Mathematical Modeling of Tumour Invasion of Tissue

BY

Lemessa Berewak

A Thesis Submitted to Applied Mathematics Department School of Applied Natural Science

Presented in partial fulfillment of the requirement forthe degree of master's in Applied Mathematics(Specialization in Differential)

Office of Graduate Studies

Adama Science and Technology University

ADAMA,ETHIOPIA

August, 2018

Mathematical Modeling of Tumour Invasion of Tissue

BY

Lemessa Berewak

Advisor:

Shiferaw Feyissa (PhD)

A Thesis Submitted to Applied Mathematics Department School of Applied Natural Science

Presented in partial fulfillment of the requirement for degree of master's in Applied Mathematics(Specialization in Differential)

Office of Graduate Studies

Adama Science and Technology University

ADAMA,ETHIOPIA

August, 2018

Declaration

This preliminary thesis is my original work and has not been presented before in application for a higher degree in any other university, and that all sources of the material used for the preliminary thesis have been duly acknowledged.

Dr. Shiferaw Feyissa (Advisor)
Signature .....

Lemessa Berewak
Signature .....

Dedication

I dedicate this thesis to my beloved mother **Zenebu Milki**, who poured me the spirit of hard working. Mam may God rest your soul always in peace!

Advisor's Approval Sheet

To:Applied Mathematics program

Subject:Thesis Submission

This is to certify that the thesis entitled "Mathematical Modeling of Tumor Invasion of Tissue"submitted in partial fulfillment of the requirements for MSc.degree in Applied Mathematics, and has been carried out by Lemessa Berewak under my supervision. Therefore, I recommend that the student has fulfilled the requirements and hence hereby he can submit the thesis to the department.

Name	Signature	Date
Student		
Advisor		

Certification

This is to certify that the thesis prepared by Lemessa Berewak, entitled "Mathematical Modeling of Tumor Invasion of Tissue"and submitted in partial fulfillment of the requirements for the degree of Master's of Science in Applied Mathematics(Specialization in Differential).

As a member of the board of examiners of the MSc.Thesis open defense examination, we certify that we have read and evaluated the thesis prepared by Lemessa Berewak and examined the candidate. We recommended that the thesis be accepted as fulfilling the thesis requirement for the degree of Master's of Science in Applied Mathematics.

Name	Signature	Date
Student		
Advisor		
External Examiner		
Internal Examiner		
Chair person		
HoD		
School Dean		
GSD		

Table of Contents

List of Figures

List of Tables

List of Abbreviations

SoCNPDE	System of Coupled Nonlinear partial differential equation
LADM	Laplace-Adomian Decomposition method
LDM	Laplace decomposition method
ADM	Adomian decomposition method
MDEs	Matrix-degradative enzymes
MMPs	Matrix metalloproteinases
uPA	Urokinase-type plasminogen activator
uPAR	Urokinase plasminogen activator receptor
PAI-1	Urokinase plasminogen activator inhibitor type-1
ECM	Extracellular matrix
MM	Micro-molecule
$\partial\Omega$	boundary of Ω
$\bar{\Omega}$	Union of Ω and $\partial\Omega$
1-D	one-Dimensional domain
2-D	Two-Dimensional domain
3-D	Three-Dimensional domain

Abstract

In this study we develop a mathematical model using a system of partial differential equation which describes tumor invasion of tissues by focusing on the role of a generic matrix degrading enzyme such as urokinase plasminogen activator. The model consists of a system of reaction-diffusion-taxis partial differential equations describing the interactions between tumor cells, the urokinase plasminogen activator components and the host tissue. We develop a method to obtain an approximate solution of this non-linear system of partial differential equation by applying Laplace-Adomian decomposition method. In the developed method, the higher order derivative is reduced using the Laplace decomposition method and the non-linear terms are handled by Adomian decomposition method. By the developed mathematical model, we examined the invasive behaviours of tumor cells by plotting the graph of the obtained approximate solution from which the biological meaning of the solution is discussed. The results obtained from numerical computations carried out on the model equations produce, after undergoing morphological changes malignant and invasive tumour cells, i.e., cancer cells, break away from the primary tumour by loss of cell-cell adhesion, degrade their basement membrane(through the urokinase plasminogen activator system) and migrate through the extracellular matrix(via taxis) by enhancement of cell-matrix adhesion. The important factors governing the final tumour cell density distribution are extracellular matrix heterogeneity and the haptotactic response of the cells to the gradients created in the degraded matrix. Thus the only gradients in the extracellular matrix are a result of protaese degradation and hence the cells at the leading edge of the tumour are mostly affected by haptotaxis even though small clusters of cells can break away from the central mass of the tumour and invade further leading to possible metastasis. These results may lead to broadening our understanding of cancer cell invasion and in the long term, contributing to methods of patient treatment.

Acknowledgements

First and foremost, I offer my humble thanks to Almighty God for giving me the opportunity, strength and guidance to undertake my study.
Secondly, I would like to thank my Advisor, Shiferaw Feyissa (PhD) for his valuable assistance, counselling, support, patience,and kindness during my thesis work.
My sincere thanks also go to all staffs in the Department of Applied Mathematics who contributed for the success of both my courses and thesis work, for their suggestions and help over the past two years; especially, Legessa Lemecha (PhD), his constructive comments and encouragements cannot be evaluated.
Most importantly, I would like to give my special thanks to all my families whose love and support have sustained me during my studies and my relatives, for their consistence support, concern and encouragement throughout my studies.
And last but not least, all my friends and colleagues surely have provided support that I can never thank enough. I am very grateful with this life that I have been bestowed with, in which I have and know you all in my life.

Adama Science and Technology University — Lemessa Berewak
August, 2018

Chapter 1

Introduction

1.1 Background of the Study

All living organisms are composed of a collection of cells, which grow and divide in a controlled manner with a certain order for the proper functioning of the organism[1]. Sometimes cells start to grow without considering the normal balance between the cell growth and the death. Also, there is uncontrollable cell migration between neighboring tissues. Cells with these behaviors (that grow in uncontrollable fashion) are called cancer cells or tumor [2, 3]. In healthy tissues, cells work in perfect order. They collaborate and follow the rules governing normal tissue structure and maintenance, such as whether to divide, differentiate, or to die. But in cancer cells, which starts from mutations at the genetic level, cells acquire novel, often abnormal phenotypes which cause the cells to ignore the governing rules. Cancer cells grow uncontrollably, they may invade surrounding tissue (which is the topic of this study) and eventually spread throughout the body or metastasize. Cancer, in its most virulent form, is thus not only a disease of uncontrolled cell growth, but also a disease of uncontrolled cell migration and its formation begins with failure in the replication of a cell's DNA which leads to the uncontrolled division of the cell [4, 5]. When metastasis happens, cancer or tumour can cause the death of individuals. There are two broad categories of tumours: Benign and Malignant. The growth of benign tumours is self-limiting and their cells tend to stay in the original place. Benign tumours

remain localized to the tissue in which they arise and although they may grow large, they will not spread to other parts of the body. If found early, benign tumours can be cured either by surgical removal or by radiation therapy [6].

Unlike benign tumours, and even though both benign and malignant tumours grow in an uncontrolled way, malignant (cancerous) tumours are a far more serious matter. Some of their cells break off from the main primary tumour mass, invading and destroying surrounding tissue or traveling through the blood or lymph system to distant parts of the body, where new tumours might form. These malignant cells could break off again and establish even more colonies. The ability of malignant cancer to invade the local tissue and to spread throughout the organism is also their most insidious and dangerous property[7].

The first step in metastasis is the migration of cancer cells away from the primary tumour a process called tumour invasion. Tumour invasion consists of several important steps involving the interplay between the cells themselves and their micro-environment: reduction in or loss of cell-cell adhesion, enhanced tumour cell adhesion to the extracellular matrix, secretion of matrix degrading enzymes such as matrix metalloproteinases (MMPs) and urokinase-type plasminogen activator (uPA), leading to degradation of the basement membrane and the surrounding tissue or extracellular matrix (ECM) components; extracellular matrix degradation, and the movement or migration of the cancer cells coupled with their proliferation [8, 9].

Tumour may also be classified as solid tumour and liquid tumour. The name solid tumour is used for tumours that develop within an organ in opposition to liquid tumours (blood cancers, leukaemia which are not treated here).

Solid tumours grow through two distinct phases: the avascular and the vascular phase [10, 11]. During the avascular growth phase, the size of a solid tumour is restricted by a diffusion-limited nutrient supply and the solid tumour remains localized and grows to a maximum of a few millimeters in diameter. However, during the vascular growth stage

the process of tumour invasion of peritumoral tissue can and does take place. At the early growth stage, the tumour is relatively harmless and is still avascular that is, it lacks its own network of blood vessels for supplying nutrients, including oxygen, and for removing wastes. The critical event that converts a self-contained pocket of aberrant cells into a rapidly growing malignancy comes when the tumour becomes vascularized [12]. Therefore, one of the most important steps in malignant tumour growth is angiogenesis, which is the process by which tumours develop their own blood supply. For this reason, novel drugs are being developed specifically to target tumour blood vessels. Once the tumours have acquired their own blood supply, the tumour cells can escape the primary tumour via the circulatory system (metastasis) and set up secondary tumours elsewhere in the body. After angiogenesis and metastasis, the patient is left with multiple tumours in different parts of the body that are very difficult to detect and even more difficult to treat [13].
Classifying, grading and staging tumour is done to help health professionals more clearly about the tumor to determine treatment recommendation and to better understanding the patient's current health and prognosis.

Mathematical modelling of the various phases of tumour, in particular solid tumour growth, has been developing and expanding over the years in order to detect the progression of tumour in a relatively less time without a huge cost of laboratory experiments. These models can be classified into three categories: (i) ordinary differential equation (ODE) models, (ii) partial differential equation (PDE) models, and (iii) discrete models. ODE models describe the evolution of the cancer cells population growth rather than the growth of an individual cancer cell. Since the tumour growth decelerates as it grows bigger, dynamic growth models have also been used in the ODE models.

Even though the ODE models have successfully been used to compute the time evolution of the cancer cell population, lack of the consideration of spatial is the most apparent shortcoming of the ODE models. It necessitates the PDE models in the field of cancer biology. In addition to the tumor invasion, the spread of primary tumour cells to other

parts of the body to establish secondary tumours (metastasis) is the main cause of mortality among cancer patients [11, 14] . Therefore, the spatial dependency of the tumour invasion and the metastasis are also need to be considered in the mathematical models to realistically model tumour progression involves processes that interact with one another and occur at multiple scales of time and space. The time scales involved vary from nanoseconds to years: the signalling events in the cell typically occur over fractions of a second to a few seconds, the transcriptional events may take hours, it takes days for cell division, growth and tissue remodelling, months for tumour doubling times, and years for tumour growth, etc. The spatial scales range from nanometers for protein DNA interactions to centimeters for tumour mass development, angiogenesis, tissue invasion, etc. These scales are strongly linked with each other. A phenomenon cannot be considered using a single scale, fully isolated, without taking into account what happens at other smaller or larger scales.

In general, when incorporating the temporal and spatial scales, there are three commonly used viewpoints: the subcellular level, the cellular level, and the tissue level. Or, from a modeling point of view those levels can be referred as the microscopic scale, the mesoscopic scale, and the macroscopic scale, respectively. Cancer usually starts at the subcellular level marked by events that occur within the cell, such as genetic mutations, transduction of chemical signals between proteins and a large number of intracellular components that regulates activities at the cellular level such as uncontrolled cell division, cell detachment etc. Interactions between tumour cells and host cells, intravasation and extravasation processes are viewed from a larger scale, that is the mesoscopic scale. The macroscopic scale concerns activities that occur at the tissue level such as cell migration, convection and diffusion of chemical factors, which are all typical for continuum processes [15, 16].

Here we will present a mathematical model of tumor invasion of tissue that focus on the role of the urokinase plsminogen activasion enzyatic system and approximate the solution

of the model equation using the combination of Laplace decomposition method and Adomian decomposition method. The Laplace Decomposition Method (LDM) is a numerical algorithm to solve nonlinear ordinary and partial differential equations. It illustrates how the Laplace transform may be used to approximate the solutions of the nonlinear differential equations by manipulating the Adomian decomposition.

Adomian Decomposition Method (ADM), first developed by George Adomian [24], is a nonnumerical method for solving non-linear differential equations, both ordinary and partial. The technique uses a decomposition of the non-linear operator as a series of Adomian functions. Each term of this series is a generalized polynomial called the Adomian polynomial. ADM consists of splitting the given equation into linear, remainder and non-linear parts, inverting the highest order differential operator contained in the linear operator on both sides, identifying the initial or boundary conditions and the terms involving the independent variable alone as initial approximation. ADM provides the solution in a rapidly convergent series with easily computable components.

In this thesis we presented a continuum PDE model of tumor invasion and then we solve the model equation by the combination of Laplace decomposition and Adomian decomposition method.

1.2 Statement of the problem

Tumor is a very complex and multi-faceted, dynamic disease with underlying processes occurring over the full range of biological scales from genetic, through proteomic, cellular, tissue, organ, to the organism and sometimes even the whole population level [17, 18]. The most dangerous feature of a malignant tumour and the main cause of cancer deceases is the ability to metastasize. Metastasis is the formation of a secondary tumour foci at a site discontinuous from a primary tumour and involves complex molecular cascades comprising many interconnected steps. The steps are connected to each other through a series of adhesive interactions, invasive processes, and responses to chemotactic stimuli.

According to Vivi Andasari *et al.* [16] the major steps can be summarized as follows: (1) the detachment of tumour cells from the primary tumour mass, by down-regulation of cell-cell adhesion components such as cadherins and catenins; (2) invasion of the basement membrane and the extracellular matrix (ECM) components by over-expression of proteolytic enzymes such as matrix metalloproteinases (MMPs) and urokinase-type plasminogen activator (uPA), and migration through the ECM mediated by cell-matrix adhesion components such as integrins and fibronectin; (3) intravasation of the tumour cells into the blood vessels and lymphatic vessels which gives them access to the circulatory system to travel to distant anatomical sites; (4) extravasation or escape from the circulatory system and penetration into the surrounding tissue of new sites by adhesion of the circulating tumour cells to the endothelial cell lining at the capillary bed of the target organ site; (5) invasion of the basement membrane and target organ tissue; and (6) the growth of secondary tumours at the target organ site Tumour-induced angiogenesis also provides a route for metastatic spread. In the work by Chaplain and Lolas [7], the important process occurring during metastasis is invasion: and the metastatic cascade that we will mathematically investigate and model in this thesis is the local invasion of normal or host tissues by over expression of proteolytic enzymes which involved in step (2) of the above mentioned sequence of steps critical for metastasis.

This study is intended to answer the following basic questions:

- How we formulate a mathematical model that describes the way in which tumour cells invade the surrounding normal tissue?
- What is the role of proteolytic enzymes in the local invasion of the extracellular matrix (ECM) components?
- Does ECM displacement and density have an impact on the deceleration of the spatio-temporal evolution of tumour?
- What is the biological implication of the solution of the developed mathematical

model?

1.3 The Objective of the study

This study aims at achieving the following major and specific objectives.

1.3.1 General objective

The general objective of this study is to examine the way in which tumour cell invade the surrounding normal tissue

1.3.2 Specific Objective

The specific objectives of this study are to:

- develop a mathematical model that describes the way in which cancerous cells invade the surrounding normal tissue,
- examine the role of proteolytic enzymes in the local invasion of the ECM components,
- investigate the impact of ECM displacement and ECM density in the deceleration of the spatio-temporal evolution of a tumour and
- interpret the biological meaning of the solution of the developed mathematical model.

1.4 Significant and Beneficiaries

There is a genuine need for theoretical approaches and studies that may help to better understand various aspects of this phenomenon. The literature concerning the mathematical modelling of many of the key aspects of cancer growth, spread and treatment are now quite extensive.(see Dumitru *et al.*[19] and Zuzunna *et al.* [20]).This study provides a reliable information on how we can use the mathematical modelling to know the effects of

matrix degrading enzymes and tumour cells on ECM components. Since the mathematical model is the useful approach to determine and predict the stage, size and progression of tumours in realistic geometries, so does this study. This study may also improve our understanding of the effects of tumours which in turn may contribute to improving treatment strategies and initiates other researchers to undertake further extension and rigorous mathematical analysis and construction of numerical method on mathematical model of tumour growth and invasion. Thus, model may use to generate several hypotheses on how to slow tumour growth and invasion.

1.5 Expected Outcome

The expected outcomes of the proposed study are:

- A mathematical model that might provide a detailed description of the spatio-temporal evolution of the tumour, and may also help us in the understanding of the mechanism of the invasion process.

- mathematical model that describe interactions between tumour cells, extra cellular matrix, matrix degrading enzymes and other multiple cell distinct types from the surrounding micro-environment.

- Numerical solution (which may converge to the exact solution) of the developed mathematical model, from which the biological implication of the solution of the model interpreted.

Chapter 2

Literature Review

Using mathematical models to simulate dynamic biological processes has a long history. Over the years an increasing number of mathematical models of various aspects of tumor growth and tumor-host interactions, in particular solid tumour growth has been developing and expanding with the ultimate goal of understanding the response of the cancer population to clinical intervention, predicting patient's specific response to various dose schedules or treatment combinations and sequencing are on the way to becoming an invaluable tool to optimize patient care.

Alexender R.A. Andersen [4] presented a mathematical model of the invasion of healthy tissue by a solid tumor. The hybrid model they developed focuses on four key variables implicated in the invasion process: tumour cells, host tissue (extracellular matrix), matrix-degradative enzymes and oxygen. The model is considered to be hybrid since the latter three variables are continuous (i.e. concentrations) and the tumour cells are discrete (i.e. individuals). They based their mathematical model on the growth of a generic solid tumour, which they assumed has just been vascularized, i.e. a blood supply has been established. They choose to focus on four key variables involved in tumour cell invasion, thereby producing a minimal model, namely tumour cell density (denoted by n), MDE concentration (denoted by m), ECM concentration (denoted by f) and oxygen concentration (denoted by c). Each of the four variables is a function of the spatial variable x and time t. Their governing model describing the interactions of the tumour cells, MM,

MDEs and oxygen were formulated as:

$$\frac{\partial n}{\partial t} = \overbrace{D_n \nabla^2 n}^{\textbf{random motility}} - \overbrace{\chi \nabla .(n \nabla f)}^{\textbf{haptotaxis}}$$

$$\frac{\partial f}{\partial t} = - \overbrace{\delta m f}^{\textbf{degradation}}$$

$$\frac{\partial m}{\partial t} = \overbrace{D_m \nabla^2 m}^{\textbf{diffusion}} + \overbrace{\mu n}^{\textbf{production}} - \overbrace{\lambda m}^{\textbf{decay}}$$

$$\frac{\partial c}{\partial t} = \overbrace{D_c \nabla^2 c}^{\textbf{diffusion}} + \overbrace{\beta f}^{\textbf{production}} - \overbrace{\gamma n}^{\textbf{uptake}} - \overbrace{\alpha c}^{\textbf{decay}}$$

They examined how the geometry of the growing tumour is affected by tumour cell heterogeneity caused by genetic mutations. As the tumour grows, mutations occur leading to a heterogeneous tumour cell population with some cells having a greater ability to migrate, proliferate or degrade the surrounding tissue. All of these cell properties are closely controlled by cell-cell and cell-matrix interactions and as such the physical geometry of the whole tumour will be dependent on these individual cell interactions.

They also examined the effects of cell-cell and cell-matrix adhesion upon a growing invading tumour. In particular, they examined the effects of cell-matrix adhesion by considering three different initial matrix MM distributions, homogenous, heterogeneous and random. These results illustrated the importance of tumour cell-matrix interactions in aiding or hindering the migration of individual cells that define the tumour geometry. This is dependent on the fact that the tumour cells must mutate to an aggressive phenotype in order to exploit the changes in local MM gradients. Where aggressiveness is defined to be those phenotypes that have low proliferation age, zero cell-cell adhesion, a large haptotaxis coefficient and a low oxygen consumption rate. Their result indicated that local tumour cell-matrix interactions are ultimately what control the overall geometry of the tumour and not the cell-cell interactions.

In addition, cell-matrix interactions may also enhance natural selection, since the more

random the MM distribution the more likely the most aggressive phenotype will be selected. Thus, their result shown the importance of considering both cell-cell and cell-matrix interactions in a model of tumour invasion and perhaps the strong dependence of the tumour geometry on local cell-matrix interactions points the way for subsequent cancer research and treatment.

M.A.J Chaplain and G. Lolas [7] developed a mathematical model of cancer cell invasion of tissue (extracellular matrix) which focuses on the role of a generic matrix degrading enzyme such as uPA. The model consists of a system of partial differential equations describing the interactions between cancer cells(denoted by c), the matrix degrading enzyme (denoted by u) and the host tissue(denoted by v). They assumed that there is a change in cell number density due to dispersion; arising from random locomotion, that of the directional flow of cells due to spatial gradients of environmental stimuli, such as those stimulating chemotactic or haptotactic responses and the proliferation of cancer cells.

