there exists a $t_r = t(r) \in (0, T]$ such that

$$\|w(t_r)\|_p^{(1)} > r.$$

Hence,

- For $r = 1$, there exists $t_1 \in [0, T]$ such that $\|w(t_1)\|_p^{(1)} > 1$,
- For $r = 2$, there exists $t_2 \in [0, T]$ such that $\|w(t_2)\|_p^{(1)} > 2$,
- \vdots
- For $r = n$, there exists $t_n \in [0, T]$ such that $\|w(t_n)\|_p^{(1)} > n$.

There exists a sequence $(t_r)_r \in [0, T]$ such that

$$\|w(t_r)\|_p^{(1)} > 2^r \quad \forall r. \quad (5.83)$$

From (5.83) and (5.81) we have

$$2^r < \|w(t_r)\|_p^{(1)} \leq \|w_0\|_p^{(1)} \text{const.} t_r^{-\beta} \quad \forall r,$$

which shows that, since $\beta > 0$,

$$t_r \longrightarrow 0, \text{ as } r \longrightarrow \infty.$$

Taking the limit on both sides of (5.83) as $r \longrightarrow \infty$ and knowing that $w \in C^0([0, T], W^{1,p}(\Omega))$ we obtain

$$\|w_0\|_p^{(1)} > \infty,$$

which contradicts the fact that $w_0 \in W_p^{(1)}(\Omega)$.

We then draw the conclusion that $\|w\|_p^{(1)}$ is bounded and its bound is a function of $T, \|w_0\|_p^{(1)}, \|u_0\|_1$ and $\|v_0\|_\infty$ since they are all positive. This achieves the proof of Lemma 5.79. \square

Therefore we state the main global result below.

Theorem 5.3.5. *Let $(w_0, v_0) \in W_p^{(1)}(\Omega) \times W_\infty^{(1)}(\Omega)$. If the assumptions (5.4) are satisfied, then for any $T > 0$ the system given by (5.19) has a unique solution $(w, v) \in Y \times Y^{1,\infty}$ and*

$$\begin{aligned} w &\in C^1((0, T); W_p^{(1)}(\Omega)) \cap C^0((0, T); W_p^{(2)}(\Omega)), \\ v &\in C^1((0, T); W_\infty^{(1)}(\Omega)). \end{aligned} \quad (5.84)$$

Moreover, if $w_0, v_0 \geq 0$ then

$$w(t) \geq 0, \quad v(t) \geq 0, \quad t \in [0, T]. \quad (5.85)$$

Proof. Let $(w_0, v_0) \in W_p^{(1)}(\Omega) \times W_\infty^{(1)}(\Omega)$ and let us assume that the assumptions (5.4) are satisfied. From Theorem 5.2.1, there exists $T > 0$ such that system given by (5.19) has a unique solution $(w, v) \in Y \times Y^{1,\infty}$ and

$$\begin{aligned} w &\in C^1((0, T); W_p^{(1)}(\Omega)) \cap C^0((0, T); W_p^{(2)}(\Omega)), \\ v &\in C^1((0, T); W_\infty^{(1)}(\Omega)). \end{aligned}$$

Moreover, if $w_0, v_0 \geq 0$ then

$$w(t) \geq 0, v(t) \geq 0, t \in [0, T].$$

Now let T_{max} be the maximal existence time. If we set

$$\begin{aligned} \omega &: (0, +\infty) \longrightarrow (0, +\infty) \\ \tau &\longmapsto \max(C_1(\|v_0\|_\infty^{(1)} + C_2), \text{const}1\|w_0\|_p^{(1)}). \end{aligned}$$

Since ω is a constant function, it is continuous and for each $\tau > 0$, we have

$$\|w\|_p^{(1)} \leq \omega(\tau) \quad \text{and} \quad \|v\|_\infty^{(1)} \leq \omega(\tau),$$

which means that for each $\tau > 0$,

$$\|w(t)\|_p^{(1)} \leq \omega(\tau) \quad \text{and} \quad \|v(t)\|_\infty^{(1)} \leq \omega(\tau) \quad \forall \quad 0 < t < T.$$

Consequently for all $0 < t < \min(\tau, T_{max})$. Therefore from Corollary 5.2.2

$$T_{max} = +\infty.$$

Which shows that the solution exists for any $T > 0$. Therefore we have the global existence result. \square

