ADAMA SCIENCE AND TECHNOLOGY UNIVERSITY

SCHOOL OF APPLIED NATURAL SCIENCES

APPLIED MATHEMATICS PROGRAM

THESIS ON

MATHEMATICAL MODELING OF TUMOR INVASION AND TREATMENT

BY: ZELEKE HAILU KETEMA

ADVISOR: SHIFERAW FEYISSA (PH.D)

JANUARY, 2018

ADAMA- ETHIOPIA

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A THESIS SUBMITTED TO THE SCHOOL OF APPLIED NATURAL SCIENCES OF ADAMA SCIENCE AND TECHNOLOGY UNIVERSITY IN PARIAL FULFILLMENT OF THE REQUIREMENTS FOR MASTER OF SCIENCE DEGREE IN MATHEMATICS (M.SC.)

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Certification

I, Zeleke Hailu Ketema, declare that this thesis, submitted in partial fulfillment of the requirements for the award of Masters of Science degree in Mathematics in the school of applied Natural sciences, University of Adama Science and Technology, is wholly my own work unless and otherwise referenced or acknowledged. The document has not been submitted for qualifications at any other academic institutions.

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Abstract

Using mathematical models to simulate dynamic biological processes has a long history. Over the past couple of decades or so, many approaches have also made their way into cancer research. An increasing number of mathematical, physical, computational and engineering techniques have been applied to various aspects of tumor growth, with the ultimate goal of understanding the response of the cancer population to clinical intervention. Herein I present mathematical model which describe the invasion of host tissue by tumor cells and treatment. In the models, I focus on three key variables implicated in the invasion process and treatment; namely, tumor cells denoted by c, host tissue or extracellular matrix denoted by v and urokinase plasminogen activator (uPA) protease secreted by tumor cells and denoted by u. This model focuses on the macro-scale structure (cell population level) and considers the tumor as a single mass. The mathematical model consists of a system of partial differential equations describing the production and/or activation of degradative enzymes by the tumor cells, the degradation of the matrix and the migratory response of the tumor cells. I describe the stability of the equilibrium points which are locally and globally stable. As rate of proliferation tumor cell increases the rate of production of uPA also increases. After treatment this rate decreases and the tumor is in quiescent state. This is shown by mathematical simulation at the last.

Keywords*:* Tumor cells, invasion, metastasis. Extracellular matrix, urokinase plasminogen Activator

CHAPTER ONE

INTRODUCTION

1.1. Background of the study

1.1.1. What is Cancer/tumor?

Cancer is the result of loss of coordination among different cell processes, such as cell-cell communication, cell proliferation, cell differentiation and cell migration. In many cases, the same cell-cell communication pathways control multiple processes involved in cancer progression (Andreas D. et al 2014).

The cell is the basic building block of all living things. All cells normally grow and divide (multiply) to replace old cells to keep the body healthy. A cell becomes cancerous when it grows quickly and uncontrollably. In most cancers, this process leads to the growth of tumors. A tumor is an abnormal growth of tissue resulting from uncontrolled cell growth. Tumors are either benign or malignant. Benign tumor is not cancer. Cells from benign tumor do not spread to other parts of the body. Benign tumor is not usually life threatening. Malignant tumor is cancer. Cancer cells can spread to other tissues and organs near the tumor (angiogenesis). They can also spread to other sites in the body through the bloodstream or lymphatic system. This spreading is called metastasis (M.A.J Chaplain and G. Lolas 2006).

1.1.2. What Causes Cancer?

Current knowledge of the mechanisms of cancer suggests that all cancers are both environmental and genetic, meaning that there are multiple causes that involve exposures originating outside the body as well as hereditary or genetic changes that converge to produce the disease. Persons with particular genetic predispositions may be more susceptible to the effects of environmental exposures than others. The major environmental causes of cancer are tobacco and diet; which account for almost two thirds of all cancer deaths and are among the most correctable (Richard C.et al 2005).

Some factors that increase the risk of developing cancer include behaviors such as smoking, heavy alcohol consumption, on the job exposure to chemicals, radiation and sun exposure, and

some viruses and bacteria. Substances known to cause cancer are called carcinogens. Coming into contact with a carcinogen does not mean you will get cancer. It depends on what you were exposed to, how often you were exposed, and how much you were exposed to, among other things.

Table 1. *Cancers Associated with Various Occupations or Occupational Exposure*

Types of Cancer	**Substances or processes which cause cancer**
Lung	Arsenic, asbestos, cadmium, coke oven fumes, chromium compounds, coal gasification, nickel refining, foundry substances, radon, soot, tars, oils, silica
Bladder	Aluminum production, rubber industry, leather industry, 4-aminobiphenyl, benzidine
Nasal cavity and sinuses	Formaldehyde, isopropyl alcohol manufacture, mustard gas, nickel refining, leather dust, wood dust
Larynx	Asbestos, isopropyl alcohol, mustard gas
Pharynx	Formaldehyde, mustard gas
Mesothelioma	Asbestos
Lymphatic and hematopoietic	Benzene, ethylene oxide, herbicides, x-radiation system
Skin	Arsenic, coal tars, mineral oils, sunlight
Soft-tissue sarcoma	Chlorophenols, chlorophenoxyl herbicides
Liver	Arsenic, vinyl chloride
Lip	Sunlight

Agency for Toxic Substances and Disease Registry (ATSDR),2009.

1.1.3. Cell Proliferation

Each cell's proliferation subsystem decides whether cell will proliferate or not (**A.** R. A. A. et al 2000). Both quiescence and proliferate cells could be tested for proliferation. If cell's state is quiescence cell's age and free space around cell is tested, and all these parameters are satisfied then the cell state is changed to proliferative. Even cell's state is proliferative; the cell is still a

candidate for proliferation. It is assumed that the maximum proliferation rate, will take place at optimal conditions. When cell's microenvironment conditions become closer to optimal conditions proliferation probability increases otherwise probability decreases. Parameters used for proliferation decision are oxygen concentration, glucose concentration and PH. Genetic effects are also used in probability function. After a cell decides for proliferation, next question is about finding most convenient place around cell.

1.1.4. Tumor Invasion/spread

After a cell decides for proliferation, next question is about finding most convenient place around cell. Invasion system answers this question based on micro environment conditions. In order to invade normal tissue tumor cells must lose their connection to each other, and invade and integrate into the surrounding normal structures. Normal tissue is designed to resist such breaches, making invasion an active process on the part of the cancer cell. Tumor angiogenesis requires active remodeling and integration of new cells into existing structures (Hanchen L. et al 2007). Invasion system uses oxygen, glucose and H^+ concentration as input parameters. When scanning neighbor cells with traditional methods for invasion, a strange effect is occurred small blood vessels provide oxygen and nutrients to tumor cells. The walls of these blood capillaries are not obstacles for a cancer cell. With the help of collagen digesting enzymes, a cancer cell can "eat" its way into the lumen of the small blood vessel and into the blood stream. The blood can then carry away cancer cells, by which they can spread and invade other organs **(**Matthias Rath and M.D 2001).

Tumors grow like a tree with branches. Tumor cell invasion is an essential hallmark in the progression of malignant cancer. Thereby, cancer cells migrate through the surrounding tissue (normal cells, extracellular matrix, and interstitial fluid) towards blood or lymph vessels which they penetrate and thus access the blood flow (M.A.J Chaplain and G. Lolas 2006). They are carried by blood circulation to distant locations where they settle and develop new tumors, a phenomenon known as metastasis. The invasive spread of cancer cells is highly complex, it involves several mechanisms, like diffusion, chemo taxis and hapto taxis; these in turn are conditioned by and influence the sub cellular dynamics (Andreas Deutsch et al. 2014)

Metastasis is the mechanism in which primary tumor colonies disseminate cancer cells to distance tissue where those cells subsequently adapt to the foreign tissue micro environments

and form secondary colony at these sites (M.A.J Chaplain and G. Lolas 2006). The process of invasion and metastases is often described by a series of distinct steps known as the invasion metastases cascade (Kanchi Lakshmi K. 2011). The series steps are

1. local invasion by the primary tumor
2. invasion of cancer cells into nearby blood and lymphatic vessels (intravasation)
3. transport and survival from immune clearance of these cells through the systems until extravasations of cells in to secondary tissue sites
4. The cells then form nodules of cancer cells (micro metastases) and then undergo the final step known as colonization, in which the micro metastases grow in to macroscopic tumors.

A cell that is constantly making and breaking adhesions with molecules will move from a region of low concentration to an area where adhesive molecule is more highly concentrated. Two crucial components of tissue invasion are

1. cancer cell proliferation, and
2. Over-expression and secretion of proteolytic enzymes by the cancer cells.

The proteolytic enzymes are responsible for the degradation of the tissue, enabling the proliferating cancer cells to actively invade and migrate into the degraded tissue (Zuzanna Szyma Nska 2009).

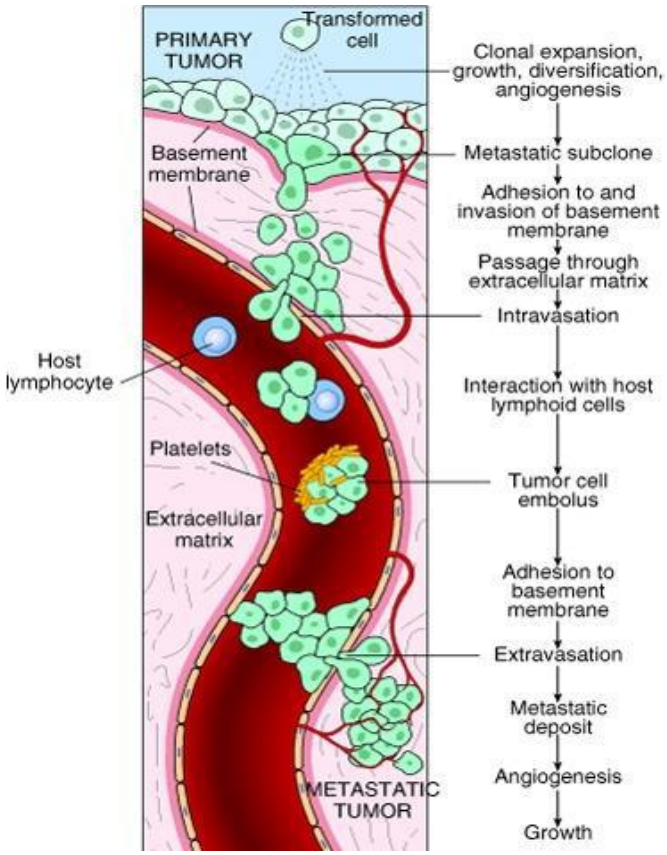


Fig 1. The major steps involved in metastasis (Yangjin Kim, Magdalena A. Stolarska, Hans G. Othmer 2011)

1.1.5. Tumor Treatment

Tumor treatment can follow two different strategies (Heiko E. and Mark A.J. C. 2014). A gross reduction in tumor volume can be inflicted by

1. inducing cell death in proliferating cancer cells
2. decreasing the tumor support via reduction of carrying capacity

