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MATHEMATICAL MODELLING OF TUMOUR DEVELOPMENT DURING ANGIOGENESIS AND TREATMENT BY ANTI-ANGIOGENESIS

A DISSERTATION SUBMITTED TO THE UNIVERSITY OF KWAZULU-NATAL

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By

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Abstract

The study focuses on mathematical modelling of tumour development during angiogenesis. It is the stage during which the tumour changes from being avascular to vascular. During this process the tumour secretes tumour angiogenetic factors which diffuse to surrounding tissues. As a result endothelial cells lining nearby blood vessels are stimulated and begin to degrade their basement membrane. Endothelial cells also excrete a chemical, fibronectin, which helps to stick cells together. Then, endothelial cells migrate towards the tumour through diffusion, chemotaxis, haptotaxis and proliferation and they then form small capillary sprouts. These sprouts with time, grow and form loops, and thus, allow a blood circulation. This process of sprout growth, extension and loop formation continue until the capillaries eventually reach and penetrate the tumour, thus completing the angiogenetic process. This formation of new blood vessels is known as angiogenesis.

In this study we present two mathematical models. The first model of nonlinear partial differential equations describing the interactions between endothelial cells, fibronectin and tumour angiogenetic factors in the development of new blood vessels. The model describe the initial migratory response of each cell population in the process during which the tumour acquires its own blood supply. The model aim to capture the spatial distribution of endothelial cells through diffusion, chemotaxis, haptotaxis, proliferation and cell loss due to decay .

The second model focuses on the treatment of tumour by introducing anti-angiogenetic

treatment. During this process chemicals, namely the tumour angiogenetic factors secreted by the tumour and anti-angiogenetic factors which is added as a treatment are seen to be opposing each other.

The continuous equations obtained are solved using the Crank-Nicolson method. The results showed that with time, the tumour angiogenectic factor decreases from the tumour and the endothelial cells migrate towards the tumour. When the anti-angiogenetic factor is added, the angiogenesis process is hindered. Results showed that the secretion of tumour angiogenetic factor by tumour is hindered and also that the presence of endothelial cells in the arbitrary region diminishes.

Declaration

The work in this dissertation was done under the supervision of Dr H. Mambili-Mamboundou and Prof P. Sibanda, School of Mathematics, Statistics and Computer Science, University of KwaZulu-Natal (Pietermaritzburg), from January 2013 to June 2016. No portion of the work referred to in this dissertation is submitted in support of an application for another degree or qualification of this or any other university or institution of learning. The dissertation is my original work except where due reference and credit is given.

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Signature (Student) Date

Sign: ....

Prof P. Sibanda Date

Sign: ....

Dr H. Mambili-Mamboundou Date

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Contents

List of Figures

List of Tables

Chapter 1

Introduction

1.1 Introduction

Cancer is a life threatening disease of epidemic proportions. World Cancer Report [1] highlighted that trends in cancer incidence and mortality worldwide is growing rapidly. It highlighted that in 2012 the world wide burden of cancer rose to an estimated fourteen million new cases per year and the figure is expected to rise to upto twenty two million annually within the next twenty years. Over the same period, cancer deaths are predicted to rise from an estimated 8.2 million annually to 13 million per year. The report indicated that they is a need for a speedy implementation of efficient prevention strategies.

The epidemic results from uncontrollable division of tumour cells with sustaining blood supply. The tumour may result from errors in cell division leading gradually to cells that are more and more abnormal. However if they survive, the damaged cells can continue to divide.[2, 3]. A tumour may also be caused by damage to the cells$'$ in the deoxyribonucleic acid, through environmental exposures, as from chemicals in tobacco smoke (leading to lung cancer) or ultraviolet radiation(leading to skin cancer)[4, 5]. Peterson [5] argued that tobacco consumption has also been implicated as the cause for cancers of the following:

oral cavity, pharynx, larynx, oesophagus, stomach, pancreas, liver, kidney, ureter, urinary bladder, uterine cervix and bone marrow (myeloid leukaemia).

The success of a tumour treatment depends on it being appropriate for the type of tumour involved. Therefore it is necessary to understand the different forms of tumours, and the processes and stages involved in their development and growth [6, 7, 8].

In this dissertation mathematical models will be used to gain insight into the processes of anti-angiogenesis, and its use in treating cancer. To this end, the next section will give an overview of the development of tumours; types of tumours that occur and the stages in tumour growth, namely angiogenesis and metastasis. Then some cancer treatment strategies are outlined, focusing on anti-angiogenesis. This is followed by a section that outlines some mathematical models used to describe these processes. Finally the study aims are given, together with an overview of the remainder of the dissertation.

1.2 Stages of Tumour Development

Tumour develop in three main phases, the avascular phase(benign), the vascular phase and the malignant phase(cancer) [9]. The stages are illustrated in Figure 1.1, and are described below. A tumour in the avascular phase is non cancerous(benign). When such a tumour is less than about two millimeters in diameter, it is unlikely to be harmful; it will only cause serious health problems if it grows in a critical body organ, or if it becomes too large. However without its own blood vessels, its survival, depends on diffusion for oxygen and nutrients from nearby blood vessels and for removal of waste products to these blood vessels [11, 12]. So at this stage, a tumour usually develops very slowly and does not proliferate or spread to other tissues or organs. In this early stage a tumour can usually be removed or be treated with radiation [4]. When removed, benign tumours do not usually regrow [9]. However, if they are not treated or removed at this stage, they may develop into

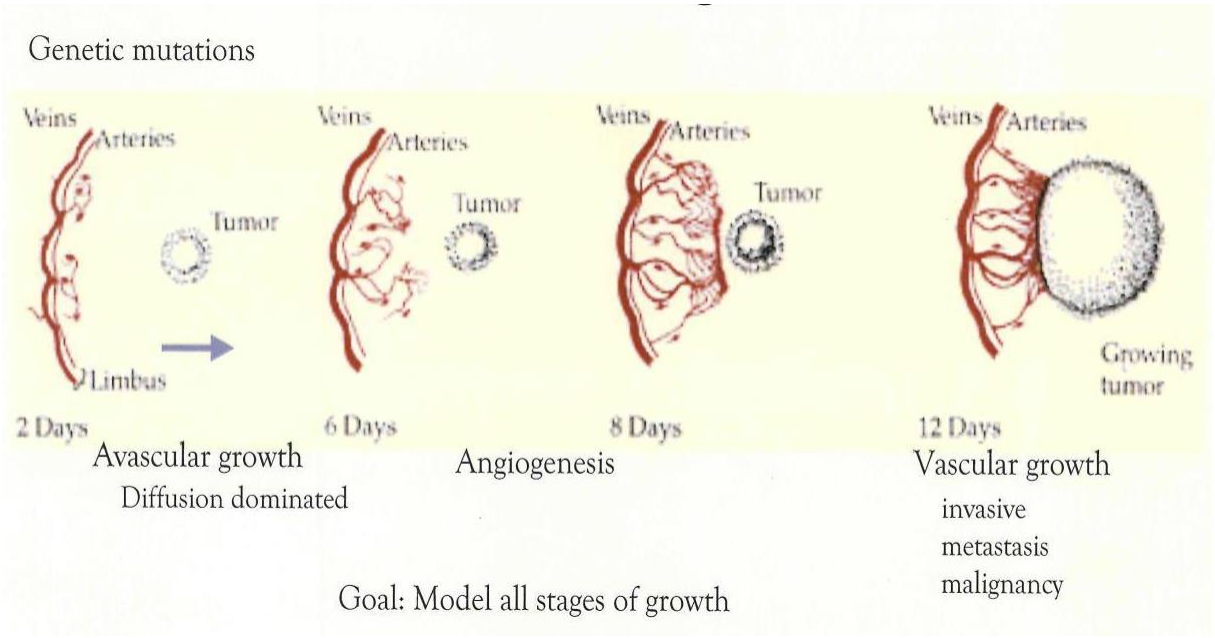

Figure 1.1: Diagram Showing Solid Tumour Development [10]

cancer. After reaching its maximal diameter of about three millimeters, the second stage of the tumour development is observed, called angiogenesis[13, 11, 14, 15].

Angiogenesis is the transition stage in which a tumour develops its own blood supply. In other words it changes from being avascular (pre-malignantor benign) to vascular (malignant) [16].

Angiogenesis may be explained as the process of tumour development, occuring between the harmless avascular growth phase and the of vascular growth [11, 14, 17, 18]. Anderson et al. [17] maintain that angiogenesis is a process that starts only when the tumour secretes several chemicals, collectively called tumour angiogenic factors (TAFs). During angiogenesis, the tumour angiogenic factors diffuse through the tissues, creating a chemical gradient between the tumour and blood vessels [18]. When these chemicals reach a neighbouring blood vessel, endothelial cells that line the blood vessel have a chemotactic response and secrete an enzyme that degrades the basement membrane , which was holding them in place. Once the basement membrane is degraded then endothelial cells are free to

migrates towards the tumour. They proliferate and form capillary sprouts, which are shown in Figure 1.1 after 6 days as finger-like extensions . Following the leading endothelial cell at a sprout tip, the sprouts can develop further into loops, called (anastomoses) and thus, permit a primitive blood circulation, see Figure 1.1 after 8 days. The processes of sprout growth, extension (through endothelial cell migration and proliferation), and loop formation continues until the capillaries so formed eventually reach and penetrate the tumour, thus completing the angiogenic process [10].

Alongside cells proliferation, the endothelial cells also secrete fibronectin; a chemical that remains bound to the extracellular matrix creating a concentration gradient. According to Anderson [19], extra cellular matrix is a mixture of macromolecules, like the collagens, laminin, fibronectin and vitronectin, which are important for cell adhesion, spreading and motility. Fibronectin allows endothelial cells to adhere to the extracellular matrix and so promotes cell proliferation up the concentration gradient. This response of endothelial cells to fibronectin is commonly called haptotaxis [14, 18, 20, 21].

Once the capilliary sprouts reach the tumour, vascularization begins, whereby the tumour forms its own blood vessels. Now the tumour is regarded as malignant because it has reached. a cancerous stage. Malignant tumours vary in size and shape. With an unlimited supply of nutrients via its own blood vessels, tumour growth can be uncontrollable. During this stage cancer cells also move away from the original tumour, or primary cancer. This process of tumour development, called metastasis, occurs as cells migrate, through the blood or lymph system and form new tumours (metastatic tumours). A metastatic tumour is thus the same type as the primary tumuor [4, 9]. Malignant tumours thus interfere with body functions and become life-threatening. Surgical and radiation treatment options are more limited, and may have less successful outcomes [4].

Consequently,this dissertation focuses on mathematical modelling of the critical stage of

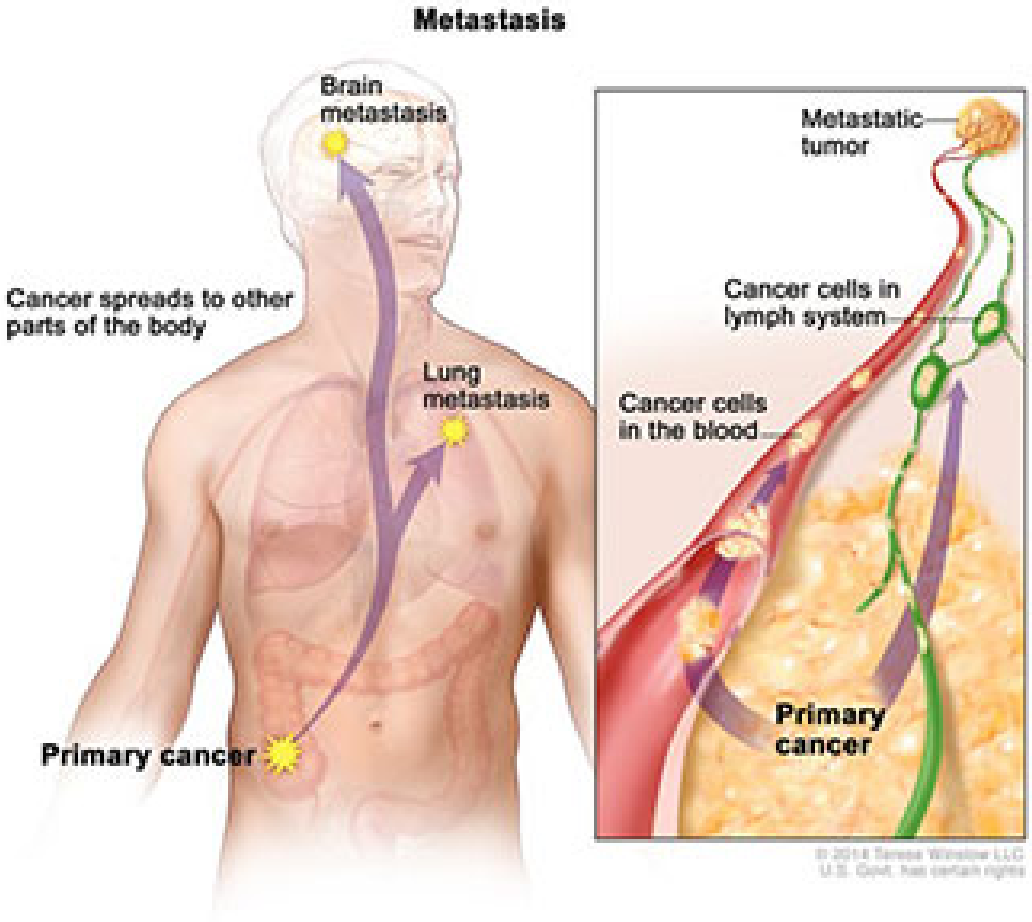

Figure 1.2: An Illustration of the spread of cancer :Source [22]

angiogenesis. It will show how the process can be inhibited before the cancer can cause life-threatening complications. When one understands tumour development, then it becomes easier to decide on appropriate treatment.

1.3 Tumour Treatment

As has been argued above, angiogenesis is a critical process in cancer development. But its complexity makes it difficulty to develop an effective treatment for it [4]. Billy et al. [23] have motivated for efforts to be directed towards identifying inhibitors of this process. Most patients with cancer receive surgery, chemotherapy, radiation therapy, or other conventional therapies or a combination as a form of treatment.

Cancer cells reproduce by dividing rapidly, and this attribute is targeted in conventional chemotherapeutic treatment. However, as Sanga et al. [4] note, some normal body cells are also dividing rapidly. The challenge with chemotherapy is that cancer cells are not like bacteria, so it becomes hard to eliminate them without also affecting some of healthy rapidly-reproducing cells. Thus chemotherapy will kill other cells, like cells in, hair follicles, gastrointestinal tract, bone marrow, and mucous membranes. That is why some patients experience side effects when undergoing chemotherapy such as loss of hair , nausea, ulcers, and mouth ulcers. Nevertheless, healthy cells can more easily repair themselves than can cancer cells [24].

Other treatment strategies are described by Sanga et al. [4]. The aim of the neovasculature strategy is to destroy a tumour′s source of oxygen and nutrients, so as to starve it. Sanga et al. [4] mention a method called vascular normalization, whose aim to normalize the abnormal structure and function of tumour vasculature and to improve the delivery of oxygen, nutrients and drugs . Another possible treatment involves the nanovectored therapy, whereby nanoscale devices are employed to deliver drug payloads to cancer cells [4].

Another strategy to treat cancer involves anti-angiogenesis. This approach harnesses a naturally occurring process in tumour development and uses it to inhibit tumour angiogenesis. Anti-angiogenesis was demonstrated in experiments with mice. Folkman [13], Anderson et al. [17] discussed an experiment on mice where numerous types of tumour were implanted in mice and were allowed to grow. The mice were then checked for the presence of secondary tumour, in particular in the lungs and results indicated little or no evidence of the presence of secondary tumour. However, upon removal of the primary tumour, rapid growth of the hidden micro-metastases were observed, leading to the growth of many large secondary tumours. They concluded that primary tumour secretes substances that inhibit angiogenesis, so-called anti-angiogenic factors. As the primary tumour is fully vascularised, these anti-angiogenic factors are transported through tissues surrounding blood vessel into the blood stream, and therefore, may hinders angiogenesis of the secondary tumour. They observed that the growth of new capillary sprout is promoted by a diffusible factor generated by primary tumour cells. They also added that in the absence of neovascularization most tumours might become dormant if they remain small; at a diameter, of about 2 to 3 mm.

Levine et al. [20] describe anti-angiogenesis as a process whereby anti-angiogenic factors (AAF) are applied to hinder the development of a tumour. Similarly Ledzewicz and Schattler [25] explained anti-angiogenesis as a cancer treatment that aims to hinder a tumuor vascularization. Anderson et al. [17] consider anti-angiogenesis to be a $'$normal$'$ tumour induced process. Specifically, they defined anti-angiogenesis as the process whereby growth of endothelial cells is hindered by the anti-angiogenic factor produced by primary tumour. In the same vein, Levine et al., Ledzewicz and Schattler [20, 25] and Rabii et al. [26] point out the two-way nature of processes occurring between tumour angiogeniic factor and endothelial cells. On the one hand, tumour cells produce a vascular endothelial growth factor to stimulate endothelial cell growth whereas on the other hand endothelial cells also have

receptors which make them sensitive to inhibitors of angiogenesis, called anti-angiostatin. This chemical thus reduce the development of new endothelial cells and capillaries and so hinders the growth of endothelial cells. The Endothelial cells of the secondary tumour thus respond chemotatically to two opposing chemical gradients in the surrounding tissue or extracellular matrix. In one direction, the concentration of tumour angiogenic factors, which are cytokines secreted by the secondary tumour, drive the angiogenesis process as described above. In the opposing direction there is the concentration of anti-angiogenic factors secreted by the primary tumour.

Orme and Chaplain [12] presented three different methods of using anti-angiogenesis in cancer treatment. One is cytotoxic treatment, which targets and destroys endothelial cells. This therapy is most beneficial if pre-existing blood vessels can be left unaffected. Another treatment uses inhibitation of mitosis(cell division). The third option prevent endothelial cell migration.

Cancer therapies are constantly changing. Developments in science and technology allow new treatments, that are more effective, and with harmful side effects. For example, advances such as tomotherapy allow for the treatment of tumours in areas that might not otherwise withstand further radiation [24]. New treatment options can be evaluated in clinical trials, but may also be explored through mathematical modelling, with no risk to patients. This is discussed in the next section. Mathematical models can even be used to develop patient-specific therapeutic schemes [4].

1.4 Role of Mathematical Modelling in Tumour Development

Mathematical modelling and computer simulations have proved to be useful tools for understanding tumour development and cancer treatment. The application of numerical methods has been facilitated by modern high speed computers[27, 28]. Computer simulations can provide valuable information into the processes of tumour development and provide a platform for analyzing the effectiveness of therapeutic treatment [4]. Sanga et.al [4]also suggest that mathematical modelling can be integrated with other tools, such as biological experiments, clinical trials and computer simulation to provide a good comprehensive framework for understanding tumour development and its response to treatments. They point out that traditional clinical or biological experiments are costly and subject to human error. Furthermore, experiments that can be run computationally through mathematical models have been difficult or impossible empirically. These models can also be invaluable in planning suitable biological experiments to test theoretical hypotheses. Nevertheless solving the equations in the models requires empirical biological data appropriate for the model constraints and parameters. Therefore modelling and practical experiments complement each other.

The importance of endothelial cell proliferation has been shown in earlier sections to be critical in tumour development. Various mathematical models have been developed for endothelial cells growth during different tumour development stages. In the following section previously published models governing tumour development will be discussed.

1.5 Review of Mathematical Models for Tumour

Several mathematical models for tumour development have been formulated; many focusing on specific cancer phases (that is, avascular, angiogenesis or vascular). The models can be categorized as either continuum or a discrete, or a hybrid of the two. Continuum models draw upon principles of fluid and continuum mechanics and they use differential equations to describe cancer related variables as continuous variables [4]. On the other hand, discrete models are used in cellular automation, which are governed by a set of rules that are deterministic or probabilistic or both. The state of discrete of these elements can be tracked through both space and time [4]. Hybrid cancer modelling approaches combine continuum models with discrete models [4]. Models that will be formulated in this dissertation are discrete in nature.

1.5.1 Avascular Tumour Models

For tumour growth during the avascular stage, Ward and King [2]. formulated a model based on a continuum phase of cells in two states, living or dead. In the living state, cells are assumed to be able to expand, due to cell production and proliferation, at a rate that is dependent on the concentration of nutrient. Cell death is an irreversible transition that is assumed to cause a spontaneous loss of cells. The reaction diffusion equations governing the living and dead cell concentrations, in relation to the local velocity of cells, are formulated. The rate of transition of living cells is determined by the difference in the rates of mitosis and death of the cells.