The coming back to the change of variable leads to Corollary 5.3.6 stated below

Corollary 5.3.6. *Let $(u_0, v_0) \in W_p^{(1)}(\Omega) \times W_\infty^{(1)}(\Omega)$. Assume (5.4) are satisfied then for every $T > 0$ the problem (5.19) has a unique solution*

$$\begin{aligned} u &\in C^0([0, T], W_p^{(1)}(\Omega)) \cap C^1((0, T), W_p^{(1)}(\Omega)) \cap C^0((0, T), W_\infty^1(\Omega)), \\ v &\in C^0([0, T]; W_\infty^{(1)}(\Omega)) \cap C^1((0, T); W_\infty^{(1)}(\Omega)). \end{aligned} \quad (5.86)$$

From the above analysis we remark that the regularity of the solutions depends on the one of the initial conditions and the kernels. From [45], under some suitable assumptions on the regularity of the initial conditions and the kernels we may obtain for any $T > 0$,

$$\begin{aligned} w &\in C^0([0, T]; W^{1,p}(\Omega)) \cap C^{1,2}((0, T) \times \Omega), \\ v &\in C^0([0, T]; C^{1+\alpha}(\bar{\Omega})) \cap C^1((0, T); C^{1+\alpha}(\bar{\Omega})), \end{aligned} \quad (5.87)$$

for $0 < 1 + \alpha < 2\beta - \frac{d}{p}$.

Chapter 6

Conclusion

The process of evolution of cancer is very complex and its modeling involves many steps. In order to understand the evolution of a tumour to become a cancer, we investigated all the stages of development of cancer using mathematical modeling. Presentation of the results is divided into five chapters. In Chapter 1, we gave a review of some mathematical modelling on tumour growth and cancer invasion. We split the models that involve tumour growth into two distinct kinds, the one based on nutrients (oxygen, carbon dioxide,...etc) consumptions and the one based on growth inhibitory factors (GIF). In Chapter 2, we presented basic concepts necessary to understand the origin of cancer. This was achieved by giving a biological background of a solid tumour formation. In Chapter 3, we incorporated some mathematical and numerical tools which were used throughout the work. We gave an insight into the semigroup method and explained how the discretisation using the finite difference method of Crank-Nicolson works.

Chapter 4 was about the examination of mathematical models describing the first stage of tumour growth which is the avascular growth and the angiogenesis, which is the process of transition from the first to the second stage (Vascular growth). In this chapter we primarily focused attention on the production of GIF within the spherical avascular nodule and showed using a non linear spatially dependent diffusion of the GIF (which reflects the heterogeneity of the multicell spheroid), that we have the internal structure of the tumour observed experimentally. Moreover, we showed how tumour cell distribution agreed with the action of GIF production, which is an improvement of the model presented by [13]. Our numerical simulations support the fact that the GIF can play an important role in the internal structure of the tumour. In the same Chapter we presented a mathematical model for the process of angiogenesis. Although it is very complicated, involving several events, we focused attention on the activity of endothelial cells, since they are mainly involved in the angiogenetic process as well as the TAF. In fact, we obtained a second order partial differential equations describing the migration, and the proliferation of EC as well as the diffusion of TAF. These equations were solved numerically

using the finite difference method of Crank Nicolson presented above. Our simulations confirmed the formation of the necrotic and the migration of EC towards the tumour.

In Chapter 5, we investigated a mathematical model of the nonlocal interactions between cancer cells and the tissue remodelling. In fact, we dealt with a system of reaction-diffusion equations with integral (nonlocal) term. We also incorporated a nonlocal degradation term. In this chapter, we were only interested in the local and global existence of the solution. Although we worked in three dimension, we proved that the solutions to the nonlocal equations exist globally and are unique in (any space dimension d) without imposing any kind of smallness conditions in the initial conditions. We achieved it using the semigroup theory together with Sobolev embeddings. Moreover, we showed that the regularity of the solutions is related to the regularity of the initial conditions and the kernels. This showed biologically that the space may play an important role in the process of cancer invasion.

Although we have a model that describes how the cancer cells and tissue densities are involved in the cancer invasion, we cannot explain how they behave depending on the parameters appearing in the equations. This is because we did not perform any simulations concerning the model.

In each of the models presented in this work, there are strengths and weaknesses. Since cancer evolution is a complicated phenomenon involving many unrelated processes, incorporating all the known and observed experimental results into a mathematical model is a formidable task. There exist many other assumptions that can be incorporated into the models. For instance, a term due to the loop formation can be added in the EC model and instead of considering constant the coefficient of diffusion of cancer cells, we can make it dependent of u ($D = D(u)$) since physically the migration of cancer cells through the ECM is like a movement in a porous medium. To have a better understanding by visualizing the whole processes, numerical simulations of the nonlocal interactions can be done.

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