

MATHEMATICAL MODEL FOR CANCER CELL INVASION OF TISSUE

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To my beloved family

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ABSTRACT

Cancer cell invasion of tissue is a complex biological process which during cell migration through extracellular matrix, facilitated by the secretion of degradative enzymes, is a central process. Cells can be deform their cytoplasm to produce pseudopodia, anchor these pseudopodia to neighbouring spatial locations in the tissue and detach earlier bonds, to enable them to move and therefore migrate in a specified direction. Genetic mutations, chemoattractant gradient or a lack of nutrients in their current location can stimulate cell motility and cause them to migrate, thereby invading new territory. In this paper, we propose a hybrid discrete-continuum model to study the early growth of solid tumour and their ability to degrade and migrate into the surrounding extracellular matrix. Considering the importance of chemoattractant gradients in the invasion process, the model consists of a system of partial differential equations describing the interactions of enzyme and the surrounding matrix. Having formulated, then the system has been simplified to simpler system which give an analytical solution in Fourier series. Results from simulation show that the degradation of the extracellular matrix mirrors the tumour's growth. High enzyme concentrations, which cause maximum degradation of extracellular matrix leads to a rise in concentration of attractant and growth factors causes cells to migrate outward and to proliferate. Finally concluding remarks are made and recommendation for future work are indicated in the last section.

ABSTRAK

Serangan sel kanser pada tisu adalah satu proses biologi yang kompleks dimana semasa migrasi sel menerusi matrik luar sel, serangan ini dibantu oleh rembesan enzim degradasi. Sel ini dapat mengubah bentuk sitoplasma mereka menjadi pseudopodia dengan mencengkam pseudopodia ini pada ruangan yang berhampiran pada tisu tersebut dan memutuskan ikatan yang sebelumnya. Ini membolehkan sel-sel bergerak dan seterusnya merebak ke arah yang tertentu. Mutasi genetik, kecerunan tarikan kimia ataupun kekurangan nutrisi pada lokasi tersebut boleh merangsang pergerakan sel dan menyebabkan sel-sel merebak, seterusnya menyerang kawasan baru. Dalam kertas kajian ini, kami mencadangkan model hybrid discrete-continuum untuk mengkaji pertumbuhan awal sel tumor dan kebolehan berdegradasi serta merebak ke sekeliling matrik di luar sel. Dengan mempertimbangkan kepentingan kecerunan tarikan kimia dalam proses serangan berlaku, model ini terdiri daripada sistem persamaan pembezaan separa yang menggambarkan interaksi antara enzim dengan matrik luar sel. Sistem yang telah diformulakan kemudian diringkaskan menjadi system yang lebih ringkas untuk memberikan penyelesaian dalam bentuk siri Fourier secara analitikal. Hasil simulasi menunjukkan kepekatan enzim yang tinggi, dimana menyebabkan degradasi matrik luar sel yang maksimum membawa kepada peningkatan kecerunan tarikan kimia dan juga faktor pertumbuhan yang menyebabkan sel merebak keluar dan terus berkembang. Akhirnya, kesimpulan dibuat dan cadangan untuk kajian masa hadapan disertakan pada seksyen terakhir.

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LIST OF SYMBOLS

MMP	-	Matrix Metalloproteinases
ECM	-	Extracellular Matrix
PDE	-	Partial Differential Equation
BC	-	Boundary Condition
IC	-	Initial Condition
ODE	-	Ordinary Differential Equation

CHAPTER 1

INTRODUCTION

1.1 Research Background

A healthy human body consists of normal growing cells which carry out the life processes in a normal and orderly manner. The body is made up of trillions of living cells. Normal body cells grow, divide, and die in an orderly fashion. During the early years of a person's life, normal cells divide faster to allow the person to grow. After the person becomes an adult, most cells divide only to replace worn-out or dying cells or to repair injuries.