1.5.2 Angiogenesis Tumour Models

Several models for angiogenesis have been published. Anderson and Chaplain and Stephanou et al. [11, 15] considered a one-dimensional model for capillary sprout formation in the absence of mitosis of endothelial-cell. They assumed that the movement of endothelial cells is influenced by three factors: random motility i.e molecular diffusion , chemotaxis in response to tumour angiogenic factor gradients haptotaxis in response to fibronectin gradients. Holmes and Sleeman [29] developed a model for the conservation of endothelial cells. The equation includes terms for mitosis, which is governed by logistic growth and depends on the level of tumour angiogenic factor. Eloundou [30] also formulated a conservation equation for endothelial cells development. This model differs from the earlier models because it does not include the term for haptotaxis, but instead included the a term for cell loss due to death.

1.5.3 Metastasis Tumour Models

Metastasis occurs when cancer cells migrate from the primary tumour to other organs where they form new (secondary) tumours. According to Franziska et al. [31] and Chaplain et al. [10], metastasis is a complex process that involvinges a series of steps. Initially tumour cells detach themselves from the primary tumour and then they attach to the neighbouring extracellular matrix, which separates the initially tumour and from adjoining tissues. When tumour cells reach the extracellular matrix, they secrete enzymes, that degrade the proteins that bind them with the extracellular matrix. Tumour cells are then able to breach the extracellular matrix and escape into the neighbouring tissue. Their movement is enhanced by adhesion and proliferation. They spread either by direct extension into adjacent tissues, or through the circulatory system, via lymphatic or blood vessels. The last stage of metastasizing is arrest or extravasion. From the circulatory system, mobile tumour cells come

to rest at another site, where they then grow and multiply. When the angiogenesis process starts again, secondary, cancer cells continue to expand, eventually forming another tumours. This new tumour is known as a metastatic or secondary tumour.

When modelling metastasis, Chaplain et al. [32], Anderson et.al [33] consider tumour cells, the extracellular matrix and matrix degradation enzymes. In both publications, the authors assumed that the model the tumour cell development is governed only by diffusion and haptotaxis, because matrix degradation enzymes can degrade the matrix only upon contact, which Anderson [19] points out is a critical part of the metastatic process. While the active matrix degradation enzymes are secreted by the tumour cells, they also decay as they diffuse through the tissue. In addition, Chaplain et al. [32] added a term for endothelial cell proliferation, They also highlight that endothelial cell movement is governed by diffusion, as well as cell to cell adhesion and cell to matrix adhesion.

The model governing cell invasion formulated by Eleondou [30] did not include haptotaxis. Nevertheless, the author indicates that during invasion under some conditions, tumour cell proliferation may be suppressed by competition for nutrients, oxygen and space. Thus, cells in the interior of the tumour do not proliferate as quickly as those on the surface.

Anderson et al. [17] focused on four key variables involved in cancer cell invasion; which are, cancer cell density, matrix degradation enzyme concentration, macromolecular concentration and oxygen concentration. Each of these four variables is a function of the spatial variable x and time t. Oxygen diffuses among the macromolecules, where it is consumed by the tumour, so its concentration is assumed to decay naturally.

1.5.4 Anti-angiogenesis Tumour Models

Besides the experimental evidence, Anderson et al. [17] argued that the dose-dependent method also confirmed that anti-angiogenic factors (such as angiostatin and endostatin)

hinders the growth of endothelial cells. Anderson et al. [17] and Collins [21] pointed out that endothelial cell migration is governed by two opposing chemicals that is a chemotatic response due to tumour angiogenetic factors and a hindrance of endothelial cells growth due to angiostatin.

The model developed by Anderson et al. [17] considered endothelial cell movement to be governed by a chemotatic response to tumour angiogenic factors and by anti-angiogenesis. The endothelial cells respond to angiostatin gradients in a dose dependent method describing cell migration.

This study will therefore strengthen models developed for angiogenesis by including terms for anti-angiogenesis. To be specific, in this dissertation a mathematical model of angiogenesis process will first be formulated, based on endothelial cells, tumour angiogenic factors and fibronectin. The equations in the model will be solved using the Crank-Nicolson scheme, then the model will be simulated using Matlab software.

From the angiogenesis model, a term for the anti-angiogenic factor that hinders tumour growth will be introduced. The anti-angiogenesis model will then be simulated with Matlab aiming to observe the tumour growth in relation to anti-angiogenetic factor therapy.

1.6 An Overview of the Dissertation

This dissertation is presented as follows: Chapter 1 has shown the different stages of cancer tumour development and some methods of cancer treatment that are available. Mathematical models formulated for avascular tumours, angiogenesis , metastasis and anti-angiogenesis were discussed. Chapter 2 will discuss the Crank-Nicolson method, which will be used to solve the Finite Difference scheme that arises from models formulated in this dissertation. Chapter 3 will present mathematical models describing the process of

angiogenesis, namely, focusing on the tumour angiogenic factor, fibronectin and endothelial cell concentration. After the application of Crank-Nicolson $'$ method, solutions of the equations from model simulation with Matlab will be presented. In Chapter4 anti - angiogenesis will be considered. An anti-angiogenic factor will be added to the equation for endothelial cell that has been formulated in Chapter 3. The governing equations for anti-angiogenesis will also be solved and results will be presented. Chapter 5 will presents the summary of all work done, conclusion and future research prospects.

1.7 Summary

Tumours can be classified into three stages: avascular, vascular and malignant. During the early avascular stages most tumours are harmless or can be treated successfully. But not early enough a tumour progress to malignancy, known as cancer. This critical stage in the tumour development depends on the tumour becoming vascular by the process of angiogenesis. Once tumour reaches vascular stage, it starts mestasise and invade to other parts of the body. It is important that proper treatment is administered as early as one discover the sickness. Anti-angiogenesis is also one of the methods that can be employed to treat cancer. The method assist to hinder the tumour growth.

Mathematical models have been formulated for different stages of tumour development. Such models can provide valuable information, which can be used to plan physical experiments including those concerning treatment therapies. Symbiotically, data from biological experiments also provide the necessary parametric values needed in the models. Thus mathematical modelling makes an important contribution to biological knowledge. Because of complexity of equations in such mathematical models, numerical methods such as the Crank-Nicolson method, and computational simulations are valuable in analyzing and solving them.

Models for avascular tumours and angiogenesis have been established. However there is little work done on including terms for anti-angiogenesis. Addressing this deficit will be the focus of the dissertation. In the next Chapter the Finite Difference scheme and the Crank-Nicolson$'$s method, which will be used to solve equations in the models to be formulated in this dissertation, will be presented.

Chapter 2

Mathematical Preliminaries

2.1 Introduction

This chapter will present the two types of numerical methods, the spectral local linearization method and finite difference method. Both methods could be applied to solve equations in models that will be generated in this dissertation although we have decided to use the finite difference scheme because of the low number of boundary conditions. The Crank-Nicolson method will also be discussed as it is an appropriate finite difference scheme for the models in this dissertation. The Crank-Nicholson method has proved itself to be a universal and stable numerical scheme . After applying the Crank-Nicolson scheme, systems of linear equations that will be generated for each row will be expressed as a matrix equation. A brief summary of matrices will be presented and resulting matrix equation will be simulated using Matlab software.

2.2 Numerical Methods

Choice of partial difference scheme depends on the partial differential equation that is required to be solved. Partial differential equations fall into three categories, that is elliptic, parabolic and hyperbolic. Not all partial differential equations can be solved analytically but numerical methods can be used to give approximate solutions [35]. Ozisik [28] points out that numerical methods are useful for solving complicated nonlinear problems with complicated boundary conditions. Finite difference methods are used worldwide in solving equations related to heat, mass and momentum transfer and each method has its own advantages depending on the nature of the problem but there is no single method that is best for all nonlinear partial differential equations [28]. According to Motsa et al. [27], methods have been developed to find efficient ways to solve such equations, the spectral local linearization method and finite difference method being amongst them. This dissertation will touch on the spectral local linearization method but discuss the finite difference method in depth because it will be used to solve the system of equations that will be generated in this study.

2.2.1 Spectral Local Linearization Method

One of the simplest and efficient method for solving highly nonlinear systems of boundary layer flow problems with exponentially decaying profiles is the spectral local linearization method (SLLM).The method is based on linearizing and decoupling systems of equations using a combination of a univariate linearization technique and a spectral collocation discretization [27, 34]. The governing systems of equations are reduced into a sequence of subsystems of differential equations. After linearizing them, they are then solved using a pseudo Chebyshev pseudospectral method. The method has proved to converge rapidly so obtains results very efficientlly. Its level of accuracy is very high especially when solving

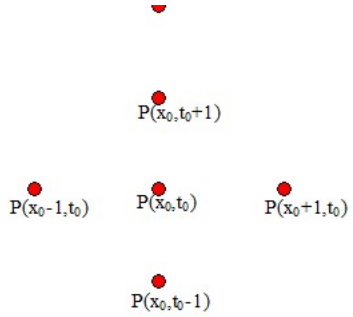

Figure 2.1: Computational Grid Showing Interior Grid Points

very large nonlinear boundary value problems. [27, 34].

2.2.2 Finite Difference Methods

Let us suppose we want to solve the heat equation, as follows:

$$\frac{\partial \theta}{\partial t} = \alpha \frac{\partial^2 \theta}{\partial x^2}, 0 \leq x \leq L, t \geq 0, \tag{2.1}$$

where $\theta = \theta(x,t)$ is a dependent variable and α is a constant co-efficient. Recktenwald [36] applies a finite difference method, as follows to solve equation(2.1) at any point (x_0, t_0), the numeral scheme is restricted to the points on the grid of discrete x values as illustrated in Figure 2.1[37]. Assume that the domain is rectangular with x, distance ranging from 0 to X and t, time ranging from 0 to T. The interval $[0, X]$ is divided into N equal subintervals of length δx. The x values are indexed by $i = 0, ..., N$. Similarly the interval $[0, T]$ is divided into M equal intervals of length δt and with t values indexed by $j = 0, ..., M$. The aim is to find an approximation for the values of θ at $(N+1) \times (M+1)$ grid points [37, 38]. The solution for equation (2.1) requires specified boundary conditions at $x = 0$ and $x = L$, and initial conditions at $t = 0$, as $\theta(0,t) = \theta_0$, $\theta(L,t) = \theta_L$ and $\theta(x,0) = f_0(x)$

[36].

Recktenwald [36] and Strikwerda [38] both point out that finite difference methods are obtained by replacing continuous derivatives with difference formulae that involves several discrete approximations given by the numerical solution at a finite number of points in the physical domain. Figure 2.1 is a schematic representation of the numerical solution, where, Δx, the local distance between adjacent points in space, and Δt, the local distance between adjacent time steps are both uniform throughout the mesh [36]. Thus, Figure 2.1 illustrates the region over which the independent variables in the partial differential equation are defined, by a finite grid of points, or a mesh, where each dependent variable is approximated. In the heat equation there are derivatives with respect to time, and derivatives with respect to space. Various combinations of mesh points, in the difference formulae, results in a variety of schemes.

In a finite difference method each partial derivative in the partial differential equation is approximated from neighbouring values using Taylor's theorem [35]. Using first order partial derivative in Taylor's theorem [35], we let:

$$a(x_0 + h) = a(x_0) + ha'(x_0) + \frac{h^2}{2!}a''(x_0) + \frac{h^3}{3!}a'''x_0 + 0(h^3) + \cdots , \tag{2.2}$$

From the Taylor series the derivative, $a'(x)$ will be

$$a'(x_0) = \frac{a(x_0 + h) - a(x_0)}{h} - \frac{h}{2}a''(x_0) - \frac{h^2}{6}a'''(x_0) + \cdots . \tag{2.3}$$

Equation (2.3) contains an unknown quantity, $0(h^3)$. If all terms with that quantity are discarded in Equation (2.3), then the approximation for $a'(x_0)$ becomes

$$a'(x_0) \approx \frac{a(x_0 + h) - a(x_0)}{h}, \tag{2.4}$$

, for a small value of h. Equation (2.4) is called the forward divided difference, with the error of $0(h^3)$ From Equation (2.3) if h is substituted with $-h$ then:

$$a'(x_0) \approx \frac{a(x_0) - a(x_0 - h)}{h}, \tag{2.5}$$

for a small value of h. equation (2.5) is called the backward divided difference. The central difference approximations of $a'(x)$: is obtained by adding equations (2.4) and (2.5) and it becomes:

$$a'(x_0) \approx \frac{a(x_0+h) - a(x_0-h)}{2h}, \tag{2.6}$$

for a small value of h, with an error of the order h^2.

The second order central difference approximations can be obtained with the additional manipulations of the Taylor series expansion as it appears in equation (2.2) and making $a''(x_0)$ the subject and it becomes:

$$a''(x_0) = \frac{2!}{h^2}[a(x_0+h) - a(x_0) - ha'(x_0)]. \tag{2.7}$$

Substituting h with $-h$, equation (2.2.2) becomes:

$$a''(x_0) = \frac{2!}{h^2}[a(x_0-h) - a(x_0) + ha'(x_0)]. \tag{2.8}$$

By adding equations and , then the central difference approximation becomes:

$$a''(x_0) \approx \frac{a(x_0+h) - 2a(x_0) + a(x_0-h)}{h^2}, \tag{2.9}$$

[35, 39]. In a finite difference scheme the points x_0 and $x_0 + h$ are points on the grid and $a(x_0)$ and the value of $a(x_0 + h)$ are known. Then using equation (2.3) allows one to get the finite difference approximation to derivatives with $O(h^n)$ errors.

If one lets a be a function of two variables t and x, then one can approximate derivatives of a with respect to x_0. If t is held constant then Taylor's theorem in equation (2.2) can be used where a simple derivative terms is changed to a partial derivative. If h is replaced by δx, then equation (2.2) can be written as:

$$a(t, x_0+\delta x) = a(t, x_0) + \delta x \frac{\partial a(t, x_0)}{\partial x} + \frac{(\delta x)^2}{2!}\frac{\partial^2 a(t, x_0)}{\partial x^2} + \frac{(\delta x)^3}{3!}\frac{\partial^3 a(t, x_0)}{\partial x^3} + \cdots . \tag{2.10}$$

On Truncation equation (2.10) yields :

$$a(t, x_0 + \delta x) = a(t, x_0) + \frac{\partial a(t, x_0)}{\partial x} + \frac{(\delta x^2)}{2!}\frac{\partial^2 a(t, x_0)}{\partial x} + O(\delta x)^2. \tag{2.11}$$

First Order Forward Difference Approximation

Re - arranging Equation (2.11) allows us to obtain the forward and backward finite difference approximations to the partial derivatives as shown below:

$$\frac{\partial a(t,x_0)}{\partial x} \approx \frac{a(t,x_0+\delta x)-a(t,x_0)}{\delta x} + O(\delta x), \tag{2.12}$$

and the approximation error is $O(\delta x)$ and that leads to:

$$\frac{\partial a(t,x_0)}{\partial x} \approx \frac{a(t,x_0+\delta x)-a(t,x_0+\delta x)}{\delta x}. \tag{2.13}$$

Similarly:

$$\frac{\partial a(t_j,x_i)}{\partial x} \approx \frac{a^j_{i+1}-a^j_i}{\delta x}, \tag{2.14}$$

, where $a^j_{i+1} = a(t_j, x_{i+1})$ ana $a^j_i = a(t_j, x_i$. Equation (2.14) is called the first order forward difference approximation to $\frac{\partial a(t_j,x_i)}{\partial x}$,

First Order Backward Difference Approximation

If δx is changed to $-\delta x$ in equation (2.14) the backward difference approximation to $\frac{\partial a(t_j,x_i)}{\partial x}$ is obtained as:

$$\frac{\partial a(t_j,x_i)}{\partial x} \approx \frac{a^j_i-a^j_{i-1}}{\delta x}. \tag{2.15}$$

First Order Central Approximation

The first order central difference approximation to $a(t_j, x_i)$ is obtained by adding equations (2.14), (2.15), then re-arranging terms to obtain:

$$\frac{\partial a(t_j,x_i)}{\partial x} \approx \frac{a^j_{i+1}-a^j_{i-1}}{2\delta x}. \tag{2.16}$$

Higher order partial derivatives approximations can also be made by taking more terms in Taylor's theorem.

Second Order Finite Difference Approximation

$$a(t, x_0 + \delta x) = a(t, x_0) + \delta x \frac{\partial a(t, x_0)}{\partial x} + \frac{(\delta x)^2}{2!} \frac{\partial^2 a(t, x_0)}{\partial x^2} + \frac{(\delta x)^3}{3!} \frac{\partial^3 a(t, x_0)}{\partial x^3} + 0(\delta x)^4), \tag{2.17}$$

and if (δx) is replaced by $-(\delta x)$

$$a(t, x_0 - \delta x) = a(t, x_0) - \delta x \frac{\partial a(t, x_0)}{\partial x} + \frac{(\delta x)^2}{2!} \frac{\partial^2 a(t, x)}{\partial x^2} - \frac{(\delta x)^3}{3!} \frac{\partial^3 a(t, x_0)}{\partial x^3} + 0(\delta x)^4. \tag{2.18}$$

Adding equation (2.17) and equation (2.18)

$$a(t, x_0 + \delta x) + a(t, x_0 - \delta x) = 2a(t, x_0) + (\delta x)^2 \frac{\partial^2 a(t, x_0)}{\partial x^2} + 0(\delta x)^4, \tag{2.19}$$

at $t^j; x_i$ Equation (2.19) becomes

$$a^j_{i+1} + a^j_{i-1} = 2a^j_i + (\delta)x^2 \frac{\partial^2 a^j_i}{(\partial x)^2} + \delta x)^4. \tag{2.20}$$

Which means that the second order finite difference approximation will be :

$$\frac{\partial^2 a^j_i}{\partial x^2} \approx \frac{a^j_{i+1} - 2a^j_i + a^j_{i-1}}{(\delta x)^2}. \tag{2.21}$$

Table 2.1: Finite Difference Toolkit

Partial Derivatives	Finite Difference Approximation	type	order
$\frac{\partial u}{\partial x}$	$\frac{u^j_{i+1} - u^j_i}{\delta x}$	forward	first in x
$\frac{\partial u}{\partial x}$	$\frac{u^j_i - u^j_{i-1}}{\delta x}$	backward	first in x
$\frac{\partial u}{\partial x}$	$\frac{u^{j+1}_{i+1} - u^{j+1}_{i-1} + u^j_{i+1} - u^j_{i-1}}{4\delta x}$	central	first in x
$\frac{\partial^2 u}{\partial x^2}$	$\frac{u^j_{i+1} - 2u^j_i + u^j_{i-1}}{2\delta x^2} + \frac{u^{j-1}_{i+1} - 2u^{j-1}_i + u^{j-1}_{i-1}}{2\delta x^2}$	central	second in x
$\frac{\partial u}{\partial t}$	$\frac{u^{j+1}_i - u^j_i}{\delta t}$	forward	first in t
$\frac{\partial u}{\partial t}$	$\frac{u^j_i - u^{j-1}_i}{\delta t}$	backward	first in t
$\frac{\partial u}{\partial t}$	$\frac{u^{j+1}_i - u^{j-1}_i}{2\delta t}$	central	first in t

There are various methods of attaining numerical solutions to partial differential equations each with relation to the kind of problem that is required to be solved as indicated on the Table 2.1 [35]. The most common finite difference methods are the explicit method, implicit method and Crank-Nicolson Method. These methods are closely related but differ in stability, accuracy and in speed of execution [28, 36, 39].

2.3 The Crank-Nicolson Method

A method for getting the value of u_i^{j+1} in parabolic partial differential equations was formulated by John Crank and Phyllis Nicolson in the mid-20th century .

Consider the equation:

$$\frac{u_i^{j+1} - u_i^j}{\delta t} = \alpha \frac{u_{i+1}^j - 2u_i^j + u_{i-1}^j}{\delta x^2}, \tag{2.22}$$

$$\frac{u_i^{j+1} - u_i^j}{\delta t} = \alpha \frac{u_{i+1}^j - 2u_i^j + u_{i-1}^j}{\delta x^2}, \tag{2.23}$$

Then Figure 2.2, illustrates the Crank-Nicolson schemes, which is the average of the forward method at j and the backward method at $j+1$ as given in equation (2.23)

There are implicit and explicit Crank-Nicolson scheme. In this dissertation the implicit scheme will be used. The implicit Crank-Nicolson scheme is a highly recommended, stable method, for steps δx in position and δt in time. Errors are of order $(\delta x)^4$ and order $(\delta t)^2$ respectively.