There are three traditional therapy procedures practiced for treatment of tumors; surgery, radiation therapy, and chemotherapy. Further treatment strategies are immunotherapy (the prevention or treatment of disease with substances that stimulate the immune response) and monoclonal antibody therapy (an antibody produced by a single clone of cells or cell line and consisting of identical antibody molecules).

a. surgery

Some cancerous tumors can be removed by surgery. Surgery attempts to directly remove tumors and hence reduces tumor burden. By this method some surrounding healthy cells are also

removed to get all cancerous cells (Heiko Enderling and Mark A.J. Chaplain 2014). Surgery, often the first treatment, is used to remove solid tumors. It may be the only treatment necessary for early stage cancers and benign tumors (Beth addson-smith 2010). When the tumor is too big or metastasis already settled down it is very difficult to eliminate the whole tumor. At this time Chemotherapy can also be used.

b. Chemotherapy

Chemotherapy is a treatment for cancer with cytotoxic drugs that mainly affect and harm cells that have a high proliferation rate. Consequently chemotherapy does not kill only cells that divide rapidly, but also harms cells that divide rapidly under normal circumstances, like cells in the bone marrow and hair follicles. So it is important not to overdose the drug. Furthermore, the cytotoxins also have a Cancer causing effect and the mutating cancer cells generate resistance against them. Nevertheless these cytotoxic drugs are not only poisonous, but they also affect more or less important pathways concerning proliferation and growth of the cells. Modern chemotherapy strategies mainly do not aim at rapidly destroying the cancer cells but try to prevent further proliferation of the malignant cells and thus to restrict tumor growth. In chemotherapy different cytotoxic agents affect the death rate of the differentiated cancer cells as well as that of cancer stem cells, depending on the treatment dose. Cancer stem cells are less sensitive to this treatment, resulting in a lower death rate in comparison to the differentiated cancer cells (Deep S. 2012).

c. Radiation Therapy

In radiation therapy ionizing radiation similar to X-rays is used to control or kill malignant cells. It damages the DNA of exposed tissue leading to cellular death of cancer cells; unlike normal cells they lack a repair mechanism. In order to spare normal tissues, shaped radiation beams are sent from several angles to intersect at the tumor, providing a much larger absorbed dose than in the surrounding healthy tissue. Instead of trying to directly kill the cancer cells modern therapies aim at implicitly altering important molecules of malignant tumor cells. These changes are supposed to initiate cell death via biological pathways: Radiation leads to the emergence of aggressive molecules especially in the tumor tissue that is well supplied with blood and oxygen. Especially oxygen ions attack the genetic information of the cancer cells in the form of free radicals. Furthermore, these reactive molecules destroy important enzymes and molecules that play a vital role in the high proliferation rate of the cancer cells. Consequently, the ability of tumor cells to divide rapidly is sorely afflicted and thus the tumor can no longer

expand. Additionally the malignant cells are marked by the reactive molecules and thus can be detected by the immune system and specifically eliminated.

Radiation as chemotherapy, also damages normal cells; in addition the cancer cells mutate and develop resistance against the rays. So the aim again is to minimize the deaths of the normal cells and to maximize the ones of the cancer cells, as to avoid too large doses.

d. Emerging and targeted therapies

Surgery, radiation therapy and chemotherapy either alone or in various combinations are successful only when the tumor is identified in the initial stages. But, still there are some cancers (pancreas, liver or lungs) which are detected only at their aggressive stages. Now, cancer scientists are putting lot of efforts in developing novel and effective treatment strategies with higher selectivity such that only cancer cells are targeted while sparing the normal cells. Thus, these therapies are known as targeted therapies (Kanchi L. 2011). These include immunotherapy, gene therapy, and viral therapy. In immunotherapy, the main idea is to identify and extract the immune cells which are cytotoxic to tumor cells to improve the selectivity and cyto toxicity.

Gene therapy exploits the role of oncogenes and tumor suppressor genes in cancer development based on discoveries over the past two decades. In gene therapy, the defective genes are replaced by the normal genes.

A tumor's response to treatment depends on many factors, including the severity of the disease, the application of the treatment, and the strength of patient's own immune response. Mathematical modeling of this process is viewed as a potentially powerful tool in the development of improved treatment regimens (Heiko E. and Mark A. 2014).

1.2. **Statement of the problem**

Solid tumor growth has attracted the attention of scholars from many different fields, becoming one of the most important areas of active research in the theoretical biology community. The number of models analyzing the different stages in tumor development, from its initial avascular phase to invasion and metastasis through vascularization via tumor-induced angiogenesis, is huge. Nevertheless, almost all of these models neglect a factor which can, eventually, influence many features of the growth and invasion process.

Tumor cells embedded the biochemical and mechanical state of their environment, convert the extracellular signals in to intracellular signals, integrate these signals, and respond accordingly (Yangjin Kim et al. 2011).

Chemotactic factors found in the tumor microenvironment can promote the motility and invasion of tumor cells and therefore facilitate metastasis. Epidermal growth factor (EGF) is a potent chemotactic factor for many cells of epithelial origin and is expressed in many tumor types (Sumanta Goswami et al. 2005). To induce the death of tumor cells and minimize the tumor invasion the patient should be treated by a single method or combination of the methods. For my case I want to concentrate on the treatment of tumor by chemotherapy. Because still the interaction between the chemotherapy drug and tumor especially the adaptation of tumor cell to chemotherapy drug is not clearly shown.

Hence this thesis work will try to address the following basic questions.

1. What are basic assumptions in developing a mathematical model which describes the tumor invasion and treatment?
2. What are the main factors that influence invasion of tumor?
3. What is the rate of tumor cell interaction with the host tissue?
4. How we show the interaction of chemotherapy drug with tumor cell and what is its effect on the tumor cell?

1.3. Objective of the study

1.3.1. General objective

This thesis work enables to know how mathematical models are used in tumor invasion and the treatment methods.

1.3.2. Specific objective

The specific objectives of this thesis are to

1. examine the basic assumption in developing the mathematical model which describes tumor invasion and treatment.
2. list the factors that influence tumor invasion.
3. indicate the rate of tumor interaction with the host tissue.
4. show the interaction of chemotherapy with tumor cells and the effect of drugs on tumor cells.

1.4. Significance of the study

The Significance of the study is

1. It save time and resource to prepare the model, and it is simple to understand the model.
2. It is simple to transfer knowledge about the cause, prevention, and treatment of the disease.
3. Researchers will be encouraged for further investigation using this material as a base or as a reference.
4. Persons who get the chance to read this material or have the chance to listen to the presentation will get awareness in reading/ knowing about the disease.

CHAPTER TWO

REVIEW RELATED LITERATURE

2.1. Cell proliferation

When a cell is mutated its property is changed and as a result uncontrolled cell division occurs. Different Authors write on the issue as follows.

The response of tumor cells to their environment at the cell level may involve changes in metabolic state, gene expression, growth, differentiation, cell division, cell movement, or apoptosis. Maintenance of homeostasis at the tissue level involves the tissue-wide integration of and response to signals from within the tissue and its surroundings, and disruption at any of the detection, transduction or response steps may lead to neoplastic growth, i.e., abnormal, unchecked growth of the tissue, producing what is called a neoplasm or tumor. Tumors can be benign, pre-malignant or malignant, and when they become malignant they become a cancer. More precisely, cancer denotes diseases that give rise to abnormal cells that proliferate indefinitely, and that can invade nearby tissues and spread to other parts of the body through the blood and lymph systems (Yangjin Kim et al. 2011).

The number of cancer cells in a tumor is difficult to estimate due to continuous changes in time. Tumor cells may proliferate, rest in a quiescent state, or die. Describing the number of tumor cells as a function of time is therefore remarkably challenging. It is, however, straightforward to formalize what changes in cell number are expected as time changes (Heiko Enderling and Mark A.J. Chaplain 2014).

Malignant individuals are seen to have also a higher proliferation rate than to their not mutated counterparts. In particular, as suggested by a number of experimental works the time between cell divisions has a stochastic distribution, which depends on both the internal state of each cell and on the time from its last mitotic process (M. Scianna and L. Preziosi 2012).

2.2. Tumor invasion

Cancer cells invade the surrounding tissue either as individuals or as small groups of cells, and may secrete enzymes that degrade the ECM to facilitate passage of cells. Migration is to nearby vessels (if the tumor enters the circulatory system directly) or to the lymph system (M.A.J Chaplain and G. Lolas 2006). In the former case it may involve chemotaxis to attractants

released by nearby stromal cells in response to stimuli from the tumor (Yangjin Kim et al. 2011).

Invasion of tumor cells is an important step for metastasis and is governed by several subcellular processes. As a tumor grows in healthy tissue it is producing a cell mass that pushes healthy cells aside. Different scholars with their ideas have been cited by Thomas Hillen,Robert Gatenby and Peter Hinow 2015 as; the mechanical interactions of tumor cells with healthy tissue have been modeled in several ways, including continuum equations (Preziosi, Byrne, Loewengrub, Macklin,Chauviere) 2007, multi-phase flow models (Byrne, Owen) 2006, transport equations (Hillen, Painter) 2012, and individual based models (Anderson, Deutsch, Drasdo) 2011. Thomas Hillen et al. 2015 take an example of white matter tracks and grey matter regions as well as macroscopic barriers such as the falx celebri in which tumors in brain tissue are exposed to. They said that the models become complicated very quickly and sophisticated methods are needed for analysis and simulations. One powerful tool is scaling limits, homogenization and moment closure methods which enable us to reduce the full (physical) PDE to macroscopic models that can be analyzed as stated by Thomas Hillen et al. 2015.

According to Thomas Hillen et al.2015 after the tumor has grown to a certain size, it starts to actively invade into healthy tissue. This can have two forms; active movement to nearby sites (invasion) or passive transport by the blood system or the lymphatic system (metastasis which leads to eventual death of the patient). Recent mathematical modeling has focused on various aspects of tumor invasion. They also cited the paper of Swanson 2003, Konukoglu et al 2010, Hillen and Painter 2012 from recent studies in order to indicate reaction-diffusion models which can be used to describe glioma growth in the heterogeneous environment of the brain. The brain is made out of white and grey matter. While the grey matter is mostly homogeneous, the white matter is a fibrous structure. Tumor cells are known to use these fibrous structures to invade new areas.

The mathematical modeling of evolution in cancer is in full swing and many methods from ecological modeling are already implemented into cancer modeling. They cited different Authors with their respected contributions: Nagy 2005 wrote a review highlighting recent success in the modeling of cancer evolution; Merlo et al 2006 explain cancer as an evolutionary process; and Gatenby 2009, 2011 highlight the interaction between evolution, selection and the tumor microenvironment; Anderson et al 2001 used the genetic makeup of tumor cells to

successfully model reoccurrence of breast tumors; An emerging focus of interest is the role played by Cancer Stem Cells (Enderling, Hahnfeldt, Hillen, oewengrub) 2012.

2.3. Tumor Control and Treatment

A specific challenge of cancer treatment is the way how a cytotoxic agent (or radiation) gets delivered to the tumor cells. According to Thomas Hillen et al. 2015 the complicated spatial extend of a tumor must be understood, as well as the connection to the vascular system. Unfortunately, treatments have side effects on the healthy tissue and they impose selection pressures on the tumor. The tumor control probability (TCP) mostly used in radiation treatment describes the probability that a tumor is eradicated by a given treatment. Mathematically it is the same object as the extinction probability, which describes the probability that a certain species goes extinct.