A normal living cell can, for various unfortunate reasons, turn abnormal or cancerous. Cancer is a disorder of cells and although it usually appears as a tumour made up of a mass of cells, the visible tumours is the end of result of whole series of changes which may have taken many years to develop (Knowles, M.A. and Selby, P.J. 2005). It multiplies in the body rapidly and excessively, forming a group of cells of

uncontrollable growth resulting in a swelling. Tumours are usually recognized by the fact that the cells have shown abnormal proliferation, so that a reasonably acceptable definition is that tumour cells differ from normal cells in their lack of response to normal control mechanisms. Tumours can be classified into three main groups (Knowles, M.A. and Selby, P.J. 2005):

- (1) **Benign tumours** may arise in any tissue, grow locally, and cause damage by local pressure or obstruction. However, the common feature is that they do not spread to distant sites.
- (2) ***In situ* tumours** usually develop in epithelium and are usually but not invariably, small. The cells have morphological appearance of cancer cells but remain in the epithelial layer. They do not invade the basement membrane and supporting mesenchyme.
- (3) **Cancer** are fully developed (malignant) tumours with a specific capacity to invade and destroy underlying mesenchyme.

The formation of a tumor begins with the failure in the replication of a cell's DNA which leads to the uncontrolled division of the cell. People can inherit abnormal DNA, but most DNA damage is caused by mistakes that happen while the normal cell is reproducing or by something in the environment. Sometimes the cause of the DNA damage may be something obvious like cigarette smoking or sun exposure. But it's rare to know exactly what caused any one person's cancer.

This initial failure in DNA replication occurs at a molecular level in the cell nucleus. The result of such instability are new daughter cells which interact with the environment in a two-scale physical-chemical framework. At the cellular level, dynamics have in general a much longer space scale and a slower time scale than events

at the molecular level. For example, a reaction such as the enzymatic degradation of a substrate can occur in milliseconds whereas the replication of a cell can take about one day. This difference in space and time scales is evident at the edge of a cancerous cell mass as it tries to penetrate the extracellular matrix (ECM) and thereby invade surrounding territory or spread to other locations. (Ramis-Conde, I. et al, 2008) and (Wolf, K. et al, 2003)

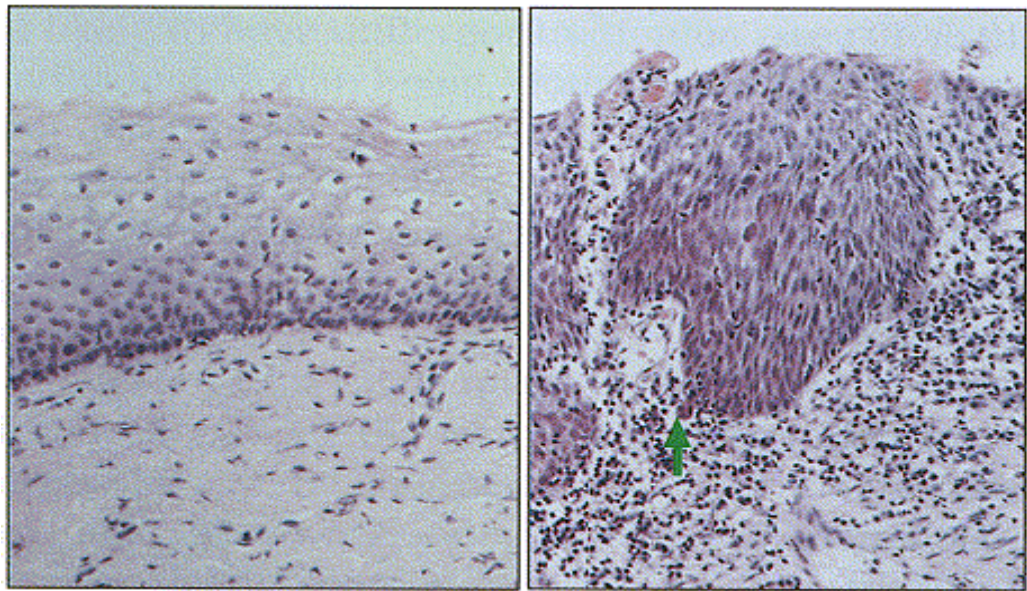


Figure 1.1 The photo on the right shows a carcinoma of the uterine cervix that is just beginning to invade into underlying tissue (at the point indicated by the green arrow). The photo on the left shows the corresponding healthy tissue, for comparison. (<http://www.macs.hw.ac.uk/~jas/researchinterests/cancerinvasion.html>)

