Some Mathematical Models of Cancer Tumors

by
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Abstract

In this project, we consider using partial differential equations to model the growth of a cancer tumor. Using the diffusion and conservation laws, we will derive a general system of partial differential equations for the nutrient concentration and density of proliferating, quiescent and dead cells. We proceed to simplify to a symmetric model in R^3, and then prove some existence and uniqueness results for this simplified model.

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CHAPTER 1

Introduction

1. Nutrient Distribution

We begin by considering a growing multicell spheroid to be surrounded by nutrient-rich serum. For the purpose of modelling, we consider the effect of a single nutrient; usually assumed to be oxygen. The diffusion of oxygen is assumed to be very rapid, if we let the diffusion coefficient be D, and the consumption of oxygen by living cells to be dependent on the local oxygen concentration $C(x,t)$, the oxygen concentration maintains a quasi-static distribution determined by

$$D\nabla^2 C = N\sigma(C) \tag{1.1}$$

where $\sigma(C)$ describes the rate of oxygen consumption per cell and N represents the number of living cells per unit volume of the multicell spheroid.

2. Cell Kinetics

In this paper we make the assumption that the cells that constitute the multicell spheroid may be in one of three possible states; a proliferating state, a non-proliferating state (also known as a quiescent state) and a dead state. Each of these states may be interpreted as representing components of the cell cycle. It is an intrinsic element of our model that cells will exhibit a set of kinetic and dynamic behaviour characteristic of the part of the cell cycle in which they reside. The proliferative part of the cell cycle known as interphase is broken down into phases known as G_1, S, G_2 and M. These individual stages play very important roles in the growth and synthesis of cellular DNA which leads to cell division at the end of the M-phase. Cells in the proliferative part of the cell cycle grow and divide at intervals dependent upon their size, environment and internal cell cycling mechanisms. In the G_1 phase, cellular content, excluding the chromosomes are duplicated. In the S phase, each of the 46 chromosomes are duplicated by the cell. In the G_2 phase, the cell checks for any errors and makes any repairs necessary. The M phase stands for mitosis, where cells replicate. Quiescent cells are those in the G_0 phase and persist in a dormant or non-proliferative state. Cells may move to the quiescent phase from the proliferative phase due to a lack of available nutrients although growth inhibitors can also trigger such a conversion. Cells may also return to the proliferative part of the cycle either by an increase in nutrient supply or in response to external stimuli such as growth factors.