Deep Shikha Dixit et al. 2012 by themselves write the function and the procedures of using chemotherapy as follows.

Chemotherapy uses powerful drugs to kill cancer cells, control their growth, or relieve pain symptoms. Chemotherapy may involve one drug, or a combination of two or more drugs, depending on the type of cancer and its rate of progression. Chemotherapy can be used in combination with other treatments such as surgery or radiation, to make sure all cancer cells have been eliminated.

CHAPTER THREE

METHODS AND PROCEDURES

3.1. Methodology

On this thesis work, I used partial differential equation using continuum approach to model the invasion/spread of tumor cells by considering time and ignoring space to develop mathematical model for my particular problem.

3.2. Procedures

In this study, Model analysis has been done by using the governor equation to find the steady state solutions and then Jacobean matrix has been created to find the eigenvalues and determine the stability. Tables have been used and graphs have been presented using matlab code. At last, the result has been interpreted and then discussions and conclusions have been put.

3.3. Source of information

To conduct this study, I have used different reference books, Journals and articles that are related to the applications of mathematical modeling of tumor invasion and treatment.

CHAPTER FOUR

MATHEMATICAL MODELING AND ANALYSIS

4.1. Basic Assumptions used to develop the model

The basic assumptions are (Andrew B. 2015)

1. Both normal and tumor cells are governed by logistic growth;
2. Normal cell and tumor cell undergo cell diffusion. Furthermore the diffusion coefficients may be dependent on the other respective cell density;
3. There is a population competition relationship between the normal and tumor tissues;
4. The tumor tissue produce H^+ ions as a result of aerobic glycolysis at a rate proportional to the tumor cell density;
5. The normal tissue interacts with the excess H^+ ions, leading to the death rate proportional to the H^+ concentration;
6. Excess H^+ ions diffuse chemically with a constant diffusion rate and are produced at a rate proportional to the tumor cell density. Moreover an uptake turn is included to take account of mechanisms for increasing pH;
7. The chemotherapy drug is infused equally across the system at a rate given by a function time. A term is included for a removal of drug from the system by metabolic process and the drug is assumed to be diffuse chemically with a constant rate of diffusion;
8. The tumor tissue interact with the chemotherapy drug leading to destruction of tumor tissue at a rate proportional to the concentration of drug;
9. The chemotherapy drug concentration is decreased as a result of interaction with the tumor tissue;
10. The rate of degradation of ECM decreases as a result of interaction of chemotherapy drug with the tumor tissue (my assumption).

4.2. Partial Differential Equation Models of Tumor invasion

Although ordinary differential equation models have proven to be a useful tool to simulate the evolution of the total tumor cell number over time, the most apparent shortcoming of this approach is the lack of spatial consideration. Patients do not die because of the total number of cancer cells in their bodies but because the primary tumors locally invade the tissue and spread (metastasize) to distant sites of the body to establish secondary tumors (Heiko E. and Mark A. 2014). It is these metastatic masses that are the main cause of death in cancer patients. Cancer invasion and metastatic spread are two crucial and inherently spatial processes, which can be

simulated using partial differential equation (PDE) models. In such models, a population *c* at spatial positions in one, two, or three dimensional space, respectively, is often described as a density, or fraction of maximum available volume at this position. The variable *c* is no longer only dependent on changes in time *t*, but also on variations in considered spatial dimensions. The equation for *c* therefore involves the partial derivatives of its independent variables. Omitting the considered spatial domain, the partial derivative of *c* with respect to time *t* is written as $\frac{\partial c}{\partial t}$.

4.2.1. Cancer cells

Assuming that there is a change in cell number density due to dispersion, arising from random locomotion and let take D_c as the cell random motility coefficient, characterizing how cells would disperse from higher to lower densities. However, in some cases a physically meaningful expression to describe their random motion other than the common linear diffusion and therefore nonlinear diffusion will be used.

In addition, the important features that the nonlinearity of the random motility captures are the finite speed of dispersion as well as the preservation of initial conditions of compact support. In other words, this means that if the initial cancer cell profile is localized in a finite region then at all subsequent times it will be confined to a finite region whose size however could change over time. On the other hand by choosing D_c to be constant and imposing that an infinitesimally small density of cancer cells penetrates the entire spatial domain immediately which is physically unrealistic. However such a choice does not affect the general framework of the process since the contribution of the chemo kinetic term D_c is always the smallest in cancer cell locomotion.

The second most important term that quantifies the change in cell number density is that of the "directional flow" of cells due to spatial gradients of environmental stimuli, such as those stimulating chemotactic or hapto tactic responses. This directional movement of tumor cells in the urokinase plasminogen activation model as chemotaxis and haptotaxis - namely a response to gradients of diffusible and non-diffusible macromolecules such as urokinase plasminogen activator and vitronectin respectively is referred (M.A.J Chaplain and G. Lolas 2006). To incorporate this response into the mathematical model the cancer cell flux (due to gradients) is taken as

$J_{flux} = J_{chemo} + J_{hapto}$, namely $J_{flux} = \chi_c c\nabla u + \xi_c c\nabla v$, where χ_c, $\xi_c > 0$ are the chemotactic and haptotactic coefficients respectively, characterizing biased directional movement in response to spatial gradients. Regarding the proliferation of cancer cells, assuming that in the absence of any extracellular matrix (ECM), cancer cell proliferation satisfies a logistic growth law. The presence of ECM leads to competition for space between the cancer cells and the ECM; modeling this by including a crowding term which is proportional to the product cv (the product of tumor cells and the ECM). To summarize, the conservation of mass applied to the cancer cell density c leads to the following equation:

$$\frac{\partial c}{\partial t} + \nabla\cdot(J_{random} + J_{chemotaxis} + J_{haptotaxis}) = R_c ,$$

where R_c is the net rate of production or loss of cells by mechanisms other than migration (e.g. proliferation or death) and hence the resulting partial differential equation for the cancer cell motion is,

$\frac{\partial c}{\partial t}$ = dispersion −chemotaxis − haptotaxis + proliferation, which is denoted as

$$\frac{\partial c}{\partial t} = \nabla.(D_c \nabla c) - \nabla.(\chi_c c\nabla u) - \nabla.(\xi_c c\nabla v) + \mu_1 c\left(1 - \frac{c}{c_o} - \frac{v}{v_o}\right) \qquad \text{.....(4.1)}$$

where D_c is (linear or nonlinear) the random motility coefficient; χ_c and ξ_c are the chemotactic and haptotactic functions respectively. Furthermore, μ_1 is the proliferation rate of the cells, while c_0 and v_0 are the maximum sustainable tumor cell and extracellular matrix densities respectively.

4.2.2. Extracellular matrix

ECM is known to contain many macromolecules such as vitronectin, laminin and fibronectin which can be degraded by several matrix degrading enzymes and especially by plasminogen activation (Zuzanna S. 2009). Since ECM is "static", neglect any random motion and focus solely on its degradation by the uPA protease. Assuming that uPA degrades the ECM upon contact and also suggesting that ECM components re-establish or re-model while they are competing for space with the invasive cells in a manner similar to that describing cancer cell proliferation. Thus, in the absence of cancer cells, extracellular matrix remodels in a logistic manner. On the other hand, the presence of cancer cells leads to competition for space between the cancer cells and the ECM which again modeled by incorporating a crowding term into the logistic growth. Using a modified logistic growth with rate constant μ_2 to describe the ECM

production, and taking δuv to represent the rate of degradation, we have the following equation for the extracellular matrix$\left(\frac{\partial v}{\partial t}\right)$.

$\frac{\partial v}{\partial t}$ = proteolysis + re-establishment, which is denoted as

$\frac{\partial v}{\partial t}$ = $-\delta uv + \mu_2 v\,(1 - c - v)$, where $\mu_1 \neq \mu_2$ …… (4.2)

4.2.3. urokinase Plasminogen Activator (uPA) protease

Factors influencing the protease (an enzyme which breaks down proteins and peptides) concentration are assumed to be diffusion, protease production and protease decay. Specifically, uPA is produced by cancer cells, diffuses throughout the extracellular matrix, with constant diffusion coefficient D_u, and undergoes decay of the form βu (M.A.J Chaplain and G. Lolas 2006). The equation governing the evolution of uPA concentration is therefore given by

$\frac{\partial u}{\partial t}$ = Dispersion + production – decay, which is denoted as

$\frac{\partial u}{\partial t} = D_u\nabla^2 u + \alpha c - \beta u$ …… (4.3)

Hence, the complete system of equations describing the interactions between the tumor cells, extracellular matrix and uPA is

$$\begin{cases} \frac{\partial c}{\partial t} = \nabla.(D_c\,\nabla c) - \nabla.\left(\chi_c c\nabla u\right) - \nabla.\left(\xi_c c\nabla v\right) + \mu_1 c\left(1 - \frac{c}{c_o} - \frac{v}{v_o}\right) \\ \frac{\partial v}{\partial t} = -\delta_1 uv + \mu_2 v\,(1 - c - v) \\ \frac{\partial u}{\partial t} = D_u\nabla^2 u + \alpha c - \beta u \end{cases} \quad \ldots\ldots\ldots\ldots\ldots (4.4)$$

Which is equivalent to

$$\begin{cases} \frac{\partial c}{\partial t} = D_c\frac{\partial^2 c}{\partial x^2} - \frac{\partial}{\partial x}\left(\chi_c\, c\frac{\partial u}{\partial x} + \xi_c\frac{\partial v}{\partial x}\right) + \mu_1 c\left(1 - \frac{c}{c_0} - \frac{v}{v_0}\right) \\ \frac{\partial v}{\partial t} = -\delta_1 uv + \mu_2 v(1 - c - v) \\ \frac{\partial u}{\partial t} = D_u\frac{\partial^2 u}{\partial x^2} + \alpha c - \beta u \end{cases} \quad \ldots\ldots\ldots\ldots\ldots (4.5)$$

where D_c is (linear or nonlinear) the random motility coefficient; χ_c and ξ_c are the chemotactic and haptotactic coefficients respectively.

4.2.4. Treatment

The factors that influence the invasion of tumor are immune system response and variety of tumor treatments. The cancer cells are decreased by mortality caused by the concentration of drug, by surgery done to decrease the burden of tumor cell, by application of radiotherapy or by combination of two or more methods. This can be represented mathematically as follows.

Treatment $=$ Chemotherapy $+$ Surgery (if there) $+$ radiotherapy (if there). Here I want to concentrate on chemotherapy.