At a molecular level cells need to produce those reactions that facilitate their migration through ECM, a process which often involves the degradation of this matrix. The pathways involved in tumor growth can be classified as; intracellular, such as the

formation of actin filaments to produce pseudopodia; extracellular, for example, the reorganization of the collagen filaments of the ECM; and certain others that connect intracellular dynamics with the extracellular stroma, for instance, the uptake of growth factors release from the remodeled ECM, which promote cell mitosis. (Trusolina, L. and Comoglio, P.M., 2002)

From a cellular perspective, physical interactions with the ECM are crucial in determining the nature of the tumour's invasion-front. Invasion of surrounding tissue normally occurs after the tumour had reached a certain size and the peripheral rim of cells has started to disaggregate. At this point the cells on the tumour surface initiate different invasion mechanisms including the fingering process, Indian lines, cluster detachment, etc.

Invasion is the main feature that allows a tumour to be characterized as malignant. The progression of a benign tumour and delimited growth to a tumour that is invasive and potentially metastatic is the major cause of poor clinical outcome in cancer patients, in terms of therapy and prognosis. Understanding tumour invasion could potentially lead to a design of therapeutical strategies. Biomedically, invasion involves the following tumour cell processes:

- Tumour cell migration, which is a result of down-regulation of cadherins, that is loss of cell-cell adhesion
- Tumour cell-extracellular matrix (ECM) interactions, such as cell-ECM adhesion, and ECM degradation. These processes allow for the penetration of the migrating tumour cells into host tissue barriers
- Tumour cell proliferation

All these processes are characterized by a loss of compactness at the tumour surface and are the hallmarks of metastasis. This loss of compactness differentiates malignant and benign tumours and seems to be a biological process similar to the epithelial-mesenchymal transition in embryogenesis where a well organized and bipolar layer of cells becomes more diffuse and semidetached (Preziosi, L., 2003). In this transition, cell adhesion plays an important role in maintaining the compactness of the tissue. For a tumour to become harmful and to invade distant organs in the body, a loss of compactness is crucial. This dictates that cell-cell bonds must be able to detached.

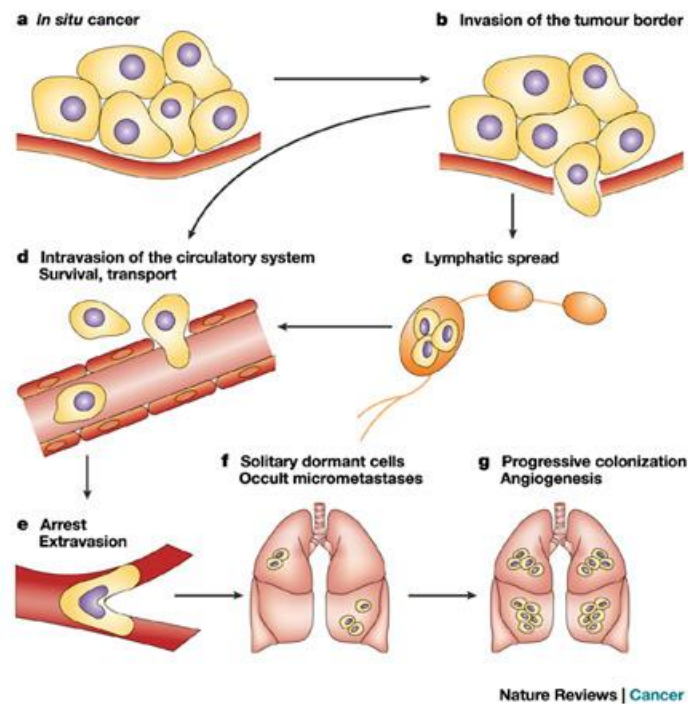


Figure 1.2 A schematic of metastasis process (Steeg, P.S., 2003)