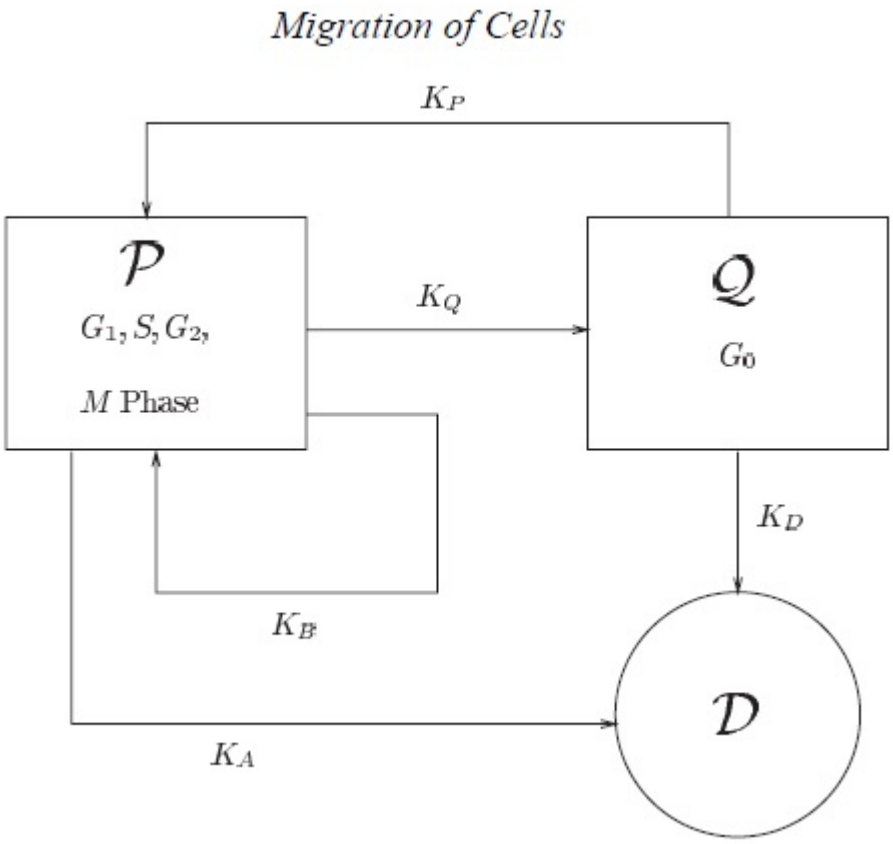


FIGURE 1. Schematic diagram of the three state models used showing the rate functions for conversion between states. P=proliferating, Q=quiescent, D=dead

In comparison the lack of nutrient supply to cells in the quiescent state may trigger necrosis and hence cell death. Those cells that undergo apoptotic cell death at the end of G_1 and the onset of S phases may be represented in this model by the conversion of cells in the proliferative state to cells in the death state. The model does not assume all cells that are deprived of adequate oxygen are quiescent, but rather considers the rate at which cells make the transition between the phases to be oxygen dependent. It is worth noting that the equation above assumes that all cells use the nutrients at the same rate. We assume that the rate at which cells transfer between states is only dependent upon the local extracellular nutrient concentration. The rate functions for each of the possible transfers in our model of cell kinetics are summarized in the figure. More explicitly we have:

- cells in the proliferative state proliferate at a rate $K_B(C)$ and are converted to the quiescent state at the rate $K_Q(C)$ and undergo apoptotic death at a rate $K_A(C)$
- cells in the quiescent state may revert to the proliferating state at a rate $K_P(C)$ and undergo necrotic death at a rate $K_D(C)$.

CHAPTER 2

Biology of Cancer Tumors

The cells within cancer tumors can either be in a living state or in a necrotic state. A necrotic state can be described as the premature death of cells. For cells to be considered in a living state they must grow, divide to make new cells and die in an orderly way.

The human body replaces millions of cells a second. Apoptosis is a form of cell death in which cells are eliminated from the body without releasing harmful substances. Living cells are either in a proliferating phase or in a quiescent phase. In the proliferating phase, the extra cells that are created due to the cell growth and cell division are called proliferating cells. They die as a result of apoptosis.

When a living cell is in a quiescent phase, the cells are at a period of rest in the cell cycle. These types of cells die partially of apoptosis but mostly of starvation. Some cells, such as nerve cells become quiescent when they are terminally differentiated but continue to perform their main functions in order to maintain the organisms life. Living cells undergo cell division in a process called mitosis, but for proliferating cells that part of the cell cycle is much shorter than normal. As the nutrient levels increase in the body, cells change from being in a quiescent phase into being in a proliferating phase at a rate similar to the change in nutrient levels. The cells die at a rate that increases as the level of nutrients in the body decreases. Additionally, as the nutrient concentration decreases in the body proliferating cells become quiescent. For this reason the proliferation rate increases with the nutrient concentration.

According to the above expectation, when talking about cancer tumors, it is typically assumed that proliferating cells will form near the surface. This assumption is due to the fact that the nutrient concentration is the highest near the surface of the tumor. Within the inner core of the tumor, also known as the necrotic core, dead cells will reside as the nutrient concentration is the smallest. Quiescent cells however, are usually found between the outer proliferating layer of a tumor and its necrotic core. Dead cells can be removed from the tumor by large migratory macrophages which engulf and digest cancer cells through a process called phagocytosis. In this way, even though the tumor may grow, its necrotic core may not increase in size. A particular feature of cancer modeling revolves around the idea that a tumors size and shape change over time. A tumor that grows over time is called a malignant tumor, whereas a tumor that stays dormant, decreases in size or disappears completely is called a benign tumor.

The tumors surface is itself a free boundary. Free boundary problems are predominantly challenging because you must solve a system of PDEs in an unknown region. Some

physical conditions are usually evident at the free boundary, and at the same time one seeks to determine the unknown free boundary and the solution of differential equations within the domain enclosed by the free boundary.

There are two types of PDE models to help calculate the free boundary problems on a tumors surface: mixed models and segregated models. Mixed models calculate the different populations of cells that are continuously present everywhere in the tumor. Segregated models however calculate the different populations of cells that are separated by borders, which themselves are free boundaries. Mixed models give a more accurate representation of a tumors surface; though segregated models represent a good approximation. An illustration of this idea is true in vitro experiments. Multicellular tumors have a virtually spherical shape, so the necrotic core is nearly a concentric ball. Tumors who are spherically symmetric have an (outer) free boundary defined as the function $r = R(t)$.