They also assumed that the ECM is degraded by uPA upon contact and its component re-established or re-modeled while they are competing for space with the invasive cells in a manner similar to that describing cancer cell proliferation. In their model factors influencing the protease concentration were assumed to be diffusion, protease production and protease decay. The governing equations describing the interactions between the tumour cells, extracellular matrix and uPA in the model was:

$$\frac{\partial c}{\partial t} = \overbrace{\nabla.(D_c \nabla c)}^{\textbf{dispersion}} - \overbrace{\nabla.(\chi_c c \nabla u)}^{\textbf{chemotaxis}} - \overbrace{\nabla.(\xi_c c \nabla v)}^{\textbf{haptotaxis}} + \overbrace{\mu_1 c(1 - \frac{c}{c_0} - \frac{v}{v_0})}^{\textbf{proliferation}}$$

$$\frac{\partial v}{\partial t} = - \overbrace{\delta u v}^{\textbf{proteolysis}} + \overbrace{\mu_2(1 - \frac{c}{c_0} - \frac{v}{v_0})}^{\textbf{re-establishment}}$$

$$\frac{\partial u}{\partial t} = \overbrace{D_u \nabla^2 u}^{\textbf{dispersion}} + \overbrace{\alpha c}^{\textbf{production}} - \overbrace{\beta u}^{\textbf{decay}}$$

The results obtained from numerical computations carried out on the model equations produce dynamic, heterogeneous spatio-temporal solutions and demonstrate the ability of

a rather simple model to produce complicated dynamics, all of which are associated with tumour heterogeneity and cancer cell progression and invasion.

By incorporating the proliferation function as well as the extracellular matrix re-establishment function as an function of variables they overcame a certain weakness of continuum models due to the fact that they normally only consider constant reproduction terms for cancer cells they deduced that when cancer cells secrete uPA,this resulted in an increase in their proliferation rate while when there is a decay of uPA, e.g. due to the presence of the inhibitors, the cancer cell proliferation rate will slow down. The results of the simulations of the model showed a very rich dynamic spatio-temporal behavior. The observed spatio-temporal heterogeneities in the solution profiles arise from the complex interplay between proliferative effects, cancer cell proliferation and matrix re-modeling and gradient-driven migration (chemotaxis and haptotaxis).

They also examined the effects that changing several key parameter values have on the solution. From the haptotaxis-only model they observed that by increasing the haptotactic coefficient, a large cluster of cancer cells breaks away from the primary tumour and migrates into the region. However, by the time that this secondary tumour reaches the boundary, it reverses its direction driven by the gradient of the undegraded extracellular components. They presumed that their boundary represents a hard tissue or bone that they assumed biologically that,the cancer cells unable to penetrate the hard tissue or bone and thus reverse their direction directed by ECM components gradient. They observed that addition of the tumour cell proliferation term and tissue remodeling term affected only the speed of the invasion since once again the invasion was successful.

Vivi Andasari [16] also presented the mathematical model of the uPA system and cancer cell invasion of tissue looking at the role of cell adhesion, using continuum approach. They focused on a model of the urokinase plasminogen activation (uPA) system and the role of cell adhesion in cancer invasion. The model explicitly considered the production of plasmin and the interactions between cancer cells (with uPAR located on their surface),

uPA, PAI-1, plasmin, and the extracellular matrix component vetronectin. In their model they assumed an unrestricted supply of plasminogen. Furthermore, they assumed a fixed average number of uPARs located on each cancer cells surface. This implies that the concentration of uPAR is proportional to the cancer cell density and they do not explicitly modeled the evolution of uPAR. They denoted the cancer cell density by $c(t,x)$, the uPA concentration by $u(t,x)$, the PAI-1 concentration by $p(t,x)$, the plasmin concentration by $m(t,x)$, and the VN concentration by $v(t,x)$ and the mathematical model depicting the interactions between all those variables , in its full dimensional form, was given by:

$$\frac{\partial c}{\partial t} = \overbrace{D_1\nabla^2 c}^{\textbf{random motility}} - \nabla.[\overbrace{\xi_u c\nabla u}^{\textbf{uPA-chemo}} + \overbrace{\xi_p c\nabla p}^{\textbf{PAI-1-chemo}} + \overbrace{\xi_c c\nabla v]}^{\textbf{VN-hapto}} + \overbrace{\alpha_1 c(1-\frac{c}{c_0})}^{\textbf{proliferation}}$$

$$\frac{\partial v}{\partial t} = -\overbrace{\beta v m}^{\textbf{degradation}} + \overbrace{\Phi_{21} u p}^{\textbf{uPA/PAI-1}} - \overbrace{\Phi_{22} v p}^{\textbf{PAI-1/VN}} + \overbrace{\alpha_2 v(1-\frac{v}{v_0})}^{\textbf{remodelling}}$$

$$\frac{\partial u}{\partial t} = \overbrace{D_3\nabla^2 u}^{\textbf{diffusion}} - \overbrace{\Phi_{31} p u}^{\textbf{uPA/PAI-1}} - \overbrace{\Phi_{33} c u}^{\textbf{uPA/uPAR}} + \overbrace{\gamma_{31} c}^{\textbf{production}}$$

$$\frac{\partial p}{\partial t} = \overbrace{D_4\nabla^2 p}^{\textbf{diffusion}} - \overbrace{\Phi_{41} p u}^{\textbf{PAI-1/uPA}} - \overbrace{\Phi_{42} p v}^{\textbf{PAI-1/VN}} + \overbrace{\gamma_{41} m}^{\textbf{production}}$$

$$\frac{\partial m}{\partial t} = \overbrace{D_5\nabla^2 m}^{\textbf{diffusion}} + \overbrace{\Phi_{52} p v}^{\textbf{PAI-1/VN}} + \overbrace{\Phi_{53} u c}^{\textbf{uPA/uPAR}} - \overbrace{\Phi_{54} m}^{\textbf{degradation}}$$

They performed a linear stability analysis and computational simulations of the model. Their main contribution and finding is the observation of a very rich (dynamic) spatio-temporal heterogeneity of the solutions. They showed that by varying key parameters of the model, the qualitative character of the solution, either of traveling-wave-like form or heterogeneous dynamics, can be changed. Cell adhesion has been shown to be critical in cancer progression, from local invasion where the cancer originates to the dissemination of cancer to distant anatomical sites or metastasis.

However, the effect of extra cellular matrix displacement from the foci of tumour is not included in the model equation to show the dynamics of the invasion process and the exact solution of mathematical modeling of tumour invasion is not tried. But, approximate

solution by laplace-adomian decomposition method may converge to the exact solution which is not considered in none of these studies. In the proposed study we tried to develop a mathematical model and numerical solution which fill this gap.

Chapter 3

Methodology of the Study

3.1 Study Design

The aim of this study is to develop a mathematical model using a system of partial differential equation which describes the interaction between tumour cell, urokinase plasminogen activator enzymatic system (mainly consist UPAR, UPA, PAI-1, matrix like protein-VN and degrading enzymes plasmin) and the surrounding tissue. In order to investigate the effect of the extracellular matrix(ECM) on the invasion process, we included the displacement of ECM (as the dependent variable) in the model. After we non-dimensionalized the formulated mathematical model, the numerical solution and simulation are conducted to understand the physical meaning of the governing equation. The numerical methods we used for this investigation is Laplace-Adomian decomposition method in which Laplace transform is used for reducing derivative and Adomian decomposition method is used for handling nonlinear terms in the equation. The method is applied to the system of coupled nonlinear partial differential equation(SoCNLPDE) by appropriately choosing the system parameter values and initial condition. Then we discussed the solution of system of the nonlinear system of partial differential equation with its graph.

3.2 Procedures of the Study

To attain the objective of the study, the following procedures will be undertaken:

- Defining the problem,
- Collecting information,
- Developing the model (modifying the existing model),
- Analysis of the model,
- Solving the model equation using numerical methods,
- discussing the solution with its graph.

Chapter 4

Model Formulation and Analysis

4.1 Biological Background

4.1.1 Component of the uPA system and it's Role in ECM proteolysis

Tumor is a very complex disease and its prognosis is primarily dependent on its ability to invade and metastasize. Therefore, there is a need for theoretical approaches and studies that may help to better understand various aspects of this phenomenon. This understanding is facilitated by an understanding of the interactions of the key components of invasion for matrix degradation. A crucial part of the invasive/metastatic process is the ability of the cancer cells to degrade the surrounding tissue or extracellular matrix (ECM). Many steps that occur during tumour invasion and metastasis require the regulated turnover of extracellular matrix (ECM) macromolecules. Breakdown of the ECM is accomplished by the concerted action of two general classes of the enzymatic system (or proteases): the large family of matrix metalloproteinases(MMPs) and the serine proteases/the plasminogen activator (PA) system. Both of these proteases have been repeatedly implicated in tumour invasion and metastasis. But, the plasminogen activation system has an important position among the extracellular proteases engaged in these degradation reactions and so we focus on this enzymatic system.

The urokinase plasminogen activation system (uPA system) is organized as a proteolytic

cascade with active proteases and their pro-enzymes, protease inhibitors, and extracellular binding proteins.The urokinase plasminogen activation system is consists of: the urokinase receptor (uPAR), urokinase plasminogen activator (uPA), the matrix-like protein vitronectin (VN) and plasminogen activator inhibitors: type-1 (PAI-1) and type-2 (PAI-2).

Urokinase Plasminogen Activator/uPA

uPA is an extracellular serine protease produced by cells as a single-chain proenzyme pro-uPA. Both pro-uPA and uPA, bind to uPA receptors (uPAR) located on the cell membrane. Two major functional domains of the uPA molecule are the protease domain and the growth factor domain. The protease part activates plasminogen (i.e. a ubiquitous protein produced mainly in the liver and present in blood and the matrix) and turns it into plasmin, which is able to digest basement membrane and extracellular matrix proteins. Indeed secreted uPA is often associated with plasminogen activator inhibitor-1 (PAI-1) and remains inactive. The growth factor domain has no protease activity but can bind a specific high-affinity cell-surface receptor, uPAR. Finally, uPA has a zymogen form, pro-uPA, which can be activated by plasmin and binds to uPAR.

Urokinase Plasminogen Activator Receptor/uPAR

uPAR is expressed in considerable amounts on the cell surface of various cell types such as blood leukocytes, endothelial cells, macrophages, fibroblasts, and by different types of cells in human cancer. In addition, uPAR is a high-affinity cell surface receptor for uPA(and of its zymogen form pro-uPA),which via the binding process localises the uPA and pro-uPA to the cell surface. uPAR mediates the binding of the zymogen pro-uPA to the plasma membrane where plasmin converts pro-uPA to the active zymogen, uPA, which in turn converts plasma membrane-associated plasminogen into plasmin. Importantly, uPAR contains another binding site for the ECM component called vitronectin(VN). uPAR contains a vitronectin binding site(s) distinct form the urokinase binding site and

since VN and uPA binding sites are distinct, uPAR can simultaneously bind both ligands, allowing coordinated regulation of proteolysis, cell adhesion and signalling. The strength of interaction between uPAR and VN is not mutually exclusive; rather inactive pro-uPA, as well as active uPA promote VN binding. uPAR is also expressed in many human cancers. It indicates poor prognosis and in some cases is predictive of invasion and metastasis. Importantly, uPAR expression in tumours can occur in tumour cells and/or tumour-associated stromal cells, such as fibroblasts and macrophages. Moreover, there is a certain crosstalk between these two binding processes, as the ligand binding of uPA to uPAR enhances the VN binding by uPAR.

Urokinase Plasminogen Activator Inhibitor Type-1/PAI-1

Secreted urokinase plasminogen activator is associated with inhibitors and remains inactive. In other words, for cells to protect themselves they must secrete a surplus of inhibitors to guarantee restraint of pericellular proteolysis. The inhibitor of uPA, belongs to the serpin (serine protein inhibitors) family and can specifically bind to and inhibit not only free, but also receptor bound uPA. One of these inhibitors is PAI-1, which is believed to be the most abundant, fast-acting inhibitor of uPA. It can specifically bind to soluble and membrane-bound uPA to inhibit plasminogen activation. In other words, as a major binding protein of VN, PAI-1 competes with uPAR for binding to VN and bring PAI-1 in close approximation with uPA, thereby promoting inhibition and clearance of uPA

Extracellular Matrix

The extracellular matrix (ECM) is known to contain many macromolecules such as vetronectin, laminin and fibronectin which can be degraded by several matrix degrading enzymes. Vitronectin is a versatile glycoprotein that is found in the extracellular matrix of endothelial cells, and within various tissues of the human body and promotes cell adhesion and spreading. As the name indicates, VN binds strongly to glass surfaces (vitro =

glass) and it has binding sites for several ligands, including, urokinase plasminogen activator receptor (uPAR), plasminogen activator inhibitor type-1(PAI-1). Interactions with an assortment of biological molecules are responsible for the multiple functions exhibited by vitronectin. Other functions of the protein that are confined to surfaces or tissues include cell-adhesion and regulation of pericellular proteolysis. Moreover VN functions as the major high-affinity binding protein of PAI-1, uPAR and integrins.

Vetronectin is recognized as the major binding protein of PAI-1, and its binding to uPAR could be expected to bring PAI-1 in close approximation with uPA, thereby promoting inhibition and clearance of uPA from its receptor uPAR. This process may effect a lower avidity of cellular attachment to vitronectin. In this paradigm, PAI-1, although decreasing uPA activity, would also promote detachment of the cell from its contact site. Thus, PAI-1 in circumstances where sustained proteolytic activity is not vital to movement could promote rather than retard migration. However, proteolytic degradation of the extracellular matrix is essential for the processes of tissue remodelling as well. These processes take place in a number of distinct physiological events in the healthy organism, such as trophoblast invasion, mammary gland involution, and skin wound healing.

Plasmin

Plasmin is a widespread enzyme(or a serine protease) capable of digesting basement membrane and many extracellular matrix proteins such as fibronectin, laminin, vitronectin and thrombospondin. In addition, plasmin can also activate many matrix metalloproteinases (MMPs), enhancing even more the degradation of extracellular matrix. It can also influence the composition of the extracellular environment by affecting the activity of cytokines and growth factors, for example, decreasing the activation of $TGF - \beta_1$. Therefore, the unrestrained generation of plasmin from plasminogen by the action of plasminogen activator (PA) is potentially hazardous to cells. In this regard, the process of plasminogen activation in a healthy organism is strictly controlled through the availability of PAs,

localized activation and interaction with specific inhibitors (PAIs). activity of plasmin is inhibited by α_2 -antiplasmin.

4.1.2 Proteolytic stimulation of Cell migration

Cell migration is the locomotion of a cell on a substratum of ECM proteins. Many of the activities of mammalian cells, such as embryogenesis, mitosis,morphogenesis, shape maintenance, cell orientation, survival, and motility depend on the attachment of cells to their surroundings such as the extracellular matrix (ECM) and other neighbouring cells. Most cells possess multiple mechanisms that enable them to bind to other neighbouring cells (cell-cell adhesion) and to the extracellular matrix (cell-matrix adhesion).

The maintenance, formation or disruption of cell-cell and cell-matrix adhesion are particularly important cellular events in cancer invasion and metastasis. Cell-cell adhesion functions to maintain a tumours compactness. Loss of cell-cell adhesion facilitates the detachment of tumour cells from the primary tumour mass. This event is then followed by the formation of cell-matrix adhesion that mediate the migration of tumour cells through the ECM. Disruption of cell-cell adhesion is essential for the first step of local invasion of cancer, in which malignant cells detach and break free from the primary tumour mass.

Cancer cells possess a broad spectrum of motility mechanisms, depending importantly on cell type and matrix structure. They can migrate as individual cells, referred to as individual cell migration, or expand in solid cell strands, sheets, files or clusters, called collective cells migration.

In general, cell movement through tissue may involve several different mechanisms. However, the two most important types of movement for invading cancer cells are diffusion (no preferred direction) and directed motion, with the latter usually dominating. Directed movement of cancer cells through the extracellular matrix (ECM) is possible due to the breakdown of ECM components, with the cancer cells generally secreting the enzymes which degrade one or more of the ECM constitutive proteins. Through a combination of

proliferation and migration the cancer cells then invade and spread into the ECM.

Chemotaxis and Haptotaxis

Tumour cells encounter a variety of soluble and substratum-bound factors which may influence their directed migration at different stages in the process of tumour invasion and metastasis. Such factors can promote the directed movement of tumour cells by at least two mechanisms, termed chemotaxis and haptotaxis. Chemotaxis is defined as cellular locomotion directed in response to a concentration gradient of a chemical factor in solution. Cells sense the chemical and migrate toward higher concentrations of this substance until they reach the source secreting it. On the other hand, gradients do not have to be in solution. An adhesive molecule could be present in increasing amounts along an extracellular matrix. A cell that was constantly making and breaking adhesions with such a molecule would move from a region of low concentration to an area where that adhesive molecule was more highly concentrated. Such a phenomenon is called haptotaxis.

The potential importance of a chemotactic response to ECM components is apparent when considering that during the process of tumour invasion and metastasis, proteolytic degradation results in solubilization of ECM components. As a result, tumour cells could conceivably detect and respond to the soluble fragments as well as to the insoluble intact matrix molecules. Therefore, chemotaxis and haptotaxis to ECM components represent two separate and distinguishable means by which tumour cells penetrate membranes and interstitial stroma. Cell motility (e.g. chemotaxis, chemokinesis, migration) stimulated by active uPA can involve plasmin generation and the subsequent degradation of ECM proteins and/or proteolytic trimming of cell surface components, including adhesion receptors and uPAR itself. uPAR has been reported to associate with many signaling molecules and to mediate signal transduction.

Cell adhesion

Another phenotypic alteration that must occur for the successful invasion of neighbouring tissue is changes in cell adhesion. Each cell has its own internal adhesion value i.e. the number of neighbours that it will preferentially adhere to A_e , and the number of external neighbours each cell has A_e and if $A_e > A_i$, then the cell is allowed to migrate. Cancer cells experience both adhesion to themselves, i.e. cell-cell adhesion and adhesion to components of the extracellular matrix (e.g. collagen, laminin fibronectin, vitronectin) i.e. cell-matrix adhesion. Both cell-cell interactions and cell-stroma interactions play an important role during the invasive cascade. Extracellular matrix (ECM) has a dual role : as the substratum on which the cells move and as the physical barrier that the cells have to surpass.

Extracellular matrix proteins and signalling molecules have provided new insights into their role as molecular coordinators of cell adhesion. The classical role of plasminogen activation is one counteracting cell-substratum and cell-cell adhesion as pericellular plasmin generation leads to degradation of adhesion receptors and their extracellular matrix ligands. However, under some conditions, binding of uPA to uPAR promotes cell-substratum adhesion, in this regard, binding of uPA to uPAR stimulates the adhesion of several integrin independent cell lines to vecronectin.

4.2 Model Formulation

Previously several studies have incorporated mathematical models for tumour invasion and metastasis. Many of these papers examine how cancer cells respond to extracellular matrix gradients via chemotaxis and haptotaxis. The gradients are created through the degradation of the extracellular matrix by matrix degrading enzymes. In this study, we will base our mathematical model on generic solid tumour invasion, which its general form is the same for both at avascular and at vascular stage, since we are focusing solely on the interactions between the tumour cells, MDEs and the surrounding tissue. We develop

a mathematical model consisting of six coupled partial differential equations describing the way in which the tumour cell density (denoted by c), the urokinase plasminogen activator (uPA) concentration (denoted by u), the extracellular matrix density (denoted by v) , the ECM displacement (denoted by s), the plasminogen activator inhibitor (PAI-1) concentration (denoted by p) and the plasmin concentration (denoted by m) are involved in invasion and derive partial differential equations governing the evolution in time and space of each variable. Further, since it is assumed that a fixed average number of receptors uPAR located on each cancer cell surface, there is no explicit modeling of uPAR. Therefore, the concentration of uPAR is considered to be proportional to the cancer cell density. Another important assumption is that the supply of plasminogen is unlimited in this model. Finally, the macroscopic model is obtained by accounting for the biological considerations described in previous section in conjunction with the following presumptions:

4.2.1 Cancer cell equation

According to the work by [16, 18] it is assumed that the cancer cells migrate into the extracellular matrix through a combination of diffusion(no preferred direction), chemotaxis and haptotaxis as well as undergoing proliferation. Thus it is assumed that there is a change in tumour cell number density due to diffusion of tumour cell, which we described in our model by a flux of the form $D_1 \nabla c$. where D_1 is tumour cell diffusion coefficient which may be a constant or a function of either the MDE concentration or ECM concentration/density, the latter cases representing a chemokinetic response i.e., increased diffusion will be observed for regions of high MDE/ECM concentration/density. It characterize how tumour cells would diffuse from higher to lower densities. Although it may be more accurate and closer to biological reality to consider nonlinear (degenerate) diffusion for simplicity linear diffusion can be assumed since such a choice does not affect the general framework of the process since the contribution of the chemokinetic term D_1

is always the smallest in cancer cell locomotion.