According to Eloundou [30] to get the next value of u in time using the implicit method, the system of algebraic equations of u, $\frac{\partial u}{\partial t}$, $\frac{\partial u}{\partial x}$ and $\frac{\partial^2 u}{\partial x^2}$ are approximated as follows:

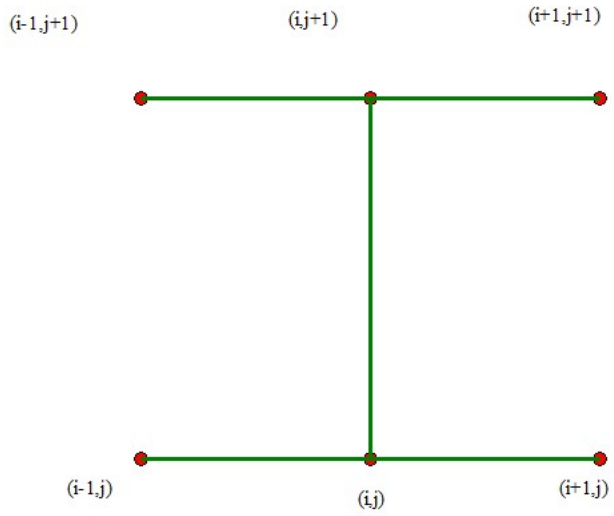

Figure 2.2: An illustration of the Crank-Nicolson Method

Table 2.2: Finite Difference Toolkit

Partial Derivatives	Finite Difference Approximation	type	order
$\frac{\partial u}{\partial x}$	$\frac{u_{i+1}^j - u_i^j}{\delta x}$	forward	first in x
$\frac{\partial u}{\partial x}$	$\frac{u_i^j - u_{i-1}^j}{\delta x}$	backward	first in x
$\frac{\partial u}{\partial x}$	$\frac{u_{i+1}^{j+1} - u_{i-1}^{j+1} + u_{i+1}^j - u_{i-1}^j}{4\delta x}$	central	first in x
$\frac{\partial^2 u}{\partial x^2}$	$\frac{u_{i+1}^j - 2u_i^j + u_{i-1}^j}{2\delta x^2} + \frac{u_{i+1}^{j-1} - 2u_i^{j-1} + u_{i-1}^{j-1}}{2\delta x^2}$	central	second in x
$\frac{\partial u}{\partial t}$	$\frac{u_i^{j+1} - u_i^j}{\delta t}$	forward	first in t
$\frac{\partial u}{\partial t}$	$\frac{u_i^j - u_i^{j-1}}{\delta t}$	backward	first in t
$\frac{\partial u}{\partial t}$	$\frac{u_i^{j+1} - u_i^{j-1}}{2\delta t}$	central	first in t

2.3.1 Unconditional Stability of the Crank-Nicolson Method

The Crank-Nicolson Method has been proved to be stable and reliable. Its stability has been proved [40] as follows: Suppose

$$\frac{\partial a}{\partial t} = \frac{\partial^2 a}{\partial x^2}, t > 0, x \in (0, L), \tag{2.24}$$

is a parabolic equation, with Diriclet boundary conditions $a(0,t) = u_1(t), a(L,t) = u_2(t)$ and initial conditions $a(x,0) = a_0(x)$. Then if one discretizes space by h such that $(n+1)h = 0, n \in \mathbb{N}$, and $h > 0$. Using Table 2.2 above and substituting for the first order forward derivative in relation to t in $\frac{\partial a}{\partial t}$ and second order central derivative in $\dfrac{\partial^2 a}{\partial x^2}$, we get a system of equations of the form:

$$\frac{a_i^{j+1} - a_i^j}{\delta t} = \frac{a_{i+1}^{j+1} - 2a_i^{j+1} + a_{i-1}^{j+1} + a_{i+1}^j - 2a_i^j + a_{i-1}^j}{(\delta x)^2}. \tag{2.25}$$

If we let $\alpha = \frac{\delta t}{(\delta x)^2}$ and substitute in equation (2.36), then equation (2.36) can be written as:

$$-\alpha a_{i-1}^{j+1} + 2(1+\alpha)a_i^{j+1} - \alpha a_{i+1}^{j+1} = \alpha a_{i-1}^{j+1} - 2(1+\alpha)a_i^{j+1} + \alpha a_{i+1}^{j+1}). \tag{2.26}$$

Which can be expressed as:

$$-\alpha(a_{i-1}^{j+1} + a_{i+1}^{j+1}) + 2(1+\alpha)a_i^{j+1} = \alpha(a_{i-1}^{j+1} + a_{i+1}^{j+1}) + 2(1-\alpha)a_i^{j+1}. \tag{2.27}$$

equation (2.27) results in a matrix of the form $Aa_i^{j+1} = Ba_i^j, j = 0, 1, \cdots$.

Faduga et al. [39] considered the worst case solution of equation (2.27) by letting

$$a_i^j = \rho^j(-1)^i. \tag{2.28}$$

To prove unconditional stability of the Crank Nicholson scheme, we need to show that $|\rho| < 1$.

Substituting equation (2.28) into equation (2.27) we get:

$$\begin{aligned} &-\alpha(\rho)^{j+1}(-1)^{i-1}((-1)^{i+1} + (-1)^{i-1}) + 2(1+\alpha)(\rho)^{j+1}(-1)^i \\ &\quad = \alpha(\rho)^j(-1)^{i-1}((-1)^{i+1} + (-1)^{i-1}) + 2(1+\alpha)(\rho)^j(-1)^i. \end{aligned} \tag{2.29}$$

Equation (2.30) results to:

$$\rho[-\alpha(-1) - 1 + 2(1+\alpha) - \alpha(-1) + 1] = \alpha(-1) - 1 + 2(1-\alpha) + \alpha(-1) + 1. \tag{2.30}$$

When making ρ the subject of the formula, equation (2.30) becomes:

$$\rho = \frac{1-2\alpha}{1+2\alpha}, \tag{2.31}$$

then we can conclude by:

$$\rho = |\frac{1-2\alpha}{1+2\alpha}| \implies |\rho| < 1 \ \forall \ \rho > 0 \tag{2.32}$$

The denominator is always positive, while the numerator may be positive or negative. In any case, it is clear that the absolute value of the numerator is smaller than the denominator,which means that $|\rho| < 1$ and that completes the proof.

The conclusion indicates that the Crank-Nicolson Method is unconditionally stable and has a very high order of accuracy. As mentioned earlier, it is commonly used in solving heat equations [39].

2.3.2 Application of the Crank-Nicolson Method in Nonlinear Parabolic Partial Differential Equations

Suppose we need the solution of equation (2.1) which is a one space dimensional system of equation as x is the only independent spatial variable involved, based on the following boundary conditions:

$$\theta(0,t) = 0, \;\; \theta(L,t) = 0, \;\; 0 \leq t \leq T, \tag{2.33}$$

and the initial conditions:

$$\theta(x,0) = f(x), 0 \leq x \leq L, \tag{2.34}$$

where $\theta(x,t)$ represents the concentration of a certain chemical at any time t in a specified region R. If the movement of the chemical is constant throughout the region, α from (2.23) is assumed to be a positive constant. In order to approximate the solution of equation (2.1), a network of grid points is created throughout the rectangular region [41],

$$R = \{(x,t)0 \leq x \leq L, 0 \leq t \leq T\}, \tag{2.35}$$

as shown in Figure 2.3. The region R is partitioned by dividing the interval $[0, L]$into n equal parts , each having length $h = L/n$. Similarly the interval $[0, T]$ is divided into m equal subintervals such that each of them is of length $k = T/m$. The corresponding points of the intervals are denoted by x_i for $i = 0, 1, \cdots, , n$ and t_j for $j = 0, 1, \cdots, m$. The points (x_i, t_j) are called mesh or grid points. Mesh points are defined as $x_i = hi, \;\; t_j = kj$ for $i = 0, 1, \cdots, n$ and $j = 0, 1, \cdots, m$.

The approximate solution of $\theta(x,t)$ at the mesh point (x_i, t_j) is expressed by θ_i^j and the true solution denoted by $\theta(x_i, t_j)$. To solve equation (2.1) if the space derivative $\frac{\partial^2\theta}{\partial x^2}$ is replaced with the average of the central difference scheme at the time steps $j+1$ and j and the time derivative $\frac{\partial\theta}{\partial t}$ is replaced with the forward difference scheme as tabled in Table 2.1 and we obtain:

$$\frac{\theta_i^{j+1} - \theta_i^j}{k} = \frac{\alpha}{2}\left(\frac{\theta_{i+1}^{j+1} - 2\theta_i^{j+1} + \theta_{i-1}^{j+1} + \theta_{i+1}^j - 2\theta_i^j + \theta_{i-1}^j}{h^2}\right). \tag{2.36}$$

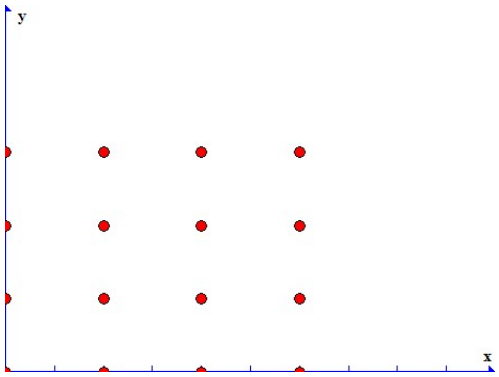

Figure 2.3: The Region R and Mesh Points

If we let $\lambda = \alpha\frac{k}{h^2}$ and substitute in equation (2.36), then equation (2.36) can be written as

$$-\lambda\theta_{i-1}^{j+1} + 2(1+\lambda)\theta_i^{j+1} - \lambda\theta_{i+1}^{j+1} = \lambda\theta_{i-1}^{j+1} - 2(1+\lambda)\theta_i^{j+1} + \lambda\theta_{i+1}^{j+1}. \tag{2.37}$$

Equation (2.37) indicates that the solution value at any point $(i, j+1)$ on the $(j+1)^{th}$ time interval depends on the solution values at the neighbouring points on the same level and three points on the j^{th} time level as shown in Figure 2.3:

2.4 Solutions of the System of Equations

Equation (2.37) results in a matrix of the form $A\theta^{j+1} = B\theta^{j}, j = 0, 1, \cdots$. let $2 + 2\lambda = \Lambda$ and $\vartheta = 2 - 2\lambda$, where

$$A = \begin{pmatrix} \Lambda & -\lambda & 0 & 0 & 0 & 0 & 0 & 0 & 0 \\ -\lambda & \Lambda & -\lambda & 0 & 0 & 0 & . & 0 & 0 \\ 0 & -\lambda & \Lambda & -\lambda & 0 & 0 & . & 0 & \\ 0 & 0 & -\lambda & \Lambda & -\lambda & . & . & .0 & 0 \\ 0 & 0 & 0 & -\lambda & \Lambda & -\lambda & 0 & 0 & \\ 0 & 0 & 0 & 0 & -\lambda & \Lambda & -\lambda. & . & .0 \\ . & . & . & . & . & . & . & . & . \\ . & . & . & . & . & . & . & . & . \\ 0 & 0 & . & . & . & . & -\lambda & \Lambda & -\lambda \\ 0 & 0 & 0 & . & . & . & . & -\lambda & \Lambda \end{pmatrix} \tag{2.38}$$

and

$$B = \begin{pmatrix} \vartheta & \lambda & 0 & 0 & 0 & 0 & 0 & 0 & 0 \\ \lambda & \vartheta & \lambda & 0 & 0 & 0 & . & 0 & 0 \\ 0 & \lambda & \vartheta & \lambda & 0 & 0 & . & 0 & \\ 0 & 0 & \lambda & \vartheta & \lambda & . & . & .0 & 0 \\ 0 & 0 & 0 & \lambda & \vartheta & \lambda & 0 & 0 & \\ 0 & 0 & 0 & 0 & \lambda & \vartheta & \lambda. & . & .0 \\ . & . & . & . & . & . & . & . & . \\ . & . & . & . & . & . & . & . & . \\ 0 & 0 & . & . & . & . & .\lambda & \vartheta & \lambda \\ 0 & 0 & 0 & . & . & . & . & .\lambda & \vartheta. \end{pmatrix} \tag{2.39}$$

Definition 1

Consider m and n to be two positive integers. We call a matrix A, having m rows and n columns, with elements on a vector space over the numerical field $\mathbb{C}$, is a set of mn scalars $a_{ij} \in \mathbb{K}$ with $i = 1, \cdots, m$ and $j = 1, \cdots, n$, $\mathbb{K}$ can be the set of real or complex numbers which can be written as $A \in \mathbb{R}^{m \times n}$ or $A \in \mathbb{C}^{m \times n}$ respectively to specify the field for A. A square matrix is an $m \times n$ with $m = n$. A matrix A can be abbreviated as $A = (a_{ij})$.

The index i is called the row index, and j is the column index. Then set $a_{i1}, a_{i2}, \cdots, a_{in}$ is called the i-th row of A and $(a_{11}, a_{22} \cdots, a_{nn})$ is called the main diagonal [42].

Definition 2

An identity matrix I is an $n \times n$ matrix such that $AI = IA = A$ for all square matrices A [42].

Definition 3

A square matrix A of order n is invertible, if there exist a square matrix B of order n such that $AB = BA = I$. Where B is called the inverse matrix of A and is denoted by A^{-1} [42].

Definition 4

If A is inevitable its inverse is also invertible, that is $(A^{-1})^{-1} = A$ [42].

Definition 5

The transpose of an $m \times n$ matrix A is denoted by A^T, and is obtained by exchanging the rows of A with the columns of A [42].

Definition 6

A matrix $A \in \mathbb{C}^n$ is positive definite in $\mathbb{C}^n$ if the number (Ax, x) is real and positive for all values of x element of complex numbers and $x \neq 0$ [42].

Definition 7

A matrix $A \in \mathbb{R}^{nxn}$ is called diagonally dominant by rows if

$$|a_{ii}| \geq \sum_{j=1, j<i}^{n} |a_{ij}|, i = 1, \cdots, n, \tag{2.40}$$

and diagonally dominant by columns if

$$|a_{ii}| \geq \sum_{j=1, j<1}^{n} |a_{ji}|, i = 1, \cdots, n. \tag{2.41}$$

Matrix A is said to be strictly diagonally dominant if is diagonally dominant by both rows and column [42].

Definition 8

(i) If A and B are two matrices of order $n \times m$, then the sum of A and B is an $n \times m$ matrix [41]. (ii) If A and B are two matrices of order $n \times m$ and λ a real number, then the product of λ and A is the $n \times m$ matrix $C = \lambda A$ [41].

According to the definitions given above, the tridiagonal matrix A that emanated from equation (2.37) is positive definite and strictly diagonally dominant. As a result A is invertible and the equation (2.37) can be solved using standard methods of solving system of equations or by using Matlab. To solve the systems of equation $Ax = B$ using Matlab, then the value of x can be expressed as $x = A^{-1}B$ as is used in this dissertation to solve all system of equations.

2.4.1 Numerical Integration:The Trapezoidal Rule

Functions that cannot be directly integrated by analytical methods can be accommodated by numerical methods of integration, which in turn can be evaluated using calculators or computers. In this dissertation, we use the trapezoidal rule, which is then simulated by a computer. The trapezoidal rule gives an approximate value of a definite integral, using the area below the curve. It approximate the areas as a set of inscribed trapezoids. This use of trapezoids reduces the error and provides better approximations [43, 44].

2.5 Summary

Many equations involving diffusion results in non linear partial differential equations(PDEs) as is the case in this dissertation. These PDEs can be hyperbolic, parabolic or elliptic. To solve them, analytical or numerical methods can be applied depending on equations complexity. The finite difference method is one of the numerical methods that can be applied according to the explicit, implicit or the Crank- Nicolson approaches. The method that is applied in this dissertation is the Crank Nicolson scheme, which has proved its self to be more valid and stable.

The chapter that follows will present a mathematical model for the process of angiogenesis, show application of the Crank-Nicolson method to formulate a system of equations from the model which are then simulated using Matlab.

Chapter 3

Mathematical Model of Angiogenesis During Tumour Development

3.1 Introduction

In Chapter 1 the stages and processes in cancer tumour development were outlined. The critical process of angiogenesis, whereby a tumour becomes vascularised and is then termed malignant, was highlighted. Angiogenesis is initiated when a tumour releases a diffusible tumour angiogenic factors into surrounding tissues (the extra cellular matrix), which eventually reach nearby blood vessels. These factors allow degradation of the basement membrane lining the blood vessels, thereby releasing endothelial cells from the lining. As the endothelial cells are stimulated to follow the chemical gradient of tumour angiogenic factors so they migrate towards the tumour until they form capilliary sprouts which eventually penetrate it. This chemotatic response to the tumour angiogenic factors secreted by a tumour, is also enhanced by fibronectin, which is secreted by the endothelial cells.

We consider a situation in which a localised tumour triggers an angiogenic response from a neighbouring blood vessel. The process can be modelled in terms of concentration of

tumour angiogenic factors, endothelial cell density and the concentration of fibronectin. Fick′s law is used to model the diffusion of the tumour angiogenic factors, which creates the concentration gradient.

Models developed in this dissertation are related to previously published models which were discussed in Chapter 1. To solve the algebraic equations comprising the new models, the Crank-Nicolson scheme, discussed in Chapter 2, will be used; particularly in relation to the approximations for each time interval.

This chapter will be presented as follows. Firstly molecular movement of endothelial cells commonly known as cell flux will be discussed. Next the conservation equations for endothelial cells, tumour angiogenic factors and fibronectin will be formulated. Then the Crank-Nicholson method will be used to solve them. At the end simulated results of systems of non linear equations will be presented.

3.2 Cell Flux

When formulating equations that model endothelial cell development, including authors like Anderson and Chaplain [11] and Holmes and Sleeman [29] consider the cell flux. Cell flux is a term used to describe the movement of endothelial cells. Some authors consider two factors which influence the cellular movement. These are first diffusion, which is the random molecular movement of chemicals, and then chemotaxis, which is a directional movement of cells along a chemical gradient [30]. However other authors also consider the third factor which is haptotaxis. Haptotaxis is thus, the motion of endothelial cells, from the basement membrane of a blood vessel at or the near the capillary sprout until they reaches the tumour, is governed by homogenous random molecular diffusion, chemotaxis in response to tumour angiogenic factors and haptotaxis in response to the fibronectin gradient [11, 29]

In this dissertation we will derive the total cell flux through on spatial position x during time t. $A(x,t)$ represents a tumour angiogenic factor concentration in spatial position x at time t. Similarly, $f(x,t)$ and $E(x,t)$ will represents fibronectin and endothelial concentration respectively in spatial position x at time t on spatial position x to derive the total cell flux on spatial position x during time t [11, 29, 45, 46]. Following the work of Anderson and Chaplain [11] and Edelstein-Keshet [47], we formulated an equation governing the total cell flux as follows:

$$E_{Total} = E_{Random} + E_{Chemo} + E_{Hapto}, \tag{3.1}$$

where E_{Total} represents the total collection of endothelial cells present, E_{Random} represents endothelial cells due to random diffusion, E_{Chemo} represents endothelial cells due to chemotaxis, E_{Hapto} represent cells due to haptostaxis. The random flux is given as

$$E_{Random} = -D_E \nabla E, \tag{3.2}$$

where D_E represents a cell random positive constant and ∇E is the rate of change of the concentration of of endothelial cells. The chemotatic flux is given by:

$$E_{Chemo} = \chi(E) \times E \nabla A, \tag{3.3}$$

where $\chi(E)$ is the term for chemotatic function. E is a term for endothelial cells and ∇E is the rate of change of tumour angiogenic factors. Following a receptor kinetic law, the chemotatic function can then be defines as:

$$\chi(E) = \chi_0 \frac{K_1}{K_1 + E}, \tag{3.4}$$

where χ_0 is the chemotatic coefficient and K_1 is a positive constant. The haptotatic flux can also be defined as follows:

$$E_{Hapto} = \rho_1 E \nabla(f), \tag{3.5}$$

where ρ_1 is a positive constant called the haptotatic coefficient and $\nabla(f)$ is the rate of change of fibronection concentration. By substituting Equations (3.2), (3.3), (3.4) and (3.5)

into (3.1) we get the equation for the total cell flux as:

$$E_{Total} = -D_E \nabla E + \chi(E) E \nabla A + \rho_1 E \nabla(f). \tag{3.6}$$

.

3.3 Conservation Equation for Endothelial Cells

The models discussed in Chapter 1 are incomplete incomplete because the equations governing density of endothelial cells do not include all relevant terms. For instance Anderson and Chaplain [11] did not include a term for proliferation, Eloundou [30] did not include the term for haptotaxis, and Holmes and Sleeman [29] did not include a term for cells lost due to decay. As a result the model that is developed in this dissertation follows one generated by McDougall et al. [46] while also incorporating work by other authors. We assume endothelial cells moves due to proliferation and are depleted due to decay. Thus the equation governing the rate of change of endothelial cells concentration in an arbitrary region can be represented as:

$$\partial_t E = -\nabla^2 E_{Total} + F(E)G(A) - H(E), \tag{3.7}$$

where $F(E)$ and $H(E)$ stands for the growth and loss of cells respectively and $G(A)$ is the equation for mitotic growth.