In this paper, the models in Section 3.5 (denoted M_3) assume three populations of cells: proliferating, quiescent and dead cells. The models in Section 3.6 (denoted by M_2) assume two populations of cells: proliferating and quiescent. The model in Section 3.7 deals with a population of cells, namely proliferating cells. Finally, in Chapter 4 we report on some mathematical results and list some open problems.

CHAPTER 3

PDE Models of Cancer Tumors

In this chapter, we study mixed models, denoted as M_3 and M_2, and a model with just proliferating cells in $\mathbb{R}^3$. We will then assume spherical symmetry in the concentration of nutrients C.

1. Background PDEs and Physical Laws

In this subsection, we discuss some PDEs and physical laws required to derive PDE models of cancer tumors: the diffusion equation, the continuity equation (or conservation of mass) and Darcy's Law.

2. The Diffusion Equation/Heat Equation

The diffusion equation in one dimension describes the temperature, $u = u(x,t)$, of a rod of length L at every point x in the rod, and every time $t \geq 0$. Using the Law of Conservation of Energy, Fourier's Law and empirical laws on heat transfer, one can derive the following heat equation

$$\frac{\partial u}{\partial t} = k\nabla^2 u, \tag{3.1}$$

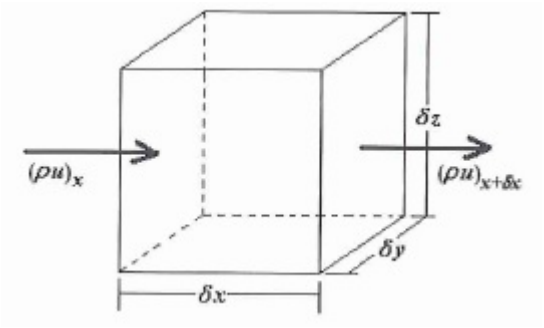
where k=thermal diffusivity is a positive constant and $\nabla^2 u = \triangle u$ is the Laplacian operation in 3 dimersions, i.e, $\nabla^2 u = \triangle u = \frac{\partial^2 u}{\partial x^2} + \frac{\partial^2 u}{\partial y^2} + \frac{\partial^2 u}{\partial z^2}$. If there is a source or sink of heat, then the heat equation becomes

$$\frac{\partial u}{\partial t} = k\nabla^2 u + G(x,t), \tag{3.2}$$

where $G(x,t)$ represents the source or sink of heat.

3. Continuity Equation

Imagine a small cube at a fixed point in space. To calculate the net change in mass contained within the cube, one must add the mass fluxes entering and leaving through each face of the cube.



Let $\overrightarrow{v}$ = velocity field of fluid, ρ = density and $\rho\overrightarrow{v}$ = mass flux, The mass flux across a face of the cube normal to the x, y and z axis is:

$$\begin{aligned}\frac{\partial m}{\partial t} &= (\rho u)_x \delta y \delta z - (\rho u)_{x+\delta x}\delta y\delta z + (\rho v)_y \delta x \delta z \\ &\quad -(\rho v)_{y+\delta y}\delta x\delta z + (\rho w)_z \delta x\delta y - (\rho w)_{z+\delta z}\delta x\delta y\end{aligned}$$

The mass in the cube can be written in terms of density as: $m = \rho\,\delta x\delta y\delta z$. Hence,

$$\frac{\partial m}{\partial t} = \frac{\partial \rho}{\partial t}\delta x\delta y\delta z, \tag{3.3}$$

and

$$\frac{\partial \rho}{\partial t} = -[\frac{(\rho u)|_{x+\delta x} - (\rho u)|_x)}{\delta x}] - [\frac{(\rho v)|_{y+\delta y} - (\rho v)|_y)}{\delta y}] - [\frac{(\rho w)|_{z+\delta z} - (\rho w)|_z)}{\delta z}].$$

Letting δx, δy, $\delta z \to 0$, we have

$$\frac{\partial \rho}{\partial t} = -\frac{\partial(\rho u)}{\partial x} - \frac{\partial(\rho v)}{\partial y} - \frac{\partial(\rho w)}{\partial z}$$

$\Longleftrightarrow$

$$\frac{\partial \rho}{\partial t} = -\nabla\cdot(\rho\overrightarrow{v}). \tag{3.4}$$

If divergence of mass flux $\nabla\cdot(\rho\overrightarrow{v}) > 0$ then density ρ will decrease. If divegence of mass flux $\nabla\cdot(\rho\overrightarrow{v}) < 0$ then density ρ will increase.