The second most important term that quantifies the change in tumour cell number density is that of the directional flow of cells due to spatial gradients of environmental stimuli, such as those stimulating chemotactic or haptotactic which are respectively, a response to gradients of diffusible and non-diffusible macromolecules such as urokinase plasminogen activator and urokinase plasminogen activator inhibitor (see [16, 18, 19]) and vitronectin [15, 16, 18, 19] respectively. These responses are incorporated into the model by taking the tumour cell flux (due to gradients) to be:

$$J_{flux} = J_{chemo} + J_{hapto} = \xi_u \nabla u + \xi_p \nabla p + \xi_v \nabla v$$

, Where $\chi_u, \xi_p, \xi_v > 0$ are the chemotactic due to uPA, PAI-1 and haptotactic due to vetronectin sensitivity function respectively. But for simpilicity, we consider them to be constant coefficients.

Regarding the proliferation of cancer cells, it assumed that in the absence of any extra-cellular matrix (ECM), cancer cell proliferation satisfies a logistic growth model. The presence of ECM leads to competition for space between the cancer cells and the ECM and this is modeled by including a crowding term which is proportional to the product cv. This distinguishes our model from the one proposed by Andasari [16] and Dumitru [19] since they do not consider any cell competition in order for them to focus entirely on cell-matrix interactions. On the contrary, Chaplain [19] considered a similar term in their work concerning cells proliferation but they do not consider chemotaxis due to PAI-1 since they do not model it explicitly.

Therefore, incorporating all the migration terms (diffusion, chemotaxis and haptotaxis) and the cell proliferation terms, the equation describing the spatio-temporal dynamics of the tumor cells reads:

$$\frac{\partial c}{\partial t} = \overbrace{D_1 \Delta c}^{\textbf{Diffusion}} - \nabla.[\ \overbrace{\xi_u c \nabla u}^{\textbf{uPA-chemo}} - \overbrace{\xi_p c \nabla p}^{\textbf{PAI-1-chemo}} - \overbrace{\xi_v c \nabla v}^{\textbf{VN-hapto}}\ ] + \overbrace{\alpha_1 (1 - \frac{c}{c_0} - \frac{v}{v_0})}^{\textbf{proliferation}},$$

where μ_1 is the proliferation rate of the cells, c_0 and v_0 are the maximum sustainable tumour cell and extracellular matrix respectively.

4.2.2 ECM density equation

We now turn our attention to the extracellular matrix. ECM is known to contain many macromolecules such as vitronectin, laminin and fibronectin which can be degraded by several matrix degrading enzymes [9]. Since extracellular matrix (ECM) is static [15, 9] any diffusion term (or other migration terms) is neglected from its model equation. Therefore, there is a change in its density due to its degradation by the uPA protease and factors facilitating and opposing its degradation.

We model the fact that plasmin degrades ECM upon contact which is accounted for by the degradation term $-\beta_1 vm$. In addition the binding of uPA and uPAR lead to plasmin formation which in turn catalyze the ECM degradation and in our model this effect is accounted for by the degradation term $-\Phi_{23}uc$. In opposition, inhibition of both uPA activity and of uPA/uPAR interactions prevents extracellular matrix degradation. The binding of PAI-1 to uPA inhibits the activation of plasminogen, leading to the protection of ECM molecular constituents and indirectly contributing to their production and hence the production term $\Phi_{22}up$ is added to the model equation. Simultaneously, the binding of PAI-1 to VN results in less binding to cell-surface receptors such as uPAR,and promoting its own production through the regulation of cell-matrix-associated signal transduction pathways,this inhibits the production of VN.This effect is accounted for by the degradation term $-\Phi_{25}vp$. In addition since binding of VN to uPAR bring PAI-1 in close approximation with uPA there by promoting inhibition and clearance of uPA from uPAR [15], it promotes the protection of VN. We accounted for this effect by the term $\Phi_{24}vc$. It also assumed that ECM components are re-established or re-modelled by other cells present in the tissue. These cells are assumed to be proliferating and competing for space with the invasive cells in a manner similar to that describing cancer cell proliferation, which again modeled by

incorporating a crowding term into the logistic equation. Using a modified logistic growth with rate constant α_2 to describe the ECM production, we have the following equation for the extracellular matrix:

$$\frac{\partial v}{\partial t} = -\overbrace{\beta_1 vm}^{\textbf{degradation}} + \overbrace{\Phi_{22} up}^{\textbf{uPA/PAI-1}} - \overbrace{\Phi_{23} uc}^{\textbf{uPA/uPAR}} + \overbrace{\Phi_{24} vc}^{\textbf{VN/uPAR}} - \overbrace{\Phi_{25} vp}^{\textbf{VN/PAI-1}} + \overbrace{\alpha_2 v(1 - \frac{v}{v_0} - \frac{c}{c_o})}^{\textbf{re-modeling}},$$

where Φ_{22} , Φ_{23} , Φ_{24} and Φ_{25} are a binding rates of uPA/PAI-1,uPA/uPAR, VN/uPAR,and VN/PAI-1 respectively.

4.2.3 ECM Displacement equation

We conclude that, the invasion process will stop where ECM is degraded a lot. Although it has not yet been explicitly demonstrated that, this captures that when cell-matrix adhesion is too low, no focal adhesions or stress fibres are formed, and the cells do not move. Therefore, the ECM displacement affect the individual cell interactions such as cell-cell and cell-matrix interaction which determine the whole property of tumour tissue and so factor affecting ECM displacement also affect the invasion process. These factors are, ECM is degraded in contact with enzyme plasmin and displaced from the tumor-host interface leading to the increase in the displacement of the ECM from the tumour foci[19, 20]. This phenomena is included into our model by the crowding term proportional to the product $\beta_2 vm$.

In opposition, since the binding of PAI-1 to uPA inhibits the activation of plasminogen, leading to the protection of VN and other ECM molecular constituents and indirectly contributing to ECM/VN production that decreases the ECM displacement. This effect is accounted in our model by inhibiting term $-\Phi_{32} up$. We also included the affect of the binding of PAI-1 to VN and that of uPA to uPAR that results in the inhibition of the production of VN and hence ECM displacement is increased by those phenomena; and those effects are included in our model by the terms $\Phi_{35} vp$ and $\Phi_{33} uc$ respectively. And also binding of VN to uPAR binds uPA to PAI-1 and hence promote the protection of

ECM leading to decrease in ECM displacement and so the term $\Phi_{34}cv$ is substructed from the model equation. Finally, ECM re-modelling opposes its displacement and this effect is subtracted from the system with a remodeling rate α_3. Therefore, governing equation for ECM displacement is given by:

$$\frac{\partial s}{\partial t} = \overbrace{\beta_2 vm}^{\textbf{degradation}} - \overbrace{\Phi_{32}up}^{\textbf{uPA/PAI-1}} + \overbrace{\Phi_{33}uc}^{\textbf{uPA/uPAR}} - \overbrace{\Phi_{34}vc}^{\textbf{VN/uPAR}} + \overbrace{\Phi_{35}vp}^{\textbf{VN/PAI-1}} - \overbrace{\alpha_3 v(1-\frac{v}{v_0}-\frac{c}{c_0})}^{\textbf{remodeling}},$$

where β_2 is a degradation rate, Φ_{32} ,Φ_{33} , Φ_{34} and Φ_{35} are respectively a binding rates of uPA/PAI-1,uPA/uPAR,VN/uPAR and VN/PAI-1.

4.2.4 uPA equation

The mathematical modelling of the uPA concentration dynamics accounts for the following aspects. Specifically, uPA is produced by cancer cells (which is considered here by $\Phi_{46}c$), diffuses throughout the extracellular matrix which is accounted for by the term $D_4\Delta u$ and removed from the system due to its binding with PAI-1 and uPAR, per unit time which is considered in our model equation by the terms $-\Phi_{42}up$ and $-\Phi_{43}uc$ respectively [16, 18, 19].

In addition, we consider that, since the binding of VN to uPAR brings PAI-1 to uPA which is in turn results in the decay of uPA. This effect is included in our model with decay term of the form $-\Phi_{44}vc$. Similarly the binding of PAI-1 to VN cause the detachment of the cell from its contact site and simultaneously the removal of PAI-1 from the system which is in turn have an additional contribution in the production of uPA and we accounted for this effect by the term $\Phi_{45}vp$. Therefore, this can be formalised mathematically as follows:

$$\frac{\partial u}{\partial t} = \overbrace{D_4\Delta u}^{\textbf{Diffusion}} - \overbrace{\Phi_{42}up}^{\textbf{uPA/PAI-1}} - \overbrace{\Phi_{43}uc}^{\textbf{uPA/uPAR}} - \overbrace{\Phi_{44}vc}^{\textbf{VN/uPAR}} + \overbrace{\Phi_{45}vp}^{\textbf{VN/PAI-1}} + \overbrace{\Phi_{46}c}^{\textbf{production}},$$

where Φ_{46} is production rate of uPA by cancer cell, D_4 is a constant diffusion coefficient, Φ_{42},Φ_{43} , Φ_{44} and Φ_{45} are respectively a binding rates of uPA/PAI-1,uPA/uPAR, VN/uPAR and VN/PAI-1.

4.2.5 PAI-1 Equation

The conservation equation for the concentration of PAI-1 include, a diffusion term, production being as a result of plasmin formation and its neutralisation in the system occurs by its binding to VN and to uPA [16, 18, 19]. Additionally, since the binding of VN to uPAR result in the binding of PAI-1 to uPA which in turn leads removal of PAI-1 from the system and also the binding of uPA to uPAR lead plasmin formation. Therefore, it has indirect contribution in PAI-1 production. Addition of these two considerations lead us to the following governing equation:

$$\frac{\partial p}{\partial t} = \overbrace{D_5 \Delta p}^{\textbf{Diffusion}} - \overbrace{\Phi_{52} up}^{\textbf{uPA/PAI-1}} + \overbrace{\Phi_{53} uc}^{\textbf{uPA/uPAR}} - \overbrace{\Phi_{54} vc}^{\textbf{VN/uPAR}} - \overbrace{\Phi_{55} vp}^{\textbf{VN/PAI-1}} + \overbrace{\Phi_{56} m}^{\textbf{production}} ,$$

where D_5 is a constant diffusion coefficient, Φ_{56} is a constant production rate as a result of plasmin formation, Φ_{55} and Φ_{52} are ,binding rates of PAI-1 to VN and uPA respectively, Φ_{54} and Φ_{53} are binding rate of VN to uPAR and uPA to uPAR respectively.

4.2.6 Plasmin equation

The evolution of plasmin concentration is modelled as follows. Plasmin exercises a local diffusion per unit time [16, 18, 19] , and it is considered that the binding of uPA to uPAR provides an opportunity for pericellular proteolytic activity through plasminogen activation leading to plasmin formation [19]. Moreover, the binding of PAI-1 to VN indirectly enhances the binding of uPA to uPAR, therefore bringing additional contribution to plasmin formation [15, 16, 18, 19]. Furthermore because the binding of uPA to PAI-1 and VN to uPAR lead to the decay of uPA which indirectly results in the additional decay of plasmin we add these affects in our model. Finally, the term $-\Phi_{66} m$ models the deactivation of plasmin by the action of the plasmin inhibitor α_2 -antiplasmin. Thus, these assumptions give us the following evolution law:

$$\frac{\partial m}{\partial t} = \overbrace{D_6 \Delta m}^{\textbf{Diffusion}} - \overbrace{\Phi_{62} up}^{\textbf{uPA/PAI-1}} + \overbrace{\Phi_{63} uc}^{\textbf{uPA/uPAR}} - \overbrace{\Phi_{64} vc}^{\textbf{VN/uPAR}} + \overbrace{\Phi_{65} vp}^{\textbf{VN/PAI-1}} - \overbrace{\Phi_{66} m}^{\textbf{degradation}} .$$

Where D_6 is a diffusion coefficient, Φ_{62} ,Φ_{63},Φ_{64} and Φ_{65} are binding rates of uPA/PAI-1, uPA/uPAR, VN/uPAR, VN/PAI-1 respectively and Φ_{66} is the decay rate of plasmin due to inhibitor.

The complete system of equations describing the interactions between the tumour cells, extracellular matrix and uPA enzymatic system is therefore:

$$\frac{\partial c}{\partial t} = \overbrace{D_1\Delta c}^{\textbf{Diffusion}} - \nabla.[\overbrace{(\xi_u c\nabla u)}^{\textbf{uPA-chemo}} + \overbrace{(\xi_p c\nabla p)}^{\textbf{PAI-1-chemo}} + \overbrace{(\xi_v c\nabla v)}^{\textbf{VN-hapto}}] + \overbrace{\alpha_1 c(1-\frac{c}{c_0}-\frac{v}{v_0})}^{\textbf{proliferation}}, \tag{4.2.1}$$

$$\frac{\partial v}{\partial t} = -\overbrace{\beta_1 vm}^{\textbf{degradation}} + \overbrace{\Phi_{22}up}^{\textbf{uPA/PAI-1}} - \overbrace{\Phi_{23}uc}^{\textbf{uPA/uPAR}} + \overbrace{\Phi_{24}vc}^{\textbf{VN/uPAR}} - \overbrace{\Phi_{25}vp}^{\textbf{VN/PAI-1}} + \overbrace{\alpha_2 v(1-\frac{v}{v_0}-\frac{c}{c_o})}^{\textbf{re-modeling}}, \tag{4.2.2}$$

$$\frac{\partial s}{\partial t} = \overbrace{\beta_2 vm}^{\textbf{degradation}} - \overbrace{\Phi_{32}up}^{\textbf{uPA/PAI-1}} + \overbrace{\Phi_{33}uc}^{\textbf{uPA/uPAR}} - \overbrace{\Phi_{34}vc}^{\textbf{VN/uPAR}} + \overbrace{\Phi_{35}vp}^{\textbf{VN/PAI-1}} - \overbrace{\alpha_3 v(1-\frac{v}{v_0}-\frac{c}{c_0})}^{\textbf{remodeling}}, \tag{4.2.3}$$

$$\frac{\partial u}{\partial t} = \overbrace{D_4\Delta u}^{\textbf{Diffusion}} - \overbrace{\Phi_{42}up}^{\textbf{uPA/PAI-1}} - \overbrace{\Phi_{43}uc}^{\textbf{uPA/uPAR}} - \overbrace{\Phi_{44}vc}^{\textbf{VN/uPAR}} + \overbrace{\Phi_{45}vp}^{\textbf{VN/PAI-1}} + \overbrace{\Phi_{46}c}^{\textbf{production}}, \tag{4.2.4}$$

$$\frac{\partial p}{\partial t} = \overbrace{D_5\Delta p}^{\textbf{Diffusion}} - \overbrace{\Phi_{52}up}^{\textbf{uPA/PAI-1}} + \overbrace{\Phi_{53}uc}^{\textbf{uPA/uPAR}} - \overbrace{\Phi_{54}vc}^{\textbf{VN/uPAR}} - \overbrace{\Phi_{55}vp}^{\textbf{VN/PAI-1}} + \overbrace{\Phi_{55}m}^{\textbf{production}}, \tag{4.2.5}$$

$$\frac{\partial m}{\partial t} = \overbrace{D_6\Delta m}^{\textbf{Diffusion}} - \overbrace{\Phi_{62}up}^{\textbf{uPA/PAI-1}} + \overbrace{\Phi_{63}uc}^{\textbf{uPA/uPAR}} - \overbrace{\Phi_{64}vc}^{\textbf{VN/uPAR}} + \overbrace{\Phi_{65}vp}^{\textbf{VN/PAI-1}} - \overbrace{\Phi_{66}m}^{\textbf{degradation}}. \tag{4.2.6}$$

4.3 Model Analysis

4.3.1 Non-dimensionalization

In order to solve the system of equation (4.2.1)-(4.2.6) numerically, we first non-dimensionalise the system of equations; So, the variables and parameters in the uPA system equations are transformed into dimensionless quantities using the following reference variables:

1. a reference length scale, L, (e.g. the maximum invasion distance of the tumor cells at this early stage of invasion 0.1 cm);

2. a reference time unit, $\tau = L^2 D^{-1}$, where, D is a reference chemical diffusion coefficient e.g. $D = 10^{-6} cm^2 s^{-1}$ (see Ref. [16]), therefore, it can be deduced that $\tau = 10^4$

3. a reference tumour cell density c_0, extracellular matrix density v_0 ,extracellular matrix displacement s_0 , uPA concentration u_0, PAI-1 concentration p_0 (where $c_0 = 6.7 \times 10^7 cell cm^{-3}$,$v_0 = 1nM$,$u_0 = 1nM$,$p_0 = 1nM$,$m_0 = 1nM$ and s_0 is an appropriate ECM reference displacement, (see [16] and [18] for details).

Then we define the dimensionless variables as:

$$\tilde{t} = \frac{t}{\tau}, \tilde{x} = \frac{x}{L}, \tilde{c} = \frac{c}{c_0} \tilde{v} = \frac{v}{v_0}, \tilde{s} = \frac{s}{s_0}, \tilde{u} = \frac{u}{u_0}, \tilde{p} = \frac{p}{p_0}, \tilde{m} = \frac{m}{m_0}. \tag{4.3.1}$$

as well as the full set of non-dimensional parameters are given by table 4.1 .

Table 4.1: Set of non-dimensional Parameter from which the non dimensional variables are obtained

$D_c = \frac{D_1}{D}$,	$\chi_u = \xi_u \frac{u_0}{D}$,	$\chi_P = \xi_p \frac{p_o}{D}$,	$\chi_v = \xi_v \frac{v_0}{D}$,	$\mu_1 = \alpha_1 c_0 \tau$,
$\delta_1 = \beta_1 m_0 \tau$,	$\phi_{22} = \Phi_{22} \frac{u_o p_0}{v_0} \tau$,	$\phi_{23} = \Phi_{23} \frac{u_0 c_0}{v_0} \tau$,	$\phi_{24} = \Phi_{24} c_0 \tau$,	$\phi_{25} = \Phi_{25} p_0 \tau$,
$\mu_2 = \alpha_2 v_0 \tau$,	$\delta_2 = \beta_1 \frac{v_0 m_0}{s_o} \tau$,	$\phi_{32} = \Phi_{32} \frac{u_0 p_0}{s_0} \tau$,	$\phi_{33} = \Phi_{33} \frac{u_0 c_0}{s_0} \tau$,	$\phi_{34} = \Phi_{34} \frac{v_0 c_0}{s_0} \tau$,
$\phi_{35} = \Phi_{35} \frac{v_0 p_0}{s_0} \tau$,	$\mu_3 = \alpha_3 \frac{v_0}{s_0} \tau$,	$D_u = \frac{D_4}{D}$,	$\phi_{42} = \Phi_{42} p_0 \tau$,	$\phi_{43} = \Phi_{43} c_0 \tau$,
$\phi_{44} = \Phi_{44} \frac{v_0 c_0}{u_0} \tau$,	$\phi_{45} = \Phi_{45} \frac{v_0 p_0}{u_0} \tau$,	$\phi_{46} = \Phi_{46} \frac{c_0}{u_0} \tau$,	$D_p = \frac{D_5}{D}$,	$\phi_{52} = \Phi_{52} u_0 \tau$,
$\phi_{53} = \Phi_{53} \frac{u_0 c_0}{p_0} \tau$,	$\phi_{54} = \Phi_{54} \frac{v_0 c_0}{p_0} \tau$,	$\phi_{55} = \Phi_{55} v_0 \tau$,	$\phi_{56} = \Phi_{56} \frac{m_0}{p_0} \tau$,	$D_m = \frac{D_6}{D}$,
$\phi_{62} = \Phi_{62} \frac{u_0 p_0}{m_0} \tau$,	$\phi_{63} = \Phi_{63} \frac{u_0 c_0}{m_0} \tau$,	$\phi_{64} = \Phi_{64} \frac{v_0 c_0}{m_0} \tau$,	$\phi_{65} = \Phi_{65} \frac{v_0 p_0}{m_0} \tau$,	$\phi_{66} = \Phi_{66} \tau$.