Assume that a concentration of the drug in the body is given as the following sequence; let ς_0 is drug taken at a time and ω is the rate of remaining drug in the body before the present dose.

$$\varsigma_1 = \omega\varsigma_0 + \varsigma_0 = (\omega + 1)\,\varsigma_0$$

$$\varsigma_2 = (\omega + 1)\,\varsigma_1 = (\omega + 1)\,(\omega + 1)\,\varsigma_0$$

$$\varsigma_2 = (\omega + 1)^2\varsigma_0$$

$$\varsigma_3 = (\omega + 1)\,\varsigma_2 = (\omega + 1)\,(\omega + 1)^2\varsigma_0 = (\omega + 1)^3\varsigma_0$$

According to this sequence the concentration of drug in the patient body after n dose is

$$\varsigma_n = (\omega + 1)^n\varsigma_0 \qquad \ldots\ldots\ldots\ldots\ldots (4.6)$$

Assume that the treatment of a patient from a tumor cell by drug is the difference between how much the drug attack the tumor cells or how much the drug block the proliferation of tumor cell and the adaptation of the tumor cell to the drug; which can be described as $\varphi\varsigma_n$c and $\psi\varsigma_n$c respectively.

Where φ is the attacking rate of the proliferating tumor cells or blocking rate of the proliferation of tumor cells,

ψ is the adaptation rate of the tumor cell to the drug and

ς_n is the concentration of the drug in the patient body after n dose.

Tr $= \varphi\varsigma_n\mathrm{c} - \psi\varsigma_n\mathrm{c} = \varsigma_n\mathrm{c}\,(\varphi - \psi)$

Introducing another constant $\mu_3 = \varphi - \psi$,

$$Tr = \mu_3\varsigma_n c \qquad \ldots\ldots\ldots\ldots\ldots (4.7)$$

After a dose the drug starts to block the proliferation of tumor cell or attack the proliferating tumor cells and to the contrary the tumor cells adapt with the drug; this continue until the patient stop taking the drug. Therefore

$\frac{\partial c}{\partial t}$ = Dispersion + chemotaxis + haptotaxis + proliferation – $treatent\ by\ chemotherapy$

$$\frac{\partial c}{\partial t} = \nabla.(D_c \nabla c) - \nabla.(\chi_c c \nabla u) - \nabla.(\xi_c c \nabla v) + \mu_1 c\left(1 - \frac{c}{c_o} - \frac{v}{v_o}\right) - \mu_3 \varsigma_n c \quad \ldots (4.8)$$

When the cancer cells are reduced by treatment as discussed above the uPA reduces and this leads to reduction of degradation in ECM which can be given in the form of $\delta_2 uv$.

Therefore $\frac{\partial v}{\partial t}$ = proteolysis + re-establishment + recovery or no more degradation, which is denoted as

$$\frac{\partial v}{\partial t} = -\delta_1 uv + \mu_2 v(1 - c - v) + \delta_2 uv \quad \ldots\ldots\ldots\ldots\ldots\ldots\ldots\ldots (4.9)$$

Assuming that the uPA protease decreases by γc (because the rate of increase/ decrease of uPA depends on the number of tumor cells), then

$$\frac{\partial u}{\partial t} = D_u \nabla^2 u + \alpha c - \beta u - \gamma c \quad \ldots\ldots\ldots (4.10)$$

$$\frac{\partial u}{\partial t} = D_u \nabla^2 u + (\alpha - \gamma) c - \beta u$$

Hence, the complete system of equations describing the interactions between the tumor cells, extracellular matrix and uPA after the treatment is

$$\begin{cases} \frac{\partial c}{\partial t} = D_c \frac{\partial^2 c}{\partial x^2} - \frac{\partial}{\partial x}\left(\chi_c c \frac{\partial u}{\partial x} + \xi_c \frac{\partial v}{\partial x}\right) + \mu_1 c\left(1 - \frac{c}{c_0} - \frac{v}{v_0}\right) - \mu_3 \varsigma_n c \\ \frac{\partial v}{\partial t} = (\delta_2 - \delta_1) uv + \mu_2 v(1 - c - v) \\ \frac{\partial u}{\partial t} = D_u \frac{\partial^2 u}{\partial x^2} + (\alpha - \gamma) c - \beta u \end{cases} \quad \ldots\ldots\ldots (4.11)$$

When the proliferation of tumor cells is blocked or the proliferating cancer cells are died by chemotherapy after adaptation by $\mu_3 \varsigma_n c$ the cancer cell reduces, and the uPA enzyme also decreases by γc for my case. This results in recovery of the extracellular matrix by $\delta_2 uv$ that is degraded by tumor cells or there is no more degradation (proteolysis).

4.3. Non dimensionalization

In order to solve the system, we first of all non-dimensionalize the equations. The variables and parameters in the uPA system equations and their associated boundary conditions are transformed into dimensionless quantities using the following reference variables: (M.A.J Chaplain and G.Lolas 2006).

1. Reference length scale, L, (e.g. the maximum invasion distance of the cancer cells at this early stage of invasion $0.1 - 1$cm),

2. Reference time unit, $\tau = \frac{L^2}{D}$, where D is a reference chemical diffusion coefficient

Example: If D = 10^{-6}cm^{2}s^{-1}, then we deduce that τ varies between $\frac{(0.1cm)^2 s}{(10^{-6})cm^2}$ and $\frac{(1cm)^2 s}{(10^{-6})cm^2}$.

$\tau \; is \; in \; the \; interval \; of$ 10^4 sec to 10^6 sec.

3. Reference tumor cell density c_0, extracellular matrix density v_0 and reference uPA concentration u_0(where c_0, v_0 and u_0 are appropriate reference variables). The non-dimensional variables are defined as:

$$\tilde{t} = \frac{t}{\tau}\,, \qquad \tilde{x} = \frac{x}{L}\,, \qquad \tilde{c} = \frac{c}{c_0}\,, \qquad \tilde{v} = \frac{v}{v_0}\,, \qquad \tilde{u} = \frac{u}{u_0}\,,$$

$$\widetilde{D_c} = \frac{D_c}{D}\,, \quad \widetilde{D_u} = \frac{D_u}{D}\,, \quad \tilde{\chi} = \chi_c \frac{u_0}{D}\,, \quad \tilde{\xi} = \xi_c \frac{v_0}{D}, \quad \widetilde{\mu_1} = \mu_1 \tau\,, \quad \widetilde{\mu_2} = \mu_2 \tau,$$

$$\tilde{\delta} = \delta u_0 \tau\,, \; \tilde{\alpha} = \alpha \tau \frac{c_0}{v_0}\,, \quad \tilde{\beta} = \beta \tau,$$

and new parameters via the following scaling:

$$\widetilde{\mu_3} = \mu_3 \tau, \quad \tilde{\gamma} = \gamma \tau, \quad \widetilde{\delta_2} = \delta_2 \tau, \quad \widetilde{\varsigma_n} = \varsigma_n \tau$$

Henceforth, omitting the tildes for notational simplicity, the dimensionless governing equations can then be written in the following general form:

$$\begin{cases} \dfrac{\partial \mathrm{c}}{\partial \mathrm{t}} = D_c \dfrac{\partial^2 c}{\partial x^2} - \dfrac{\partial}{\partial x}\left(\chi_c \, c \dfrac{\partial u}{\partial x} + \xi_c \dfrac{\partial v}{\partial x}\right) + \mu_1 c(1 - c - v) - \mu_3 \varsigma_n c \\ \dfrac{\partial \mathrm{v}}{\partial \mathrm{t}} = (\delta_2 - \delta_1)\mathrm{uv} + \mu_2 \mathrm{v}(1 - c - v) \\ \dfrac{\partial \mathrm{u}}{\partial \mathrm{t}} = D_u \dfrac{\partial^2 u}{\partial x^2} + (\alpha - \gamma)c - \beta u \end{cases} \qquad \ldots\ldots\ldots (4.12)$$

Boundary and initial conditions

In order to close the system, boundary and initial conditions for c, u and v are required.

Boundary conditions: Guided by the in vitro experimental protocol in which invasion takes place within an isolated system, M.A.J Chaplain and G. Lolas 2006 assume that there is no-flux of tumor cells or protease across the boundary of the domain, namely x = 0 and x = 1, in one-space dimension. These boundary conditions are represented by the following equations (M.A.J Chaplain and G.Lolas 2006).

$$\left.\begin{aligned}\left(-D_c\frac{\partial c}{\partial x}+\ c\chi\frac{\partial u}{\partial x}+\ c\xi\frac{\partial v}{\partial x}\right)=\ 0\ \text{at x}\ =\ 0,1\\ \frac{\partial u}{\partial x}\ =\ 0,\text{at x}\ =\ 0,1\end{aligned}\right\} \quad \text{……. (4.13)}$$

Initial conditions: Finally, the initial distribution of the tumor cells, the protease concentration and the ECM density are prescribed by the system of equations. Initially it is assumed that there is a cluster of cancer cells already present and that they have penetrated a short distance into the extracellular matrix while the remaining space is occupied by the matrix alone. Finally, it is supposed that the uPA protease initial concentration is proportional to the initial tumor density. Combining the above to get (M.A.J Chaplain and G.Lolas 2006),

$$c(x,0)\ =\ exp\left(\frac{-x^2}{\epsilon}\right), x\in[0,1]\ and\ \epsilon\ >\ 0$$

$$v(x,0)\ =\ 1\ -\ \frac{1}{2}\ exp\left(\frac{-x^2}{\epsilon}\right), x\in[0,1]\ and\ \epsilon\ >\ 0 \qquad \text{……..(4.14)}$$

$$u(x,0)\ =\ \frac{1}{2}exp\left(\frac{-x^2}{\epsilon}\right), x\in[0,1]\ and\ \epsilon\ >\ 0, \text{ where } \epsilon \text{ is taken as } 0.01.$$

Estimation of parameters

Whenever possible, parameter values are estimated from available experimental data. However, given the large number of parameters in the model to be determined, it is perhaps not surprising that several remain not quantified. Focusing on the aim of my model which is to produce certain experimentally observed events of the urokinase plasminogen activation system in a qualitative manner, in the cases where no experimental data could be found, parameter values were chosen to give the best qualitative numerical simulation results. This is in line with previous paper successfully simulating mathematical modeling of cancer invasion of tissue: dynamic heterogeneity (M.A.J Chaplain and G.Lolas 2006).

Table 2. *Numerical values and the description of parameters*

Parameter	Description	Value	source
D_c	Tumor random motility coefficient	10^{-4}	(M.A.J Chaplain and G.Lolas 2006).
D_u	diffusion coefficient of uPA	10^{-2}	(M.A.J Chaplain and G.Lolas 2006).
χ_c	coefficient of chemotaxis	0	(M.A.J Chaplain and G.Lolas 2006).
ξ_c	coefficient of haptotaxis	5×10^{-3}	(M.A.J Chaplain and G.Lolas 2006).
α	Production rate of uPA	0.05	(M.A.J Chaplain and G.Lolas 2006).
β	Decay rate of uPA	0.03	My estimation
γ	Rate of decrease of uPA because of reduction of tumor cell	10^{-5}	My estimation
δ_1	Degradation rate of ECM	10	(M.A.J Chaplain and G.Lolas 2006).
δ_2	Rate of recovery of ECM	1	My estimation
$\mu_1 = \mu_2$	Tumor cell proliferation rate and ECM re-establishment rate	0	(M.A.J Chaplain and G.Lolas 2006).
μ_3	Rate of treatment	0.1	My estimation
L	Tumor cell maximum invasion distance	0.1	(M.A.J Chaplain and G.Lolas 2006).