Note that if there is a source or sink of mass, then the conservation of mass equation (3.4) becomes

$$\frac{\partial p}{\partial t} + \nabla\cdot(\rho\overrightarrow{v}) = G(t, \overrightarrow{v}), \tag{3.5}$$

where $G(t, \overrightarrow{v})$ = source/sink of mass.

4. Darcy's Law

Darcy's Law describes the flow of a fluid through a porous medium. It is analogous to Fourier's law in the field of heat conduction where heat flow= $-k\nabla T$. Darcy's Law is a mathematical statement which summarizes many properties that groundwater flowing in aquifiers demonstrates, including:

- if there is no pressure gradient over a distance, no flow occurs (these are hydrostatic conditons),
- if there is a pressure gradient, flow will occur from high pressure towards low pressure (opposite the direction of increasing gradient - hence the negative sign in Darcy's law),
- the greater the pressure gradient (through the same formation material), the greater the discharge rate, and
- the discharge rate of fluid will often be different – through different formation materials (or even through the same material, in a different direction) – even if the same pressure gradient exists in both cases.

If we denote $\overrightarrow{v}$ as the velocity of a fluid, and σ its pressure, then Darcy's Law can be written as

$$\overrightarrow{v} = -k\nabla\sigma \tag{3.6}$$

where k is some constant.

5. Mixed Models M_3

In this subsection, we study the mixed model M_3 in $\mathbb{R}^3$ (3 dimensions).

This particular model assumes that there are three cell populations: proliferating cells, quiescent cells and dead (necrotic) cells. Their densities are represented by P, Q and D respectively. The rates of change from one phase to another are functions of the concentration C of nutrients. The tumour surface is a free boundary, and these densities satisfy a system of nonlinear first order hyperbolic equations in the tumor.

Cells of the same size and density are assumed to be mixed within the tumor in different states. The total density of cells within the tumor is assumed to be uniformly packed and constant, which can be shown by the following equation:

$$P + Q + D \equiv const. \equiv N. \tag{3.7}$$

There is a continuous movement of cells within the tumor due to proliferation and removal of necrotic cells. We can represent this movement by a velocity field $\overrightarrow{v}$ that satisfies the generalized relationship for flow in porous media known as Darcy's Law (see equation 3.6). This law shows that the volumetric flow rate is a function of the flow, area, elevation, fluid pressure and a proportionality constant:

$$\overrightarrow{v} = \nabla\sigma, \qquad \sigma = \text{pressure}; \tag{3.8}$$

In this model the following is assumed:

$\overline{K}_Q(C)$ is increasing in C (rate of change from $P \to Q$)

$\overline{K}_P(C)$ is increasing in C (rate of change from $Q \to P$)

$\overline{K}_D(C)$ is increasing in C ($Q \to D$ at a rate $\overline{K}_D(C)$)

$\overline{K}_A(C)$ is decreasing in C (death rate by apoptosis)

$\overline{K}_B(C)$ is increasing in C (proliferating rate)

$\overline{K}_B(C) > \overline{K}_A(C)$

$K_R(C)$ is a positive constant (rate of removal of dead cells)

The region occupied by the tumor at time t is denoted by $\Omega(t)$ and by $\partial\Omega(t)$ its boundary. We are under the assumption that a nutrient concentration C satisfies a linear diffusion equation with source/sink (see equation 3.2):

$$\epsilon_0 \frac{\partial c}{\partial t} = \nabla^2 c - \lambda c \qquad (\lambda > 0) \tag{3.9}$$

We know, ϵ_0 to be a small positive coefficient given by the quotient

$$\epsilon_0 = \frac{T_{\text{diffusion}}}{T_{\text{growth}}}$$

.