Inserting the non-dimensional variables (4.3.1) and parameters above into the system (4.2.1) -(4.2.6) and by omitting the tildes for notational simplicity, we obtain the non-dimensionalised form of the system of PDEs given by (4.3.2)-(4.3.7):

$$\frac{\partial c}{\partial t} = D_c \Delta c - \nabla.[(\chi_u c \nabla u) + (\chi_p c \nabla p) + (\chi_v c \nabla v)] + \mu_1 c(1 - c - v), \tag{4.3.2}$$

$$\frac{\partial v}{\partial t} = -\delta_1 v m + \phi_{22} u p - \phi_{23} u c + \phi_{24} v c - \phi_{25} v p + \mu_2 v(1 - v - c), \tag{4.3.3}$$

$$\frac{\partial s}{\partial t} = \delta_2 vm - \phi_{32} up + \phi_{33} uc - \phi_{34} vc + \phi_{35} vp - \mu_3 v(1 - v - c), \tag{4.3.4}$$

$$\frac{\partial u}{\partial t} = D_u \Delta u - \phi_{42} up - \phi_{43} uc - \phi_{44} vc + \phi_{45} vp + \phi_{46} c, \tag{4.3.5}$$

$$\frac{\partial p}{\partial t} = D_p \Delta p - \phi_{52} up + \phi_{53} uc - \phi_{54} vc - \phi_{55} vp + \phi_{56} m, \tag{4.3.6}$$

$$\frac{\partial m}{\partial t} = D_m \Delta m - \phi_{62} up + \phi_{63} uc - \phi_{64} vc + \phi_{65} vp - \phi_{66} m. \tag{4.3.7}$$

4.3.2 Initial and Boundary condition

We consider system (4.3.2)-(4.3.7) to hold for times $t \in (0, T]$ and on a bounded spatial domain $\Omega \subset \mathbb{R}^d$, for $d = 1$, $d = 2$ or $d = 3$ representing a region of tissue under consideration. We use three different cases of domains, each parameterised by a positive parameter M: the one-dimensional domain $\Omega_1 := (-M, M) \subset \mathbb{R}^1$, the two-dimensional square domain $\Omega_2 := (-M, M) \times (-M, M) \subset \mathbb{R}^2$ and the three-dimensional domain $\Omega_3 := (-M, M) \times (-M, M) \times (-M, M) \subset \mathbb{R}^3$. System (4.3.2)-(4.3.7) must be closed and in order to close the system, appropriate initial conditions for each of the dependent variables c , v , s , u ,p and m are required.

According to the studies by Vivi Andasari [16],Chaplain [15] and Chaplain *et al.* [7] it is assumed that initially there is a cluster of cancer cells already present at $x = 0$ and that they have penetrated a short distance into the extracellular matrix, while the remaining space is occupied by the matrix alone. Additionally, it is assumed that the uPA protease as well as the PAI-1 initial concentration are proportional to the initial cancer cell density. At the same time, As described in the study by Dumitru Trucu [19],the movement direction and displacement magnitude of the part of the invading edge of the tumour is determined by the plasmin in the peritumoural region; i.e. invasion started if and only if, a sufficient amount of plasmin has been produced on $\Omega|_{t_0}$ across the invading edge and its spatial distribution characterises ECM degradation. Therefore, for the initial plasmin protase entering the uPA system we suppose that it is also proportional to the

initial cancer cell density present at $x = 0$ while the ECM is not yet degraded by the plasmin protaese and so we consider a zero initial ECM displacement. Further, the initial conditions for all dependent variable are considered as follows by the system of equation (4.3.8) :

$$\begin{aligned} c(0,\mathbf{x}) &= \exp(-100\,|\mathbf{x}|^2), \\ v(0,\mathbf{x}) &= 1 - \frac{1}{2}\exp(-100\,|\mathbf{x}|^2), \\ s(0,\mathbf{x}) &= 0 \\ u(0,\mathbf{x}) &= \frac{1}{2}\exp(-100\,|\mathbf{x}|^2), \\ p(0,\mathbf{x}) &= \frac{1}{20}\exp(-100\,|\mathbf{x}|^2), \\ m(0,\mathbf{x}) &= \frac{1}{200}\exp(-100\,|\mathbf{x}|^2). \end{aligned} \tag{4.3.8}$$

and presented in figure(4.1). in $1-D$ i.e. for $t \in [0,T]$ and $x \in \mathbb{R}$. It also assumed

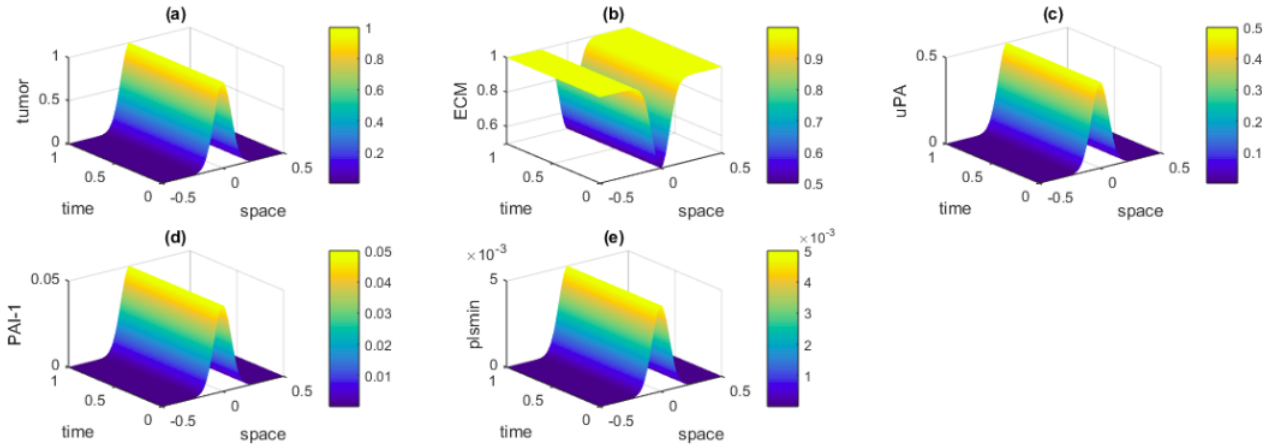

Figure 4.1: Initial conditions of the tumor cell density, ECM density and uPA and PAI-1 concentration given by (4.3.8)

.

that cancer cells, and as a consequence uPA, PAI-1, plasmin and ECM displacement remain within the domain of tissue under consideration and therefore zero-flux boundary conditions are imposed on $\partial\Omega$, the boundary of Ω. For the matrix density, $v(t,\mathbf{x})$ satisfies an ordinary differential equation (ODE) and so no boundary conditions can be prescribed.

4.3.3 Parameter estimation

In this work, whenever possible values of the parameters are estimated from available experimental data used in comparable models; i.e, we took our baseline set of parameters in line with previous comparable models of tumor cell invasion. The majority of these values of the parameters are taken from Andasari[16] and Dumiritu *et al.*[19] except for the values of the new parameters δ_2 , ϕ_{32}, ϕ_{33} , ϕ_{34} ϕ_{35} , μ_3 ϕ_{44} , ϕ_{53} ϕ_{54} , ϕ_{55} , ϕ_{62} , ϕ_{64} , ϕ_{23} , ϕ_{24} which we choose their values in order to give the best qualitative results in the simulations. A summary of the values of the non-dimensional parameter set $\mathcal{P}$ used in the solution are given in Table below:

Table 4.2: Parameter set $\mathcal{P}$ of the uPA model and their values

$D_c = 3.5 \times 10^{-4}$	$\chi_u = 3.05 \times 10^{-2}$	$\chi_p = 3.75 \times 10^{-2}$	$\chi_v = 2.85 \times 10^{-2}$
$\mu_1 = 0.25$	$\delta_1 = 0.15$	$\phi_{22} = 0.75$	$\phi_{23} = 0.2$
$\phi_{24} = 0.5$	$\phi_{25} = 0,55$	$\mu_2 = 0.15$	$\delta_2 = 0.85$
$\phi_{32} = 0.075$	$\phi_{33} = 0.75$	$\phi_{34} = 0.0025$	$\phi_{35} = 0.75$
$\mu_3 = 0.0275$	$D_u = 2.5 \times 10^{-3}$	$\phi_{42} = 0.75$	$\phi_{43} = 0.3$
$\phi_{44} = 0.00275$	$\phi_{45} = 0.55$	$\phi_{46} = 0.215$	$D_p = 3.5 \times 10^{-3}$
$\phi_{52} = 0.5$	$\phi_{53} = 0.2$	$\phi_{54} = 0.00425$	$\phi_{55} = 0.55$
$\phi_{56} = 0.5$	$D_m = 4.91 \times 10^{-3}$	$\phi_{62} = 0.2$	$\phi_{63} = 0.75$
$\phi_{64} = 0.0625$	$\phi_{65} = 0.11$	$\phi_{66} = 0.5$	

Chapter 5

Numerical Solution/Simulation

5.1 Solving System by Using LADM

Under this section we are going to solve this complicated system of coupled non linear partial differential equations model (4.3.2)-(4.3.7) supplemented by the initial conditions (4.3.8) numerically by using the analytical approximation method called the laplace-Adomian Decomposion method. The Laplace-adomian decomposition method consists of first applying the Laplace transform[21, 22]; and hence we apply the Laplace transform with respect to the variable $'t'$ to both sides of system of equations (4.3.2)-(4.3.7) and have:

$$\mathcal{L}[\frac{\partial c}{\partial t}] = \mathcal{L}[D_c\Delta c - \nabla.[(\chi_u c\nabla u) + (\chi_p c\nabla p) + (\chi_v c\nabla v)] + \mu_1 c(1-c-v)],$$

$$\mathcal{L}[\frac{\partial v}{\partial t}] = \mathcal{L}[-\delta_1 vm + \phi_{22}up - \phi_{23}uc + \phi_{24}vc - \phi_{25}vp + \mu_2 v(1-v-c)],$$

$$\mathcal{L}[\frac{\partial s}{\partial t}] = \mathcal{L}[\delta_2 vm - \phi_{32}up + \phi_{33}uc - \phi_{34}vc + \phi_{35}vp - \mu_3 v(1-v-c)],$$

$$\mathcal{L}[\frac{\partial u}{\partial t}] = \mathcal{L}[D_u\Delta u - \phi_{42}up - \phi_{43}uc - \phi_{44}vc + \phi_{45}vp + \phi_{46}c],$$

$$\mathcal{L}[\frac{\partial p}{\partial t}] = \mathcal{L}[D_p\Delta p - \phi_{52}up + \phi_{53}uc - \phi_{54}vc - \phi_{55}vp + \phi_{56}m],$$

$$\mathcal{L}[\frac{\partial m}{\partial t}] = \mathcal{L}[D_m\Delta m - \phi_{62}up + \phi_{63}uc - \phi_{64}vc + \phi_{65}vp - \phi_{66}m].$$

Using the differentiation property of Laplace transform, we get

$$\mathcal{L}[c] = \frac{c(\mathbf{x},0)}{s} + \frac{1}{s}\mathcal{L}[D_c\Delta c - \nabla.[(\chi_u c\nabla u) + (\chi_p c\nabla p) + (\chi_v c\nabla v)] + \mu_1 c(1-c-v)],$$

$$\mathcal{L}[v] = \frac{v(\mathbf{x},0)}{s} + \frac{1}{s}\mathcal{L}[-\delta_1 vm + \phi_{22}up - \phi_{23}uc + \phi_{24}vc - \phi_{25}vp + \mu_2 v(1-v-c)],$$

$$\mathcal{L}[s] = \frac{s(\mathbf{x},0)}{s} + \frac{1}{s}\mathcal{L}[\delta_2 vm - \phi_{32}up + \phi_{33}uc - \phi_{34}vc + \phi_{35}vp - \mu_3 v(1-v-c)],$$

$$\mathcal{L}[u] = \frac{u(\mathbf{x},0)}{s} + \frac{1}{s}\mathcal{L}[D_u\Delta u - \phi_{42}up - \phi_{43}uc - \phi_{44}vc + \phi_{45}vp + \phi_{46}c],$$

$$\mathcal{L}[p] = \frac{p(\mathbf{x},0)}{s} + \frac{1}{s}\mathcal{L}[D_p\Delta p - \phi_{52}up + \phi_{53}uc - \phi_{54}vc - \phi_{55}vp + \phi_{56}m],$$

$$\mathcal{L}[m] = \frac{m(\mathbf{x},0)}{s} + \frac{1}{s}\mathcal{L}[D_m\Delta m - \phi_{62}up + \phi_{63}uc - \phi_{64}vc + \phi_{65}vp - \phi_{66}m].$$

Using initial conditions from equation (4.3.8) we have:

$$\mathcal{L}[c] = \frac{exp(-100\,|\mathbf{x}|^2)}{s} + \frac{1}{s}\mathcal{L}[D_c\Delta c - \nabla.[(\chi_u c\nabla u) + (\chi_p c\nabla p) + (\chi_v c\nabla v)] + \mu_1 c(1-c-v)], \tag{5.1.1}$$

$$\mathcal{L}[v] = \frac{1-\frac{1}{2}exp(-100\,|\mathbf{x}|^2)}{s} + \frac{1}{s}\mathcal{L}[-\delta_1 vm + \phi_{22}up - \phi_{23}uc + \phi_{24}vc - \phi_{25}vp + \mu_2 v(1-v-c)], \tag{5.1.2}$$

$$\mathcal{L}[s] = \frac{0}{s} + \frac{1}{s}\mathcal{L}[\delta_2 vm - \phi_{32}up + \phi_{33}uc - \phi_{34}vc + \phi_{35}vp - \mu_3 v(1-v-c)], \tag{5.1.3}$$

$$\mathcal{L}[u] = \frac{0.5exp(-100\,|\mathbf{x}|^2)}{s} + \frac{1}{s}\mathcal{L}[D_u\Delta u - \phi_{42}up - \phi_{43}uc - \phi_{44}vc + \phi_{45}vp + \phi_{46}c], \tag{5.1.4}$$

$$\mathcal{L}[p] = \frac{\frac{1}{20}exp(-100\,|\mathbf{x}|^2)}{s} + \frac{1}{s}\mathcal{L}[D_p\Delta p - \phi_{52}up + \phi_{53}uc - \phi_{54}vc - \phi_{55}vp + \phi_{56}m], \tag{5.1.5}$$

$$\mathcal{L}[m] = \frac{\frac{1}{200}\exp(-100\,|\mathbf{x}|^2)}{s} + \frac{1}{s}\mathcal{L}[D_m\Delta m - \phi_{62}up + \phi_{63}uc - \phi_{64}vc + \phi_{65}vp - \phi_{66}m]. \tag{5.1.6}$$

The LADM defines the solutions $c(\mathbf{x},t)$, $v(\mathbf{x},t)$,$s(\mathbf{x},t)$,$u(\mathbf{x},t)$, $p(\mathbf{x},t)$ and $m(\mathbf{x},t)$ by the infinite series solution as:

$$c(\mathbf{x},t) = \sum_{n=0}^{\infty} c_n(\mathbf{x},t), v(\mathbf{x},t) = \sum_{n=0}^{\infty} v_n(\mathbf{x},t), s(\mathbf{x},t) = \sum_{n=0}^{\infty} s_n(\mathbf{x},t),$$
$$u(\mathbf{x},t) = \sum_{n=0}^{\infty} u_n(\mathbf{x},t), p(\mathbf{x},t) = \sum_{n=0}^{\infty} p_n(\mathbf{x},t), m(\mathbf{x},t) = \sum_{n=0}^{\infty} m_n(\mathbf{x},t). \tag{5.1.7}$$

And the nonlinear terms $\nabla c\nabla u$, $c\nabla^2 u$, $\nabla c\nabla p$, $c\nabla^2 p$, $\nabla c\nabla v$, $c\nabla^2 v$, c^2 , cv , v^2 , vm , up , uc and vp are represented by an infinite polynomial series of the so-called Adomian

polynomials [23, 24] as;

$$\nabla c\nabla u=\sum_{m=0}^{\infty}A_m(c,u), c\nabla^2 u=\sum_{m=0}^{\infty}\tilde{A}_m(c,u), \nabla c\nabla p=\sum_{m=0}^{\infty}B_m(c,p), c\nabla^2 p=\sum_{m=0}^{\infty}\tilde{B}_m(c,p),$$
$$\nabla c\nabla v=\sum_{m=0}^{\infty}C_m(c,v), c\nabla^2 v=\sum_{m=0}^{\infty}\tilde{C}_m(c,v), c^2=\sum_{m=0}^{\infty}D_m(c), v^2=\sum_{m=0}^{\infty}E_m(v), vc=\sum_{m=0}^{\infty}F_m(c,v),$$
$$vm=\sum_{m=0}^{\infty}G_m(v,m), up=\sum_{m=0}^{\infty}H_m(u,p), uc=\sum_{m=0}^{\infty}I_m(u,c), vp=\sum_{m=0}^{\infty}J_m(v,p). \quad (5.1.8)$$

where a few terms of these Adomian polynomials are;

$$A_0=\nabla c_0\nabla u_0 \qquad \tilde{A}_0=c_0\nabla^2 u_0$$
$$A_1=\nabla c_0\nabla u_1+\nabla u_0\nabla c_1 \qquad \tilde{A}_1=c_0\nabla^2 u_1+c_1\nabla^2 u_0$$
$$A_2=\nabla c_0\nabla u_2+\nabla u_1\nabla c_1+\nabla u_0\nabla c_2 \qquad \tilde{A}_2=c_0\nabla^2 u_2+c_1\nabla^2 u_1+c_2\nabla^2 u_0$$
$$\vdots \qquad \vdots$$
$$A_n=\sum_{i=0}^{n}\nabla c_i\nabla u_{n-i}, \qquad \tilde{A}_n=\sum_{i=0}^{n}c_i\nabla^2 u_{n-i},$$

$$B_0=\nabla c_0\nabla p_0 \qquad \tilde{B}_0=c_0\nabla^2 p_0$$
$$B_1=\nabla c_0\nabla p_1+\nabla p_0\nabla c_1 \qquad \tilde{B}_1=c_0\nabla^2 p_1+c_1\nabla^2 u_0$$
$$B_2=\nabla c_0\nabla p_2+\nabla p_1\nabla c_1+\nabla p_0\nabla c_2 \qquad \tilde{B}_2=c_0\nabla^2 p_2+c_1\nabla^2 u_1+c_2\nabla^2 p_0$$
$$\vdots \qquad \vdots$$
$$B_n=\sum_{i=0}^{n}\nabla c_i\nabla p_{n-i}, \qquad \tilde{B}_n=\sum_{i=0}^{n}c_i\nabla^2 p_{n-i},$$

$$C_0=\nabla c_0\nabla v_0 \qquad \tilde{C}_0=c_0\nabla^2 v_0$$
$$C_1=\nabla c_0\nabla v_1+\nabla v_0\nabla c_1 \qquad \tilde{C}_1=c_0\nabla^2 v_1+c_1\nabla^2 v_0$$
$$C_2=\nabla c_0\nabla v_2+\nabla v_1\nabla c_1+\nabla v_0\nabla c_2 \qquad \tilde{C}_2=c_0\nabla^2 v_2+c_1\nabla^2 v_1+c_2\nabla^2 v_0$$
$$\vdots \qquad \vdots$$
$$C_n=\sum_{i=0}^{n}\nabla c_i\nabla v_{n-i}, \qquad \tilde{C}_n=\sum_{i=0}^{n}c_i\nabla^2 v_{n-i},$$

$$D_0 = c_0^2 \qquad E_0 = v_0^2$$

$$D_1 = 2c_0c_1 \qquad E_1 = 2v_0v_1$$

$$D_2 = 2c_0c_2 + c_1^2 \qquad E_2 = 2v_0v_2 + v_1^2$$

$$\vdots, \qquad \vdots,$$

$$F_0 = c_0v_0 \qquad G_0 = v_0m_0$$

$$F_1 = c_0v_1 + v_0c_1 \qquad G_1 = v_0m_1 + v_1m_0$$

$$F_2 = c_0v_2 + v_1c_1 + v_0c_2 \qquad G_2 = v_0m_2 + v_1m_1 + v_2m_0$$

$$\vdots \qquad \vdots$$

$$F_n = \sum_{i=0}^{n} c_iv_{n-i}, \qquad G_n = \sum_{i=0}^{n} v_im_{n-i},$$

$$H_0 = u_0p_0 \qquad I_0 = u_0c_0$$

$$H_1 = u_0p_1 + u_1p_0 \qquad I_1 = u_0c_1 + u_1c_0$$

$$H_2 = u_0p_2 + u_1p_1 + u_2p_0 \qquad I_2 = u_0c_2 + u_1c_1 + u_2c_0$$

$$\vdots \qquad \vdots$$

$$H_n = \sum_{i=0}^{n} u_ip_{n-i}, \qquad I_n = \sum_{i=0}^{n} u_ic_{n-i}$$

and

$$J_0 = v_0p_0$$

$$J_1 = v_0p_1 + v_1p_0$$

$$J_2 = v_0p_2 + v_1p_1 + v_2p_0$$

$$\vdots$$

$$J_n = \sum_{i=0}^{n} v_ip_{n-i}.$$

Putting Equations (5.1.7) and (5.1.8) into Equation(5.1.1)-(5.1.6) we will get:

$$\mathcal{L}[\sum_{0}^{\infty} c_n(\mathbf{x},t)] = \frac{1}{s}(\exp(-100\,|\mathbf{x}|^2))+\frac{1}{s}\mathcal{L}[D_c\sum_{0}^{\infty}\Delta c_n(\mathbf{x},t)-\chi_u\sum_{m=0}^{\infty}A_m-\chi_u\sum_{m=0}^{\infty}\tilde{A}_m-\chi_p\sum_{m=0}^{\infty}B_m - \chi_p\sum_{m=0}^{\infty}\tilde{B}_m-\chi_v\sum_{m=0}^{\infty}C_m-\chi_v\sum_{m=0}^{\infty}\tilde{C}_m-\mu_1\sum_{m=0}^{\infty}D_m-\mu_1\sum_{m=0}^{\infty}F_m+\mu_1\sum_{m=0}^{\infty}c_n(\mathbf{x},t)]$$