τ	Time of invasion	10^4	(M.A.J Chaplain and G.Lolas 2006).
ς_n	concentration of the drug in the patient body after n dose	10^{-5}	My estimation
C_0	The initial number of cancer cells in the patient's body.	100	My estimation

4.4. Positivity of solutions

Lemma: If the initial data set $(c, v, u,) \geq (0,0,0)$ in the given domain, then the solution set (c, v, u) (t) of the equations in system (4.12) is positive for all t > 0.

Proof

Given: $c(x,0) > 0, v(x,0) > 0 \; and \; u(x,0) > 0$;

WTS: $c(x,t) > 0$,

$v(x,t) > 0 \; and$

$u(x,t) > 0$

$\frac{\partial c}{\partial t} = D_c \frac{\partial^2 c}{\partial x^2} - \frac{\partial}{\partial x}\left(\chi_c \, c \frac{\partial u}{\partial x} + \xi_c \frac{\partial v}{\partial x}\right) + \mu_1 c(1 - c - v) - \mu_3 \varsigma_n c$; From equation (4.12)

$\frac{\partial c}{\partial t} = D_c \frac{\partial^2 c}{\partial x^2} + \mu_1 c - \frac{\partial}{\partial x}\left(\chi_c \, c \frac{\partial u}{\partial x} + \xi_c \frac{\partial v}{\partial x}\right) - \mu_1 c^2 - \mu_1 cv - \mu_3 \varsigma_n c$

$$\int \frac{\partial c}{c} = \int \left(\frac{D_c}{c}\frac{\partial^2 c}{\partial x^2} + \mu_1 - \chi_c \frac{\partial^2 u}{\partial x^2} - \frac{\xi_c}{c}\frac{\partial^2 v}{\partial x^2} - \mu_1 c - \mu_1 v - \mu_3 \varsigma_n\right) \partial t$$

If the expression $\frac{D_c}{c}\frac{\partial^2 c}{\partial x^2} + \mu_1$ is removed from the equation the following inequality is obtained.

$$\int \frac{\partial c}{c} \geq \int \left(-\chi_c \frac{\partial^2 u}{\partial x^2} - \frac{\xi_c}{c}\frac{\partial^2 v}{\partial x^2} - \mu_1 c - \mu_1 v - \mu_3 \varsigma_n\right) \partial t$$

$$ln \; c \geq \int \left(-\chi_c \frac{\partial^2 u}{\partial x^2} - \frac{\xi_c}{c}\frac{\partial^2 v}{\partial x^2} - \mu_1 c - \mu_1 v - \mu_3 \varsigma_n\right) \partial t$$

$$ln \; c \geq -\chi_c \frac{\partial^2 u}{\partial x^2} t - \frac{\xi_c}{c}\frac{\partial^2 v}{\partial x^2} t - \mu_1 ct - \mu_1 vt - \mu_3 \varsigma_n t + k$$

$c \geq \exp\left(-\chi_c \frac{\partial^2 u}{\partial x^2} t - \frac{\xi_c}{c}\frac{\partial^2 v}{\partial x^2} t - \mu_1 ct - \mu_1 vt - \mu_3 \varsigma_n \mathrm{t} + k\right)$

$c \geq \exp\left(-\chi_c \frac{\partial^2 u}{\partial x^2} t - \frac{\xi_c}{c}\frac{\partial^2 v}{\partial x^2} t - \mu_1 ct - \mu_1 vt - \mu_3 \varsigma_n \mathrm{t}\right) . exp(k)$

$c \geq \mathrm{A} \exp\left(-\chi_c \frac{\partial^2 u}{\partial x^2} t - \frac{\xi_c}{c}\frac{\partial^2 v}{\partial x^2} t - \mu_1 ct - \mu_1 vt - \mu_3 \varsigma_n \mathrm{t}\right)$, where A = exp(k)

For t = 0, $c \geq \mathrm{A} \exp(0)$, where A = exp(k)

$c \geq \mathrm{A}.$

Obviously we can conclude that c is positive for any $\mathrm{t} \geq 0$.

Similarly,

$\frac{\partial \mathrm{v}}{\partial \mathrm{t}} = (\delta_2 - \delta_1)\mathrm{uv} + \mu_2 \mathrm{v}(1 - c - v)$

$\frac{\partial \mathrm{v}}{\partial \mathrm{t}} = (\delta_2 \mathrm{uv} - \delta_1 uv) + \mu_2 \mathrm{v} - \mu_2 \mathrm{vc} - \mu_2 \mathrm{v}^2$

$\frac{\partial \mathrm{v}}{\partial \mathrm{t}} = \delta_2 \mathrm{uv} + \mu_2 \mathrm{v} - \delta_1 uv - \mu_2 \mathrm{vc} - \mu_2 \mathrm{v}^2$

$\int \frac{\partial \mathrm{v}}{\mathrm{v}} = \int (\delta_2 \mathrm{u} + \mu_2 - \delta_1 u - \mu_2 \mathrm{c} - \mu_2 \mathrm{v})\, \partial \mathrm{t}$

If the expression $\delta_2 \mathrm{u} + \mu_2$ is removed from the equation the following inequality is obtained.

$\int \frac{\partial \mathrm{v}}{\mathrm{v}} \geq \int (-\delta_1 u - \mu_2 \mathrm{c} - \mu_2 \mathrm{v})\, \partial \mathrm{t}$

$ln\, v \geq -\delta_1 ut - \mu_2 \mathrm{ct} - \mu_2 \mathrm{vt} + k$

$v \geq exp\,(-\delta_1 ut - \mu_2 \mathrm{ct} - \mu_2 \mathrm{vt} + k)$

$v \geq exp\,(-\delta_1 ut - \mu_2 \mathrm{ct} - \mu_2 \mathrm{vt}) . \exp(k)$

$v \geq A\, exp\,(-\delta_1 ut - \mu_2 \mathrm{ct} - \mu_2 \mathrm{vt})$, where A = exp(k)

For t = 0, $v \geq A\, exp\,(0)$, where A = exp(k)

$v \geq A.$

This also indicates v is positive for any $\mathrm{t} \geq 0$.

In the same way,

$$\frac{\partial \mathrm{u}}{\partial \mathrm{t}} = D_u \frac{\partial^2 u}{\partial x^2} + (\alpha - \gamma)c - \beta u$$

$$\frac{\partial \mathrm{u}}{\partial \mathrm{t}} = D_u \frac{\partial^2 u}{\partial x^2} + \alpha c - \gamma c - \beta u$$

$$\int \frac{\partial \mathrm{u}}{\mathrm{u}} = \int \left(\frac{D_u}{u} \frac{\partial^2 u}{\partial x^2} + \frac{\alpha c}{\mathrm{u}} - \frac{\gamma c}{u} - \beta \right) \partial t$$

If the expression $\frac{D_u}{u}\frac{\partial^2 u}{\partial x^2} + \frac{\alpha c}{\mathrm{u}}$ is removed from the equation the following inequality is obtained.

$$\int \frac{\partial \mathrm{u}}{\mathrm{u}} \geq \int \left(-\frac{\gamma c}{u} - \beta \right) \partial t$$

$$ln\, u \geq -\frac{\gamma c}{u} t - \beta t + \mathrm{k}$$

$$ln\, u \geq \left(-\frac{\gamma c}{u} t - \beta t + k \right)$$

$$u \geq exp\left(-\frac{\gamma c}{u} t - \beta t + k \right)$$

$$u \geq exp\left(-\frac{\gamma c}{u} t - \beta t \right).exp(k)$$

$u \geq A\, exp\left(-\frac{\gamma c}{u} t - \beta t \right)$, where A= exp(k)

For t = 0, $u \geq A\, exp(0)$, where A= exp(k)

$u \geq A$, which means u is positive for any value $of\ t \geq 0$.

Therefore the solution set $(\mathrm{c}, \mathrm{v}, \mathrm{u})$ (t) of the equations in system (4.12) is positive for all t > 0.

4.5. Model Analysis

$$Let\ k(c,v,u) = \frac{\partial c}{\partial t}, g(c,v,u) = \frac{\partial v}{\partial t}, and\ h(c,v,u) = \frac{\partial u}{\partial t}$$

$$\begin{cases} \mathrm{k}(c,v,u) = D_c \frac{\partial^2 c}{\partial x^2} - \frac{\partial}{\partial x}\left(\xi_c \frac{\partial v}{\partial x} \right) + \mu_1 c(1 - c - v) - \mu_3 \varsigma_n c \\ \mathrm{g}(c,v,u) = (\delta_2 - \delta_1)\mathrm{uv} + \mu_2 \mathrm{v}(1 - c - v) \\ \mathrm{h}(c,v,u) = D_u \frac{\partial^2 u}{\partial x^2} + (\alpha - \gamma)c - \beta u \end{cases}$$

By substituting the corresponding values for parameters we can get the following system.

$$\begin{cases} \mathrm{k}(c,v,u) = D_c \dfrac{\partial^2 c}{\partial x^2} - \dfrac{\partial}{\partial x}\left(\xi_c \dfrac{\partial v}{\partial x}\right) + 0 - \mu_3 \varsigma_n c \\ \mathrm{g}(c,v,u) = (1 - 10)\mathrm{uv} + 0 \\ \mathrm{h}(c,v,u) = D_u \dfrac{\partial^2 u}{\partial x^2} + (0.049)c - 0.03u \end{cases}$$

4.5.1. Steady State Solutions (The equilibrium points)

To find the steady state solutions we have to make k(c,v,u) =0, g(c,v,u) =0, h(c,v,u) =0 and then solve the system as follows.

$$\begin{cases} D_c \dfrac{\partial^2 c}{\partial x^2} - \dfrac{\partial}{\partial x}\left(\xi_c \dfrac{\partial v}{\partial x}\right) + 0 - 0.1\varsigma_n c = 0 \\ -9\mathrm{uv} + 0 = 0 \\ D_u \dfrac{\partial^2 u}{\partial x^2} + (0.049)c - 0.03u = 0 \end{cases}$$

The trivial solution or the trivial equilibrium point is obviously E_0 = (0, 0, 0). And the other equilibrium points are calculated as follows.

First let us solve the third equation.

$D_u \frac{\partial^2 u}{\partial x^2} + (0.049)c - 0.03u$= 0, provided that $\frac{\partial u}{\partial x}$ = 0, it is B.C (from 4.13)

This implies $\frac{\partial^2 u}{\partial x^2}$ is also zero.

Therefore $(0.049)c - 0.03u$ = 0

0.03u = 0.049c

c = $\frac{0.03}{0.049}$ u

This shows or indicates if there is tumor, the uPA also presents. Therefore both c and u are not equals to zero.*

Next let us take the second row of the matrix.

$-9\mathrm{uv} + 0 = 0$

$(9)uv = 0$

uv = 0

v = 0, because u ≠0 as (*) from the above.