The term for logistic growth can be expressed as follows:

$$F(E) = \rho_2 E \left(1 - E/E_0\right), \tag{3.8}$$

where ρ_2 is a positive constant related to the maximum mitotic rate E_0 and is the maximum amount of endothelial cells that can be carried within the specified boundary.

The growth of endothelial cells is influenced by two processes. At first endothelial cells respond chemotatically to tumour angiogenic factors, then later proliferation takes place.

It is assumed that until tumour angiogenic factors reach a certain threshold concentration level of A^* no proliferation takes place. Thus proliferation only occurs once the level of A is bigger than the level of A^* . This means that if the level of tumour angiogenic factors are below the threshold level proliferation does not occur. It only takes place when the level of tumour angiogenic factors are above the threshold. Taking $G(A)$ as a non decreasing function, it can be expressed as:

$$G(A) = \begin{cases} 0 & \text{if } A \leq A^*, \\ \frac{A-A^*}{A_0} & \text{if } A > A^* \end{cases}, \tag{3.9}$$

where A_0 is the maximum constant value of tumour angiogenic factors at the boundary of the tumour.

The function of cell loss is as follows:

$$H(E) = \mu E, \tag{3.10}$$

where μ is a positive constant related to maximum loss rate. It can be concluded that the rate of increase of endothelial cell concentration can be written as follows: if $A \leq A^*$ no proliferation will take place and

$$\partial_t E = D_E \nabla^2 E - \nabla \chi_1 \frac{K_1}{K_1 + E} E \nabla A - \nabla \rho_e E \nabla (f) - \mu E, \tag{3.11}$$

but if $A > A^*$ mitosis will take place and

$$\partial_t E = D_E \nabla^2 E - \nabla \chi_1 \frac{K_1}{K_1 + E} E \nabla A - \nabla \rho_1 E \nabla (f) + \rho_2 E \left(1 - \frac{E}{E_0}\right) \left(\frac{A^* - A}{A_0}\right) - \mu E, \tag{3.12}$$

for $A^* \leq A_0$.

3.4 Conservation Equation for Tumour Angiogenic Factors

The critical role played by tumour angiogenic factors in degrading the blood vessel basement membrane, and so releasing endothelial cells. The equation that will be presented in this dissertation for tumour angiogenic factors is based on previously published models of Anderson and Chaplain [11], Eleondou [30] and Holmes and Sleeman [29]. We assume that the tumour angiogenic factors diffuses, depletes and decays. Thus the rate of change of tumour angiogenic factors concentration in a particular region can be represented by:

$$\partial_t A = D_A \nabla^2 A - f(A)g(E) - h(A), \tag{3.13}$$

where D_A, is tumour angiogenic factors diffusion coefficient.

The function $f(A)$ represents the local uptake of tumour angiogenic factor by endothelial cells, which is linearly dependent on cell density and so it can be expressed as follows:

$$f(A) = \frac{QA}{K_{max} + A}, \tag{3.14}$$

where K_{max} is the Michaelis–Menten kinetic law constant which is equivalent to the concentration of tumour angiogenic factors required to achieve a reaction rate of $Q/2$, where Q is maximum reaction uptake rate.

The function $g(E)$ is a strongly increasing function which can be expressed as $g(E) = E/E_0$, where E_0 is the maximum amount of endothelial cells that can use the tumour angiogenic factors within the specified boundary with zero flux boundary condition. $h(A)$ is the decay rate for tumour angiogenic factors which are taken as:

$$h(A) = dA \tag{3.15}$$

where d is the tumour angiogenic factors decay rate. The rate of change of the tumour

angiogenic factor then written as:

$$\partial_t A = D_A \nabla^2 A - \left(\frac{QA}{K_{max} + A} \right) (E/E_0) - dA, \tag{3.16}$$

[11, 29, 30].

3.5 Conservation Equation for Fibronectin

Endothelial cells secrete fibronectin which helps them adhere together. This dissertation makes use of the conservation equation for fibronectin in an arbitrary region, as formulated by Holmes and Sleeman [29]. We assume that the equation governing the rate of change of fibronectin concentration has terms for: diffusion, secretion by endothelial cells, loss due to cell-cell adhesion and loss due to decay. Thus it can be expressed as follows:

$$\partial_t f = D_f \nabla^2 f + \frac{\alpha_f E f}{\beta + f} - s_f E f - \lambda_f f, \tag{3.17}$$

where α_f is the secretion rate, β is a positive constant, s_f is the uptake rate of fibronectin by endothelial cells and λ_f is the decay rate of fibronectin. The term

$\frac{\alpha_f E f}{\beta + f}$

represents the concentration of fibronectin which is secreted by endothelial cells. Models already developed do not consider concentration of oxygen and glucose because as Ward and King [2] suggest it can be neglected in the interior of larger spheroids.

3.6 Numerical Solution in one Space Dimension

The systems of equations shown in Equations (3.12), (3.16) and (3.17) are all non linear parabolic differential equations. They are one space dimensional, because x is the only independent spatial variable involved [35]. Solving them requires that they are first non-dimensionalized as in Holmes and Sleeman [29]. The distance from the parent blood vessel

to tumour is given to be L is, and the time $\tau = \frac{L^2}{D_A}$, and by setting appropriate reference variables. Accordingly, we obtain : $\overline{A} = \frac{A}{A_0}$; $\overline{E} = \frac{E}{E_0}$; $\overline{x} = \frac{x}{L}$; $\overline{t} = \frac{t}{\tau}$; $\overline{f} = \frac{f}{f_0}$, We also let: $\omega = \frac{TQ}{A_0}$; $\gamma = \frac{k_m}{A_0}$; $\sigma = \frac{Td}{A_0}$; $\xi = \frac{\beta}{f_0}$; $\varepsilon = \frac{\alpha_f T E_0}{f_0}$; $\eta = TS_f E_0$; $\kappa = \lambda_f T$; $\psi = \mu T$; $\rho = \frac{\rho_1 T A_0}{L^2}$; $\rho_0 = \rho_2 T$; $\chi(1) = \frac{\chi_0 T A_0}{L^2}$; $d_f = \frac{TD_f}{L^2}$; $d_A = \frac{TD_A}{L^2}$; $d_E = \frac{TD_E}{L^2}$[29]. Dropping the bars, the following non-dimensionalized systems are obtained from (3.16), (3.17) and (3.12) respectively:

$$\frac{\partial f}{\partial t} = d_f \frac{\partial^2 f}{\partial x^2} + \frac{\varepsilon E f}{\xi + f} - \eta E f - \kappa f, \tag{3.18}$$

$$\frac{\partial A}{\partial t} = d_A \frac{\partial^2 A}{\partial x^2} - \left(\frac{\omega E A}{\gamma + A}\right) - \sigma A, \tag{3.19}$$

and

$$\begin{aligned}\frac{\partial E}{\partial t} = d_E \frac{\partial^2 E}{\partial x^2} - \chi_0 \frac{K_1}{K_1 + E} \frac{\partial E \partial A}{\partial x \partial x} - E \frac{\partial^2 A}{\partial x} \\ - \rho \frac{\partial E \partial f}{\partial x \partial x} - E \frac{\partial^2 f}{\partial x^2} + \rho_0 E(1 - E) G(A) - \psi E.\end{aligned} \tag{3.20}$$

3.6.1 Application of the Crank-Nicolson Method in the Model for Fibronectin

When solving equation (3.18) using the Crank-Nicolson scheme it becomes:

$$\begin{aligned}\frac{f_i^{j+1} - f_i^j}{\Delta t} = d_f \frac{[f_{i-1}^{j+1} - 2f_i^{j+1} + f_{i+1}^{j+1} + f_{i-1}^j - 2f_i^j + f_{i+1}^j]}{2\Delta x^2} \\ + \varepsilon \frac{E_i^j f_i^j}{\xi + f_i^j} - \eta E_i^j f_i^j - \kappa \frac{f_i^{j+1} - f_i^j}{2}.\end{aligned} \tag{3.21}$$

Letting, $P = \frac{\Delta t d_f}{\Delta x^2}$, $H_i^j = \frac{\Delta t \varepsilon E_i^j}{\xi + f_i^j}$, $C_i^j = \Delta t \eta E_i^j$ and $R = \frac{\Delta t \kappa}{2}$, and substituting for P, H_i^j, C_i^j and R equation (3.21) will be:

$$f_i^{j+1} - f_i^j = P[f_{i-1}^{j+1} - 2f_i^{j+1} + f_{i+1}^{j+1} + f_{i-1}^j - 2f_i^j + f_{i+1}^j] + H_i^j f_i^j - C_i^j f_i^j - R\left(f_i^{j+1} - f_i^j\right). \tag{3.22}$$

By re-arranging terms we get:

$$-Pf_{i+1}^{j+1}+(1+2P+R)f_i^{j+1}-Pf_{i-1}^{j+1}=Pf_{i+1}^{j}+(1-2P+H_i^j-C_i^j+R)f_i^j+Pf_{i-1}^{j}. \quad (3.23)$$

Let $1+2P+R=\varrho_0$ and $(\varrho_1)_i^j=1-2P+R_i^j-C_i^j+R.$ After equation (3.6.1) we then obtain a tridiagonal matrix like this for $j=0,1,2.....n$

$$\begin{pmatrix} \varrho_0 & -P & 0 & 0 & 0 & 0 & \\ -P & \varrho_0 & -P & . & 0 & 0 & \\ 0 & -P & \varrho_0 & -P & . & 0 & \\ 0 & 0 & -P & \varrho_0 & -P & . & 0 \\ 0 & 0 & -P & \varrho_0 & -P & 0 & \\ 0 & 0 & -P & \varrho_0 & -P & 0 & \\ . & . & . & . & . & . & \\ . & . & . & . & . & . & \\ 0 & . & . & -P & \varrho_0 & -P & \\ 0 & . & . & . & -P & \varrho_0 & \end{pmatrix} \begin{pmatrix} f_1^{j+1} \\ f_2^{j+1} \\ f_3^{j+1} \\ f_4^{j+1} \\ . \\ . \\ . \\ . \\ f_{i-1}^{j+1} \\ f_i^{j+1} \end{pmatrix} = \begin{pmatrix} (\varrho_1)_i^j & P & . & . & 0 & 0 \\ P & \varrho_1 & P & . & . & 0 \\ 0 & P & (\varrho_1)_i^j & P & . & 0 \\ 0 & 0 & P & (\varrho_1)_i^j & P & 0 \\ . & . & . & . & . & . \\ . & . & . & . & . & . \\ 0 & . & . & P & (\varrho_1)_i^j & P \\ 0 & 0 & . & . & P & (\varrho_1)_i^j \end{pmatrix} \quad (3.24)$$

$$\times \begin{pmatrix} f_1^j \\ f_2^j \\ f_3^j \\ f_4^j \\ . \\ . \\ . \\ f_i^j \end{pmatrix} + \begin{pmatrix} 2P \times f_1^j \\ 0 \\ 0 \\ 0 \\ . \\ . \\ 0 \\ 2P \times f_i^j \end{pmatrix} \quad (3.25)$$

3.6.2 Application of the Crank-Nicolson Method in The Model for Tumour Angiogenic Factors

As in the previous section, the solution of equation (3.19) is obtained by applying the Crank-Nicolson scheme in discrete form as:

$$\frac{A_i^{j+1}-A_i^j}{\Delta t}=d_A\frac{[A_{i-1}^{j+1}-2A_i^{j+1}+A_{i+1}^{j+1}+A_{i-1}^j-2A_i^j+A_{i+1}^j]}{2\Delta x^2} - \frac{\omega E_i^j A_i^j}{\gamma+A_i^j}-\sigma\frac{A_i^{j+1}-A_i^j}{2}.$$

By letting $B = \frac{\Delta t d_A}{2\Delta x^2}$, $D = \frac{\Delta t \sigma}{2}$, $X_i^j = \Delta t \frac{\omega E_i^j}{\gamma + A_i^j}$ and substituting for B, D and X_i^j, Equation (3.26), becomes:

$$A_i^{j+1} - A_i^j = B\left(A_{i-1}^{j+1} - 2A_i^{j+1} + A_{i+1}^{j+1} + A_{i-1}^j - 2A_i^j + A_{i+1}^j\right) - X_i^j A_i^j - D\left(A_i^{j+1} - A_i^j\right). \quad (3.26)$$

Rearranging terms we get:

$$-BA_{i+1}^{j+1} + (1+2B+D)A_i^{j+1} - BA_{i-1}^{j+1} = BA_{i+1}^j + (1-2B-X_i^j+D)A_i^j + BA_{i-1}^j. \quad (3.27)$$

Let $\upsilon_0 = 1 + 2B + D$ and $(\upsilon_1)_i^j = 1 - 2B - X_i^j + D$ For $j = 0, 1, 2.....n$, Equation (3.27) can be written as a tridiagonal matrix, like shown below:

$$\begin{pmatrix} \upsilon_0 & -B & 0 & 0 & 0 & 0 & . & 0 \\ -B & \upsilon_0 & -B & 0 & 0 & . & 0 & 0 \\ 0 & -B & \upsilon_0 & -B & 0 & 0 & 0 & 0 \\ 0 & 0 & -B & \upsilon_0 & -B & 0 & 0 & 0 \\ 0 & 0 & 0 & -B & \upsilon_0 & -B & 0 & 0 \\ . & . & . & . & . & . & . & . \\ . & . & . & . & . & . & . & . \\ . & . & . & . & -B & \upsilon_0 & -B & 0 \\ 0 & 0 & . & . & 0 & -B & \upsilon_0 & -B \\ 0 & 0 & . & . & . & . & -B & \upsilon_0 \end{pmatrix} \begin{pmatrix} A_1^{j+1} \\ A_2^{j+1} \\ A_3^{j+1} \\ A_4^{j+1} \\ . \\ . \\ . \\ . \\ A_i^{j+1} \end{pmatrix} = \begin{pmatrix} (\upsilon_1)_i^j & B & 0 & 0 & 0 & 0 & 0 & 0 \\ B & (\upsilon_1)_i^j & B & 0 & 0 & . & . & 0 \\ 0 & B & (\upsilon_1)_i^j & B & 0 & 0 & . & 0 \\ 0 & 0 & B & (\upsilon_1)_i^j & B & 0 & . & 0 \\ 0 & 0 & 0 & B & (\upsilon_1)_i^j & B & . & 0 \\ . & . & . & . & . & . & . & . \\ . & . & . & . & . & . & . & . \\ . & . & . & . & B & (\upsilon_1)_i^j & B & 0 \\ 0 & 0 & 0 & . & . & B & (\upsilon_1)_i^j & B \\ 0 & 0 & 0 & . & . & . & B & (\upsilon_1)_i^j \end{pmatrix}$$

$$\begin{pmatrix} A_1^j \\ A_2^j \\ A_3^j \\ A_4^j \\ . \\ . \\ . \\ . \\ A_i^j \end{pmatrix} + \begin{pmatrix} 2B \times A_1^j \\ 0 \\ 0 \\ 0 \\ . \\ . \\ . \\ . \\ 0 \\ 2B \times A_i^j \end{pmatrix}$$

3.6.3 Application of the Crank-Nicolson Method in The Model for Endothelial Cells

Using equation (3.20), which is the conservation equation for endothelial cells,

$$\frac{\partial E}{\partial t} = d_E \frac{\partial^2 E}{\partial x^2} - \chi(1)\frac{K_1}{K_1 + E}\frac{\partial(E\partial A)}{\partial x \partial x} - \rho\frac{\partial(E\partial f)}{\partial x \partial x} + \rho_0 E(1-E)G(A) - \psi E. \quad (3.28)$$

By applying the product rule equation (3.20) becomes:

$$\frac{\partial E}{\partial t} = d_E \frac{\partial^2 E}{\partial x} - \chi(1)\frac{K_1 \partial A^2 E}{(K_1+E)\partial x} - \chi(1)\frac{K_1}{K_1+E}\frac{\partial E \partial A}{\partial x \partial x} - \rho E \frac{\partial f^2}{\partial x} \rho \frac{\partial E \partial f}{\partial x \partial x} + \rho_0 E(1-E)G(A) - \psi E. \tag{3.29}$$

Where

$$G(A) = \begin{cases} 0 & \text{if } A \leq A^*, \\ \frac{A-A^*}{A_0} & \text{if} A > A^* \end{cases}. \tag{3.30}$$

Dividing by A^* Equation (3.30) gives

$$G(A) = \begin{cases} 0 & \text{if} A \leq 1, \\ \frac{A-1}{A_0} & \text{if } > 1. \end{cases} \tag{3.31}$$

Then applying the Crank-Nicolson method approximation from Table **??**, to equation (3.29), we get

$$\begin{aligned} \frac{E_i^{j+1}-E_i^j}{\Delta t} &= d_E \frac{E_{i-1}^{j+1} - 2E_i^{j+1} + E_{i+1}^{j+1} + E_{i-1}^j - 2E_i^j + E_{i+1}^j}{2(\Delta x)^2} \\ &- \frac{\chi(1)K_1}{K_1+E_i^j} \times \frac{[E_{i+1}^{j+1} - E_{i-1}^{j+1} + E_{i+1}^j - E_{i-1}^j]}{4\Delta x} \times \frac{[A_{i+1}^{j+1} - A_{i-1}^{j+1} + A_{i+1}^j - A_{i-1}^j]}{4\Delta x} \\ &+ E_i^j \chi(1) K_1 \frac{[A_{i-1}^{j+1} - 2A_i^{j+1} + A_{i+1}^{j+1} + A_{i-1}^j - 2A_i^j + A_{i+1}^j]}{2\Delta x^2} \\ &- \rho \frac{[E_{i+1}^{j+1} - E_{i-1}^{j+1} + E_{i+1}^j - E_{i-1}^j]}{4\Delta x} \times \frac{[F_{i+1}^{j+1} - F_{i-1}^{j+1} + F_{i+1}^j - F_{i-1}^j]}{4\Delta x} \\ &+ E_i^j - \rho \frac{F_{i-1}^{j+1} - 2F_i^{j+1} + F_{i+1}^{j+1} + F_{i-1}^j - 2F_i^j + F_{i+1}^j}{2\Delta x^2} \\ &+ \rho_0 E_i^j (1-E_i^j) G(A_j^j) - \psi \frac{E_i^{j+1} - E_i^j}{2}. \end{aligned} \tag{3.32}$$

Let

$$Q = \frac{\Delta t d_E}{2(\Delta x)^2},$$

$$U_i^j = \frac{\chi(1)K_1 \Delta t \{(A_{i+1}^{j+1} - A_{i-1}^{j+1} + A_{i+1}^j - A_{i-1}^j\})}{16(\Delta x)^2(K_1+E_i^j}},$$

$$R_i^j = \frac{\chi(1)k_1\Delta t\{(A_{i+1}^{j+1} - 2A_i^{j+1} + A_{i-1}^{j+1} + A_{i+1}^j - 2A_i^j - A_{i-1}^j\})}{2(\Delta x)^2(k_1 + E_i^j},$$

$$M_i^j = \frac{\rho\Delta t\{(f_{i+1}^{j+1} - f_{i-1}^{j+1} + f_{i+1}^j - f_{i-1}^j\})}{16(\Delta x)^2},$$

$$N_i^j = \frac{\rho\Delta t E_i^j\{(f_{i+1}^{j+1} - 2f_i^{j+1} + f_{i-1}^{j+1} + f_{i+1}^j - 2f_i^j - A_{i-1}^j\})}{2(\Delta x)^2},$$

$$Z = \frac{\psi\Delta t}{2},$$

and

$$W_i^j = \rho_0\Delta t\left(1 - E_i^j\right)G(A_i^j).$$

Substituting for $Q, R_i^j, M_i^j, N_i^j, Z$, and W_i^j in equation (3.34) it becomes:

$$\begin{aligned} E_i^{j+1} - E_i^j =& Q[E_{i-1}^{j+1} - 2E_i^{j+1} + E_{i+1}^{j+1} + E_{i-1}^j - 2E_i^j + E_{i+1}^j] \\ & - U_i^j[E_{i+1}^{j+1} - E_{i-1}^{j+1} + E_{i+1}^j - E_{i-1}^j] - R_i^j E_i^j - M_i^j[E_{i+1}^{j+1} - E_{i-1}^{j+1} + E_{i+1}^j - E_{i-1}^j] \\ & - N_i^j E_i^j + W_i^j E_i^j - Z[E_i^{j+1} - E_i^j]. \end{aligned} \tag{3.33}$$

Let $\psi_0 = (1 + 2Q + Z), (\psi_1)_i^j = (-Q - U_i^j - M_i^j), (\psi_2)_i^j = (-Q + U_i^j + M_i^j), (\psi_3)_i^j = (1 - 2Q - R_i^j - N_i^j + W_i^j + Z), (\psi_4)_i^j = (Q + U_i^j + M_i^j)$ and $(\psi_5)_i^j = (Q - U_i^j - M_i^j)$

Rearranging terms in equation (3.33) gives

$$(\psi_2)_i^j)E_{i+1}^{j+1} + \psi_0 E_i^{j+1} + (\psi_1)_i^j E_{i-1}^{j+1} = (\psi_5)_i^j E_{i+1}^j + (\psi_3)^j E_i^j + (\psi_4)_i^j E_{i-1}^j. \tag{3.34}$$

After substituting for for $j = 0, 1, 2.....n$ in equation (3.34) then we got system of linear

equations which is then expressed as this tridiagonal matrix :

$$\begin{pmatrix} \psi_0 & (\psi_2)_i^j & 0 & 0 & . & 0 \\ (\psi_1)_i^j & \psi_0 & (\psi_2)_i^j & 0 & . & 0 \\ 0 & (\psi_1)_i^j & \psi_0 & (\psi_2)_i^j & 0 & 0 \\ 0 & 0 & (\psi_1)_i^j & \psi_0 & (\psi_2)_i^j & 0 \\ . & . & . & . & . & . \\ . & . & . & . & . & . \\ . & . & . & . & . & . \\ 0 & . & (\psi_1)_i^j & \psi_0 & (\psi_2)_i^j & 0 \\ 0 & . & . & (\psi_1)_i^j & \psi_0 & (\psi_2)_i^j \\ 0 & . & . & . & (\psi_1)_i^j & \psi_0 \end{pmatrix} \begin{pmatrix} E_1^{j+1} \\ E_2^{j+1} \\ E_3^{j+1} \\ E_4^{j+1} \\ . \\ . \\ . \\ . \\ . \\ E_i^{j+1} \end{pmatrix} = \begin{pmatrix} (\psi_3)_i^j & (\psi_5)_i^j & 0 & 0 & . & 0 \\ (\psi_4)_i^j & (\psi_3)_i^j & (\psi_5)_i^j & 0 & . & 0 \\ 0 & (\psi_4)_i^j & (\psi_3)_i^j & (\psi_5)_i^j & 0 & 0 \\ 0 & 0 & (\psi_4)_i^j & (\psi_3)_i^j & (\psi_5)_i^j & 0 \\ 0 & 0 & 0 & . & . & 0 \\ . & . & . & . & . & . \\ . & . & . & . & . & . \\ 0 & . & (\psi_4)_i^j & (\psi_3)_i^j & (\psi_5)_i^j & 0 \\ 0 & . & . & (\psi_4)_i^j & (\psi_3)_i^j & (\psi_5)_i^j \\ 0 & . & . & . & (\psi_4)_i^j & (\psi_3)_i^j \end{pmatrix}$$

$$\times \begin{pmatrix} E_1^j \\ E_2^1 \\ E_3^j \\ E_4^j \\ . \\ . \\ . \\ . \\ . \\ E_i^j \end{pmatrix} + \begin{pmatrix} 2Q \times E_1^j \\ 0 \\ 0 \\ 0 \\ . \\ . \\ . \\ . \\ 0 \\ 2Q \times E_i^j \end{pmatrix} \tag{3.35}$$

3.7 Results and Discussion

Matrices (3.25), (3.28) and (3.35), were solved numerically using Matlab software. Parameter values, boundary and initial conditions are taken from published literature, and the results obtained are discussed below.