$$\mathcal{L}[\sum_{0}^{\infty} v_n(\mathbf{x},t)] = \frac{1}{s}(1-\frac{1}{2}\exp(-100\,|\mathbf{x}|^2))-\frac{1}{s}\mathcal{L}[\delta_1\sum_{m=0}^{\infty}G_m+\phi_{22}\sum_{m=0}^{\infty}H_m-\phi_{23}\sum_{m=0}^{\infty}I_m + \phi_{24}\sum_{m=0}^{\infty}F_m-\phi_{25}\sum_{m=0}^{\infty}J_m-\mu_2\sum_{m=0}^{\infty}E_m-\mu_2\sum_{m=0}^{\infty}F_m+\mu_2\sum_{m=0}^{\infty}v_n(\mathbf{x},t)],$$

$$\mathcal{L}[\sum_{0}^{\infty} s_n(\mathbf{x},t)] = \frac{1}{s}\mathcal{L}[\delta_2\sum_{m=0}^{\infty}G_m-\phi_{32}\sum_{m=0}^{\infty}H_m+\phi_{33}\sum_{m=0}^{\infty}I_m - \phi_{34}\sum_{m=0}^{\infty}F_m+\phi_{35}\sum_{m=0}^{\infty}J_m+\mu_3\sum_{m=0}^{\infty}E_m+\mu_3\sum_{m=0}^{\infty}F_m-\mu_3\sum_{n=0}^{\infty}v_n(\mathbf{x},t)],$$

$$\mathcal{L}[\sum_{0}^{\infty} u_n(\mathbf{x},t)] = \frac{1}{s}(\frac{1}{2}\exp(-100\,|\mathbf{x}|^2))+\frac{1}{s}\mathcal{L}[D_u\Delta u_n(\mathbf{x},t)-\phi_{42}\sum_{m=0}^{\infty}H_m-\phi_{43}\sum_{m=0}^{\infty}I_m-\phi_{44}\sum_{m=0}^{\infty}F_m + \phi_{45}\sum_{m=0}^{\infty}J_m+\phi_{46}\sum_{m=0}^{\infty}c_n(\mathbf{x},t)],$$

$$\mathcal{L}[\sum_{0}^{\infty} p_n(\mathbf{x},t)] = \frac{1}{s}(\frac{1}{20}\exp(-100\,|\mathbf{x}|^2))+\frac{1}{s}\mathcal{L}[D_p\Delta p_n(\mathbf{x},t)-\phi_{52}\sum_{m=0}^{\infty}H_m+\phi_{53}\sum_{m=0}^{\infty}I_m-\phi_{54}\sum_{m=0}^{\infty}F_m - \phi_{55}\sum_{m=0}^{\infty}J_m+\phi_{56}\sum_{m=0}^{\infty}m_n(\mathbf{x},t)],$$

$$\mathcal{L}[\sum_{0}^{\infty} m_n(\mathbf{x},t) = \frac{1}{s}(\frac{1}{200}\exp(-100\,|\mathbf{x}|^2))+\frac{1}{s}\mathcal{L}[D_m\Delta m_n(\mathbf{x},t)-\phi_{62}\sum_{m=0}^{\infty}H_m+\phi_{63}\sum_{m=0}^{\infty}I_m - \phi_{64}\sum_{m=0}^{\infty}F_m+\phi_{65}\sum_{m=0}^{\infty}J_m-\phi_{66}\sum_{m=0}^{\infty}m_n(\mathbf{x},t)].$$

Using the linearity of Laplace transformation:

$$\sum_{n=0}^{\infty}\mathcal{L}[c_n(\mathbf{x},t)] = \frac{1}{s}(\exp(-100\,|\mathbf{x}|^2))+\frac{D_c}{s}\sum_{n=0}^{\infty}\mathcal{L}[\Delta c_n(\mathbf{x},t)]-\frac{\chi_u}{s}\sum_{m=0}^{\infty}\mathcal{L}[A_m]-\frac{\chi_u}{s}\sum_{m=0}^{\infty}\mathcal{L}[\tilde{A}_m]$$
$$-\frac{\chi_p}{s}\sum_{m=0}^{\infty}\mathcal{L}[B_m]-\frac{\chi_p}{s}\sum_{m=0}^{\infty}\mathcal{L}[\tilde{B}_m]-\frac{\chi_v}{s}\sum_{m=0}^{\infty}\mathcal{L}[C_m]-\frac{\chi_v}{s}\sum_{m=0}^{\infty}\mathcal{L}[\tilde{C}_m]+\frac{\mu_1}{s}\sum_{m=0}^{\infty}\mathcal{L}[D_m]$$
$$-\frac{\mu_1}{s}\sum_{m=0}^{\infty}\mathcal{L}[F_m]+\frac{\mu_1}{s}\sum_{m=0}^{\infty}\mathcal{L}[c_n(\mathbf{x},t)], \quad (5.1.9)$$

$$\sum_{n=0}^{\infty}\mathcal{L}[v_n(\mathbf{x},t)] = \frac{1}{s}(1-\frac{1}{2}\exp(-100\,|\mathbf{x}|^2))-\frac{\delta_1}{s}\sum_{n=0}^{\infty}\mathcal{L}[G_m]+\frac{\phi_{22}}{s}\sum_{m=0}^{\infty}\mathcal{L}[H_m]-\frac{\phi_{23}}{s}\sum_{m=0}^{\infty}\mathcal{L}[I_m]$$
$$+\frac{\phi_{24}-\mu_2}{s-\mu_2}\sum_{m=0}^{\infty}\mathcal{L}[F_m]+\frac{\phi_{25}}{s}\sum_{m=0}^{\infty}\mathcal{L}[J_m]-\frac{\mu_2}{s}\sum_{m=0}^{\infty}\mathcal{L}[E_m]+\frac{\mu_2}{s}\sum_{m=0}^{\infty}\mathcal{L}[v_n(\mathbf{x},t)], \quad (5.1.10)$$

$$\sum_{n=0}^{\infty}\mathcal{L}[s_n(\mathbf{x},t)] = \frac{1}{s}\left(\frac{1}{2-\exp(-100\,|\mathbf{x}|^2)}\right)+\frac{\delta_2}{s}\sum_{n=0}^{\infty}\mathcal{L}[G_m]-\frac{\phi_{32}}{s}\sum_{m=0}^{\infty}\mathcal{L}[H_m]+\frac{\phi_{33}}{s}\sum_{m=0}^{\infty}\mathcal{L}[I_m]$$
$$-\frac{(\phi_{34}-\mu_3)}{s}\sum_{m=0}^{\infty}\mathcal{L}[F_m]-\frac{\phi_{35}}{s}\sum_{m=0}^{\infty}\mathcal{L}[J_m]+\frac{\mu_3}{s}\sum_{m=0}^{\infty}\mathcal{L}[E_m]-\frac{\mu_3}{s}\sum_{m=0}^{\infty}\mathcal{L}[v_n(\mathbf{x},t)], \quad (5.1.11)$$

$$\sum_{n=0}^{\infty}\mathcal{L}[u_n(\mathbf{xx},t)] = \frac{1}{s}(\frac{1}{2}\exp(-100\,|\mathbf{x}|^2))+\frac{D_u}{s}\sum_{n=0}^{\infty}\mathcal{L}[\Delta u_n(\mathbf{x},t)]-\frac{\phi_{42}}{s}\sum_{m=0}^{\infty}\mathcal{L}[H_m]+\frac{\phi_{43}}{s}\sum_{m=0}^{\infty}\mathcal{L}[I_m]$$
$$-\frac{\phi_{44}}{s}\sum_{m=0}^{\infty}\mathcal{L}[F_m]-\frac{\phi_{45}}{s}\sum_{m=0}^{\infty}\mathcal{L}[J_m]+\frac{\phi_{46}}{s}\sum_{m=0}^{\infty}\mathcal{L}[c_n(\mathbf{x},t)], \quad (5.1.12)$$

$$\sum_{n=0}^{\infty}\mathcal{L}[p_n(\mathbf{x},t)] = \frac{1}{s}(\frac{1}{20}\exp(-100\,|\mathbf{x}|^2))+\frac{D_p}{s}\sum_{n=0}^{\infty}\mathcal{L}[\Delta p_n(\mathbf{x},t)]-\frac{\phi_{52}}{s}\sum_{m=0}^{\infty}\mathcal{L}[H_m]+\frac{\phi_{53}}{s}\sum_{m=0}^{\infty}\mathcal{L}[I_m]$$
$$-\frac{\phi_{54}}{s}\sum_{m=0}^{\infty}\mathcal{L}[F_m]-\frac{\phi_{55}}{s}\sum_{m=0}^{\infty}\mathcal{L}[J_m]+\frac{\phi_{56}}{s}\sum_{m=0}^{\infty}\mathcal{L}[m_n(\mathbf{x},t)], \quad (5.1.13)$$

$$\sum_{n=0}^{\infty}\mathcal{L}[m_n(\mathbf{x},t)] = \frac{1}{s}(\frac{1}{200}\exp(-100\,|\mathbf{x}|^2))+\frac{D_m}{s}\sum_{n=0}^{\infty}\mathcal{L}[\Delta m_n(\mathbf{x},t)]-\frac{\phi_{62}}{s}\sum_{m=0}^{\infty}\mathcal{L}[H_m]+\frac{\phi_{63}}{s}\sum_{m=0}^{\infty}\mathcal{L}[I_m]$$
$$-\frac{\phi_{64}}{s}\sum_{m=0}^{\infty}\mathcal{L}[F_m]+\frac{\phi_{65}}{s}\sum_{m=0}^{\infty}\mathcal{L}[J_m]-\frac{\phi_{66}}{s}\sum_{m=0}^{\infty}\mathcal{L}[m_n(\mathbf{x},t)]. \quad (5.1.14)$$

On comparing both side of equations(5.1.9)-(5.1.14) we have;

$$\begin{aligned}
\mathcal{L}[c_0(\mathbf{x},t)] &= \frac{1}{s}(\exp(-100\,|\mathbf{x}|^2)),\\
\mathcal{L}[v_0(\mathbf{x},t)] &= \frac{1}{s}(1-\frac{1}{2}\exp(-100\,|\mathbf{x}|^2)),\\
\mathcal{L}[s_0(\mathbf{x},t)] &= 0,\\
\mathcal{L}[u_0(\mathbf{x},t)] &= \frac{1}{s}(\frac{1}{2}\exp(-100\,|\mathbf{x}|^2)),\\
\mathcal{L}[p_0(\mathbf{x},t)] &= \frac{1}{s}(\frac{1}{20}\exp(-100\,|\mathbf{x}|^2)),\\
\mathcal{L}[m_0(\mathbf{x},t)] &= \frac{1}{s}(\frac{1}{200}\exp(-100\,|\mathbf{x}|^2)).
\end{aligned}$$

$$\begin{aligned}
\mathcal{L}[c_1(\mathbf{x},t)] = \mathcal{L}^{-1}[&\frac{D_c}{s}\mathcal{L}[\Delta c_0(\mathbf{x},t)] - \frac{\chi_u}{s}\mathcal{L}[A_0] + \frac{\chi_u}{s}\mathcal{L}[\tilde{A}_0] - \frac{\chi_p}{s}\mathcal{L}[B_0] - \frac{\chi_p}{s}\mathcal{L}[\tilde{B}_0]\\
&+ \frac{\chi_v}{s}\mathcal{L}[C_0] + \frac{\chi_v}{s}\mathcal{L}[\tilde{C}_0] + \frac{\mu_1}{s}\mathcal{L}[D_0] - \frac{\mu_1}{s}\mathcal{L}[F_0]],
\end{aligned}$$

$$\mathcal{L}[v_1(\mathbf{x},t)] = \frac{\delta_1}{s}\mathcal{L}[G_0]+\frac{\phi_{22}}{s}\mathcal{L}[H_0]-\frac{\phi_{23}}{s}\mathcal{L}[I_0]-\frac{(\phi_{24}-\mu_2)}{s}\mathcal{L}[F_0]+\frac{\phi_{25}}{s}\mathcal{L}[J_0]-\frac{\mu_3}{s}\mathcal{L}[E_0]+\frac{\mu_3}{s}\mathcal{L}[v_0(\mathbf{x},t)],$$

$$\mathcal{L}[s_1(\mathbf{x},t)] = \frac{\delta_2}{s}\mathcal{L}[G_0]-\frac{\phi_{32}}{s}\mathcal{L}[H_0]+\frac{\phi_{33}}{s}\mathcal{L}[I_0]-\frac{(\phi_{34}+\mu_3)}{s}\mathcal{L}[F_0]-\frac{\phi_{35}}{s}\mathcal{L}[J_0]+\frac{\mu_3}{s}\mathcal{L}[E_0]-\frac{\mu_3}{s}\mathcal{L}[v_0(\mathbf{x},t)],$$

$$\mathcal{L}[u_1(\mathbf{x},t)] = \frac{D_u}{s}\mathcal{L}[\Delta u_0(\mathbf{x},t)]-\frac{\phi_{42}}{s}\mathcal{L}[H_0]+\frac{\phi_{43}}{s}\mathcal{L}[I_0]-\frac{\phi_{44}}{s}\mathcal{L}[F_0]-\frac{\phi_{45}}{s}\mathcal{L}[J_0]+\frac{\phi_{46}}{s}\mathcal{L}[c_0(\mathbf{x},t)],$$

$$\mathcal{L}[p_1(\mathbf{x},t)] = \frac{D_p}{s}\mathcal{L}[\Delta p_n(\mathbf{x},t)]-\frac{\phi_{52}}{s}\mathcal{L}[H_0]+\frac{\phi_{53}}{s}\mathcal{L}[I_0]-\frac{\phi_{54}}{s}\mathcal{L}[F_0]-\frac{\phi_{55}}{s}\mathcal{L}[J_0]+\frac{\phi_{56}}{s}\mathcal{L}[m_0(\mathbf{x},t)],$$

$$\mathcal{L}[m_1(\mathbf{x},t)] = \frac{D_m}{s}\mathcal{L}[\Delta m_0(\mathbf{x},t)]-\frac{\phi_{62}}{s}\mathcal{L}[H_0]+\frac{\phi_{63}}{s}\mathcal{L}[I_0]-\frac{\phi_{64}}{s}\mathcal{L}[F_0]+\frac{\phi_{65}}{s}\mathcal{L}[J_0]-\frac{\phi_{66}}{s}\mathcal{L}[m_0(\mathbf{x},t)].$$

In general for $n \geq 1$, the LADM presents recursive relation as follow [25, 26];

$$\begin{aligned}
\mathcal{L}[c_{n+1}(\mathbf{x},t)] &= \tfrac{D_c}{s}\mathcal{L}[\Delta c_n(\mathbf{x},t)] - \tfrac{\chi_u}{s}\mathcal{L}[A_m] + \tfrac{\chi_u}{s}\mathcal{L}[\tilde{A}_m] - \tfrac{\chi_p}{s}\mathcal{L}[B_m] - \tfrac{\chi_p}{s}\mathcal{L}[\tilde{B}_m]\\
&\quad + \tfrac{\chi_v}{s}\mathcal{L}[C_m] + \tfrac{\chi_v}{s}\mathcal{L}[\tilde{C}_m] + \tfrac{\mu_1}{s}\mathcal{L}[D_m] - \tfrac{\mu_1}{s}\mathcal{L}[F_m] + \tfrac{\mu_1}{s}\mathcal{L}[c_n(\mathbf{x},t)],
\end{aligned}$$

$$\begin{aligned}
\mathcal{L}[v_{n+1}(\mathbf{x},t)] &= \tfrac{\delta_1}{s}\mathcal{L}[G_m] + \tfrac{\phi_{22}}{s}\mathcal{L}[H_m] - \tfrac{\phi_{23}}{s}\mathcal{L}[I_m] + \tfrac{\phi_{24}-\mu_2}{s}\mathcal{L}[F_m] + \tfrac{\phi_{25}}{s}\mathcal{L}[J_m] - \tfrac{\mu_2}{s}\mathcal{L}[E_m]\\
&\quad + \tfrac{\mu_2}{s}\mathcal{L}[v_n(\mathbf{x},t)],
\end{aligned}$$

$$\begin{aligned}\mathcal{L}[s_{n+1}(\mathbf{x},t)] &= \tfrac{\delta_2}{s}\mathcal{L}[G_m] - \tfrac{\phi_{32}}{s}\mathcal{L}[H_m] + \tfrac{\phi_{33}}{s}\mathcal{L}[I_m] - \tfrac{\phi_{34}-\mu_3}{s}\mathcal{L}[F_m] - \tfrac{\phi_{35}}{s}\mathcal{L}[J_m] + \tfrac{\mu_3}{s}\mathcal{L}[E_m] \\ &\quad -\tfrac{\mu_3}{s}\mathcal{L}[v_n(\mathbf{x},t)],\end{aligned}$$

$$\mathcal{L}[u_{n+1}(\mathbf{x},t)] = \tfrac{D_u}{s}\mathcal{L}[\Delta u_n(\mathbf{x},t)] - \tfrac{\phi_{42}}{s}\mathcal{L}[H_m] + \tfrac{\phi_{43}}{s}\mathcal{L}[I_m] - \tfrac{\phi_{44}}{s}\mathcal{L}[F_m] - \tfrac{\phi_{45}}{s}\mathcal{L}[J_m] + \tfrac{\phi_{46}}{s}\mathcal{L}[c_n(\mathbf{x},t)],$$

$$\mathcal{L}[p_{n+1}(\mathbf{x},t)] = \tfrac{D_p}{s}\mathcal{L}[\Delta p_n(\mathbf{x},t)] - \tfrac{\phi_{52}}{s}\mathcal{L}[H_m] + \tfrac{\phi_{53}}{s}\mathcal{L}[I_m] - \tfrac{\phi_{54}}{s}\mathcal{L}[F_m] - \tfrac{\phi_{55}}{s}\mathcal{L}[J_m] + \tfrac{\phi_{56}}{s}\mathcal{L}[m_n(\mathbf{x},t)],$$

$$\mathcal{L}[m_{n+1}(\mathbf{x},t)] = \tfrac{D_m}{s}\mathcal{L}[\Delta m_n(\mathbf{x},t)] - \tfrac{\phi_{62}}{s}\mathcal{L}[H_m] + \tfrac{\phi_{63}}{s}\mathcal{L}[I_m] - \tfrac{\phi_{64}}{s}\mathcal{L}[F_m] + \tfrac{\phi_{65}}{s}\mathcal{L}[J_m] - \tfrac{\phi_{65}}{s}\mathcal{L}[m_n].$$