Therefore the equilibrium points are E_0(0,0,0) and E_1 (c,0, u)

4.5.2. Stability of the equilibrium points.

Cayley- Hamilton theorem

Consider a square matrix A with dimension n and with a characteristic polynomial

$P(\lambda)= |\lambda I - A| = \lambda^n + a_{n-1}\lambda^{n-1} + a_{n-2}\lambda^{n-2} + \ldots + a_0$ formed by substituting A for λ above

$P(A) = A^n + a_{n-1}A^{n-1} + a_{n-2}A^{n-2} + \ldots + a_0 I_0$

where I is the identity matrix. The Cayley-Hamilton theorem states that every matrix satisfies its own characteristic equation, that is $P(A) \equiv [0]$ where [0] is the null matrix.(Note that the normal characteristic equation $P(\lambda)= 0$ is satisfied only at the eigenvalues ($\lambda_1, \lambda_2, \lambda_3, \ldots, \lambda_n$).

1. **Local stability**

By using Jacobean matrix for linearization and Cayley- Hamilton theorem to find the eigenvalues, it is possible to determine the stability as follows.

If the equilibrium point is (c, v, u) for functions k, g and h, then the Jacobean matrix is calculated as

$$J(c,v,u) = \frac{\partial(k,g,h)}{\partial(c,v,u)} = \begin{pmatrix} \frac{\partial k}{\partial c}(c,v,u) & \frac{\partial k}{\partial v}(c,v,u) & \frac{\partial k}{\partial u}(c,v,u) \\ \frac{\partial g}{\partial c}(c,v,u) & \frac{\partial g}{\partial v}(c,v,u) & \frac{\partial g}{\partial u}(c,v,u) \\ \frac{\partial h}{\partial c}(c,v,u) & \frac{\partial h}{\partial v}(c,v,u) & \frac{\partial h}{\partial u}(c,v,u) \end{pmatrix}$$

$$J(c,v,u) = \frac{\partial(k,g,h)}{\partial(c,v,u)} = \begin{pmatrix} -0.1\varsigma_n & 0 & 0 \\ 0 & -10u + u & -10v + v \\ 0.049 & 0 & -0.03 \end{pmatrix}$$

$$= \begin{pmatrix} -0.1\varsigma_n & 0 & 0 \\ 0 & -9u & -9v \\ 0.049 & 0 & -0.03 \end{pmatrix}$$

In particular taking the critical points

i. $\boldsymbol{E_0 = (0,0,0)}$

$$A = J(0,0,0) = \frac{\partial(k,g,h)}{\partial(0,0,0)} = \begin{pmatrix} \frac{\partial k}{\partial c}(0,0,0) & \frac{\partial k}{\partial v}(0,0,0) & \frac{\partial k}{\partial u}(0,0,0) \\ \frac{\partial g}{\partial c}(0,0,0) & \frac{\partial g}{\partial v}(0,0,0) & \frac{\partial g}{\partial u}(0,0,0) \\ \frac{\partial h}{\partial c}(0,0,0) & \frac{\partial h}{\partial v}(0,0,0) & \frac{\partial h}{\partial u}(0,0,0) \end{pmatrix}$$

$$J(0, 0, 0) = A = \begin{pmatrix} -0.1\varsigma_n & 0 & 0 \\ 0 & 0 & 0 \\ 0.049 & 0 & -0.03 \end{pmatrix}$$

$$|A - \lambda I| = 0$$

$$A - \lambda I = \begin{pmatrix} -0.1\varsigma_n & 0 & 0 \\ 0 & 0 & 0 \\ 0.049 & 0 & -0.03 \end{pmatrix} - \lambda \begin{pmatrix} 1 & 0 & 0 \\ 0 & 1 & 0 \\ 0 & 0 & 1 \end{pmatrix}$$

$$A - \lambda I = \begin{pmatrix} -0.1\varsigma_n - \lambda & 0 & 0 \\ 0 & 0 - \lambda & 0 \\ 0.049 & 0 & -0.03 - \lambda \end{pmatrix}$$

$$|A - \lambda I| = 0$$

$$\begin{vmatrix} -0.1\varsigma_n - \lambda & 0 & 0 \\ 0 & -\lambda & 0 \\ 0.049 & 0 & -0.03 - \lambda \end{vmatrix} = \begin{vmatrix} 0 & 0 & 0 \\ 0 & 0 & 0 \\ 0 & 0 & 0 \end{vmatrix}$$

Taking the first row and finding the determinant, it is possible to get the eigenvalue(s) as follows.

$|A - \lambda I| = a_{11}\, c_{11} + a_{12}\, c_{12} + a_{13}\, c_{13} = 0$, $a_{12} = a_{13} = 0$

$a_{11}\, c_{11} = 0$

$$|A - \lambda I| = (-0.1\varsigma_n - \lambda)\,(-1)^{1+1} \begin{vmatrix} -\lambda & 0 \\ 0 & -0.03 - \lambda \end{vmatrix} = \begin{vmatrix} 0 & 0 \\ 0 & 0 \end{vmatrix}$$

$$(-0.1\varsigma_n - \lambda)\,\big((-\lambda)(-0.03 - \lambda) - 0\big) = 0$$

$$(-0.1\varsigma_n - \lambda)((\lambda)(0.03 + \lambda)) = 0$$

$$(-0.1\varsigma_n - \lambda) = 0 \text{ or } \lambda = 0 \text{ or } \lambda = -0.03$$

$$\lambda_1 = -0.1\varsigma_n, \lambda_2 = 0, \lambda_3 = -0.03.$$

From the above, we can observe that $\lambda_1 < 0$, $\lambda_3 < 0, and\ \lambda_2 = 0$; Therefore the equilibrium point E_0 (0,0,0) is locally stable.

ii. $\boldsymbol{E_1 = (c, 0, u)}$

$$J(c,0,u) = \frac{\partial(c,0,u)}{\partial(c,0,u)} = \mathrm{B} = \begin{pmatrix} -0.1\varsigma_n & 0 & 0 \\ 0 & -9u & 0 \\ 0.049 & 0 & -0.03 \end{pmatrix}$$

$$\lambda I - B = \lambda \begin{pmatrix} 1 & 0 & 0 \\ 0 & 1 & 0 \\ 0 & 0 & 1 \end{pmatrix} - \begin{pmatrix} -0.1\varsigma_n & 0 & 0 \\ 0 & -9u & 0 \\ 0.049 & 0 & -0.03 \end{pmatrix}$$

$$\lambda I - B = \begin{pmatrix} \lambda & 0 & 0 \\ 0 & \lambda & 0 \\ 0 & 0 & \lambda \end{pmatrix} - \begin{pmatrix} -0.1\varsigma_n & 0 & 0 \\ 0 & -9u & 0 \\ 0.049 & 0 & -0.03 \end{pmatrix}$$

$$\lambda I - B = \begin{pmatrix} \lambda + 0.1\varsigma_n & 0 & 0 \\ 0 & \lambda + 9u & 0 \\ 0.049 & 0 & \lambda + 0.03 \end{pmatrix}$$

$$|\lambda I - B| = 0$$

$$\begin{vmatrix} \lambda + 0.1\varsigma_n & 0 & 0 \\ 0 & \lambda + 9u & 0 \\ 0.049 & 0 & \lambda + 0.03 \end{vmatrix} = \begin{vmatrix} 0 & 0 & 0 \\ 0 & 0 & 0 \\ 0 & 0 & 0 \end{vmatrix}$$

$$(\lambda + 0.1\varsigma_n)\,(-1)^{1+1} \begin{vmatrix} \lambda + 9u & 0 \\ 0 & \lambda + 0.03 \end{vmatrix} = \begin{vmatrix} 0 & 0 \\ 0 & 0 \end{vmatrix}$$

$$(\lambda + 0.1\varsigma_n)\,(\lambda + 9u)(\lambda + 0.03) = 0$$

$$\lambda + 0.1\varsigma_n = 0 \text{ or } \lambda + 9u = 0 \; or \; \lambda + 0.03 = 0$$

$$\lambda_1 = -0.1\varsigma_n\,,\ \lambda_2 = -9u, \lambda_3 = -0.03$$

Routh-Hurwitz stability criteria:

$(\lambda + 0.1\varsigma_n)\,(\lambda + 9u)(\lambda + 0.03) = 0$

$\lambda^3 + (9\mathrm{u} + 0.1\varsigma_n + 0.03)\lambda^2 + (0.9u\varsigma_n + 0.27u + 0.003\varsigma_n)\lambda + 0.027\mathrm{u}\varsigma_n = 0$

$a_1 = 9\mathrm{u} + 0.1\varsigma_n + 0.03$

$a_2 = 0.9u\varsigma_n + 0.27u + 0.003\varsigma_n$

$a_3 = 0.027\mathrm{u}\varsigma_n$

$a_1 > 0, a_2 > 0, a_3 > 0$, and clearly, $a_1 a_2 - a_3 > 0$: Routh-Hurwitz stability criteria is satisfied.

Therefore the equilibrium point (c, 0, u) is locally asymptotically stable.

2. **Global stability:** Lyapunov's Indirect Method

Definition: A matrix A$\in \mathbb{R}^{n\times n}$ is called Huwitz or asymptotically stable, if and only if

Re(λ_i) < 0,$\forall_{i=1,2,3,\ldots,n}$, where λ_i's are the eigenvalues of the matrix A.

Consider the system $\dot{x}$ = Ax, we look for a quadratic function

V(x) = x^TPx where P = P^T > 0. Then

$\dot{V}(x)$ = $\dot{x}^T$Px + x^TP$\dot{x}$ = x^T(A^TP + PA)x = $-x^T Qx$. If there exist Q = Q^T > 0 such that

A^TP + PA = $-Q$, then V is a Lyapunov function and x = 0 is Globally stable. This is called the matrix Lyapunov equation.