For simplicity, we take $\epsilon_0 = 0$, so that

$$\nabla^2 C - \lambda C = 0 \text{ in } \Omega(t), \qquad (\lambda > 0),$$
$$C = C_0 \text{ on } \partial\Omega(t).$$

The rates explained above can be written as:

$$\overline{K}_B(C) = k_B(C), \overline{K}_D(C) = k_D(C_0 - C), \overline{K}_P(C) = k_P(C),$$
$$\overline{K}_Q(C) = k_Q(C_0 - C), \overline{K}_A(C) = k_A(C_0 - C);$$

the removal rate K_R is independent of C. One may go about replacing these linear rates, as long as the nonlinear rates have the same monotonic behaviour in C.

Since the densities P, Q and D satisfy conservation of mass/continuity equation (3.3), we have

$$\frac{\partial P}{\partial t} + \text{div}(Pv) = [\overline{K}_B(C) - \overline{K}_Q(C) - \overline{K}_A(C)]P + K_P(C)Q, \tag{3.10}$$

$$\frac{\partial Q}{\partial t} + \text{div}(Qv) = \overline{K}_Q(C)P - [\overline{K}_P(C) + \overline{K}_D(C)]Q, \tag{3.11}$$

and

$$\frac{\partial D}{\partial t} + \text{div}(Dv) = \overline{K}_A(C)P + \overline{K}_D(C)Q - \overline{K}_R D. \tag{3.12}$$

Adding the density systems (3.10)-(3.12) for P, Q and D, we get an equation for the pressure σ:

$$N\nabla^2\sigma = \overline{K}_B(C)P - K_R D. \tag{3.13}$$

It is clear that the density system for D may be replaced by Darcy's Law if we also replace D by $N - P - Q$ and set

$$c = \frac{C}{C_0},\ p = \frac{P}{N},\ q = \frac{Q}{N}.$$

From this we arrive at the following system of equations:

$$\nabla^2 c - \lambda c = 0 \text{ in } \Omega(t), \tag{3.14}$$

$$c = 1 \text{ on } \partial\Omega(t), \tag{3.15}$$

$$\frac{\partial p}{\partial t} + \text{div } (p\nabla\sigma) = (K_B(c) - K_Q(c) - K_A(c))p + K_P(c)q \text{ in } \Omega(t), \tag{3.16}$$

$$\frac{\partial q}{\partial t} + \text{div } (q\nabla\sigma) = K_Q(c)p - (K_P(c) + K_D(c))q \text{ in } \Omega(t), \tag{3.17}$$

$$\nabla^2\sigma = -K_R(c) + (K_B(c) + K_R(c))p + K_R(c)q \text{ in } \Omega(t), \tag{3.18}$$

where

$$K_i(c) = \overline{K}_i(C) \text{ for } i = B, Q, A, D$$

We assume that the pressure σ on the surface of the tumor is equal to the surface tension, that is,

$$\sigma = \gamma\kappa \text{ on } \partial\Omega(t) \qquad (\gamma > 0) \tag{3.19}$$

where κ is the mean curvature.

There are certain conditions that surround tumors and tumor growth: (i) The medium of a tumor is essentially in a state of diffusive equilibrium at all times. A two-layer structure is assumed for tumors that are currently in a stage of growth. This consists mainly of an outer shell of viable or proliferating cells that envelops a larger core of necrotic debris; (ii) the local thickness h of the thin layer of living cells depends only on a critical level a_1 and the value of $\sigma = \sigma(x, y, z, t)$ the concentration of a vital nutrient at the outer surface of the tumor by the relation $h = v(a - a_1)^{1/2}$ when $a > a_1$ and $h = 0$ (i.e. the cell dies) when $a > a_1$; (iii) the mitotic index is a constant; (iv) necrotic debris disintegrates continually into simpler compounds and the rate of loss of necrotic mass is a constant; (v) a surface-tension force T is proportional to the mean curvature; and (vi) the birth or death of cells produces internal pressure differentials which are governed by $q = \nabla p$ where $q(x, y, z, t)$ is the particle velocity and $p(x, y, z, t)$ is proportional to the internal pressure. The constants λ and μ are relating respectively to the new cells created and nutrient consumed.

Instability is manifested as either a pinch or a corrugation of the boundary surface which can cause a spheroidal distortion of colony shape and may possibly lead to subdivision or disintegration. It is further shown that colonies which share the same food supply repel each other and move apart.