Taking the inverse Laplace transform of both sides of equation above; with a parameter set $\mathcal{P}$, the required recursive relation in one dimensional domain ($\mathbf{x} \in \mathbb{R}$) is given by;

$$\begin{aligned}c_0(x,t) &= \mathcal{L}^{-1}[\frac{1}{s}(\exp(-100x^2))] = \exp(-100x^2), \\ v_0(x,t) &= \mathcal{L}^{-1}[\frac{1}{s}(1 - \frac{1}{2}\exp(-100x^2))] = 1 - \frac{1}{2}\exp(-100x^2), \\ s_0(x,t) &= 0, \\ u_0(x,t) &= \mathcal{L}^{-1}[\frac{1}{s}(\frac{1}{2}\exp(-100x^2))] = \frac{1}{2}\exp(-100x^2), \\ p_0(x,t) &= \mathcal{L}^{-1}[\frac{1}{s}(\frac{1}{20}\exp(-100x^2))] = \frac{1}{20}\exp(-100x^2), \\ m_0(x,t) &= \mathcal{L}^{-1}[\frac{1}{s}(\frac{1}{200}\exp(-100x^2))] = \frac{1}{200}\exp(-100x^2).\end{aligned}$$

$$\begin{aligned}c_1(x,t) &= \mathcal{L}^{-1}[\tfrac{D_c}{s}\mathcal{L}(\Delta c_0(x,t))] - \mathcal{L}^{-1}[\tfrac{\chi_u}{s}\mathcal{L}(A_0)] - \mathcal{L}^{-1}[\tfrac{\chi_u}{s}\mathcal{L}(\tilde{A}_0)] - \mathcal{L}^{-1}[\tfrac{\chi_p}{s}\mathcal{L}(B_0)] \\ &\quad -\mathcal{L}^{-1}[\tfrac{\chi_p}{s}\mathcal{L}(\tilde{B}_0)] - \mathcal{L}^{-1}[\tfrac{\chi_v}{s}\mathcal{L}(C_0)] - \mathcal{L}^{-1}[\tfrac{\chi_v}{s}\mathcal{L}(\tilde{C}_0)] - \mathcal{L}^{-1}[\tfrac{\mu_1}{s}\mathcal{L}(D_0)] \\ &\quad -\mathcal{L}^{-1}[\tfrac{\mu_1}{s}\mathcal{L}(F_0)] + \mathcal{L}^{-1}[\tfrac{\mu_1}{s}\mathcal{L}c_0(x,t)] \\ &= ((14x^2 - 0.07)t)\exp(-100x^2) + ((3.85 - 230x^2)t)\exp(-200x^2),\end{aligned}$$

$$\begin{aligned}v_1(x,t) &= \mathcal{L}^{-1}[\tfrac{\delta_1}{s}\mathcal{L}(G_0)] + \mathcal{L}^{-1}[\tfrac{\phi_{22}}{s}\mathcal{L}(H_0)] - \mathcal{L}^{-1}[\tfrac{\phi_{23}}{s}\mathcal{L}(I_0)] + \mathcal{L}^{-1}[\tfrac{\phi_{24}-\mu_2}{s}\mathcal{L}(F_0)] \\ &\quad +\mathcal{L}^{-1}[\tfrac{\phi_{25}}{s}\mathcal{L}(J_0)] - \mathcal{L}^{-1}[\tfrac{\mu_2}{s}\mathcal{L}(E_0)] + \mathcal{L}^{-1}[\tfrac{\mu_2}{s}\mathcal{L}(v_0(x,t))] \\ &= (0.39675t)\exp(-100x^2) - 0.279625t\exp(-200x^2),\end{aligned}$$

$$\begin{aligned}s_1 &= \mathcal{L}^{-1}[\tfrac{\delta_2}{s}\mathcal{L}(G_0)] - \mathcal{L}^{-1}[\tfrac{\phi_{32}}{s}\mathcal{L}(H_0)] + \mathcal{L}^{-1}[\tfrac{\phi_{33}}{s}\mathcal{L}(I_0)] - \mathcal{L}^{-1}[\tfrac{(\phi_{34}-\mu_3)}{s}\mathcal{L}(F_0)] - \mathcal{L}^{-1}[\tfrac{\phi_{35}}{s}\mathcal{L}(J_0)] \\ &\quad +\mathcal{L}^{-1}[\tfrac{\mu_3}{s}\mathcal{L}(E_0)] - \mathcal{L}^{-1}[\tfrac{\mu_3}{s}\mathcal{L}(v_0(x,t))] \\ &= 0.025t\exp(-100x^2) + 037725t\exp(-200x^2),\end{aligned}$$

$$\begin{aligned} u_1 &= \mathcal{L}^{-1}[\tfrac{D_u}{s}\mathcal{L}(\Delta u_0(x,t))] - \mathcal{L}^{-1}[\tfrac{\phi_{42}}{s}\mathcal{L}(H_0)] + \mathcal{L}^{-1}[\tfrac{\phi_{43}}{s}\mathcal{L}(I_0)] - \mathcal{L}^{-1}[\tfrac{\phi_{44}}{s}\mathcal{L}(F_0)] \\ &\quad -\mathcal{L}^{-1}[\tfrac{\phi_{45}}{s}\mathcal{L}(J_0)] + \mathcal{L}^{-1}[\tfrac{\phi_{46}}{s}\mathcal{L}(c_0(x,t))] \\ &= ((50x^2 - 0.01025)t)\exp(-100x^2) - 0.181125t\exp(-200x^2), \end{aligned}$$

$$\begin{aligned} p_1 &= \mathcal{L}^{-1}[\tfrac{D_p}{s}\mathcal{L}(\Delta p_0(x,t))] - \mathcal{L}^{-1}[\tfrac{\phi_{52}}{s}\mathcal{L}(H_0)] + \mathcal{L}^{-1}[\tfrac{\phi_{53}}{s}\mathcal{L}(I_0)] - \mathcal{L}^{-1}[\tfrac{\phi_{54}}{s}\mathcal{L}(F_0)] \\ &\quad -\mathcal{L}^{-1}[\tfrac{\phi_{55}}{s}\mathcal{L}(J_0)] + \mathcal{L}^{-1}[\tfrac{\phi_{56}}{s}\mathcal{L}(m_0(x,t))] \\ &= ((7x^2 - 0.06675)t)\exp(-100x^2) + 0.1035t\exp(-200x^2), \end{aligned}$$

$$\begin{aligned} m_1 &= +\mathcal{L}^{-1}[\tfrac{\phi_{65}}{s}\mathcal{L}(J_0)] - \mathcal{L}^{-1}[\tfrac{\phi_{66}}{s}\mathcal{L}(m_0(x,t))] \\ &= \pounds^{-1}[\tfrac{D_m}{s}\mathcal{L}(\Delta m_0(x,t))] - \mathcal{L}{-}1[\tfrac{\phi_{62}}{s}\mathcal{L}(H_0)] + \mathcal{L}^{-1}[\tfrac{\phi_{63}}{s}\mathcal{L}(I_0)] - \mathcal{L}^{-1}[\tfrac{\phi_{64}}{s}\mathcal{L}(F_0)] \\ &\quad ((0.491x^2 - 0.06441)t)\exp(-100x^2) + 0.3985t\exp(-200x^2). \end{aligned}$$

and so on for other components. Using equation (5.1.7), by truncating the solution, we have a second approximation of the solution in $1 - D$;

$$\begin{aligned} c(x,t) &= c_0(x,t) + c_1(x,t) \\ &= ((14x^2 - 0.07)t + 1)\exp(-100x^2) + ((3.85 - 230x^2)t)\exp(-200x^2), \end{aligned}$$

$$\begin{aligned} v(x,t) &= v_0(x,t) + v_1(x,t) \\ &= 1 + (0.39675t - 0.5)\exp(-100x^2) - 0.279625t\exp(-200x^2), \end{aligned}$$

$$\begin{aligned} s(x,t) &= s_0(x,t) + s_1(x,t) \\ &= 0.0255t\exp(-100\mathbf{x}^2) + 0.37725t(-200\mathbf{x}^2), \end{aligned}$$

$$\begin{aligned} u(x,t) &= u_0(x,t) + u_1(x,t) \\ &= ((50x^2 - 0.01025)t + 0.5)\exp(-100x^2) - 0.181125t\exp(-200x^2), \end{aligned}$$

$$\begin{aligned} p(x,t) &= p_0(x,t) + p_1(x,t) \\ &= ((7x^2 - 0.06675)t + 0.05)\exp(-100x^2) + 0.1035t\exp(-200x^2), \end{aligned}$$

$$\begin{aligned} m(x,t) &= m_0(x,t) + m_1(x,t) \\ &= ((0.491x^2 - 0.06441)t + 0.005)\exp(-100x^2) + 0.3985t\exp(-200x^2). \end{aligned}$$

By Similar calculation, in two dimensional domain,$\mathbf{x} \in \mathbb{R}^2$, the system of equation (4.3.2)-(4.3.7) have a solution components:

$$
\begin{aligned}
c_0(\mathbf{x},t) &= \mathcal{L}^{-1}[\frac{1}{s}(\exp(-100\,|\mathbf{x}|^2))] = \exp(-100\,|\mathbf{x}|^2),\\
v_0(\mathbf{x},t) &= \mathcal{L}^{-1}[\frac{1}{s}(1-\frac{1}{2}\exp(-100\,|\mathbf{x}|^2))] = 1-\frac{1}{2}\exp(-100\,|\mathbf{x}|^2),\\
s_0(\mathbf{x},t) &= 0,\\
u_0(\mathbf{x},t) &= \mathcal{L}^{-1}[\frac{1}{s}(\frac{1}{2}\exp(-100\,|\mathbf{x}|^2))] = \frac{1}{2}\exp(-100\,|\mathbf{x}|^2),\\
p_0(\mathbf{x},t) &= \mathcal{L}^{-1}[\frac{1}{s}(\frac{1}{20}\exp(-100\,|\mathbf{x}|^2))] = \frac{1}{20}\exp(-100\,|\mathbf{x}|^2),\\
m_0(\mathbf{x},t) &= \mathcal{L}^{-1}[\frac{1}{s}(\frac{1}{200}\exp(-100\,|\mathbf{x}|^2))] = \frac{1}{200}\exp(-100|\mathbf{x}|^2).
\end{aligned}
$$

$$
\begin{aligned}
c_1 &= \mathcal{L}^{-1}[\tfrac{D_c}{s}\mathcal{L}(\Delta c_0(\mathbf{x},t))] - \mathcal{L}^{-1}[\tfrac{\chi_u}{s}\mathcal{L}(A_0)] - \mathcal{L}^{-1}[\tfrac{\chi_u}{s}\mathcal{L}(\tilde{A}_0)] - \mathcal{L}^{-1}[\tfrac{\chi_p}{s}\mathcal{L}(B_0)]\\
&\quad -\mathcal{L}^{-1}[\tfrac{\chi_p}{s}\mathcal{L}(\tilde{B}_0)] - \mathcal{L}^{-1}[\tfrac{\chi_v}{s}\mathcal{L}(C_0)] - \mathcal{L}^{-1}[\tfrac{\chi_v}{s}\mathcal{L}(\tilde{C}_0)] - \mathcal{L}^{-1}[\tfrac{\mu_1}{s}\mathcal{L}(D_0)]\\
&\quad -\mathcal{L}^{-1}[\tfrac{\mu_1}{s}\mathcal{L}(F_0)] + \mathcal{L}^{-1}[\tfrac{\mu_1}{s}\mathcal{L}(c_0(\mathbf{x},t))]\\
&= (14\,|\mathbf{x}|^2 - 0.14)t\exp(-100\,|\mathbf{x}|^2) + (1.025 - 230\,|\mathbf{x}|^2)t\exp(-200\,|\mathbf{x}|^2),
\end{aligned}
$$

$$
\begin{aligned}
v_1 &= -\mathcal{L}^{-1}[\tfrac{\delta_1}{s}\mathcal{L}(G_0)] + \mathcal{L}^{-1}[\tfrac{\phi_{22}}{s}\mathcal{L}(H_0)] - \mathcal{L}^{-1}[\tfrac{\phi_{23}}{s}\mathcal{L}(I_0)] + \mathcal{L}^{-1}[\tfrac{(\phi_{24}-\mu_2)}{s}\pounds(F_0)]\\
&\quad +\mathcal{L}^{-1}[\tfrac{\phi_{25}}{s}\mathcal{L}(J_0)] - \mathcal{L}^{-1}[\tfrac{\mu_2}{s}\mathcal{L}(E_0)] + \mathcal{L}^{-1}[\tfrac{\mu_2}{s}\mathcal{L}(v_0(\mathbf{x},t))]\\
&= 0.39675t\exp(-100\,|\mathbf{x}|^2) - 0.279625t\exp(-200\,|\mathbf{x}|^2),
\end{aligned}
$$

$$
\begin{aligned}
s_1 &= \mathcal{L}^{-1}[\tfrac{\delta_2}{s}\mathcal{L}(G_0)] - \pounds^{-1}[\tfrac{\phi_{32}}{s}\mathcal{L}(H_0)] + \mathcal{L}^{-1}[\tfrac{\phi_{33}}{s}\mathcal{L}(I_0)] - \mathcal{L}^{-1}[\tfrac{(\phi_{34}-\mu_3)}{s}\mathcal{L}(F_0)] - \mathcal{L}^{-1}[\tfrac{\phi_{35}}{s}\mathcal{L}(J_0)]\\
&\quad +\mathcal{L}^{-1}[\tfrac{\mu_3}{s}\mathcal{L}(E_0)] - \mathcal{L}^{-1}[\tfrac{\mu_3}{s}\mathcal{L}(v_0(\mathbf{x},t))]\\
&= 0.0255t\exp(-100\,|\mathbf{x}|^2) + 0.37725t\exp(-200\,|\mathbf{x}|^2),
\end{aligned}
$$

$$
\begin{aligned}
u_1 &= \mathcal{L}^{-1}[\tfrac{D_u}{s}\mathcal{L}(\Delta u_0(x,t))] - \mathcal{L}^{-1}[\tfrac{\phi_{42}}{s}\mathcal{L}(H_0)] + \pounds^{-1}[\tfrac{\phi_{43}}{s}\mathcal{L}(I_0)] - \mathcal{L}^{-1}[\tfrac{\phi_{44}}{s}\mathcal{L}(F_0)]\\
&\quad -\mathcal{L}^{-1}[\tfrac{\phi_{45}}{s}\mathcal{L}(J_0)] + \mathcal{L}^{-1}[\tfrac{\phi_{46}}{s}\mathcal{L}(c_0(x,t))]\\
&= (50\,|\mathbf{x}|^2 - 0.26025)t\exp(-100\,|\mathbf{x}|^2) - 0.181125t\exp(-200\,|\mathbf{x}|^2),
\end{aligned}
$$

$$
\begin{aligned}
p_1 &= \mathcal{L}^{-1}[\tfrac{D_p}{s}\mathcal{L}(\Delta p_0(\mathbf{x},t))] - \mathcal{L}^{-1}[\tfrac{\phi_{52}}{s}\mathcal{L}(H_0)] + \mathcal{L}^{-1}[\tfrac{\phi_{53}}{s}\mathcal{L}(I_0)] - \mathcal{L}^{-1}[\tfrac{\phi_{54}}{s}\mathcal{L}(F_0)]\\
&\quad -\mathcal{L}^{-1}[\tfrac{\phi_{55}}{s}\mathcal{L}(J_0)] + \mathcal{L}^{-1}[\tfrac{\phi_{56}}{s}\mathcal{L}(m_0(\mathbf{x},t))]\\
&= ((7\,|\mathbf{x}|^2 - 0.10175)t)\exp(-100\,|\mathbf{x}|^2) + 0.1035t\exp(-200\,|\mathbf{x}|^2),
\end{aligned}
$$

$$\begin{aligned} m_1 &= \pounds^{-1}[\tfrac{D_m}{s}\mathcal{L}(\Delta m_0(\mathbf{x},t))] - \mathcal{L}{-}1[\tfrac{\phi_{62}}{s}\mathcal{L}(H_0)] + \mathcal{L}^{-1}[\tfrac{\phi_{63}}{s}\mathcal{L}(I_0)] - \mathcal{L}^{-1}[\tfrac{\phi_{64}}{s}\mathcal{L}(F_0)] \\ &\quad +\mathcal{L}^{-1}[\tfrac{\phi_{65}}{s}\mathcal{L}(J_0)] - \mathcal{L}^{-1}[\tfrac{\phi_{66}}{s}\mathcal{L}(m_0(\mathbf{x},t))] \\ &= ((0.491\,|\mathbf{x}|^2 - 0.00742)t)\exp(-100\,|\mathbf{x}|^2) + 0.3985t\exp(-200\,|\mathbf{x}|^2). \end{aligned}$$

and so on for other components. The second approximation of the solution in $2-D$ is therefore;

$$\begin{aligned} c(\mathbf{x},t) &= c_0(\mathbf{x},t) + c_1(\mathbf{x},t) \\ &= ((14\,|\mathbf{x}|^2 - 0.14)t + 1)\exp(-100\,|\mathbf{x}|^2) + ((3.85 - 230\,|\mathbf{x}|^2)t)\exp(-200\,|\mathbf{x}|^2), \end{aligned}$$

$$\begin{aligned} v(\mathbf{x},t) &= v_0(\mathbf{x},t) + v_1(\mathbf{x},t) \\ &= 1 + (0.39675t - 0.5)\exp(-100\,|\mathbf{x}|^2) - 0.279625t\exp(-200\,|\mathbf{x}|^2), \end{aligned}$$

$$\begin{aligned} s(\mathbf{x},t) &= s_0(\mathbf{x},t) + s_1(\mathbf{x},t) \\ &= 0.0255t\exp(-100\,|\mathbf{x}|^2) + 0.37725t\exp(-200\,|\mathbf{x}|^2), \end{aligned}$$

$$\begin{aligned} u(\mathbf{x},t) &= u_0(\mathbf{x},t) + u_1(\mathbf{x},t) \\ &= ((50\,|\mathbf{x}|^2 - 0.01025)t + 0.5)\exp(-100\,|\mathbf{x}|^2) - 0.181125t\exp(-200\,|\mathbf{x}|^2), \end{aligned}$$

$$\begin{aligned} p(\mathbf{x},t) &= p_0(\mathbf{x},t) + p_1(\mathbf{x},t) \\ &= ((7\,|\mathbf{x}|^2 - 0.06675)t + 0.05)\exp(-100\,|\mathbf{x}|^2) + 0.1035t\exp(-200\,|\mathbf{x}|^2), \end{aligned}$$

$$\begin{aligned} m(\mathbf{x},t) &= m_0(\mathbf{x},t) + m_1(\mathbf{x},t) \\ &= ((0.491\,|\mathbf{x}|^2 - 0.06441)t + 0.005)\exp(-100\,|\mathbf{x}|^2) + 0.3985t\exp(-200\,|\mathbf{x}|^2). \end{aligned}$$

And similarly,in three dimensional domain,$\mathbf{x} \in \mathbb{R}^3$;

$$\begin{aligned} c_0(\mathbf{x},t) &= \mathcal{L}^{-1}[\frac{1}{s}(\exp(-100\,|\mathbf{x}|^2))] = \exp(-100\,|\mathbf{x}|^2), \\ v_0(\mathbf{x},t) &= \mathcal{L}^{-1}[\frac{1}{s}(1 - \frac{1}{2}\exp(-100\,|\mathbf{x}|^2))] = 1 - \frac{1}{2}\exp(-100\,|\mathbf{x}|^2), \\ s_0(\mathbf{x},t) &= 0, \\ u_0(\mathbf{x},t) &= \mathcal{L}^{-1}[\frac{1}{s}(\frac{1}{2}\exp(-100\,|\mathbf{x}|^2))] = \frac{1}{2}\exp(-100\,|\mathbf{x}|^2), \\ p_0(\mathbf{x},t) &= \mathcal{L}^{-1}[\frac{1}{s}(\frac{1}{20}\exp(-100\,|\mathbf{x}|^2))] = \frac{1}{20}\exp(-100\,|\mathbf{x}|^2), \\ m_0(\mathbf{x},t) &= \mathcal{L}^{-1}[\frac{1}{s}(\frac{1}{200}\exp(-100\,|\mathbf{x}|^2))] = \frac{1}{200}\exp(-100|\mathbf{x}|^2). \end{aligned}$$

$$
\begin{aligned}
c_1 &= \mathcal{L}^{-1}[\tfrac{D_c}{s}\mathcal{L}(\Delta c_0(\mathbf{x},t))] - \mathcal{L}^{-1}[\tfrac{\chi_u}{s}\mathcal{L}(A_0)] + \mathcal{L}^{-1}[\tfrac{\chi_u}{s}\mathcal{L}(\tilde{A}_0)] - \mathcal{L}^{-1}[\tfrac{\chi_p}{s}\mathcal{L}(B_0)] \\
&\quad -\mathcal{L}^{-1}[\tfrac{\chi_p}{s}\mathcal{L}(\tilde{B}_0)] - \mathcal{L}^{-1}[\tfrac{\chi_v}{s}\mathcal{L}(C_0)] - \mathcal{L}^{-1}[\tfrac{\chi_v}{s}\mathcal{L}(\tilde{C}_0)] - \mathcal{L}^{-1}[\tfrac{\mu_1}{s}\mathcal{L}(D_0)] \\
&\quad -\mathcal{L}^{-1}[\tfrac{\mu_1}{s}\mathcal{L}(F_0)] + \mathcal{L}^{-1}[\tfrac{\mu_1}{s}\mathcal{L}(c_0(\mathbf{x},t))] \\
&= ((14\,|\mathbf{x}|^2 - 0.21)t)\exp(-100\,|\mathbf{x}|^2) + ((1.025 - 230\,|\mathbf{x}|^2)t)\exp(-200\,|\mathbf{x}|^2),
\end{aligned}
$$

$$
\begin{aligned}
v_1 &= -\mathcal{L}^{-1}[\tfrac{\delta_1}{s}\mathcal{L}(G_0)] + \mathcal{L}^{-1}[\tfrac{\phi_{22}}{s}\mathcal{L}(H_0)] - \mathcal{L}^{-1}[\tfrac{\phi_{23}}{s}\mathcal{L}(I_0)] + \mathcal{L}^{-1}[\tfrac{(\phi_{24}-\mu_2)}{s}\pounds(F_0)] \\
&\quad +\mathcal{L}^{-1}[\tfrac{\phi_{25}}{s}\mathcal{L}(J_0)] - \mathcal{L}^{-1}[\tfrac{\mu_2}{s}\mathcal{L}(E_0)] + \mathcal{L}^{-1}[\tfrac{\mu_2}{s}\mathcal{L}(v_0(\mathbf{x},t))] \\
&= 0.39675t\exp(-100\,|\mathbf{x}|^2) - 0.279625t\exp(-200\,|\mathbf{x}|^2),
\end{aligned}
$$