3.7.1 Length Scale

We denoted L to be the distance between the blood vessel and the tumour. Holmes and Sleeman [29] stated that if the distance between the tumour and a neighbouring blood vessel was beyond a critical distance of 2.5 mm , then the tumour angiogenic factor failed to stimulate the basement membrane lining the blood the vessel. Hence, they took $2,5$mm as their reference length scale. Anderson et al. [17], vary their reference length between

0.1 mm and 2 mm. The reference length scale in this dissertation is assumed to vary from 1 mm to 2 mm as suggested by Anderson et al. [17] .

3.7.2 Time Scale

In this dissertation T represents the time taken by endothelial cells to move from the blood vessel to the tumour. Holmes and Sleeman [29] used 48 hours as the reference time scale in their model whereas Anderson and Chaplain [11] chose 14 days. In this dissertation T is chosen to be 10 days which is within the range of reference time scales cited, that is between 2 days to 14 days.

3.7.3 The Concentration of Tumour Angiogenic Factor During Angiogenesis

In this section we present initial conditions, boundary conditions and parametric values of tumour angiogenic factors.

Initial and Boundary Conditions for Tumour Angiogenic Factor

The initial condition that will be used in this dissertation are derived from those given by Holmes and Sleeman [29]and Eleondou [30]. For $0 < x < L; 0 < t < L$, $A(x,0) = 10 - x^2$, $A(L,t) = 0$, $A(0,t) = A_0$ and $\nabla A = 0$. To be more specific, in this dissertation the initial condition for the concentration of the tumour angiogenic factor are as follows: $A(x,0) = 10 - (i-1)dx^2$ for $i = 1, \cdots, n$, where n is the number of space steps and dx is the length scale, which is the number of space steps and $A(0,1) = 10$. The boundary conditions are then $A(0,j) = 10$ and $A(n,j) = 0$ for $j = 0, \cdots, k$ with zero flux boundary conditions.

Figure 3.1 displays the boundary conditions of tumour angiogenic factors before angiogenesis. The figure illustrates that concentration of tumour angiogenic factors is maximum at the boundary of the tumour and it decreases with increasing distance between the tumour and blood vessel it is zero at the boundary of the blood vessel.

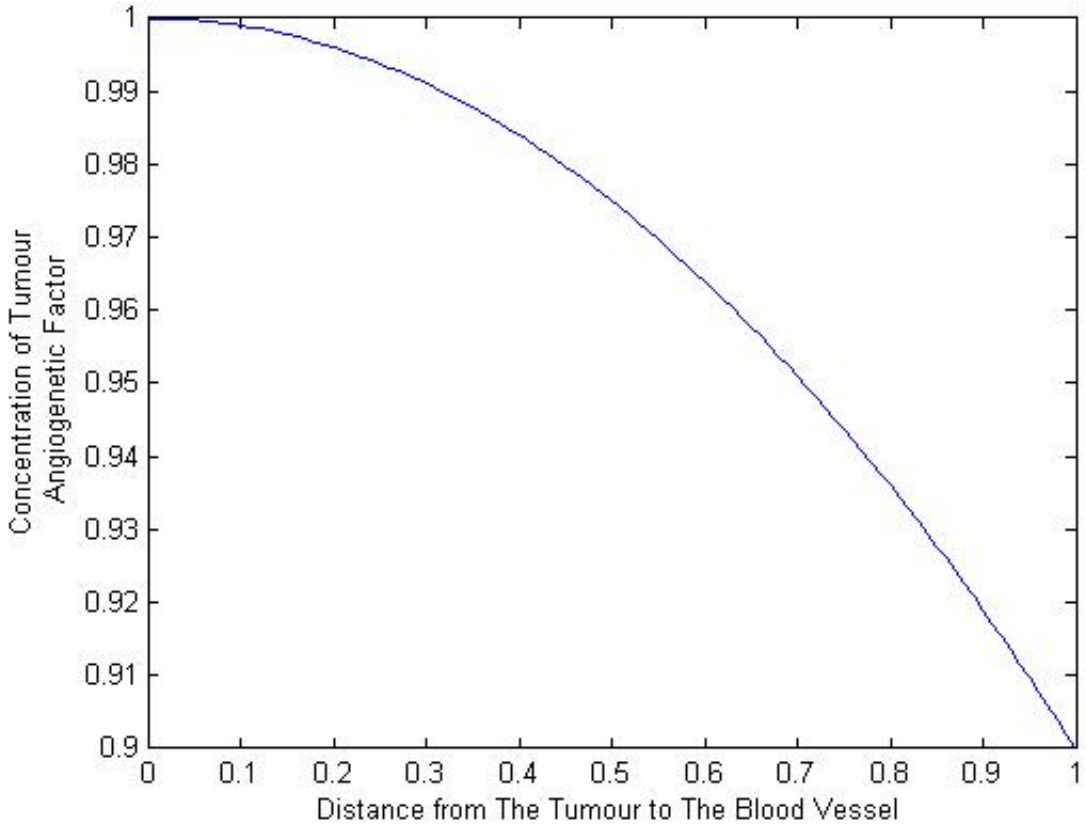

Figure 3.1: Plot of Initial and Boundary Values for the Concentration of Tumour Angiogenic Factors

Parameter Values for Tumour Angiogenic Factors

Holmes and Sleeman [29] stated that the value for the non- dimensionalized tumour angiogenic factors diffusion coefficient, d_A ranges from 9.0×10^{-2} to 1.6×10. Anderson

and Chaplain [11] used a dimensional value of $2.9 \times 10^{-7} cm^2 s^{-1}$ for their simulation. The non-dimensionalized value for d_A used in this study is 4.55×10^{-2} which is close to the value used by Holmes and Sleeman [29].

Holmes and Sleeman [29] estimated the tumour angiogenic factors decay rate, to be between 2.7×10^{-3} and 2.7×10^{-1} but in this study it has been kept to 2.7×10^{-3} as used by Holmes and Sleeman [29]. The chosen value for Q, the tumour angiogenic factors maximum reaction rate chosen is 1.0 and k_m, Michaelis– Mentes Kinetic law constant is 0.1. Appendix 2 at the end indicates non-dimensional parametric values that are used in this study.

Results for Tumour Angiogenic Factors

Matrix (3.28) generated earlier in this chapter was then converted to matlab codes, following previously published approaches [41, 48] for generating Matlab codes.

Accordingly Figure 3.2 illustrates the concentration of tumour angiogenic factors in the space between the tumour and blood vessel during angiogenesis specifically at $1, 3, 7, 9$ and 10 days from the start. In this dissertation we assume the angiogenesis process is completed after 10 days. Results indicate that the concentration of tumour angiogenic factor in the space between the tumour and blood vessel at different times. Results indicate that as time progresses, that is as the value of t increases, the level of tumour angiogenic factors decreases. This would occur because some of the tumour angiogenic factors was used to degrade the basement membrane on the blood vessel and other chemical is lost due to decay.

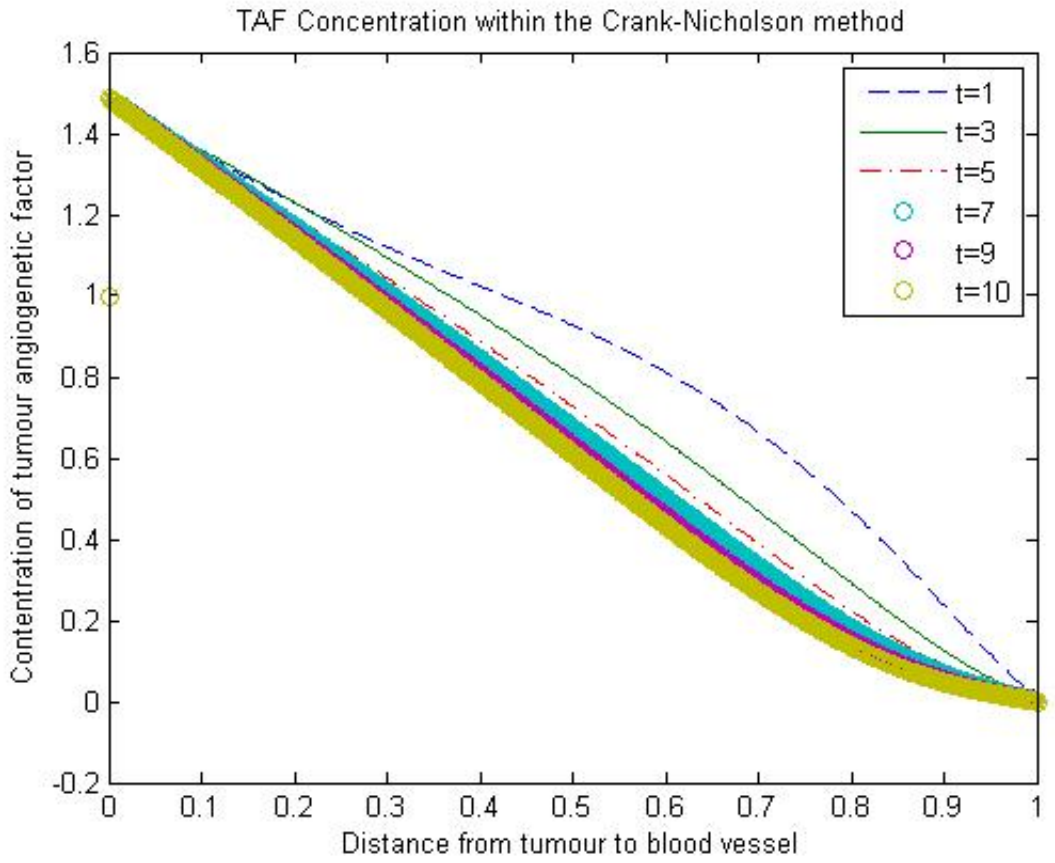

Figure 3.2: Spatial Distribution of the Concentration of Tumour Angiogenic Factors at Different Times

3.7.4 Results for the Concentration of Fibronectin During Angiogenesis

This section shows the initial conditions, boundary conditions and parametric values of fibronectin that are used for simulation.

Initial and Boundary Conditions for Fibronectin

Because fibronectin is secreted by the endothelial cells there is a strong relationship between the endothelial cell profile and the fibronectin distribution. An initial condition is imposed as used in Orme and Chaplain [12] of $f(x,0) = 0.5E(x,0)$. Then $f(x,0) = 0$ elsewhere in the domain.

The zero- flux boundary condition is $\nabla f = 0$, at $x = 0$ and at $x = L$ and for t in $[0,T]$. For simulation in this dissertation the initial condition is taken as:

$$f(x,0) = \begin{cases} 0 & \text{if } x \leq n, \\ 5 & \text{else where in the domain} \end{cases}, \tag{3.36}$$

and boundary conditions were as follows: $f(0,j)$ and $f(n,j) = 5$ for $j = 0 \cdots k$ with zero flux boundary conditions as illustrated in Figure 3.3. Figure 3.3 shows the boundary conditions of fibronectin before angiogenesis takes place. The figure indicates the concentration of fibronectin to be maximum at the boundary of the blood vessel and zero elsewhere in the domain region.

Parametric Values for Fibronectin

Holmes and Sleeman [29] stated that the value for the non-dimensional fibronectin diffusion constant, d_f may vary from 2.7×10^{-2} to 2.7 and in this dissertation the value used for d_f is chosen randomly as 2.7×10^{-2} which falls within the range given by Holmes and Sleeman [29]. Non-dimensionalized values chosen for fibronectin secretion, uptake rate and decay rate are 2.0×10^{-2} , 3.9×10^{-2} and 5.4×10^{-2} respectively as shown in Appendix 2. These chosen values are in line with parametric values whi ch were used by Holmes and Sleeman [29] as follows,for the secretion rate α, the uptake rate is $\S_f$ and the decay rate λ_f were 2.0×10^{-2} to 2.0×10, 5.2×10^{-3} to 3.9 and 2.7×10^{-3} to 2.6×10^{-1} respectively.

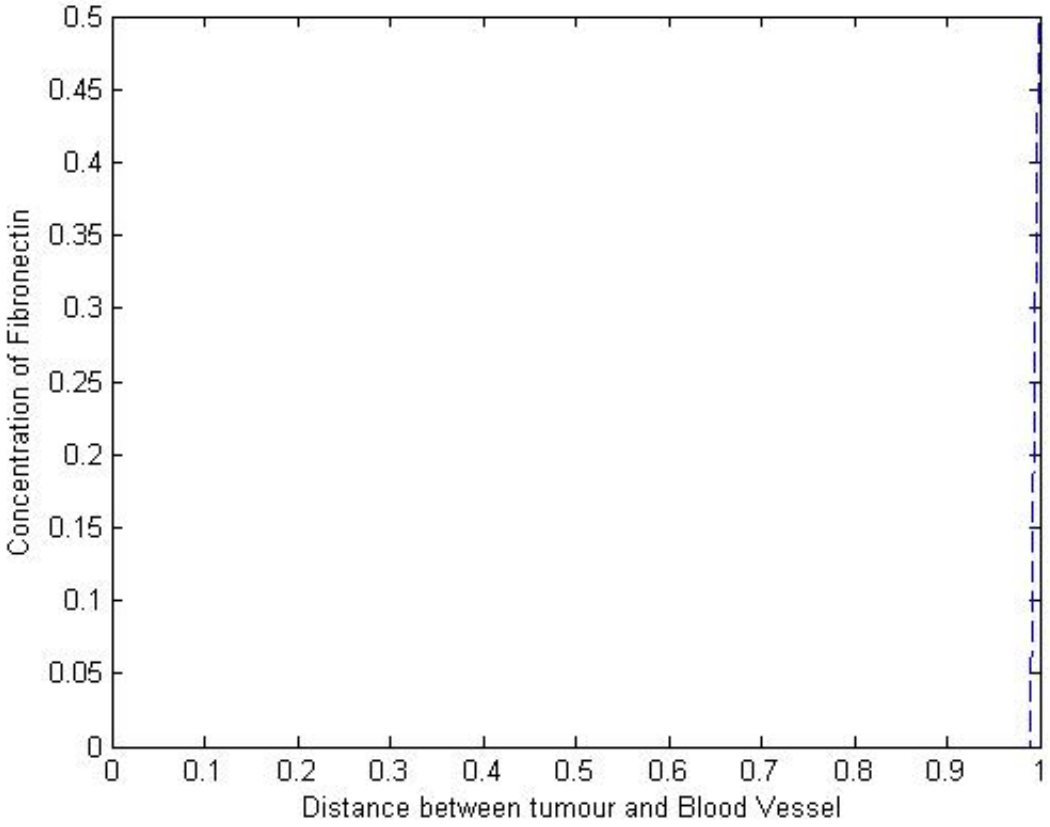

Figure 3.3: Plot of Initial and Boundary Conditions of Fibronectin

Results Simulated for Fibronectin Concentration

Matrix (3.25) generated earlier in this chapter was then converted to matlab codes, following previously published approaches [41, 48] for generating Matlab codes.

Figure 3.4 illustrates the concentration of fibronectin in the region during different times of angiogenesis; that is $1, 3, 5, 7, 9,$ and 10 days. The graphs indicates that, fibronectin behaved in the same way as endothelial cells. Graphs indicate that as time progresses, fibronectin concentration decreases with distance away from the blood vessel.

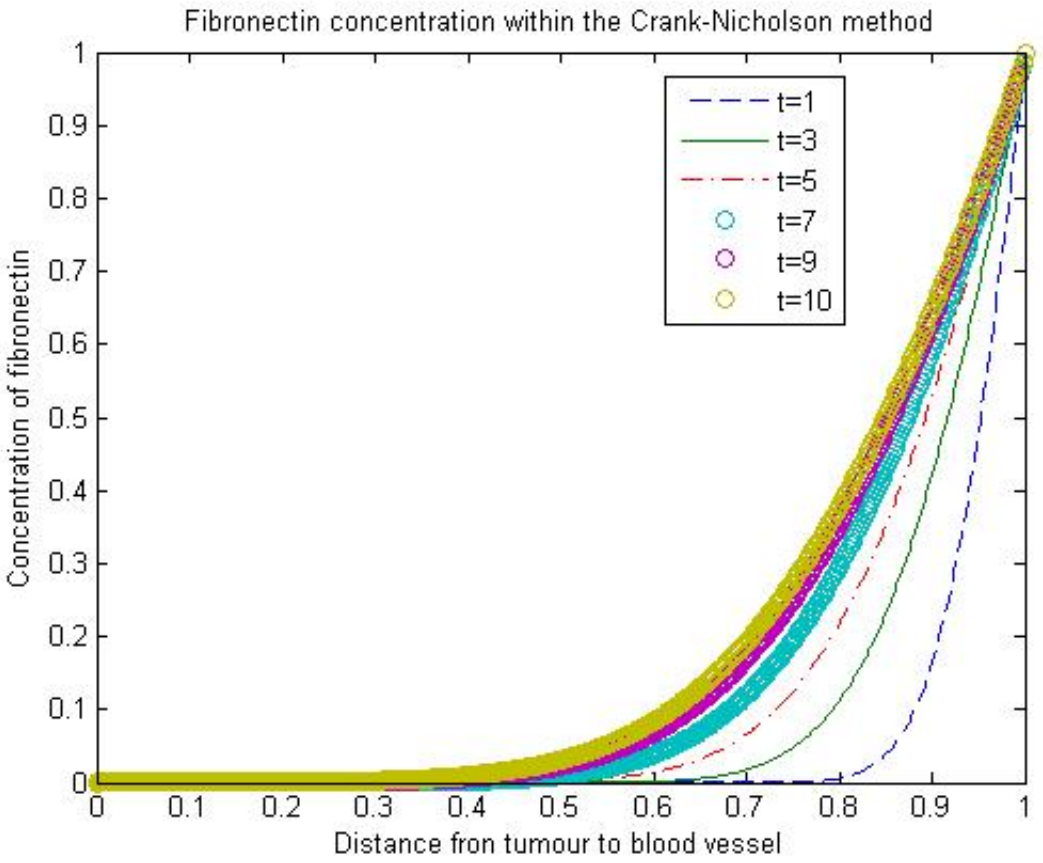

Figure 3.4: A Plot Showing Spatial Distribution of Fibronectin concentration at Different Times

3.7.5 The Concentration of Endothelial Cells During Angiogenesis

This section reports the initial conditions, boundary conditions and parametric values that will be used to simulate the concentration of endothelial cells in this dissertation.