In many tumours mutations related to the cells' adhesive system have been found. These abnormalities are often related to other intracellular biological pathways that may promote further abilities related to invasion. For instance, the beta catenin

pathways is thought to be related to tumour invasion: up-regulation of beta-catenin in the cytoplasm is linked to a poor prognosis for cancer patients (Wong, A. & Gumbiner, M., 2003). This increased invasive ability can be associated with cell-cycle progression or increased cellular motility but, in addition, the beta catenin pathway is closely related to the intracellular domain of the E-cadherin adhesive system. Even if increased cell motility and proliferation contribute greatly to the invasive ability of the tumour, in order for metastasis to occur the detachment of intercellular bonds is necessary.

Cancer cells employ different methods of invasion both individually and in combination to allow tumours to grow. Before a tumour becomes invasive, the roughness of its surface is caused by variations in how groups of peripheral cells degrade the ECM they are in contact with. This degradation is achieved by the tumour cells secreting matrix-degrading enzymes, mainly of the type Matrix Metalloproteinases (MMPs) and Urokinase Plasminogen Actovators (uPAs). Cancer –induced degradation leads to the reorganization of the protein network that forms the ECM and, in many cases, to the production of chemicals that promote cell migration and proliferation. (Bogenrieder, T. & Herlyn, M., 2003)

1.2 Problem statement

Modelling aspect of cancer growth has been approached using a wide range of mathematical models. Most models fall into two broad categories based on how the tumour tissue is represented: discrete cell-based models and continuum models. Although the continuum and discrete approaches have each provided important insight into cancer-related processes occurring at particular length and time scales, the

complexity of cancer and the interactions between the cell-and tissue-level scales may be elucidated further by means of multiscale (hybrid) approach that uses both continuum and discrete representations of tumor cells and components of the tumor microenvironment (Cristini, V. and Lowengrub, J., 2010).

Continuum models using PDEs are usually too large scale and are inappropriate when the problem focuses on a relatively small number of individual cancer cells. In discrete model, it is relatively easy to describe the detailed behaviour of individual cells, which includes random and biased migration, cell-cell and cell-ECM interactions. On the other hand, global population interactions among the group of cancer cells that interact with cannot be captured by discrete approach.

Recently, third category of models has emerged; hybrid model that allows the modellers to maximise the advantages and minimize drawbacks of both continuum and discrete models, thus providing more comprehensive understanding of cell migration leading to more accurate and efficient prediction of tumour morphology and potential of invasion. The advantages are clear when dealing with organisms that involve processes at different scales; microscale and macroscale since cancer cells employ different methods of invasion both individually and in combination to allow tumours to grow.

1.3 Objectives

The purpose of this dissertation of hybrid model for cancer invasion are:

- To formulate the governing equation of enzyme's interaction with the adjacent stroma proposed by Ramis-Conde et al (2008).
- To obtain the solution of interactions of one cell in one spatial dimension interaction analytically.

1.4 Scope

Scope of this study is based on international journal of Mathematical and Computer Modelling entitled "Mathematical Modelling of Cancer Cell Invasion of Tissue" by Ramis-Conde et al (2008) which a hybrid discrete-continuum mathematical model for cancer invasion have been presented in this paper. The continuum part of the hybrid model describe the interaction of the chemicals with the ECM whereas the discrete part models the individual cells. The equations that governs the enzymes's interactions with the adjacent stroma are given in form of nonhomogeneous system of partial differential equation which then been simplified to one spatial dimension, give an analytical solution in Fourier series. Cells are considered to be discrete particles that interact with each other physically via a potential function and with surrounding environment reacting to the contact with the ECM.