$$
\begin{aligned}
s_1 &= \mathcal{L}^{-1}[\tfrac{\delta_2}{s}\mathcal{L}(G_0)] - \pounds^{-1}[\tfrac{\phi_{32}}{s}\mathcal{L}(H_0)] + \mathcal{L}^{-1}[\tfrac{\phi_{33}}{s}\mathcal{L}(I_0)] - \mathcal{L}^{-1}[\tfrac{(\phi_{34}-\mu_3)}{s}\mathcal{L}(F_0)] - \mathcal{L}^{-1}[\tfrac{\phi_{35}}{s}\mathcal{L}(J_0)] \\
&\quad +\mathcal{L}^{-1}[\tfrac{\mu_3}{s}\mathcal{L}(E_0)] - \mathcal{L}^{-1}[\tfrac{\mu_3}{s}\mathcal{L}(v_0(\mathbf{x},t))] \\
&= 0.0255t\exp(-100\,|\mathbf{x}|^2) + 0.37725t\exp(-200\,|\mathbf{x}|^2),
\end{aligned}
$$

$$
\begin{aligned}
u_1 &= \mathcal{L}^{-1}[\tfrac{D_u}{s}\mathcal{L}(\Delta u_0(\mathbf{x},t))] - \mathcal{L}^{-1}[\tfrac{\phi_{42}}{s}\mathcal{L}(H_0)] + \pounds^{-1}[\tfrac{\phi_{43}}{s}\mathcal{L}(I_0)] - \mathcal{L}^{-1}[\tfrac{\phi_{44}}{s}\mathcal{L}(F_0)] \\
&\quad -\mathcal{L}^{-1}[\tfrac{\phi_{45}}{s}\mathcal{L}(J_0)] + \mathcal{L}^{-1}[\tfrac{\phi_{46}}{s}\mathcal{L}(c_0(\mathbf{x},t))] \\
&= ((50\,|\mathbf{x}|^2 - 0.26025)t)\exp(-100\,|\mathbf{x}|^2) - 0.181125t\exp(-200\,|\mathbf{x}|^2),
\end{aligned}
$$

$$
\begin{aligned}
p_1 &= \mathcal{L}^{-1}[\tfrac{D_p}{s}\mathcal{L}(\Delta p_0(\mathbf{x},t))] - \mathcal{L}^{-1}[\tfrac{\phi_{52}}{s}\mathcal{L}(H_0)] + \mathcal{L}^{-1}[\tfrac{\phi_{53}}{s}\mathcal{L}(I_0)] - \mathcal{L}^{-1}[\tfrac{\phi_{54}}{s}\mathcal{L}(F_0)] \\
&\quad -\mathcal{L}^{-1}[\tfrac{\phi_{55}}{s}\mathcal{L}(J_0)] + \mathcal{L}^{-1}[\tfrac{\phi_{56}}{s}\mathcal{L}(m_0(\mathbf{x},t))] \\
&= ((7\,|\mathbf{x}|^2 - 0.10175)t)\exp(-100\,|\mathbf{x}|^2) + 0.1035t\exp(-200\,|\mathbf{x}|^2),
\end{aligned}
$$

$$
\begin{aligned}
m_1 &= \pounds^{-1}[\tfrac{D_m}{s}\mathcal{L}(\Delta m_0(\mathbf{x},t))] - \mathcal{L}{-}1[\tfrac{\phi_{62}}{s}\mathcal{L}(H_0)] + \mathcal{L}^{-1}[\tfrac{\phi_{63}}{s}\mathcal{L}(I_0)] - \mathcal{L}^{-1}[\tfrac{\phi_{64}}{s}\mathcal{L}(F_0)] \\
&\quad +\mathcal{L}^{-1}[\tfrac{\phi_{65}}{s}\mathcal{L}(J_0)] - \mathcal{L}^{-1}[\tfrac{\phi_{66}}{s}\mathcal{L}(m_0(\mathbf{x},t))] \\
&= ((0.491\,|\mathbf{x}|^2 - 0.00742)t)\exp(-100\,|\mathbf{x}|^2) + 0.3985t\exp(-200\,|\mathbf{x}|^2).
\end{aligned}
$$

and so on. Therefore,the second approximation in $3-D$ is;

$$
\begin{aligned}
c(\mathbf{x},t) &= c_0(\mathbf{x},t) + c_1(\mathbf{x},t) \\
&= ((14\,|\mathbf{x}|^2 - 0.21)t + 1)\exp(-100\,|\mathbf{x}|^2) + ((3.85 - 230\,|\mathbf{x}|^2)t)\exp(-200\,|\mathbf{x}|^2),
\end{aligned}
$$

$$
\begin{aligned}
v(\mathbf{x},t) &= v_0(\mathbf{x},t) + v_1(\mathbf{x},t) \\
&= 1 + (0.39675t - 0.5)\exp(-100\,|\mathbf{x}|^2) - 0.279625t\exp(-200\,|\mathbf{x}|^2),
\end{aligned}
$$

$$
\begin{aligned}
s(\mathbf{x},t) &= s_0(\mathbf{x},t) + s_1(\mathbf{x},t) \\
&= 0.0255t\exp(-100\,|\mathbf{x}|^2) + 0.37725t\exp(-200\,|\mathbf{x}|^2),
\end{aligned}
$$

$$
\begin{aligned}
u(\mathbf{x},t) &= u_0(\mathbf{x},t) + u_1(\mathbf{x},t) \\
&= ((50\,|\mathbf{x}|^2 - 0.01025)t + 0.5)\exp(-100\,|\mathbf{x}|^2) - 0.181125t\exp(-200\,|\mathbf{x}|^2),
\end{aligned}
$$

$$
\begin{aligned}
p(\mathbf{x},t) &= p_0(\mathbf{x},t) + p_1(\mathbf{x},t) \\
&= ((7\,|\mathbf{x}|^2 - 0.06675)t + 0.05)\exp(-100\,|\mathbf{x}|^2) + 0.1035t\exp(-200\,|\mathbf{x}|^2),
\end{aligned}
$$

$$
\begin{aligned}
m(\mathbf{x},t) &= m_0(\mathbf{x},t) + m_1(\mathbf{x},t) \\
&= ((0.491\,|\mathbf{x}|^2 - 0.06441)t + 0.005)\exp(-100\,|\mathbf{x}|^2) + 0.3985t\exp(-200\,|\mathbf{x}|^2).
\end{aligned}
$$

5.2 Numerical Result

In this section,the plots of the approximate solution of $c(x,t)$, $v(x,t)$, $u(x,t)$, $s(x,t)$, $p(x,t)$ and $m(x,t)$ which are obtained by LADM, in a one-dimensional spatial domain are presented. At this stage, from those graph biological meaning of the solution of system of equation (4.3.2)-(4.3.7) which is computed by LADM is interpreted. We use an equidistant covering of the spatial domain of length $\Delta x = 0.01$ and time step sizes $\Delta t = 10^{-6}$. We ran the simulations for a dimensionless time$t = 0$ up to $t = 500$ on the domain $\Omega \in [-1,1]$,$\Omega \in [-5,5]$,$\Omega \in [0,1]$ and $\Omega \in [0,10]$. In the interest of a clearer,we present that obtained with $\Omega = [-1,1]$ and $\Omega \in [0,1]$. The figures show clearly,tumor cells density distribution, the ECM degradation by the enzyme plasmin, the ECM displacement, the uPA, PAI-1, and plasmin concentration. Figures capture the dynamic heterogeneity of cancer cell density that evolves over time by interacting with components of the uPA system. Initially, at $t = 0$, we assume a cluster of tumor cells are already present and they have penetrated a small area in the extracellular matrix. In figure (5.1) by the time $t = 1(\sim 3$ hours) we see that tumour cells density distribution has changed considerably; a build up of a small cluster of tumour cells are appeared at the leading edges, which

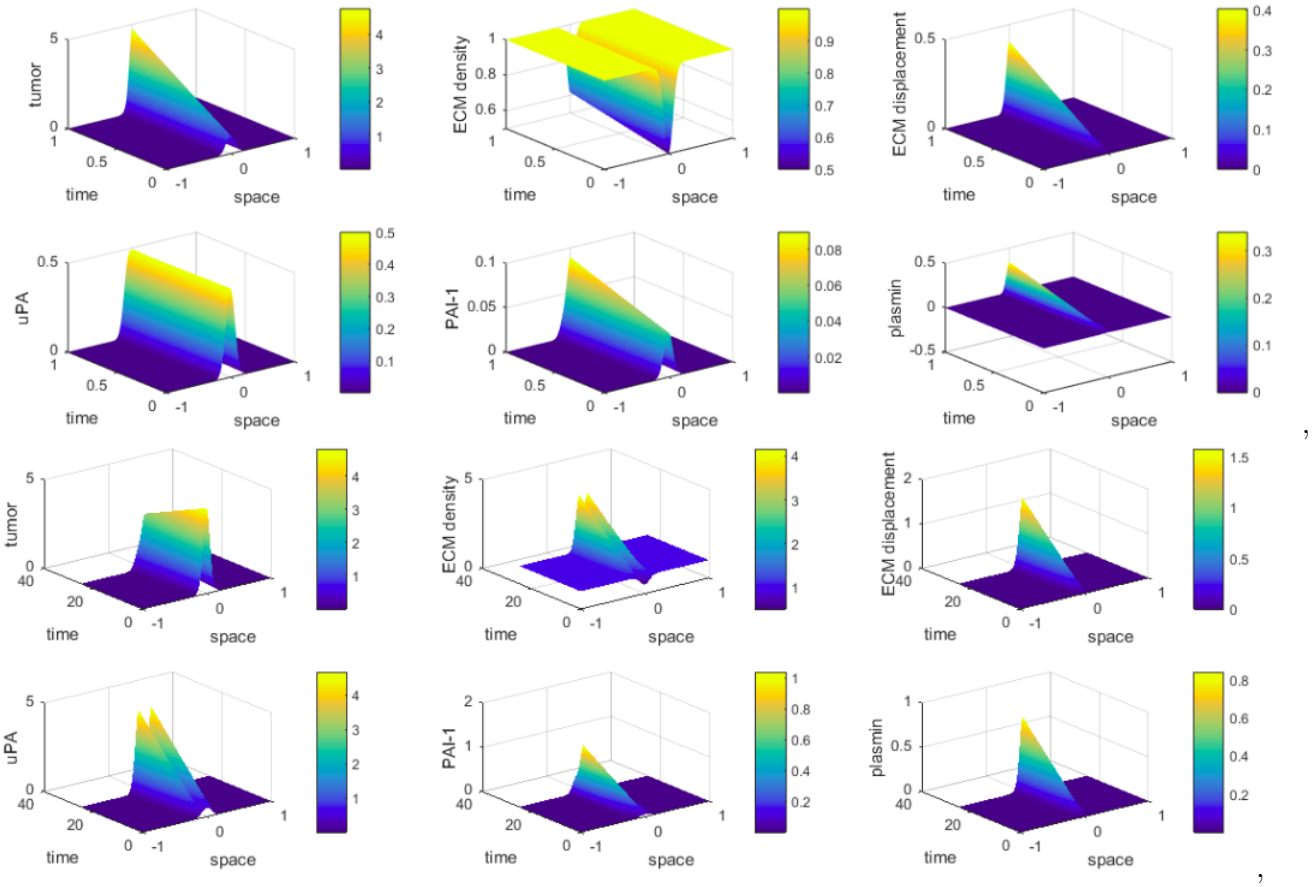

Figure 5.1: Figure showing the spatio-temporal evolution of tumor cells, invading extracellular matrix along with the other components of the model: ECM displacement, uPA protease concentration, PAI-1 concentration and plasmin concentration for model equation (4.3.2)-(4.3.7) with model parameter set $\mathcal{P}$ on a domain $\Omega = [-1.1]$ at dimensionless times $t = 1$, and $t = 25$.

then breaks away from the main body of the tumour. Clearly at this time the impact on the ECM profile is minimal. The ECM displacement, the uPA, PAI-1 and plasmin concentration are increasing.

Again in Figure (5.1) by the time $t = 10$ ($\sim$ 28 hours) larger cluster of tumor cells have formed at the leading edge of the primary tumour and some of the ECM has been degraded; and by that time,the increased levels of ECM displacement, uPA, and plasmin concentration are observed while PAI-1 is decreased. As time evolves, $t = 20$ ($\sim$ 2.5 days) the invading cluster of cancer cells has migrated all the way through the domain driven mainly by ECM mediated haptotaxis. If a small cluster of cells breaks away from

the main body of the tumour, there is then the potential for these cells to intravasate any neighbouring vessels and start the metastatic cascade. Also if the main body of the tumour were to be surgically removed (resected), the smaller cluster of cells that has invaded further into the ECM may go unnoticed by the surgeon and lead to a possible recurrence. These results indicate the importance of haptotaxis as a mechanism for invasion and implicate its role in the metastatic cascade. Figure(5.2) as time evolves, by

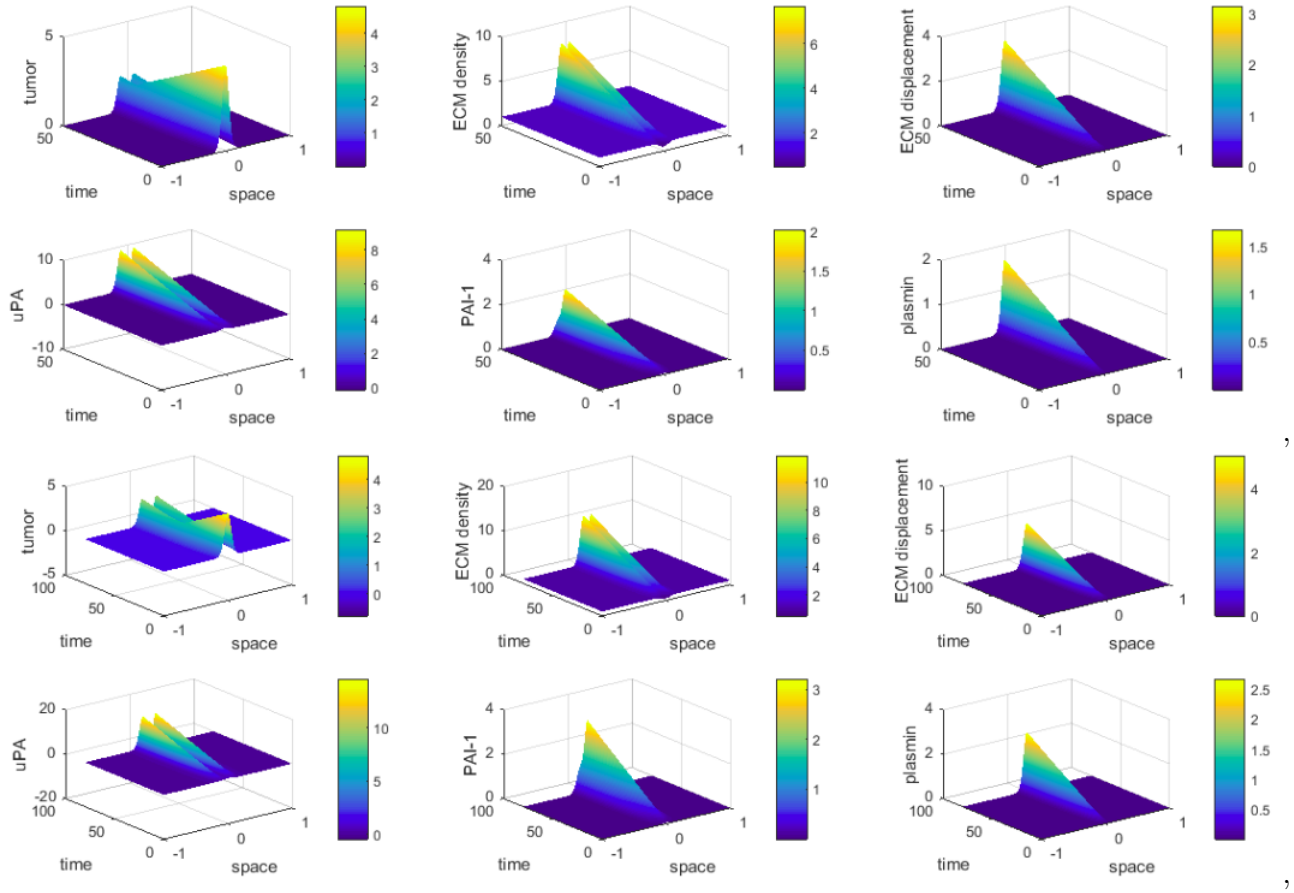

Figure 5.2: Figure showing the spatio-temporal evolution of tumor cells, invading extracellular matrix along with the other components of the model: ECM displacement and uPA, PAI-1 and plasmin concentration for model equation (4.3.2)- (4.3.7) with model parameter set $\mathcal{P}$ on a domain $\Omega = [-1.1]$ at a dimensionless times $t = 50$ and $t = 80$.

$t = 50(\sim 6$ days), two large clusters cancer cells are formed and migrates much further into the ECM have seen and invaded the remaining of the ECM; at the same time$t = 55$ ($\sim$6.5 days), most of the ECM has been degraded and cancer cell locomotion is driven

mainly by the uPA-mediated chemotaxis.

As time evolves this clusters of cells migrate further from the main body of the tumor which continues to invade the ECM but at slower rate. The main body of the tumour however, invades more slowly than was observed in Figure(5.1) while the ECM displacement, uPA , PAI-1 and plasmin concentration profile curves show that a very slow growth is observed.

However, by $t = 80$ ($\sim$ 9.25 days), in Figure 5.2, the previously mentioned cluster of cells situated near the boundary (which could represent a region of hard tissue or bone) and starts to migrate towards the left-hand boundary as a result of the uPA-mediated gradient.

Comparing the plot at $t = 10$ ($\sim$28 hours), in Figure (5.1) with that at $t = 80$ ($\sim$9.25 days), in Figure (5.2), we see that the tumor cells driven both by haptotaxis and chemotaxis migrate at a slightly slower rate than those driven by haptotaxis alone. This is a consequence of the uPA chemotaxis, namely the uPA gradient slows the migration of the cancer cells towards the ECM due to their opposite directions.

As time evolves, at $t = 100$ ($\sim$11. 5 days) two groups of cells are observed while by $t = 105$ ($\sim$12 days) these two cluster of cells start to join to form a continuous band of tumor cell density and at the same time in Figure (5.2) only a single large cluster of cells has formed. As time evolves, these group of cells are static and a spatially heterogeneous profile/pattern is observed. Therefore, we could assume that in this stage the tumour is a dormant state. Considering the successive times between t = 105 ($\sim$ 12 days) to $t = 155$ ($\sim$18 days) we observe that the system remains in a "pause"state where the cluster of cells are almost static. Therefore, we could once again assume that for several days the tumour in the absence of ECM remains in an stationary state for several days.

To examine the importance of the role of ECM in the invasive process, we now consider a ECM with an initial distribution given in Figure (4.3.2) i.e. there are now regions of high density of ECM and regions of low density of ECM. Using this initial ECM data, the same

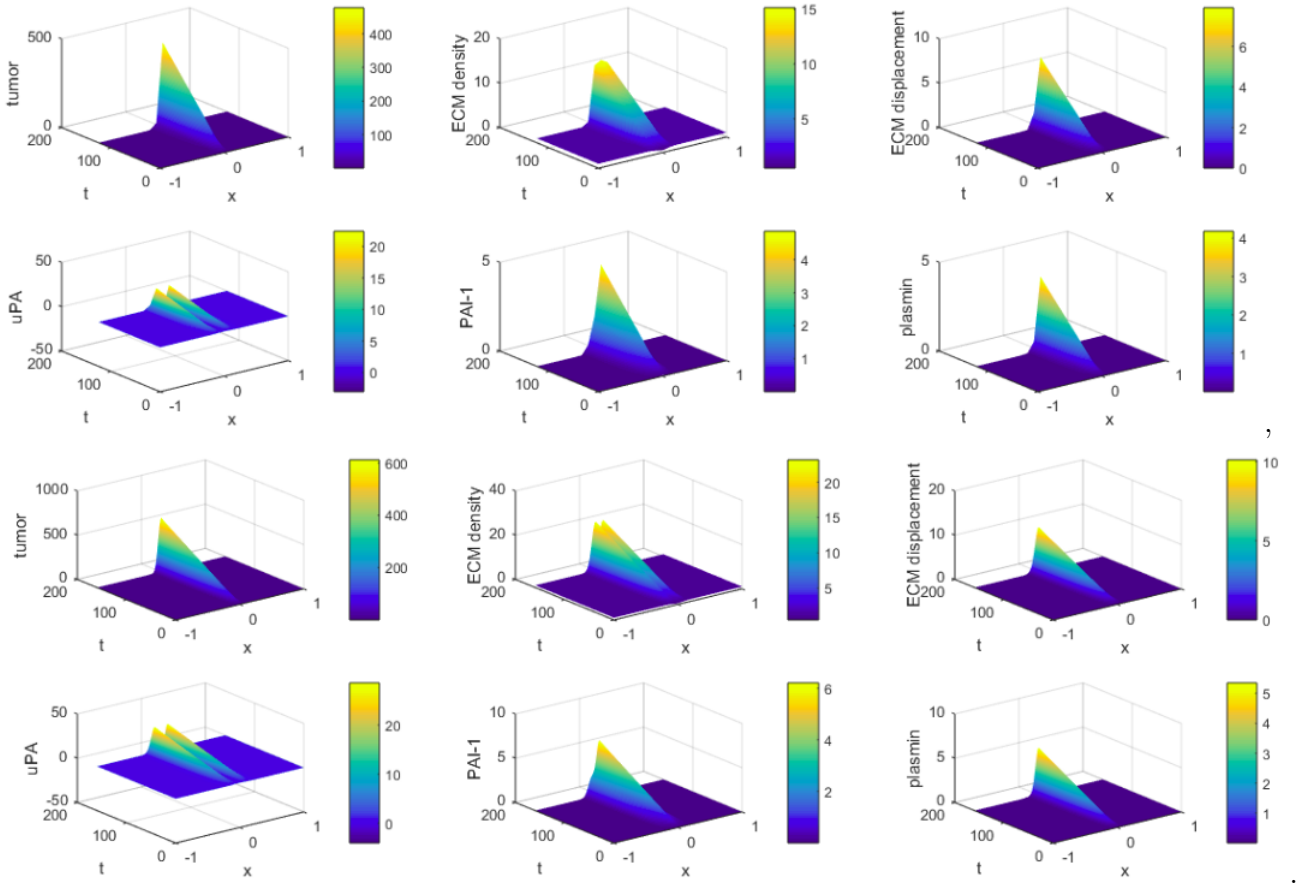

Figure 5.3: Figure showing the spatio-temporal evolution of tumor cells, invading extracellular matrix along with the other components of the model: ECM displacement, uPA, PAI-1 and plasmin concentration for model equation (4.3.2) (4.3.7) with model parameter set $\mathcal{P}$ on a domain $\Omega = [-1, 1]$ at a dimensionless times $t = 125$ and $t = 160$.

initial tumour cell distribution, ECM displacement,uPA,PAI-1 and plasmin concentration as for figure (4.3.2), we note that the same behaviour is observed at the early stages ($t = 1$) as for figure(5.1) with a basic radial expansion. However, by $t = 10$the perfect symmetry of the initial tumour cell distribution is broken and there are several regions of higher tumour cell density, the distinction between cells which are mainly driven by diffusion and those driven by haptotaxis is no longer obvious. The main body of the tumour is approximately bounded by these higher density regions of ECM, although by $t = 40$ the higher density regions have fragmented and a new profile has appeared. Thus the particular choice of initial ECM distribution shows the importance of ECM gradients.