Initial and Boundary Condition for Endothelial Cells

The initial conditions that will be used in this dissertation are in line with those used by Holmes and Sleeman [29] and Eleondou [30]. The initial condition for endothelial cells in

this dissertation for $0 < x < L$ and $0 < t < T$ is :

$$E(x,0) = \begin{cases} 0 & \text{if } x < L, j \leq n \\ 10 & \text{else where in the domain} \end{cases} , j = n+1. \tag{3.37}$$

The boundary conditions were as follows: $E(0,j) = 0$ and $E(L,j) = 10$ for $j = 0, \cdots, k$ with zero flux boundary conditions, which means that $\nabla E = 0$, at $x = 0$ and at $x = L$ Figure 3.5 indicates the boundary conditions of endothelial cells before angio-

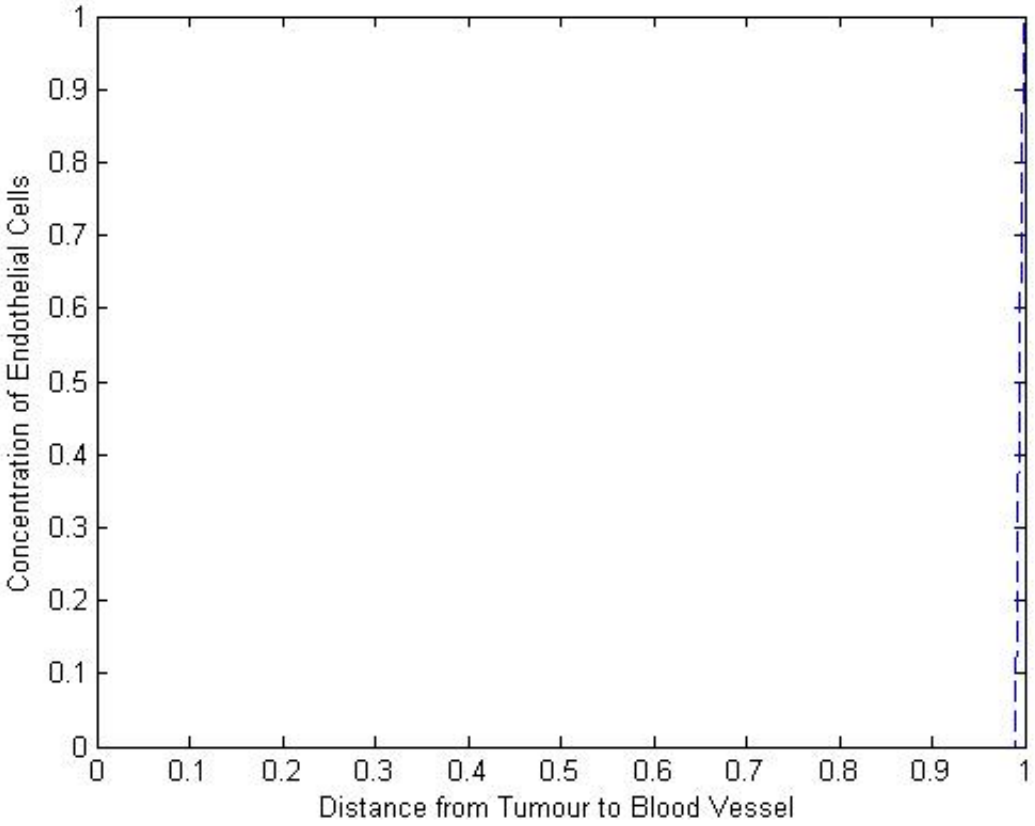

Figure 3.5: Plot of Initial and Boundary Conditions of Endothelial cells

genesis. The figure illustrates that the concentration of endothelial cell is maximum at the boundary of the blood vessel and is zero at the boundary of the tumour.

Parametric Values for Endothelial Cells

Anderson and Chaplain [11] on the other hand use the non-dimensionalized value for endothelial diffusion constant d_E to be equal to 3.5×10^{-4} while Holmes and Sleeman [29] on the other hand choose a range from $2.8 \times 10^{-4} - 2.8 \times 10^{-2}$. Eleondou [30] also used 3.5×10^{-10} cm^2 s^{-1}for the dimensionalized value of d_E. Other parametric values values used by Holmes and Sleeman [29] are given in Table 3.1 Parameters which are used in

Table 3.1: Parametric Values Used by Holmes and Sleeman

chemotaxis positive constant	χ_1	$3.5 \times 10^{-4} - 4.8 \times 10^{-1}$
maximum decay rate of EC	ψ	6.94×10^{-6}
haptotaxis coefficient t	ρ_1	$2.8 \times 10^{-6} - 3.9 \times 10$
mitotic coefficient	ρ_2	$9.5 - 2.7 \times 10$

this dissertation for the migration of endothelial cells are in Table 3.2 and they are in line with parametric values as used by Holmes and Sleeman [29] Other parameters appear on

Table 3.2: Non-dimemsionalized Parametric Values for Endothelial Cells that are used in the Dissertation

endothelial diffusion constant	d_E	2.8×10^{-3}
endothelial positive constant	K_1	1
haptotaxis coefficient	ρ_1	4.8×10^{-5}
decay rate	ψ	9.4×10^{-7}
chemotaxis positive constant	χ_1	3.5×10^{-5}

Appendix 2 at the end of this dissertation and were were randomly.

Results for Endothelial Cells

Matrix (3.35) generated earlier in this chapter was then converted to Matlab codes, following previously published approaches [41, 48] for generating Matlab codes. Figure 3.6 illustrates the concentration of fibronectin in the region during these different times of angiogenesis; $1, 3, 5, 7, 9$ and 10 days.

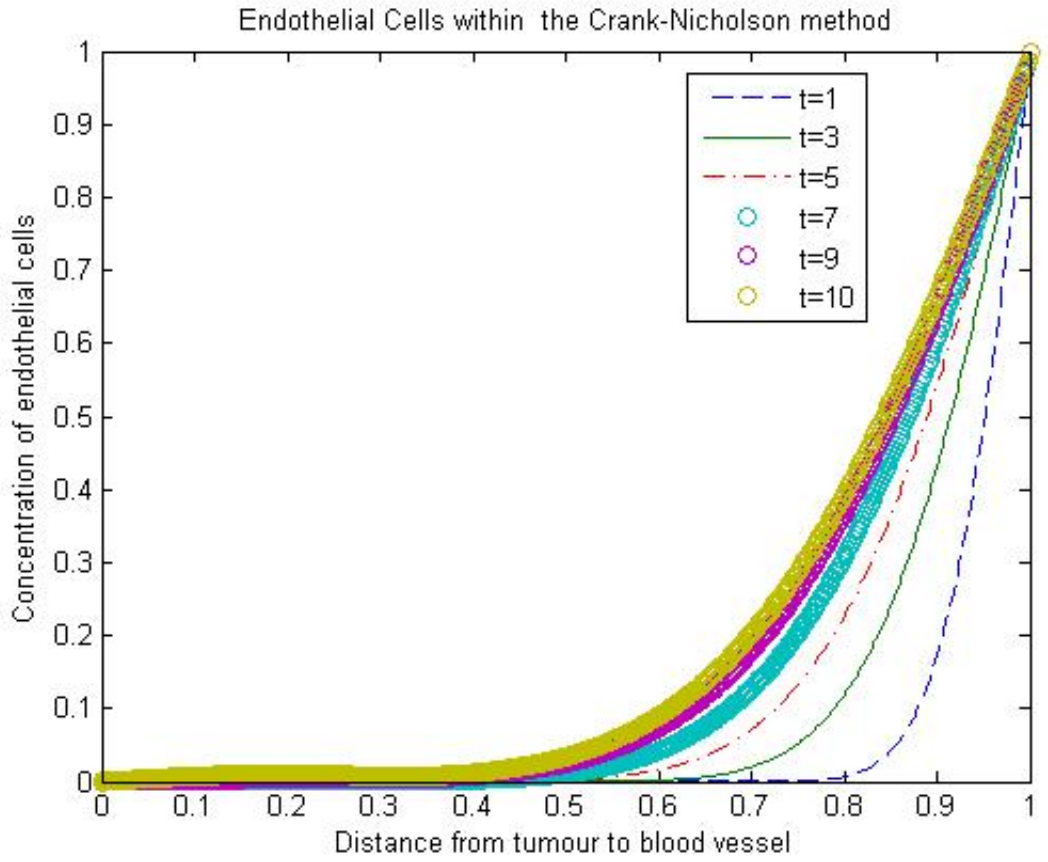

Figure 3.6: A Plot of the Concentration of Endothelial Cells at Different Times

Results indicate that the endothelial cells escape from the blood vessel and they migrate towards the tumour. It is noticed that as time progresses the distance between the endothelial cells and the tumour decreases until and they eventually reach the tumour. In this way they complete the process of angiogenesis. Figure 3.6 indicates that endothelial cells reach the

tumour after 10 days, which is in accordance with the assumption given at the beginning of this chapter.

3.8 Summary

Parabolic equations governing the conservation of tumour angiogenic factors, fibronectin and endothelial cells have been developed. A finite method, the Crank- Nicolson method, is applied to solve them. The matrices acquired are then simulated with the aid of Matlab, using parametric values already published or those chosen to suit this study. The results indicate the concentration of tumour angiogenic factors is greater near the tumour boundary, but shifts towards the blood vessel as time progresses. At the same time fibronectin and endothelial cells are also observed to migrate towards the tumour, and eventually reach it. That indicates that angiogenesis is the process of transition for the tumour from being avascular to become vascular. As such this confirms that our model is reasonable.

The next chapter will demonstrate the role of the anti-angiogenic factor in angiogenesis, when the relevant terms will be added to the system of equations. The equations in the new model formulated will also be solved using the Crank-Nicolson method.

Chapter 4

Modelling Anti-angiogenesis Treatment

4.1 Introduction

In this chapter we consider a situation in which anti-angiogenesis treatment is administered before a tumour is vascularized. The process of anti-angiogenesis was described in the literature review in Chapter 1. It occurs as the primary tumour secrets an anti-angiogenic factors, which impedes secondary tumour growth, by preventing vascularization. Thus anti-angiogenesis can also be harnessed as a treatment for cancer. As was pointed out in Chapter 1, the work in this dissertation will strengthen the existing models for tumour growth by including terms for the process of anti-angiogenesis. This will be effected by applying the dose dependent method, wherein an anti-angiogenic factors will be added to the equation for endothelial cells concentration and results will be generated by simulation. New models that will be presented in this chapter are for the anti-angigenic factors and the conservation of endothelial cells being the aspects that influence and are a response to the treatment. Models for tumour angiogenic factors and for fibronectin will be used as they were in Chapter 3.

4.2 Mathematical Model for Anti-Angiogenic Factors

The equation governing the conservation of the tumour will be used from Chapter 3 as follows:

$$\partial_t A = D_A \nabla^2 A - f(A)g(E) - h(A). \tag{4.1}$$

The equation governing fibronectin will also be used as it appears in Chapter 3 which mathematically is expressed as:

$$\partial_t f = D_f \nabla^2 f + \frac{\alpha_f E f}{\beta + f} - s_f E f - \lambda_f f. \tag{4.2}$$

The anti-angiogenic factor is the treatment administered in this dissertation. It will be added to the region of interest, and then its conservation equation will be based on diffusion, uptake of the factor by endothelial cells and its loss due to decay as had been assumed with the tumour angiogenic factors [17]. Consequently its equation will be as follows:

$$\frac{\partial a}{\partial t} = D_a \frac{\partial^2 a}{\partial x^2} - \lambda_1 a - \varsigma \frac{ae}{(K_0 + a)}, \tag{4.3}$$

where λ_1 represents the decay rate, ς is the anti-angiogenesis factor reaction rate and K_0 is anti-angiogenic factors reaction constant.

4.3 The Mathematical Model for Endothelial Cells During Treatment

As was noted in Chapter 1, biological experiments and mathematical models complement each other. In particular, this work builds on the empirical and theoretical work reported by Anderson et al. [17] and Folkman [13], as was outlined in Chapter 1. The model formulated by Anderson et al. [17] for an equation governing the concentration of endothelial cells during anti-angiogenesis considers the roles of neither haptotaxis nor mitosis in migration

of endothelial cells towards a tumour. They also assume that the function for angiostatin, follow a simple linear form.

In this dissertation the model to govern the development of endothelial cells during anti-angiogenesis is based on diffusion, the chemotatic effect by the tumour angiogenetic factors, endothelial cell-cell adherence through fibronection, cell mitosis, the chemotatic effect by anti-angiogenic factors and endothelial cell lost due to decay. In this dissertation it is assumed that the function describing conservation of anti-angiogenic factors follows a simple logistic form just like the funtion for tumour angiogenic factors. The function for anti-angiogenic factors is as follows: $\alpha(a) = \alpha_0 a \frac{K_0}{(K_0+a)}$, where α_0 (a positive constant coefficient) is the anti-angiogenic chemotatic factor indicting strength of the chemotactic response due to angiostatin and K_0 is also positive constant of the desensitisation of endothelial cell due to anti-angiogenic factors. When the term for the anti-angiogenic factor is added, the equation (3.12) governing the conservation of endothelial cell becomes :

$$\frac{\partial E}{\partial x} = D_E \nabla^2 E - \nabla \chi_1 \frac{K_1}{K_1 + E} E \nabla A - \nabla \rho_1 E \nabla f + \rho_2 E \left(1 - \frac{E}{E_0}\right)\left(\frac{A^* - A}{A_0}\right) - \alpha_0 \frac{K_0 \partial^2 a E}{(K_0 + a)\partial x^2} - \alpha_0 \frac{K_0}{K_0 + a} a \frac{\partial e}{\partial x} - \mu E \tag{4.4}$$

The anti-angiogenic factor concentration satisfies the following boundary conditions:

$a = a_m$, $x = L$, $a = 0$ and $x = 0$.

We note that the concentration of anti-angiogenic factor at the blood vessel varies depending on the dose applied. The dose that is added to the region during each time interval is given by: a_k for $0 \leq k \leq t$.

4.4 Numerical Solution in One Space Dimension

To solve Equation (4.4), which is a nonlinear parabolic differential equation, the implicit finite difference method of Crank-Nicolson will be used, as was applied in Chapter 3.

4.4.1 Non-dimensionalizing

Equation (4.4) is non-dimensionalized by rescaling the distance between the blood vessel and the tumour with L, time with $\tau = \frac{L^2}{D_A}$, (where D_A, is the tumour angiogenic factor diffusion coefficient), endothelial cell density with E_0, and tumour angiogenetic factors and anti-angiogenesis concentrations with A_0 and a_0, respectively where A_0 is the tumour angiogenic factor concentration at the tumour. Therefore, setting: $a^* = \frac{a}{a_0}$, $d_a = \frac{TD_a}{L^2}$, $\lambda = \frac{T\lambda_1}{L^2}$, $\varpi = \varsigma T$and $K_a = \frac{Tk_0}{L^2}$ $\iota = \frac{TK_0(0)}{L^2}$ and other variables as they were set in Chapter 3, and dropping the bars for notational simplicity, then the non-dimensionalised equation becomes:

$$\frac{\partial a}{\partial t} = d_a \frac{\partial^2 a}{\partial x^2} - \lambda a - \varpi \frac{ae}{(\iota + a)} \tag{4.5}$$

and the equation for endothelial cells concentration becomes:

$$\begin{aligned}\frac{\partial e}{\partial t} = d_e \frac{\partial^2 e}{\partial x^2} - \chi(1) \frac{K_1 \partial A^2 e}{(K_1 + e)\partial x^2} - \chi(1) \frac{K_1}{K_1 + e} \times \frac{\partial e \partial A}{\partial x^2} - \rho e \frac{\partial f^2}{\partial x^2} \\ - \rho \frac{\partial e \partial f}{\partial x^2} + \rho_0 e\,(1 - E)\,G(A) - \psi E - \alpha e \frac{\partial a^2}{\partial x^2} - \alpha \frac{\partial e \partial a}{\partial x^2}.\end{aligned} \tag{4.6}$$

4.5 Solution for the Anti-angiogenic Factor

Equation (4.5) stands for the non-dimensionalized anti-angiogenic factors equation is as follows:

$$\frac{\partial a}{\partial t} = d_a \frac{\partial^2 a}{\partial x^2} - \lambda a - \varpi \frac{ae}{(\iota + a)}. \tag{4.7}$$

We apply the Crank-Nicholson method as tabulated on Table **??** and Equation (4.3) becomes:

$$\begin{aligned}\frac{a_i^{j+1} - a_i^j}{\Delta t} = d_a \frac{a_{i-1}^{j+1} - 2a_i^{j+1} + a_{i+1}^{j+1} + a_{i-1}^j - 2a_i^j + a_{i+1}^j}{2\Delta x^2} \\ - \lambda \frac{\left(a_i^{j+1} - a_i^j\right)}{2} - \varpi \frac{\left(a_i^{j+1} - a_i^j\right) e_i^j}{2(\iota + a)},\end{aligned} \tag{4.8}$$

where $g = \frac{\Delta t d_a}{2\Delta x^2}$, $h = \frac{\Delta t \lambda}{2}$ and $m_i^j = \frac{\Delta t \varpi e_i^j}{2(\iota + a_i^j)}$. Substituting for g, h, and m we obtain:

$$\begin{aligned} a_i^{j+1} - a_i^j = g\left(a_{i-1}^{j+1} - 2a_i^{j+1} + a_{i+1}^{j+1} + a_{i-1}^j - 2a_i^j + a_{i+1}^j\right) \\ - h\left(a_i^{j+1} - a_i^j\right) - m_i^j\left(a_i^{j+1} - a_i^j\right). \end{aligned} \tag{4.9}$$

On rearranging terms, equation (4.9) then becomes:

$$-ga_{i+1}^{j+1} + (1 + 2g + h + m_i^j)a_i^{j+1} - ga_i^{j+1} = ga_{i+1}^j + (1 - 2g + h + m_i^j)a^{j_i} + ga_i^j. \tag{4.10}$$

Let $\rho_a = 1 + 2g + h + m_i^j$, $(\rho_b)_i^j = 1 - 2g + h + m_i^j$, then the above equation can be written in a tridiagonal form, that is;

$$\begin{pmatrix} \rho_a & -g & 0 & 0 & 0 & 0 & 0 & 0 \\ -g & \rho_a & -g & 0 & 0 & . & . & 0 \\ 0 & -g & \rho_a & -g & 0 & 0 & . & . \\ 0 & 0 & -g & \rho_a & -g & 0 & . & . \\ 0 & 0 & 0 & -g & \rho_a & -g & . & . \\ . & . & . & . & . & . & . & . \\ 0 & . & . & . & . & -g & \rho_a & -g \\ 0 & 0 & . & . & . & . & -g & \rho_a \end{pmatrix} \begin{pmatrix} [a_1^{j+1} \\ a_2^{j+1} \\ a_3^{j+1} \\ a_4^{j+1} \\ . \\ . \\ . \\ a_i^{j+1} \end{pmatrix} = \begin{pmatrix} (\rho_b)_i^j & -g & 0 & 0 & 0 & 0 & . & 0 \\ g & (\rho_b)_i^j & g & 0 & 0 & 0 & . & 0 \\ 0 & g & (\rho_b)_i^j & g & 0 & 0 & . & 0 \\ 0 & g & (\rho_b)_i^j & g & 0 & . & . & 0 \\ . & . & . & . & . & . & . & . \\ . & . & . & . & . & . & . & . \\ 0 & 0 & . & . & . & g & (\rho_b)_i^j & g \\ 0 & . & . & . & . & .g & (\rho_b)_i^j & \end{pmatrix} \begin{pmatrix} a_1^j \\ a_2^j \\ a_3^j \\ a_4^j \\ . \\ . \\ . \\ a_i^j \end{pmatrix} + \begin{pmatrix} 2g \times a_1^j \\ . \\ . \\ . \\ . \\ . \\ . \\ 2g \times a_{n+1}^j \end{pmatrix}.$$