In my case, from the equilibrium points E_0 *and* E_1 , E_1(c,0,u) satisfies the criteria of Lyapunov's indirect method.(i.e all eigenvalues are negative in case of E_1(c,0,u)). Therefore

$$A = J(c,0,u) = \begin{pmatrix} -0.1\varsigma_n & 0 & 0 \\ 0 & -9u & -9v \\ 0.049 & 0 & -0.03 \end{pmatrix}$$

$$\dot{x} = Ax = \begin{pmatrix} -0.1\varsigma_n & 0 & 0 \\ 0 & -9u & -9v \\ 0.049 & 0 & -0.03 \end{pmatrix}\begin{pmatrix} x_1 \\ x_2 \\ x_3 \end{pmatrix}$$

$$\text{Let } P = P^T = \begin{pmatrix} P_1 & P_2 & P_3 \\ P_2 & P_3 & P_1 \\ P_3 & P_1 & P_2 \end{pmatrix} \neq \begin{pmatrix} 0 & 0 & 0 \\ 0 & 0 & 0 \\ 0 & 0 & 0 \end{pmatrix}$$

$$V(x) = x^T Px = \begin{pmatrix} x_1 & x_2 & x_3 \end{pmatrix}\begin{pmatrix} P_1 & P_2 & P_3 \\ P_2 & P_3 & P_1 \\ P_3 & P_1 & P_2 \end{pmatrix}\begin{pmatrix} x_1 \\ x_2 \\ x_3 \end{pmatrix} \quad \ldots\ldots\ldots\ldots \quad \text{Lyapunov function}$$

$$\dot{V}(x) = \dot{x}^T Px + x^T P\dot{x} = (Ax)^T Px + x^T P(Ax) = x^T A^T Px + x^T PAx = x^T(A^T P + PA)x$$

$\dot{V}$(x) = $x^T(A^T P + PA)x$

$$A^T = \begin{pmatrix} -0.1\varsigma_n & 0 & 0.049 \\ 0 & -9u & 0 \\ 0 & -9v & -0.03 \end{pmatrix}$$

$$A^T \text{ P} = \begin{pmatrix} -0.1\varsigma_n & 0 & 0.049 \\ 0 & -9u & 0 \\ 0 & -9v & -0.03 \end{pmatrix} \begin{pmatrix} P_1 & P_2 & P_3 \\ P_2 & P_3 & P_1 \\ P_3 & P_1 & P_2 \end{pmatrix}$$

$$= \begin{pmatrix} -0.1\varsigma_n P_1 + 0.049P_3 & -0.1\varsigma_n P_2 + 0.049P_1 & -0.1\varsigma_n P_3 + 0.049P_2 \\ -9uP_2 & -9uP_3 & -9uP_1 \\ -9vP_2 - 0.03P_3 & -9vP_3 - 0.03P_1 & -9vP_1 - 0.03P_2 \end{pmatrix}$$

$$\text{PA} = \begin{pmatrix} P_1 & P_2 & P_3 \\ P_2 & P_3 & P_1 \\ P_3 & P_1 & P_2 \end{pmatrix} \begin{pmatrix} -0.1\varsigma_n & 0 & 0 \\ 0 & -9u & -9v \\ 0.049 & 0 & -0.03 \end{pmatrix} =$$

$$\begin{pmatrix} -0.1\varsigma_n P_1 + 0.049P_3 & -9uP_2 & -9vP_2 - 0.03P_3 \\ -0.1\varsigma_n P_2 + 0.049P_1 & -9uP_3 & -9vP_3 - 0.03P_1 \\ -0.1\varsigma_n P_3 + 0.049P_2 & -9uP_1 & -9vP_1 - 0.03P_2 \end{pmatrix}$$

A^T P + PA=

$$-\begin{pmatrix} 2(0.1\varsigma_n P_1 - 0.049P_3) & 0.1\varsigma_n P_2 - 0.049P_1 + 9uP_2 & 0.1\varsigma_n P_3 - 0.049P_2 + 9vP_2 + 0.03P_3 \\ 0.1\varsigma_n P_2 - 0.049P_1 + 9uP_2 & 2(9uP_3) & 9uP_1 + 9vP_3 + 0.03P_1 \\ 0.1\varsigma_n P_3 - 0.049P_2 + 9vP_2 + 0.03P_3 & 9uP_1 + 9vP_3 + 0.03P_1 & 2(9vP_1 + 0.03P_2) \end{pmatrix}$$

$= -Q$; And Q = $Q^T > 0, as\ required$. Therefore the equilibrium point E_1(c,0,u) is Globally asymptotically stable.

CHAPTER FIVE

MATHEMATICAL SIMULATION

5.1. Preconditions

From the initial conditions:

$c(x,0) = exp\left(\frac{-x^2}{\epsilon}\right), x \in [0,1]\ and\ \epsilon > 0$

$v(x,0) = 1 - \frac{1}{2}\ exp\left(\frac{-x^2}{\epsilon}\right), x \in [0,1]\ and\ \epsilon > 0$ and

$u(x,0) = \frac{1}{2} exp\left(\frac{-x^2}{\epsilon}\right), x \in [0,1]\ and\ \epsilon > 0$, where ϵ is taken as 0.01 as eq.(4.14) it is possible to determine $\frac{\partial^2 c}{\partial x^2}, \frac{\partial^2 u}{\partial x^2}, \frac{\partial^2 v}{\partial x^2}$ as follows.

1. $c(x,0) = c_0 = exp\left(\frac{-x^2}{\epsilon}\right)$

$\frac{\partial c}{\partial x} = \frac{dc}{dx} = \frac{d}{dx}(e^{\frac{-x^2}{\epsilon}})$

$= \frac{-2x}{\epsilon} e^{\frac{-x^2}{\epsilon}}$

$\frac{\partial^2 c}{\partial x^2} = \frac{d}{dx}\left(\frac{-2x}{\epsilon} e^{\frac{-x^2}{\epsilon}}\right)$

$= \frac{-2}{\epsilon} e^{\frac{-x^2}{\epsilon}} + \frac{-2x}{\epsilon}\left(\frac{-2x}{\epsilon}\right) e^{\frac{-x^2}{\epsilon}}$

$$\frac{\partial^2 c}{\partial x^2} = \frac{-2}{\epsilon} e^{\frac{-x^2}{\epsilon}} + \frac{4x^2}{\epsilon^2} e^{\frac{-x^2}{\epsilon}}$$

2. $v(x,0) = v_0 = 1 - \frac{1}{2}\ exp\left(\frac{-x^2}{\epsilon}\right)$

$\frac{\partial v}{\partial x} = \frac{dv}{dx} = \frac{d}{dx}\left(1 - \frac{1}{2}\ exp\left(\frac{-x^2}{\epsilon}\right)\right)$

$\frac{\partial v}{\partial x} = \frac{x}{\epsilon} e^{\frac{-x^2}{\epsilon}}$

$\frac{\partial}{\partial x}\left(\xi_c \frac{\partial v}{\partial x}\right) = \xi_c \frac{\partial^2 v}{\partial x^2}$, and $\frac{\partial^2 v}{\partial x^2} = \frac{1}{\epsilon} e^{\frac{-x^2}{\epsilon}} - \frac{2x^2}{\epsilon^2} e^{\frac{-x^2}{\epsilon}}$

$$\frac{\partial}{\partial x}\left(\xi_c \frac{\partial v}{\partial x}\right) = \xi_c \left(\frac{1}{\epsilon} e^{\frac{-x^2}{\epsilon}} - \frac{2x^2}{\epsilon^2} e^{\frac{-x^2}{\epsilon}}\right)$$

3. $u(x,0) = u_0 = \frac{1}{2} exp\left(\frac{-x^2}{\epsilon}\right)$

$\frac{\partial u}{\partial x} = \frac{du}{dx} = \frac{d}{dx}\left(\frac{1}{2} exp\left(\frac{-x^2}{\epsilon}\right)\right)$

$= \frac{-x}{\epsilon} e^{\frac{-x^2}{\epsilon}}$

$\frac{\partial^2 u}{\partial x^2} = \frac{d}{dx}\left(\frac{-x}{\epsilon} e^{\frac{-x^2}{\epsilon}}\right)$

$$\frac{\partial^2 u}{\partial x^2} = \frac{-1}{\epsilon} e^{\frac{-x^2}{\epsilon}} + \frac{2x^2}{\epsilon^2} e^{\frac{-x^2}{\epsilon}}$$

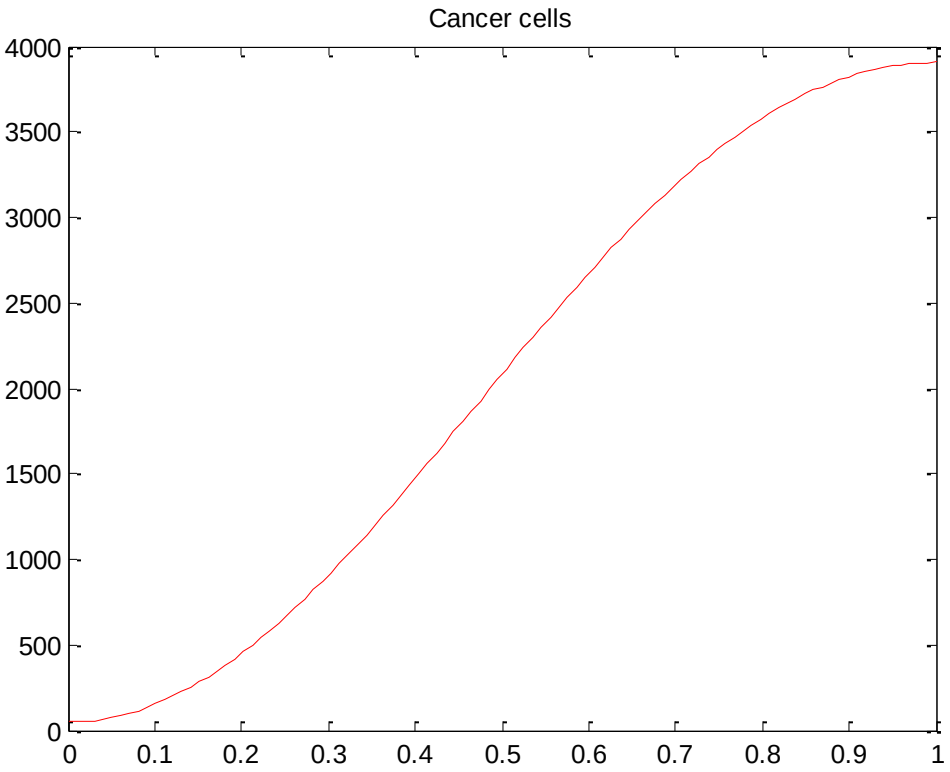
Let $f_1 = \frac{\partial^2 c}{\partial x^2}$, $f_2 = \frac{\partial^2 u}{\partial x^2}$, $f_3 = \frac{\partial^2 v}{\partial x^2}$, $f_4 = \mu_1 c(1-c-v)$, $f_5 = \mu_3 \varsigma_n c$, and

$k(c,v,u) = \frac{\partial c}{\partial t}$, $g(c,v,u) = \frac{\partial v}{\partial t}$, $h(c,v,u) = \frac{\partial u}{\partial t}$.

The values of parameters which are used to simulate the graphs in the following sub-topic are taken from table 2.