Chapter 6

Result and Discussion

In this study we have presented a mathematical model of tumor cell invasion of tissue and investigated the interactions of tumor cells with the ECM and the degradation of the ECM by MDE. The model was formulated as a system of partial differential equations with the nonlocal terms modeling competition for nutrient and space between the tumor cells and tissue re-modelling. Additionally, we incorporated ECM displacement and the indirect and direct contribution of the binding of different uPA components in the model. The numerical solution by LADM and computational results of numerical solutions of our model were given.

In Sect. 1 through 3 respectively, the problem is defined,literature is presented and the method by which the objective achieved is identified. In Sect. 4 of this study, we extend the model developed in literature to include both the competitive and cooperative interactions between tumour and normal cells, by incorporating displacement of ECM in model equation and adding indirect contribution of:(1) the binding of uPA to PAI-1 in plasmin deactivation (2) the binding of uPAR to VN (which bring PAI-1 to uPA) and (3) the binding of PAI-1 to uPA(which in turn results in clearance of uPA from the system, the neutralization of PAI-1 and the production VN) in the model equation and the model is analyzed. In Sect.5, we applied the LADM on the model equation to study the interactions of cancer cells with the ECM and the degradation of the ECM by MDE. In

this section, the approximate solution of the model equation in one ,two and three dimensional domain is obtained using LADM, the graph of the obtained approximate solution is plotted and from it the the biological meaning of the solution is discussed.

In the applied numerical method for solving this model, the nonlinear terms in the coupled equations are treated using ADM and the derivatives are reduced using Laplace transform. By the developed mathematical model, we examined the invasive behaviours of tumor cells.

The model results demonstrates,tumor cells initially degrade the matrix through the uPA system and can initially move via taxis into the degraded matrix, coupled with cell proliferation. However, as the matrix remodels, this provides the tumor cells with the opportunity to "re-degrade"this re-generated matrix with the consequence that multiple clusters of invading cancer cells appear throughout the domain. By the time that this secondary tumour reaches the boundary, it reverses its direction driven by the gradient of the un degraded extracellular components. It could be presumed that the boundary represents a hard tissue or bone and that could assumed biologically that the tumor cells were unable to penetrate the hard tissue or bone and thus reverse their direction directed by ECM components gradient. It is important also to mention that when cells move via random migration and haptotaxis and the intensity of the random movement is dependent upon extracellular matrix components i.e. vitronectin, then a large cluster of tumor cells breaks away from the primary tumour.

The ECM heterogeneity and haptotactic response of the cells to the gradients created in the degraded matrix are two important factors governing the final tumour cell density distribution. However, this result of the model is mainly due to the fact that the only gradients in the ECM are a result of protaese degradation and hence the cells at the leading edge of the tumour are mostly affected by haptotaxis. These results are in qualitative agreement with previous studies and models which are in turn in agreement with actual clinical observations i.e. it is well-known that small clusters of cells can break

away from the central mass of the tumour and invade further leading to possible metastasis. Therefore, it could assumed that a combined anti-protease therapy accompanied by a haptotactic - anti-adhesive blocking agent may result in faster cancer remission and could prevent any early increase in invasion.

Chapter 7

Conclusion and Future Work

A crucial component of tissue invasion is the over-expression by the tumor cells of proteolytic enzyme activity, urokinase-type plasminogen activator uPA. uPA initiates the activation of an enzymatic cascade that primarily involves the activation of plasminogen and subsequently its matrix degrading protein plasmin. Degradation of the matrix then enables the cancer cells to migrate through the tissue and subsequently to spread to secondary sites in the body. 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.

Our model focuses on the role of uPA enzaymatic system in matrix degradation and it consists of a system of reaction-diffusion-taxis partial differential equations terms describing the interactions between tumor cells,uPA components and the host tissue. It is well known that the tumour microenvironment can both promote and suppress tumour growth and invasion, however, most mathematical models of invasion view the normal tissue as inhibiting tumour progression via immune modulation or spatial constraint. In this study,the uPA system model is extended to a system of 6 PDEs by including the ECM displacement and direct and indirect contribution of the binding of different components of uPA system to the model equation and we have investigated, analytically and numerically, a mathematical model by the LADM but it is conceivable that similar results could be obtained.

As it was seen, differences between simulation results from comparable model from literature and solution obtained by LADM results are very small. Thus the presented method is very effective and convenient. Our suggestion is to use this numerical way to solve this and other PDEs system. It will be part of our future work to incorporate a multi-scale version of the current model in the model that has already been developed. It is clear that events at the sub-cellular and cellular level influence events at the tissue scale; we could therefore aim to extend the current model to incorporate sub-cellular and cellular information.

Bibliography

[1] M.kolev and B. zubik kowal (2010), "Numerical Solutions for a Model of Tissue Invasion and Migration of Tumour Cells ", *Computational and Mathematical Methods in Medicine*,

[2] R.A. Gatenby and E. T. Gawlinski (1996), "A reaction-diffusion model of cancer invasion", *Cancer Research*, vol. 56 , no. 24, pp.5745-5753.

[3] Tiina Roose, S. Jonathan Chapman and Philip K. Maini (2007), "Mathematical Models of Avascular Tumour Growth ", *Society for Industrial and Applied Mathematics*, Vol.49, no.2, pp. 179-208.

[4] A. R. A. Anderson , M. A. J. Chaplain, E. L. Newman, R. J. C. Steel and A. M. Thomson (1999), "Mathematical Modelling of Tumour Invasion and Metastasis ", *Journal of Theoretical Medicine*, Vol. 2, pp. 129-152.

[5] R. P. Arujo and D. L. S. Mcelwain (2004) ,"A History of the Study of Solid Tumour Growth:The Contribution of Mathematical Modelling, ", *Bulletin of Mathematical Biology*,66, 1039-1091

[6] Alexander R.A.Andersen(2005), "A hybrid mathematical model of solid tumour invasion: the importance of cell adhesion", *Mathematical Medicine and Biology* , vol. 22, pp.163-186.

[7] M.A.J. Chaplain and G. Lolas (2006),"Mathematical modelling of cancer invasion of tissue: dynamic heterogeneity ", *American Institute of Mathematical Sciences*, Vol.1, no.3, pp. 399-439.

[8] M. Scianna and L. Preziosi (2009), "A Hybrid Model Describing Different Morphologies: the role and effect of Non local interaction ", *Mathematical Models and Methods in Applied Sciences*, Vol.19, No.2, pp. 257-281.

[9] Zuzunna Szymanska(2009) , "Mathematical modelling of cancer invasion of tissue: The role and effect of nonlocal interactions ", *Mathematical Models and Methods in Applied Sciences* ,Vol.19, No.2, pp. 257-281.

[10] Jonathan A. Sherratt and Mark A.J. Chaplain (2001),"A new mathematical model for avascular tumour growth,", *J. Math. Biol.* 43, 291-312.

[11] Heiko Enderling and Mark A.J.Chaplain (2010), "Mathematical modeling of tumor growth and treatment", *J. of Mathematical Biology*,16, 147-153.

[12] Cristian Morales-Rodrigo (2009),"Local existence and uniqueness of regular solutions in a model of tissue invasion by solid tumours ", *J. of applied mathematics*24, 312-346.

[13] Natasha K. Martin , Eamonn A. Gaffney , Robert A. Gatenby and Philip K. Maini (2010),"Tumourstromal interactions in acid-mediated invasion:A mathematical model ", *Journal of Theoretical Biology* 267, 461-470

[14] Wenxiang Liu and H.I. Freedman (2005),"A Mathematical Model of Vascular Tumor Treatment by Chemotherapy ", ,*Mathematical and Computer Modelling* no.42, pp. 1089-1112

[15] Mark A. J. Chaplain (2011), "mathematical modelling of cancer invasion of tissue: The importance of cell-cell adhesion and cell-matrix adhesion ", *Mathematical Models and Methods in Applied Sciences*, Vol.21, No.4, pp.719-743.

[16] Vivi Andasari (2011), "Mathematical modelling of cancer cell invasion of tissue: discrete and continuum approaches to studying the central role of adhesion", *J. Math. Biol.*

[17] Hyun Geun Lee(2015),"Mathematical model and its fast numerical method for the tumor growth ", *Mathematical Biosciences and Engineering* Vol. 12, no. 6,pp. 1173-1187.

[18] Vivi Andasari, Georgis Lolas, Alfi Gerisch and Mark A.J. Chaplain (2011),"Mathematical modeling of cancer cell invasion of tissue: Biological insight from mathematical analysis and computational", *J. Math. Biol.*, vol.63, pp.141-171.

[19] Dumitru Trucu, Ping Lin Alastair Thomson and Mark A.J.Chaplain (2016), "Multiscale Mathematical Model of Tumour Invasive growth", *Mathematical Biology*,Vol.79, pp 389-429.

[20] Zuzanna Szymanska, Maciej Cytowski Elaine, Cicely K. Macnam and Mark A. J. Chaplain (2017) ,"Computational Modelling of Cancer Development and Growth: Modelling at Multiple Scales and Multiscale Modeling", *Math. Bio.*

[21] Majid Khan , M.Hussain, Hossein Jafari and Yasir Khan (2010), "Application of Laplace Decomposition Method to Solve Nonlinear Coupled Partial Differential Equations ", *World Applied Sciences*, vol.9, pp 13-19.

[22] Jasem Fadaei(2011), "Application of Laplace-Adomian Decomposition Method on Linear and Nonlinear System of PDEs ", *Applied Mathematical Sciences*, Vol.5, no.27, pp. 1307-1315.

[23] Sonia M. Holmouist (2007) , "An Examination of the Effective of the Adomian Decomposition Method in Fluid Dynamic Application ", *Electronic thesis and Dissertation*,

[24] G. Adomian (1988), "A of Review of the Decomposition in Applied Mathematics", *Jornal of Mathematical Analysis and Application*, vol.135, 501-544.

[25] P. Pue-on (2013), "Laplace Adomian Decomposition Method for Solving Newell-Whitehead-Segel Equation", *Applied Mathematical Sciences*, Vol.7, no. 132, pp.6593 - 6600.

[26] J. Biazar and S. M. Shafiof (2007),"A Simple Algorithm for Calculating Adomian Polynomials", *Int. J. Contemp. Math. Sciences*, Vol. 2, no. 20, pp.975 - 982.

Appendix A : Basic Idea of LADM method

The Laplace-Adomian decomposition method in the matter of fact was developed to find approximate solutions to differential equations, but in many publications (e.g.see Majid Khan et al.[21] and Jasem Fadai [22]), we could find interesting examples where obtained power series were actually summable to exact solutions. This analytic method (lADM) proposed by Adomain [24] at the begining of 1980 aims to solve nonlinear physical problems, and it is particularly valuable as a tool for scientists and applied mathematicians. It has been applied to a wide class of problems and for non-linear models, the method has shown reliable results in supplying analytical approximations that converge rapidly. consider the following equation:

$$Lu + Nu + Ru = g \tag{7.0.1}$$

where L is a linear operator (hence possibly, a Laplace transformation), N represents a non linear operator and R is the remaining linear part. By defining the inverse operator of L as L^{-1} , assuming that it exists, we get:

$$u = L^{-1}g - L^{-1}Nu - L^{-1}Ru, \tag{7.0.2}$$

The Adomian Decomposition Method assumes that the unknown function u can be expressed by an infinite series of the form:

$$u(x) = \sum_{n=0}^{\infty} u_n(x) \tag{7.0.3}$$

where the components u_n will be determined recursively. Moreover, the method defines the nonlinear term by the Adomian polynomials. More precisely, the ADM assumes that the nonlinear operator $N(u)$ can be decomposed by an infinite series of polynomials given by:

$$N(u) = \sum_{n=0}^{\infty} A_n, \tag{7.0.4}$$

where $A_n's$ are the Adomians polynomials defined as $A_n = A_n(u_0, u_1, u_2, ..., u_n)$.

Substituting ((7.0.3)) into ((7.0.2)) and using the fact that R is a linear operator, we obtain:

$$\sum_{n=0}^{\infty} u_n = L^{-1}g - L^{-1}(\sum_{n=0}^{\infty} R(u_n)) - L^{-1}(\sum_{n=0}^{\infty} A_n(u_0, u_1, u_2, \cdots)) \tag{7.0.5}$$

Therefore the formal recurrence algorithm could be defined by:

$u_0 = L^{-1}g$

$u_1 = -L^{-1}(R(u_0)) - L^{-1}(A_0(u_0))$

.....

$u_{n+1} = -L^{-1}(R(u_n)) - L^{-1}(A_0(u_0, u_1, \dots u_n)), n \geq 0$

The series solution converges to the exact solution if such a solution exists. In Adomian decomposition method, the convergence is accurate locally, mainly in a neighborhood of the boundary point(s). It is useful to note that the recursive formula is constructed on the basis that the zeroth component $u_0(x)$ is defined by all terms that arise from the initial conditions and from integrating the source terms. The remaining components $u_n(x)$, $n > 0$, can be completely determined such that each term is computed by using the previous term. As a result, the components $u_0(x), u_1(x), u_2(x), \cdots$ are identified, and the series solutions are thus entirely determined. The n^{th} term approximation Φ_n is defined by: $\Phi_n = \sum_{k=0}^{n-1} u_k$ Which can be used for numerical approximation. The ADM is similar to find the Taylors series expansion for the nonlinear function $N(u)$ around the initial function u_0.

Consider the nonlinear function $N(u)$. Then, the infinite series generated by applying the Taylors series expansion of f about the initial function u_0 is given by:

$$N(u) = N(u_0) + N'(u_0)(u - u_0) + \frac{1}{2!}f''(u_0)(u - u_0)^2 + \cdots \tag{7.0.6}$$

By substituting ((7.0.3)) into equation ((7.0.6)), we have:

$$N(u) = N(u_0) + N'(u_0)(u_1 + u_2 + \cdots) + \frac{1}{2!}N''(u_0)(u_1 + u_2 + \cdots)^2 + \cdots \tag{7.0.7}$$

Now, we expand equation ((7.0.7)) to obtain the Adomian polynomials, we need first to re-order actually depends on both the subscripts and the exponents of the $u_n's$. For instance, u_1 is of order 1; u_1^2 is of order 2; u_2^3 is of order 6 and so on.

In general,u_k^n is of order nk. In case a particular term involves the multiplication of $u_n's$, its order is determined by the sum of the terms of the $u_n's$ in each term. For example, u_2^3 $u_1^2$is of order 8 since $(3)(2) + (2)(1) = 8$. As a result, rearranging the terms in the expansion ((7.0.7)) according to the order, we have

$$N(u) = N(u_0)+N'(u_0)u_1+N'(u_0)u_2+\frac{1}{2}N''(u_0)u_1^2+N'(u_0)u_3+\frac{1}{2}N''(u_0)u_1u_2+\frac{1}{3}f'''(u_0)u_1^3 + N'(u_0)u_4 + \frac{1}{2}N''(u_0)u_2^2 + \dots \quad (7.0.8)$$

The Adomian polynomials are constructed in a certain way so that the polynomialA_1consists of all terms in the expansion ((7.0.5)) of order 1 , A_2 consists of all terms of order 2 , and so on. In general,$A_n$consists of all terms of order n . Therefore, the corrosponding terms of Adomian polynomials are listed as follows: $A_0 = f(u_0)$

$A_1 = f'(u_0)u_1$

$A_2 = f'(u_0)u_2 + \frac{1}{2}f''(u_0)u_1^2$

$A_3 = f'(u_0)u_3 + f''(u_0)u_1u_2 + \frac{1}{3}f'''(u_0)u_1^3$

. . . and so on.

The Adomian polynomials can be generated for all forms of nonlinearity. They are determined by the following relations;

$$A_n(u_0, u_1, u_2, \dots, u_n) = \frac{1}{n!}\frac{d^n}{d\lambda^n}[N(\sum_{k=0}^{\infty} u_k\lambda^k)]_{\lambda=0}, n = 0, 1, 2, \dots$$

From the above equation we can easily calculate the Adomian polynomial's as follows:

$A_0 = N(u_0)$

$A_1 = \frac{d}{d\lambda}N(u_0 + u_{1\lambda})|_{\lambda=0}$

$A_2 = \frac{1}{2}\frac{d}{d\lambda}((u_1 + 2u_2\lambda)N''(u_0 + u_1\lambda))_{\lambda=0}$

,. . . and so on.

. The LADM provides a solution which converges to the true solution as one takes more and more terms in the series solution.

Appendix B : Matlab code for plotting the graph of solution

$x = -1 : 0.1 : 1;$

$t = 0 : 0.1 : 10;$

$y = t$

$[x, t] = meshgrid(x, t);$

$c = ((14. * x.^2 - 0.07). * t + 1). * \exp(-100. * x.^2) + ((3.85 - 230. * x.^2). * t). * \exp(-200. * x.^2)$

$v = 1 + (0.39675. * t - 0.5). * \exp(-100. * x.^2) - 0.279625. * t. * \exp(-200. * x.^2)$

$s = 0.0255. * t. * \exp(-100. * \mathbf{x}^2) + 0.37725. * t. * \exp(-200. * \mathbf{x}^2)$

$u = ((50. * x.^2 - 0.01025). * t + 0.5). * \exp(-100. * x.^2) - 0.181125. * t. * \exp(-200. * x.^2)$

$p = ((7. * x.^2 - 0.06675). * t + 0.05). * \exp(-100. * x.^2) + 0.1035. * t. * \exp(-200. * x.^2)$

$m = ((0.491. * x.^2 - 0.06441). * t + 0.005). * \exp(-100. * x.^2) + 0.3985. * t. * \exp(-200. * x.^2)$

$subplot(331);$

$surf(x, t, c)$

$xlabel('space'), ylabel('time'), zlabel('tumor');$

$colorbar;$

$shadinginterp;$

$subplot(332);$

$surf(x, t, v)$

$xlabel('space'), ylabel('time'), zlabel('ECM');$

$colorbar;$

$shadinginterp;$

$subplot(333);$

$surf(x, t, s)$

$xlabel('space'), ylabel('time'), zlabel('ECMdisplacement');$

$colorbar;$

$shadinginterp;$

$subplot(334);$

$surf(x,t,u)$

$xlabel('space'), ylabel('time'), zlabel('uPA');$

$colorbar;$

$shadinginterp;$

$subplot(335);$

$surf(x,t,P)$

$xlabel('space'), ylabel('time'), zlabel('PAI-1');$

$colorbar;$

$shadinginterp;$

$subplot(336);$

$surf(x,t,m)$

$xlabel('space'), ylabel('time'), zlabel('plasmin');$

$colorbar;$

$shadinginterp;$