4.6 Solution of the Model for Endothelial Cells Conservation during Anti-angiogenesis

From equation (4.4) the non-dimensional equation for concentration of endothelial cells is:

$$\begin{aligned} \frac{\partial e}{\partial t} = d_e \frac{\partial^2 e}{\partial x^2} - \chi(1)\frac{K_1 \partial A^2 e}{(K_1 + e)\partial x^2} - \chi(1)\frac{K_1}{K_1 + e} \times \frac{\partial e \partial A}{\partial x^2} - \rho e \frac{\partial f^2}{\partial x^2} \\ - \rho \frac{\partial e \partial f}{\partial x^2} + \rho_0 e\left(1 - E\right) G(A) - \psi E - \alpha \frac{K_0}{K_0 + a} e \frac{\partial a^2}{\partial x^2} - \alpha \frac{K_0}{K_0 + a} \frac{\partial e \partial a}{\partial x^2}. \end{aligned} \tag{4.11}$$

Applying the discretization by the Crank-Nicholson scheme to equation (4.11) we obtain:

$$\begin{aligned}
\frac{e_i^{j+1}-e_i^j}{\Delta t} &= d_e\frac{\left(e_{i-1}^{j+1}-2e_i^{j+1}+e_{i+1}^{j+1}+e_{i-1}^{j}-2e_i^{j}+e_{i+1}^{j}\right)}{2(\Delta x)^2}\\
&\quad-\chi(1)\frac{\left(K_1e_{i+1}^{j+1}-e_{i-1}^{j+1}+e_{i+1}^{j}-e_{i-1}^{j}\right)}{4\Delta x(K_1+e_i^j)}\times\frac{\{A_{i+1}^{j+1}-A_{i-1}^{j+1}+A_{i+1}^{j}-A_{i-1}^{j}\}}{4(\Delta)x}\\
&\quad-\chi(1)\frac{K_1e_i^j}{K_1+e_i^j}\times\frac{\left(A_{i-1}^{j+1}-2A_i^{j+1}+A_{i+1}^{j+1}+A_{i-1}^{j}-2A_i^{j}+A_{i+1}^{j}\right)}{2(\Delta x)^2}\\
&\quad-\rho\frac{\left(e_{i+1}^{j+1}-e_{i-1}^{j+1}+e_{i+1}^{j}-e_{i-1}^{j}\right)}{4\Delta x}\times\frac{\left(F_{i+1}^{j+1}-F_{i-1}^{j+1}+F_{i+1}^{j}-F_{i-1}^{j}\right)}{4\Delta x}\\
&\quad-\rho e_i^j\frac{\left(F_{i-1}^{j+1}-2F_i^{j+1}+F_{i+1}^{j+1}+F_{i-1}^{j}-2F_i^{j}+F_{i+1}^{j}\right)}{2(\Delta x)^2}\\
&\quad+\rho_0e_i^j\left(1-e^{j}_{i}\right)G(A)\psi\frac{\left(e_i^{j+1}-e_i^j\right)}{2}\\
&\quad-\alpha\frac{K_a}{K_a+a_i^j}\frac{e_i^j\left(a_{i+1}^{j+1}-2a_i^{j+1}-a_{i-1}^{j+1}+a_{i+1}^{j}-2a_i^{j}-a_{i-1}^{j}\right)}{2(\Delta x)^2}\\
&\quad-\alpha\frac{K_a}{K_a+a_i^j}\frac{\left(a_{i+1}^{j+1}-a_{i-1}^{j+1}+a_{i+1}^{j}-a_{i-1}^{j}\right)}{4\Delta x}\times\frac{\left(e_{i+1}^{j+1}-e_{i-1}^{j+1}+e_{i+1}^{j}-e_{i-1}^{j}\right)}{4\Delta x}.
\end{aligned}\tag{4.12}$$

If we let $Q=\frac{\Delta td_e}{2(\Delta x)^2}$

$U_i^j=\frac{\chi(1)K_1\Delta t\left(A_{i+1}^{j+1}-A_{i-1}^{j+1}+A_{i+1}^{j}-A_{i-1}^{j}\right)}{16(\Delta x)^2(K_1+e_i^j)}$

$R_i^j=\frac{\chi(1)k_1\Delta t\left(A_{i+1}^{j+1}-2A_i^{j+1}+A_{i-1}^{j+1}+A_{i+1}^{j}-2A_i^{j}-A_{i-1}^{j}\right)}{2(\Delta x)^2(k_1+e_i^j}$

$M_i^j=\frac{\rho\Delta t\left(f_{i+1}^{j+1}-f_{i-1}^{j+1}+f_{i+1}^{j}-f_{i-1}^{j}\right)}{16(\Delta x)^2}$

$N_i^j=\frac{\rho\Delta t\left(f_{i+1}^{j+1}-2f_i^{j+1}+f_{i-1}^{j+1}+f_{i+1}^{j}-2f_i^{j}-A_{i-1}^{j}\right)}{2(\Delta x)^2}$

$Z=\frac{\psi\Delta t}{2}$

$W_i^j=\rho_0\Delta t\left(1-e_i^j\right)G(A_i^j)$

$y_i^j=\Delta t\alpha\frac{K_a}{K_a+a_i^j}\frac{\{a_{i+1}^{j+1}-2a_i^{j+1}-a_{i-1}^{j+1}+a_{i+1}^{j}-2a_i^{j}-a_{i-1}^{j}\}}{2(\Delta x)^2}$

$p_i^j=\Delta t\alpha\frac{K_a}{K_a+a_i^j}\frac{\{a_{i+1}^{j+1}-a_{i-1}^{j+1}+a_{i+1}^{j}-a_{i-1}^{j}\}}{16(\Delta x)^2}$, and substitute for $Q, U_i^j,\ R_i^j,\ M_i^j,\ N_i^j,\ Z,\ W_i^j,\ y_i^j,\ p_i^j$

equation (4.12), then the equations becomes:

$$\begin{aligned} e_i^{j+1} - e_i^j = Q\{e_{i-1}^{j+1} - 2e_i^{j+1} + e_{i+1}^{j+1} + e_{i-1}^j - 2e_i^j + e_{i+1}^j\} \\ - U_i^j\{e_{i+1}^{j+1} - e_{i-1}^{j+1} + e_{i+1}^j - e_{i-1}^j\} - R_i^j e_i^j \\ - M_i^j\{e_{i+1}^{j+1} - e_{i-1}^{j+1} + e_{i+1}^j - e_{i-1}^j\} - N_i^j e_i^j + W_i^j e_i^j - Z\{e_i^{j+1} - e_i^j\} \\ - y_i^j e_i^j - p_i^j\{(e_{i+1}^{j+1} - e_{i-1}^{j+1} + e_{i+1}^j - e_{i-1}^j\}). \end{aligned} \tag{4.13}$$

Rearranging terms equation (4.13) then becomes:

$$\begin{aligned} (-Q + U_i^j + M_i^j + p_i^j)e_{i+1}^{j+1} + (1 + 2Q + Z)e_i^{j+1} + (-Q - U_i^j - M_i^j - p_i^j)e_{i-1}^{j+1} \\ = (Q - U_i^j - M_i^j - p_i^j)e_{i+1}^j + (1 - 2Q - R_i^j - N_i^j + W_i^j + Z_i^j - y_i^j)e_i^j \\ + (Q + U_i^j + M_i^j + p_i^j)e_{i-1}^j. \end{aligned} \tag{4.14}$$

Let $\rho_c = 1 + 2Q + Z$, $(\rho_d)_i^j = -Q + U_i^j + M_i^j + p_i^j$, $(\rho_e)_i^j = -Q - U_i^j - M_i^j - p_i^j$, $(\rho_f)_i^j = 1 - 2Q - R_i^j - N_i^j + W_i^j + Z_i^j - y_i^j$, $(\rho_g)_i^j = Q - U_i^j - M_i^j - p_i^j$, $(\rho_h)_i^j = Q + U_i^j + M_i^j + p_i^j$
The above equation can be written in a tridiagonal matrix form to become:

$$\begin{pmatrix} \rho_c & (\rho_d)_i^j & 0 & 0 & 0 \\ (\rho_e)_i^j & \rho_c & (\rho_d)_i^j & . & 0 \\ 0 & (\rho_e)_i^j & \rho_c & (\rho_d)_i^j & 0 \\ . & . & . & . & . \\ . & (\rho_e)_i^j & \rho_c & (\rho_d)_i^j & 0 \\ . & . & (\rho_e)_i^j & \rho_c & (\rho_d)_i^j \\ 0 & . & . & (\rho_e)_i^j & \rho_c \end{pmatrix} \begin{pmatrix} e_1^{j+1} \\ e_2^{j+1} \\ e_3^{j+1} \\ e_4^{j+1} \\ . \\ . \\ e_i^{j+1} \end{pmatrix} = \begin{pmatrix} (\rho_f)_i^j & (\rho_g)_i^j & 0 & . & 0 \\ (\rho_h)_i^j & (\rho_f)_i^j & (\rho_g)_i^j & . & 0 \\ 0 & (\rho_h)_i^j & (\rho_f)_i^j & (\rho_g)_i^j & 0 \\ . & . & . & . & . \\ . & . & . & . & . \\ . & . & (\rho_h)_i^j & (\rho_f)_i^j & (\rho_g)_i^j \\ 0 & . & . & (\rho_h)_i^j & (\rho_f)_i^j \end{pmatrix} \begin{pmatrix} e_1^j \\ e_2^1 \\ e_3^j \\ e_4^j \\ . \\ . \\ e_i^j \end{pmatrix} + \begin{pmatrix} 2Q \times e_1^j \\ 0 \\ 0 \\ 0 \\ . \\ 0 \\ 2Q \times e_{n+1}^j \end{pmatrix}.$$

4.7 Model Solution for Anti-angiogenesis

In this section we show results for the concentration of the endothelial cells when the anti-angiogenic factor is added to the equation, to model would happen with treatment. Results are obtained from a simulation.

The process of angiogenesis is assumed to take 10 days. Results are shown for endothelial cells concentration as anti-angiogenic factors is added to the equation for endothelial cells during angiogenesis.

4.7.1 Results Illustrating the Concentration of Tumour Angiogenic Factor during Anti-angiogenesis

In the simulation, the anti-angiogenic factor is added 3 days after when the process of angiogenesis started, which had been taken at $t = 0$. Results are then generated for $t = 3, 5, 7$ and 10 days after angiogenesis. These values were chosen randomly. Parametric values for the model governing the tumour angiogenic factor are the same as those used in Chapter 3. The results are shown in

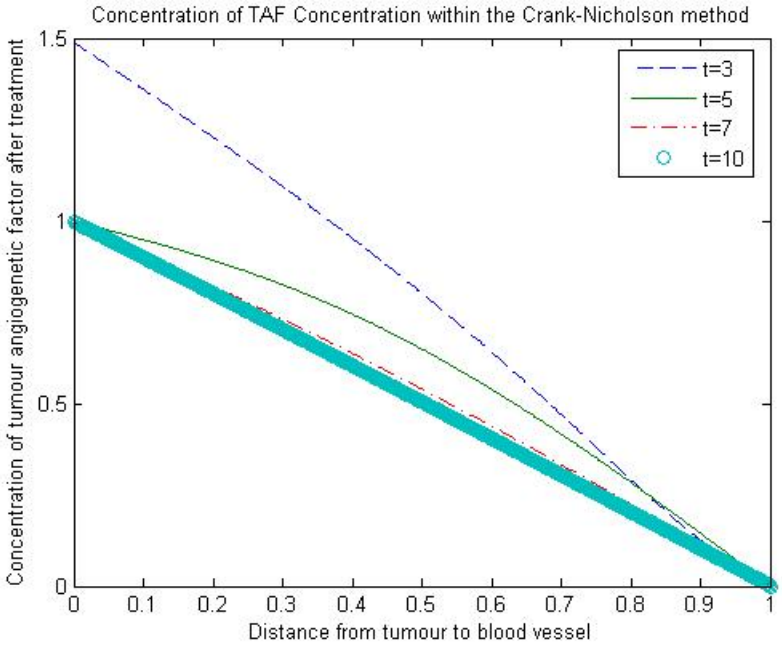

Figure 4.1: Plot of the Concentration of Tumour Angiogenic Factor After Application of Anti-angiogenic Factor

The graph in Figure 4.1 shows that after the addition of anti-angiogenic factors although the concentration of the tumour angiogenic factor decreases,it remains above zero. This means that the tumour angiogenic factor is available for degrading the basement membrane of the blood vessel so as to allow the migration of endothelial cells as was discussed in Chapter 3.

4.7.2 Results Showing the Concentration of Fibronectin during Anti-angiogenesis

Parametric values for fibronectin are the same as those used in Chapter 3. The results of the simulation are shown in Figure 4.2. Results indicate that as time increases the fibronectin

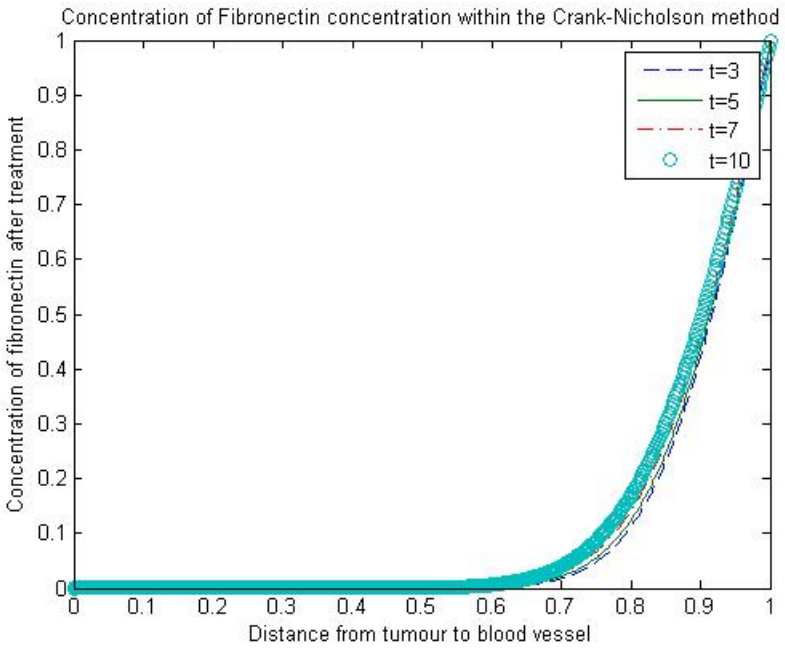

Figure 4.2: Plot of Fibronectin Concentration After Application of Anti-angiogenic Factor

concentration increases by a a small amount over its value during initial stages of no treatment. Fibronectin is therefore still being produced in the region. Because endothelial cells are the source of fibronectin, this therefore indicates that they are still present in the arbitrary region.

The concentration of fibronectin was calculated using trapezodial rule. Near the start of the treatment, 3 days after angiogenesis process had begun it was 70.06 units and after 10 days, it had increased to 86.97 units. Thus, 10 days after angiogenesis had began, the concentration of fibronectin was much less than 151.1 units, which is the value for

fibronectin after the same period without treatment. This shows that the treatment does not completely stop the growth of endothelial cells, because they are the source of fibronectin. However, the concentration of fibronectin is much reduced, which suggests that endothelial cell concentration is also reduced.

4.7.3 Results for the Concentration of Anti-Angiogenic Factor

In this section we show initial conditions, boundary conditions and parametric values of tumour angiogenetic factors , which are then used to provide results by simulation.

Initial and Boundary Conditions for Anti-angiogenic Factor

The initial, boundary conditions and parameters that are used in this paper are as follows: The initial condition for the anti-angiogenetic factor, $a(x,0)$ is 1 through out. The boundary conditions is set as follows: $a(0,t) = 1$ and $a(L,t) = 1$ for $0 \leq x \leq L$; $0 \leq t <\leq k$. The initial condition for the anti-angiogenetic factor in linear form is represented by the equation, $a(x,0) = 1 - x^2$ and its boundary conditions is $a(0,t) = 1$ and $a(L,t) = 1$ with zero flux boundary conditions. The boundary conditions $a(0,j) = 1$ and $a(n,j) = 1$ for $j = 0 \cdots k$, where k is the maximum time interval.

Parametric Values for the Anti-Angiogenic Factor

For non dimensional angiostatin chemotactic co-efficient Anderson et al. [17] used the value of 0.38 and they kept the anti-angiogenetic factor diffusion coefficient similar to the diffusion coefficient for the tumour angiogenetic factor. In this paper parametric values for the following terms were: The non-dimensional parametric values used in this dissertation for the remaining terms are given in Table 4.1.

Table 4.1: Parametric Values for Anti-Angiogenic Factor

anti-angigenetic factor diffusion coefficient	d_a	1.79×10^{-4}
anti-angigenetic factor decay rate	λ_1	$5.0 \times^1 0{-}2$
uptake rate of anti-angigenetic factor	$r(0)$	1.0×10^{-3}
Maximum constant rate of anti-angigenetic factor	q	3.0×10^{-1}
Michaelis Mentis Kinetic Constant	ϖ	3.08×10^{-1}

Results Attained for Anti-Angiogenic Factor

The simulation to show the effect of changing level on the concentration of the anti-angiogenic factor when the value K changes, are given in Figure 4.3. The figure shows

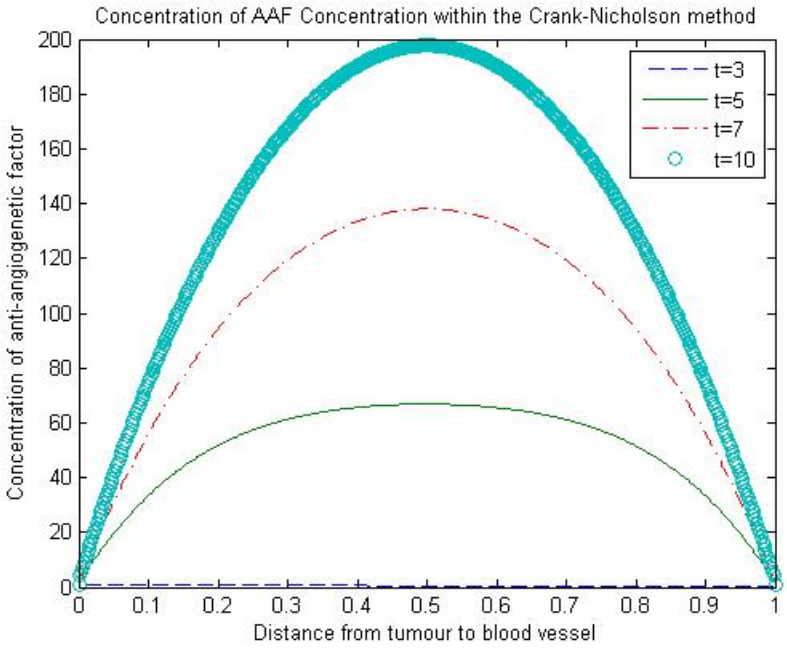

Figure 4.3: Plot of Anti-angiogenic Factor Concentration

that the concentration of anti-angiogenic factor increases as time progresses, as is shown for the increasing values of k.

4.7.4 Results Illustrating The Concentration of Endothelial Cells During Anti-angiogenesis

That density of endothelial cells when the treatment is added after 3 days are displayed in Figure 4.4, and is taken as the initial condition for anti-angiogenesis process.

The effect of anti-angiogenic factor is investigated by observing endothelial cells behaviour as initiated at two different stages of angiogenesis.

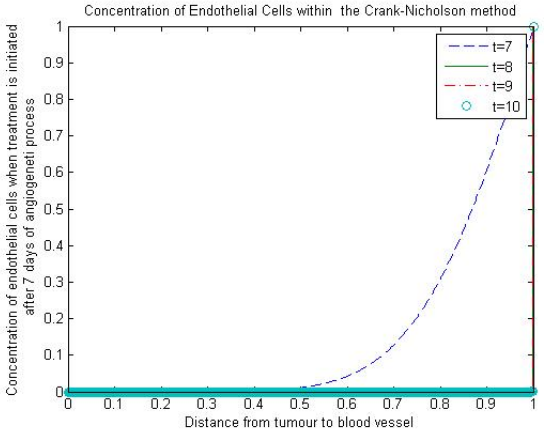

Figure 4.4: Plot of Endothelial Cell Concentration After Application of Anti-angiogenic Factor After 5 Days of Angiogenesis

Treatment is also applied after 7 days, results are displayed in Figure 4.5.

The presence of fibronectin, as shown in Figure 4.2, means that endothelial cells has escape from the basal membrane. Results in both Figure 4.4 and Figure 4.4 indicate that the treatment start working immediately when the treatment is added. Endothelial cells present in a region before the treatment also disappear after the treatment.