5.2. Simulation

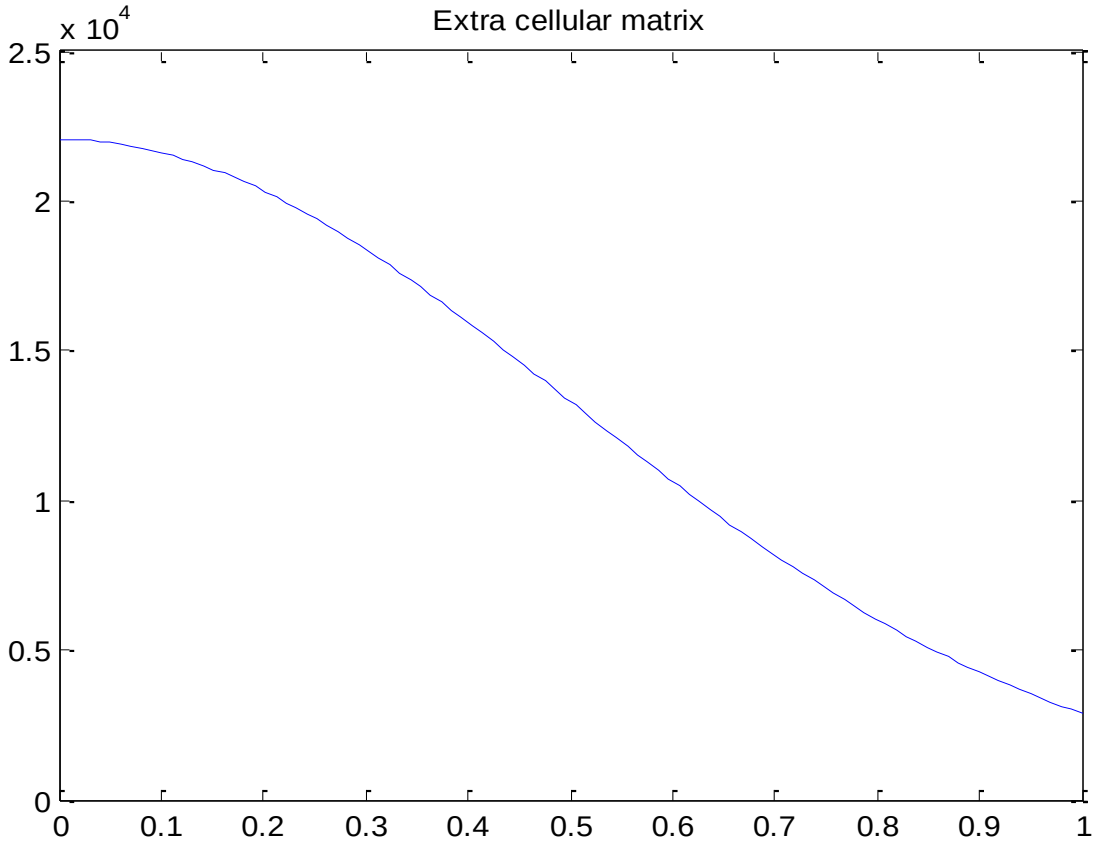
1. $\mathrm{k}(c, v, u) = D_c \frac{\partial^2 c}{\partial x^2} + \mu_1 c - \frac{\partial}{\partial x}\left(\chi_c\, c \frac{\partial u}{\partial x} + \xi_c \frac{\partial v}{\partial x}\right) - \mu_1 c^2 - \mu_1 c v - \mu_3 \varsigma_n c$



Taking the concept $\tau = \frac{L^2}{D}$ in consideration where L is the reference length scale and, D is the reference chemical diffusion coefficient, the graph can be interpreted as follows.

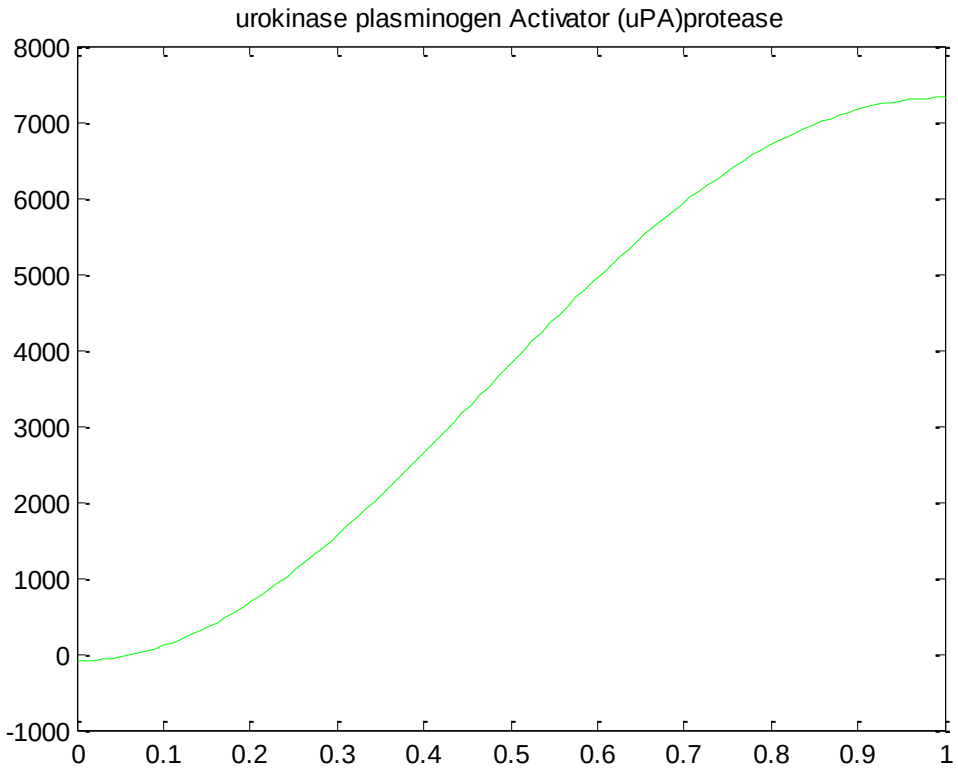
As time increases the number of tumor cells also increase in the patient body; the proliferation rate is slow from the beginning, fast at the middle and then decreases gradually.

2. $g(c, v, u) = (\delta_2 - \delta_1)uv + \mu_2 v(1 - c - v)$



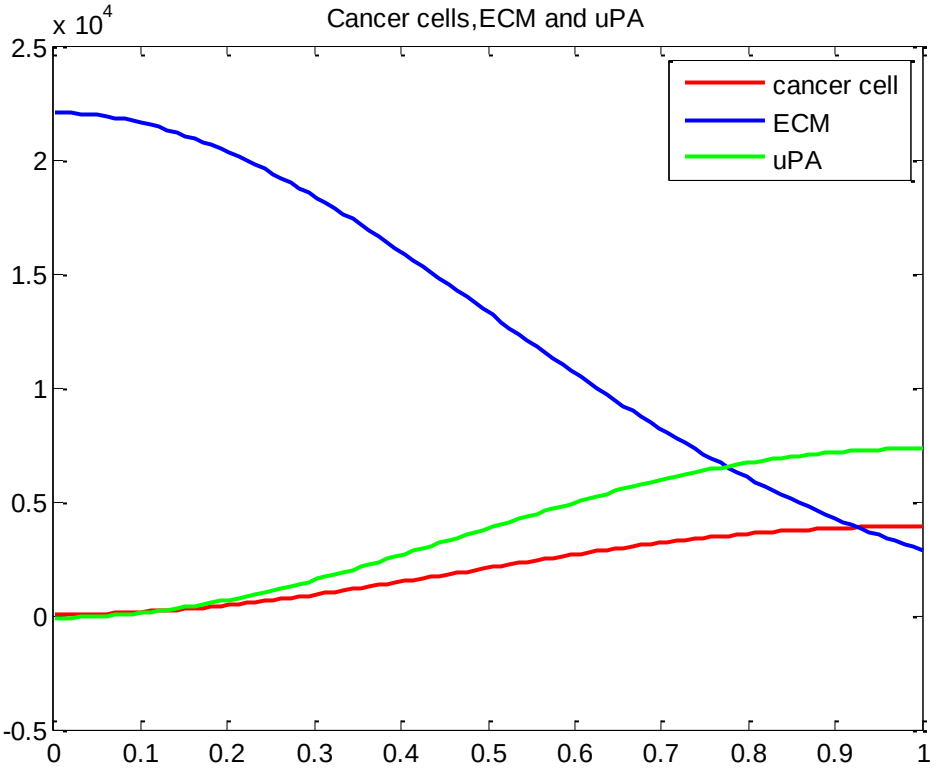
The degradation of extracellular matrix decreases gradually as time increases.

3. $\mathrm{h}(c, v, u) = D_u \frac{\partial^2 u}{\partial x^2} + (\alpha - \gamma)c - \beta u$



As shown on the graph, the rate of production of uPA in as time increase and the uPA protease secreted by tumor cell degrades the ECM and facilitate the invasion process.

4. $$\begin{cases} \frac{\partial c}{\partial t} = D_c \frac{\partial^2 c}{\partial x^2} - \frac{\partial}{\partial x}\left(\chi_c\, c \frac{\partial u}{\partial x} + \xi_c \frac{\partial v}{\partial x}\right) + \mu_1 c(1 - c - v) - \mu_3 \varsigma_n c = k(c, v, u) \\ \frac{\partial v}{\partial t} = (\delta_2 - \delta_1)uv + \mu_2 v(1 - c - v) = g(c, v, u) \\ \frac{\partial u}{\partial t} = D_u \frac{\partial^2 u}{\partial x^2} + (\alpha - \gamma)c - \beta u = h(c, v, u) \end{cases}$$



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The three in one: cancer cell, ECM, and uPA.

CHAPTER SIX

DISCUSSION AND CONCLUSION

6.1. Discussion

In this thesis I have presented a mathematical model of the invasion of tissue by cancer cells through the secretion of matrix degrading enzymes. In this regard, the model focuses specifically on the role of the urokinase plasminogen activation system.

The main achievement of this model is that fairly simple mathematical models representing the binding interactions of the components of the plasminogen activation system coupled with cell migration were able to capture the main characteristic effects of the system in cancer progression and invasion.

Initial conditions and boundary conditions are stated and used to analysis the model using Jacobian matrix and the stability of the equilibrium points are checked. The global stability of the equilibrium point (c,0,u) is checked by using Lyapunov's indirect method and finally the model is represented by a mathematical simulation. Solution profiles arise from the complex interplay between proliferative effects (cancer cell proliferation) and matrix remodeling and gradient driven migration (chemotaxis and haptotaxis). Cancer cells initially degrade the matrix through the uPA system (ultimately via plasmin activation) and can initially move via taxis into the degraded matrix, coupled with cell proliferation. However, as the matrix remodels, this provides the cancer cells with the opportunity to "re-degrade" this re-modeled matrix with the consequence that multiple clusters of invading cancer cells appear throughout the domain.

Of course, the results I have presented in this thesis are for a specific set of parameters. Other interesting dynamic spatio-temporal behavior is observed for other ranges of the parameters and for other aspects of the model.

6.2. Conclusion

I developed the model taking only time in to consideration (omitting spatial consideration). As the result indicates, the disease free equilibrium point (0,0,0) is stable which means there is no cancer cell, no degradation of the extra cellular matrix, and no uPA (the person is not affected by the disease). In the same way the equilibrium point (c,0,u) is asymptotically stable which

means there are cancer cells, and the cancer cells secret the uPA, but no degradation of ECM which means even if the ECM is not degraded the person is affected by the disease or the stage of the tumor is Benign. If the current model is extended, a more realistic treatment of the cancer cell random motility function will be considered. Although in this thesis I have considered this to be a constant (i.e. linear diffusion), from a physical point of view, migration of the cancer cells through the ECM is more like movement in a porous medium and so one may consider the cell random motility to be a function of the cancer cell density. Finally extending the current model to explicitly include the effect of matrix degrading enzymes will be considered. In this instance, the cancer cell motility may also depend upon the matrix degrading enzyme (MDE) concentration (chemokinesis). Considering such cases of nonlinear diffusion of the cancer cells naturally leads to a finite wave speed of propagation (given initial data with compact support).

On my work as I have discussed so far an attention is given to the effect of chemotheraphy drug on the tumor cell, and the model of its treatment. Now I want to leave the question ‘what happens to the tumor cell and its treatment when the tumor adapt with drugs?’

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