In order to highlight the importance of chemoattractant gradient in cell invasion, the problem formulation and procedure solution are only considering the continuum part, and then will be integrated with discrete part during numerical simulation. In this paper, we do not reproduce the simulation and therefore the results obtained by Ramis-Conde et al (2008) were made as an example of simulation results to be discussing in Chapter five.

1.5 Significance

The dynamics of tumour growth constitutes a complex process involving cell-cell and cell-ECM interactions, proliferations of individual cells, secretion of MDE, transport of nutrient, and so on, taking place at different scales both in spaces and in time. Although experimentally, it is difficult to isolate individual effects from a synchronously integrated tumour growth process while keeping other effects intact, mathematical modeling enables us to examine individual effects, one by one or in any combination, with relative ease.

Through the years there has been increasingly understanding and identifying the causes of cancer and in developing strategies for prevention, diagnose and treatment. Although cancer can develop in virtually any of the body's tissues, each cancer has its unique features based on the invaded tissues in the body originated and the particular person himself. Thus, better understanding of tumour growth and invasion would be realized with the aid of mathematical models, which could ultimately lead to treatments being developed which can localize cancer and prevent metastasis and improve therapeutic efficiency by predicting the outcome of a specific treatment on certain types

of tumours. Hence, not surprisingly there have been many attempts to mathematically and computationally describe the dynamics of tumour growth.

In order to better understand the dynamics of cancer growth, mathematical modelling, analysis and simulations have been employed to study the cancer behavior which can contribute in medical field especially in treating cancer patient. The significance of numerous developed mathematical modelling is for modelling and simulation to aid in the development of individualized therapy protocols that minimize patient suffering while maximizing treatment effectiveness. (Cristini, V. and Lowengrub, J., 2010)

1.6 Overview of Dissertation

This study contains six chapters started with introductory chapter. First chapter described briefly about the research background, problem statements, objectives, scopes, significance of this study and definition of several related biological terms.

Literature review of this study will be considered in the next chapter. This chapter explained briefly about previous study of tumour growth, illustrating the development of mathematical approaches from past few decade to the present time. The development of this field of research through the interactions of these different approaches is illuminated, demonstrating the origins of our current understanding of the invasion.

Then, the Chapter 3 will discuss the problem formulation of hybrid model which consists of both continuum and discrete part. The continuum part of the model

described the interactions of the chemicals with the ECM whereas the individual-based part models the individuals cells.

Subsequently in Chapter 4, the solution procedure is detailed out. This chapter show the mathematical analysis done in order to find the solution of the one-spatial dimension simplified system of partial differential equation analytically.

Following the mathematical modeling and procedures detailed out in the previous two chapters, analysis is made up and results are obtained presented in Chapter 5. Last but not least in Chapter 6, conclusion is drawn from the elaboration in the earlier chapters. Recommendations also will be included in this chapter to develop more future work and potential research areas which can contribute to current cancer treatments.

1.7 Terms Definition

- **Angiogenesis:** Blood vessel formation. Tumor angiogenesis is the growth of new blood vessels that tumors need to grow. This process is caused by the release of chemicals by the tumor and by host cells near the tumor.
- **Chemoattractant gradient:** The movement of a microorganism or cell in response to a chemical stimulus.
- **Chemotaxis:** Motions towards high concentration of diffusive chemical substance

- **Extracellular matrix:** Components that are extracellular and composed of secreted fibrous proteins (e.g. collagen) and gel-like polysaccharides binding cells and tissue together.
- **Haptotaxis:** Directed motion of cells along adhesion gradients of fixed substrates in the ECM, such as integrins.
- **Metastasis:** The spread of a cancer from one organ or part to another non-adjacent organ or part. Cancer spreads by metastasis, the ability of cancer cells to penetrate into lymphatic and blood vessels, circulate through the bloodstream, and then invade and grow in normal tissues elsewhere.
- **Proliferation:** To grow or multiply by rapidly producing new tissue, parts, cells, or offspring
- **Mitosis:** The process where a single cell divides resulting in generally two identical cells, each containing the same number of chromosomes and genetic content as that of the original cell.

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