The trapezoidal rule from Matlab is also used to determine the concentration of endothelial cells in the bounded region. From calculations using trapezoidal method it shows that the area below the curve for both graphs during the same interval are the same. At the beginning of the dose the endothelial cell concentration is 72.1 units and it later dropped to

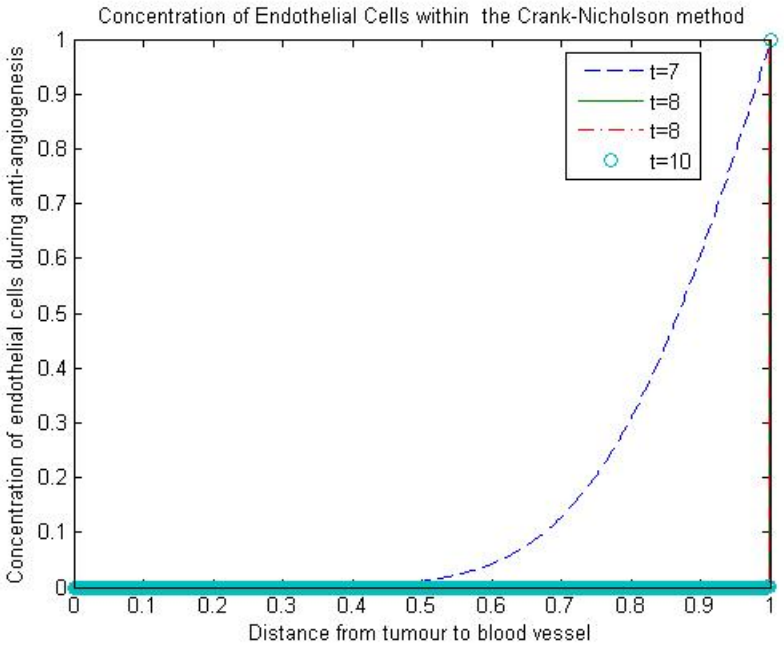

Figure 4.5: Plot of Endothelial Cells Concentration on Application of Anti-angiogenic Factor 7 days After Angiogenesis Started

5 units after 10 days. But without a treatment the concentration level of endothelial cells after 10 days is $162,87$ units. Results indicates that the concentration of endothelial cells after administering the treatment becomes very low. This leads to the conclusion that the treatment destroys endothelial cells appearing in the region .

From these observations we can therefore conclude that according to our new model, which included anti-angiogenesis as a treatment, the treatment is effective in inhibiting and destroying endothelial cells from reaching the tumour. Inhibiting angiogenesis could be a most effective way of preventing tumours progressing to the malignant stage.

4.8 Summary

Models governing the conservation of the anti-angiogenesis are developed. A discrete method for solving them, the Crank Nicholson's method is applied and the matrices so acquired are used in simulation by Matlab. Results obtained indicate that when anti-angiogenic term is added to the equation for endothelial cell concentration, endothelial cells are destroyed. This has a huge implications for cancer treatment.

The next chapter will present the summary of work done, conclusion and prospect for further work.

Chapter 5

Conclusion

The process of tumour development is very complex. The change in a tumour from avascular to vascular is called angiogenesis. During this process the tumour acquires its own blood vessels, by which it then obtains nutrients, so it will no longer depends on diffusion through the surrounding tissues for its survival.

There are three main processes in angiogenesis. It starts by tumour cells secreting tumour angiogenic factors, which migrate towards the basal membrane lining the nearby blood vessel. The tumour angiogenic factors then degrade the basal membrane and endothelial cells from the nearby blood vessel start to escape and follow the chemical gradient of the tumour angiogenic factor back to the tumour. Endothelial cells also secrete a fibronectin, which assists in their adhering together. The movement of endothelial cells is thus governed by diffusion, chemotaxis and haptotaxis.

Mathematical models for the process of angiogenesis are complicated and involve a number of processes. The equation governing tumour angiogenic factor concentration indicates that its conservation is governed by diffusion, uptake of chemical by endothelial cells, and loss of chemical due to decay. Similarly, the model governing the conservation of fibronectin is based on secretion of fibronectin by endothelial cells, diffusion, uptake of

the chemical by endothelial cells, and loss of chemical due to decay. The third model for the conservation of endothelial cells indicates that their conservation is based on diffusion, chemotaxis, haptotaxis, logistic growth of the cells and loss due to decay.

All non linear second order partial differential equations obtained here were solved using the Crank-Nicolson Method. All the numerical solutions presented here were produced from a finite difference approximation of the system with boundary, initial and zero flux boundary conditions imposed.

During angiogenesis results showed that as time progresses the concentration of tumour angiogenetic factor decreased from the boundaries of the tumour. At the same time endothelial cells migrated towards the tumour.

Then anti-angiogenic factor was introduced to the region. Initial, boundary and zero flux boundary conditions were imposed and simulations were applied, after discretisizing the models, using Matlab.

Results for anti-angiogenesis process showed that endothelial cells responded chemotactically to two opposing gradients, that is, the gradients of the anti-angiogenic chemical and also the tumour angiogenic factor. The consequent cell motion is governed by the relative strength of each. Results indicated that the anti-angiogenic factor does hinder the growth of endothelial cells, and also destroy endothelial cells appearing in the region.

Findings also indicated that anti-angiogenic factor is the effective treatment for inhibiting and destroying endothelial cells from reaching the tumour. Inhibiting angiogenesis could be one of the most effective way of preventing tumours progressing to the malignant stage.

Our numerical simulations yielded results, that are in agreement with the experimental observations obtained by Anderson et al. [17], who concluded that anti-angiogenic factors

hinders tumour growth. Results obtained here are in line with the three types of anti-angiogenesis given by Orme and Chaplain [12] in Chapter 1. Our results indicate the effectiveness of anti-angiogenesis as a treatment to prevent vascularization of non-cancerous tumours. Anderson et al. [17] showed that removal of a primary tumour promoted the change of secondary tumours (possibly still benign) into malignant tumours. By administering anti-angiogenic drugs, one could prevent this from happening.

What was challenging in this dissertation was the skill of choosing appropriate parametric values and appropriate scales. Some Parametric values used were chosen from published data and others were randomly selected.

Our findings could be particularized to investigate treating different types of tumour, especially those in breast cancer. In this regard, Enderlinga et al. [49] pointed out that, currently the only treatment for it is surgical operations removal which is then followed by radiotherapy.

Furthermore, investigations are needed concerning the best time to administer the treatment, and to find out what happens to the endothelial cell proliferation if a patient discontinues, or is inconsistent with the treatment. It will also be interesting to investigate the effectiveness of the treatment in a fully vascularised tumour.

Appendix 1- Glossary

The definitions below relate to the way the terms are used in this dissertation. Page number refer to the page of text where the definition may be found.

- ***anastomoses*** (page 4) A connection that is created between tubular structures, such as blood vessels or loops of intestine
- ***angiogenesis***pages (i & 3) A process of tumour development from avascular to vascular stage
- ***angiostatin*** (page 7) An anti-angiogenic factor that blocks the growth of new blood vessels
- ***anti-angiogenesis*** (page 6)-The process that hinders the growth of endothelial
- ***anti-angiogenic factor*** (12) A chemical that hinders the growth of endothelial cells
- ***avascular*** (page 2) A stage in cancer growth where in a tumour has not developed blood or lymphatic vessels.
- ***benign tumour*** (page 2) A non-cancerous tumour
- ***endothelial cells*** (page 3) Cells lining the interior surface of blood vessels and lymphatic vessels
- ***capillary sprout*** (page 4) A branching structure of at least three endothelial cells connected to each other in a linear manner
- ***chemotaxis*** (page 3) The movement of endothelial cells following a chemical gradient
- ***fibronectin*** (page 4) A glycoprotein of the extracellular matrix that binds extracellular matrix components together
- ***haptotaxis*** (page 4) Cell migration along a gradient of extra cellular matrix while bound by chemo-attractants
- ***malignant tumour*** (page 2) A cancerous tumour
- ***metastasis*** (page 2) The process of development of secondary malignant growths at a distance from a primary site of cancer
- ***tumour angiogenic factor*** (page 4) A chemicals that are secreted by tumour which promote tumour angiogenesis
- ***pre-malignant*** (page 2) A precancerous condition
- ***vascular*** (page 2) A stage in cancer growth where in a tumour has developed its own blood vessels.
- ***proliferation*** (3)- Reproducing or replicating of cells

Appendix 2- List of keywords

Table 5.1: Parametric Values for Anti-Angiogenic Factor

AAF	Anti-Angiogenetic Factor.
BV	Blood Vessel.
DDM	Dose Dependent Method.
EC	Endothelial Cell.
ECM	Extra cellullar Matrix.
PT	Primary Tumour.
TAF	Tumour Angiogenetic Factor.
VEGF	Vascular Endothelial Growth Factor.

Appendix 3- List of parameters

Table 5.2: Parametric Values For Tumour Angiogenic Factor

Parameters	Description	values
D_A	Tumour-angiogenic diffusion constant	2.5×10^{-4}
A_0	TAF maximum value.	1.0
Q	TAF maximum reaction rate.	0.33×10^{-2}
d	TAF decay rate.	9.0×10^{-7}

Table 5.3: Parametric Values for Fibronectin

Parameters	Description	values
D_f	Fibronectin diffusion constant	1.733×10^{-6}
f_0	Fibronectin maximum value.	1.0
α_f	Fibronection secretion rate.	6.667×10^{-6}
s_f	Fibronectin uptake rate	1.3×10^{-4}
ρ_1	Haptotatic coefficient	1.6×10^{-6}
λ_f	Fibronectin decay rate	9.0×10^{-7}

Table 5.4: Parametric Values for Endothelial Cells

Parameters	Description	values
D_E	Endothelial cell diffusion constant.	9.333×10^{-5}
χ_0	Chemotaxis coefficient.	1.3×10^{-6}
E_0	Endothelial cell maximum value.	1
ρ_2	mitotic rate.	3.667×10^{-9}
μ	Endothelial cell decay rate.	3.133×10^{-8}
K_1	chemotatic positive constant.	1.0
k_m	Michaelis Menten Kinetic law constant .	1.0

Table 5.5: Parametric Values for Anti-Angiogenic Factor

Parameters for Anti-Angiogenesis	Description	values
D_a	Anti-angiogenic diffusion constant.	1.76×10^{-4}
λ_1	AAF decay rate.	1.67×10^{-3}
ς	AAF chemotatic reaction rate.	0.27×10^{-5}
K_0	AAF chemotatic positive constant.	1.0

References

[1] World Cancer Report. (2014). Global battle against cancer won′t be won with treatment alone. Epidemiology/Etiology/Cancer Prevention.*European Society for Medical Oncology*. Available from http://www.esmo.org/Oncology-News/World-Cancer-Report-2014. Downloaded 25 August 2016.

[2] J.P. Ward and J.R. King. (1997). Mathematical modelling of avascular-tumour growth. *IMA Journal of Mathematics Applied in Medicine Biology* . **14**, 39–69.

[3] B.W. Steward and P. Kleihuis (eds). (2003). *World Cancer Report*. IARC Press. Lyon.

[4] S. Sanga, J.P. Sinek, H. B. Frieboes, M. Ferrari, J.P. Fruehauf and V. Cristini. (2006). Mathematical modeling of cancer progression and response to chemotherapy. *Expert Rev. Anticancer*. **6**, (10), 1361—1376.

[5] P.E. Peterson. (2009). Oral cancer prevention and control. The approach of the World Health Organization. *Oral Oncology* . **45**, (4–5), 454–460.

[6] L. Fallowfield and V. Jenkins. (1999). Effective communication skills are the key to good cancer care. *European Journal of Cancer*. **35**, (11), 1592–1597.

[7] A. Molassiotis, P. Fernadez-Ortega, D. Pud, G. Ozden, J.A. Scott, V. Panteli, A. Margulies, M. Browall, M. Magri, S. Selvekerova, E. Madsen, L. Milovics, I. Bruyns, G.

Gudmundsdottir, S. Hummerston, A.M.A. Ahmad, N. Platin, N. Kearney and E. Patiraki. (2005). Use of complementary and alternative medicine in cancer patients: A European survey. *Annals of Oncology*, **16**, (4), 655–663.

[8] L.S. Karliner, E.A. Jacobs, A.H. Chen and S. Mutha. (2006). Do Professional Interpreters Improve Clinical Care for Patients with Limited English Proficiency? A Systematic Review of the Literature. *Health Services Research*. **42**, (2), 727–754.

[9] CancerQuest. (2015). *Stages of Cancer Development*. Available from http://www.stagesofcancerquest.org/stages--tumor--progression.html?. Downloaded 25 November 2015.

[10] East west cancer center. *Wheel Balance Cancer Therapy, Antiangiogenesis and metastasis therapy*. Available fromhttp://www.ewcc.or.kr/en/s03/s03_03.htm?g1=s03&dte=s03_03. Downloaded 25 November 2015.

[11] A.R.A. Anderson, and M.A.J. Chaplain. (1998). Continuous and Discreet Mathematical Models of Tumour-induced Angiogenesis. *Bulletin of Mathematical Biology*,**60**, (5), 857–900.

[12] M.E. Orme and M.A.J. Chaplain. (1997). Two-dimensional models of tumour angjogenesis and anti-angiogenesis strategies. *IMA Journal of Mathematics Applied in Medicine Biology*. **14**, (3), 189–205.

[13] J. Folkman. (1972). Anti-angiogenesis: New Concept for Therapy of Solid Tumors. *Annals of Surgery*. **175**, (3), 409–416.

[14] M.A.J. Chaplain. (2000). Mathematical Modelling of Angiogenesis . *Journal of Neuro-Oncology*. **50**, (1), 37–51.

[15] A. Stephanou, S.R. McDougall, A.R.A. Anderson, M.A.J. Chaplain. (2005). Mathematical modelling of flow in 2D and 3D vascular networks: Applications to anti-angiogenic and chemotherapeutic drug strategies. *Mathematical and Computer Modelling*. **41**, (10), 1137–1156.

[16] N. Makrilia, T. Lappa, V. Xyla, I. Nikolaidis and K. Syrigos. (2009). The Role of Angiogenesis in Solid Tumours: An overview. *European Journal of Internal Medicine*. **20**, (7), 663–671.

[17] A.R.A. Anderson, M.A.J. Chaplain, C. Garcia-Reimbert and C.A. Vargas (2000). Gradient Driven Mathematical Model of Anti–Angiogenesis. *Mathematical and Computer Modelling*. **32**, (10), 1141–1152.

[18] T. Alarcon, H. Byme , P. Maini and J. Panovska. (2005). 20 Mathematical Modelling of Angiogenesis and Vascular Adaptation. In R Paton and L McNamara (Eds). *Multidisciplinary Approaches to Theory in Medicine*. Elsevier. Amsterdam. **3**, 369–387

[19] A. Anderson. (2005). A hybrid mathematical model of solid tumour invasion: the importance of cell adhesion. *Mathematical Medicine and Biology*. **22**, (2) 163–189.

[20] U. Ledzewicz, and H. Schattler. (2006). Analysis of a Mathematical Model for Tumor Anti-Angiogenesis. *Optimal Control, Applications and Methods*. **29**, (1), 41–57.

[21] P. Collins. (2009). *Combination of Chemotherapy and Antiangiogenic Therapies:A Mathematical Modelling Approach*. Unpublished thesis, University of Waterloo. Onatarion. Canada. Available from http://www.maths.dundee.ac.uk/ chaplain/publications.shtml. Downloaded 25 April 2016.

[22] National Health Institute. *Metastatic Cancer*. Available from http://www.cancer.gov/types/metastatic-cancer. Downloaded 25 November 2015.

[23] F. Billy, B. Ribba, O. Saut, H. Morre-Trouilhet, T. Colin, D. Bresch, J.P. Boissel, E. Grenier, J.P. Flandrois. (2009). A Pharmacological Multiscale Mathematical Model of Angiogenesis and its use Cancer Treatment Strategy. *Journal of Theorectical Biology*. **260**, (4), 545–562.

[24] Your Guide to Cancer Care. (nd). Available from https://www.cancercompass.com/cancer-guide/conventional-treatment/chemotherapy.html. Downloaded 01 April 2016.

[25] U. Ledzewicz, and H. Schattler. (2008). Optimal and suboptimal protocols for a class of mathematical models of tumor anti-angiogenesis. *Journal of Theorectical Biology*. **252**, (2), 295–312.

[26] S. Rafii, D. Lyden, R. Benezra1, K. Hattori and B Heissig. (2002) Vascular and haematopoietic stem cells: Novel targets for anti-angiogenesis therapy? *Nature Review Cancer*. **2**, 826–835.

[27] S. Motsa, Z. G Makukula and S.S Shateyi. (2013). Spectral Local Linearisation Approach for Natural Convection Boundary Layer Flow. *Mathematical Problems in Engineering*. **2013**.

[28] M.N. Ozisik. (1994). *Finite Difference methods in Heat Transfer*. CRC Press. Boca Raton FL.

[29] M.J. Holmes and B.D. Sleeman.(1999). *A Mathematical Model of Tumour Angiogenesis Incorporating Cellular Traction and Viscoelastic Effects*. Available from http://www.sciencedirect.com/science/article/pii/S002251939991038X. Downloaded from 25 April 2016

[30] J.M.O. Eloundou.(2011). *Mathematical Modelling of the Stages of the Tumour Growth and Non Local Interactions in Cancer Invasion*. Available from http://scholar.sun.ac.za/handle/10019.1/18056. Downloaded from 25 April 2014.

[31] F. Michor., M. A. Nowaka and Y. Iwasa. (2006). Stochastic dynamics of metastasis formation. *Journal of Theoretical Biology*. **240**. (4). 521–530.

[32] M. Chaplain, M. Lachowicz, Z. Szymanzka, D. Wrzosek. (2011). Mathematical Modelling of Cancer Invasion: The Importance of Cell-Cell Adhesion and Cell-Matrix Adhesion. *Mathematical Models and Methods in Applied Sciences*. **21**. (4). 719.

[33] A. Anderson, M. Chaplain, E. Newman, R. Steele and A. Thomson. (2000). Mathematical Modelling of Tumour Invasion and Metastasis. *Journal of Theoretical Medicine*. **2**, (2), 129–151.

[34] S. Motsa. (2013). A New Spectral Local Linearization Method for Nonlinear Boundary Layer Flow Problems. *Journal of Applied Mathematics*. **2013**.

[35] D.M. Causon and C.G. Mingham. (2010). *Introductory Finite Difference Methods for PDEs*. Ventus Publising ApS. London.

[36] G.W. Recktenwald. (2011). *Finite differences approximation to the Heat Equation*. Available fromhttp://depa.fquim.unam.mx/amyd/archivero/DiferenciasFinitas4_25730.pdf. Downloaded 01 November 2015.

[37] G. Smith. (1985). *Numerical Solution of Partial Differential Equations Finite Difference Methods*. 3^{rd} Edition. Oxford Applied and Computing Science Series. Clarendon Press. Oxford.

[38] J.C. Strikwerda. (1989). *Finite Difference Scheme and Partial Differential Equations*. 2^{nd} Edition. University of Winconsin-Madison. Madison. Winconsin.

[39] S.E. Fadugba, O.H. Edogbanya, and S.C Zelib. (2013). Crank Nicolson Method for Solving Parabolic Partial Differential Equations. *International Journal of Applied Mathematics and Modeling IJA2M*. **1** , (3), 8–23.

[40] *Unconditional Stability of Crank - Nicholson Method*. (nd). Available from http://www.science.unitn.it/AnalisiInfoTLC/NumMethFin/CN.pdf. Downloaded 11 November 2015.

[41] A. Kharab and R. Guenther.(2006). *An Introduction to Numerical Methods. A Matlab Approach*. 2^{nd} Edition. CRC Press. Boca Raton FL.

[42] A. Quarteroni, R. Sacco and F. Saleri. (2007). *Texts in Applied Mathematics. Numerical Mathematics*. 2^{nd} Edition. Springer. New York.

[43] A.J. Washington. (2009). *Basic Technical Mathematics with Calculus*. 9^{th} Edition. Pearson. London.

[44] S.T. Tan. (2008). *College Mathematics for the Managerial, Life and Social Sciences*. 7^{th} edition. Brooks/Cole. Asia

[45] N.V. Mantzaris , S. Webb and S.G. Othmer. (2004). Mathematical Modelling of Tumour induced Angiogenesis. *Mathematical Biology*. **49**, (2), 111–187.

[46] S.R. McDougall, A.R.A. Anderson, M.A.J. Chaplain and J.A. Sherratti. (2002). Mathematical Modelling of Flow Through Vascular Networks: Implications for Tumour - Induced Angiogenesis and Chemotherapy Strategies. *Bulletin of Mathematical Biology*. **64**, (4) 673–702.

[47] L. Edelstein-Keshet. (1988). *Mathematical Models in Biology*. Random House. New York.

[48] A. Bergara. (nd). *Finite difference Numerical Methods of Partial Differential Equations in Finance Using Matlab*. Available from http://www.ehu.eus/aitor/irakas/fin/apuntes/pde.pdf. Downloaded 11 November 2015.

[49] H. Enderlinga, A.R.A. Anderson, M.A.J. Chaplain,A.J. Munr and J.S. Vaidya. (2006) Mathematical modelling of radiotherapy strategies for early breast cancer. *Journal of Theorectical Biology*. **241**, (4), 158–171.