The motion of the free boundary is given by the continuity equation

$$\nabla \overrightarrow{v} \cdot \overrightarrow{n} = V_n, \text{ or } \quad \frac{\partial\sigma}{\partial n} = V_n \text{ on } \partial\Omega(t), \tag{3.20}$$

where $\overrightarrow{n}$ is the outward normal and V_n is the velocity of the free boundary in the outward normal direction.

If we were to write $\partial\Omega(t)$ locally in the form

$$\Phi(x, t) = 0 \text{ where } \nabla_x\Phi(x, t) \neq 0,$$

then the motion of the free boundary takes the form

$$\frac{\partial\sigma}{\partial n} = \frac{\Phi_t}{\mid \nabla_x\Phi \mid}. \tag{3.21}$$

In conclusion, we can summarize the M_3 problem precisely as follows:

Problem (M_3) Given initial domain $\Omega(0)$ and initial data $p_0(x)$, $q_0(x)$ in $\Omega(0)$ such that $p_0(x) \geq 0$, $q_0(x) \geq 0$, $p_0(x) + q_0(x) \leq 1$, find a family of domains $\Omega(t)$ and functions $p(x,t)$, $q(x,t)$, $\sigma(x,t)$, c which satisfy the system (3.14)-(3.20) and the inital conditions

$$p(x,0) = p_0(x), \qquad q(x,0) = q_0(x)$$

such that

$$p(x,t) \geq 0, \quad q(x,t) \geq 0, \quad p(x,t) + q(x,t) \leq 1.$$

,

The free boundary problem (M_2) is an elliptic-hyperbolic problem in the region

$$\Omega_\infty = \{(\Omega(t) \times t); \quad 0 \ < \ t \ < \ \infty\}$$

Set

$$\partial\Omega_\infty = \{\partial\Omega(t) \times t; \quad 0 \ < \ t \ < \ \infty\}.$$

6. Mixed Models M_2

In this subsection, we derive system M_2 : a simplified model of M_3.

The system in Section 5 can be simplified by assuming that the removal rate K_R is extremly large so that dead cells are effectively removed instantaneously. From this assumption, and dividing (3.18) by K_R and letting $K_R \to \infty$, we obtain $p + q = 1$. Therefore we can eliminate $q = 1 - p$ from the differential equation in the M_3 model. By taking $K_A = 0$, we obtain the following system:

$$\nabla^2 c - \lambda c = 0 \text{ in } \Omega(t), \tag{3.22}$$

$$c = 1 \text{ on } \partial\Omega(t), \tag{3.23}$$

$$\frac{\partial p}{\partial t} + \nabla\sigma \cdot \nabla p = K_P(c) + (K_M(c) - K_N)p - K_M(c)p^2 \text{ in } \Omega(t),$$

$$\text{where } K_M(c) = K_B(c) + K_D(c), K_N(c) = K_P(c) + K_Q(c),$$

$$\nabla^2\sigma = -K_D(c) + K_M(c)p \text{ in } \Omega(t), \tag{3.24}$$

with boundary and initial conditions:

$$\sigma = \gamma\kappa \text{ on } \partial\Omega(t), \tag{3.25}$$

$$\frac{\partial\sigma}{\partial n} = V_n \text{ on } \partial\Omega(t), \tag{3.26}$$

and

$$p(x,0) = p_0(x) \text{ in } \Omega(0),\ \Omega(0) \text{ is given.} \tag{3.27}$$

Problem (M_2) Find $\Omega(t)$ and p, σ, c satisfying system (3.22)-(3.26). In the spherically symmetric case, problem (M_1) with

$$\overrightarrow{v} = \nabla\sigma = u\frac{x}{|x|}$$

takes the following form:

$$c'' + \frac{2}{r}c' = \lambda c, \qquad 0 < r < R(t), \tag{3.28}$$

(since in spherical coordinates $\nabla^2 f = \frac{\partial^2 f}{\partial r^2} + \frac{2}{r}\frac{\partial f}{\partial r}$)

$$c'(0) = 0, \quad c(R(t)) = 1, \tag{3.29}$$

$$\frac{\partial p}{\partial t} + u\frac{\partial p}{\partial r} = K_P(c) + (K_M(c) - K_N(c))\,p - K_M(c)\,p^2, \quad 0 < r < R(t), \tag{3.30}$$

$$\frac{\partial u}{\partial r} + \frac{2}{r}\,u = -K_D(c) + K_M(c)\,p, \quad 0 < r < R(t), \tag{3.31}$$

$$u(0,t) = 0, \tag{3.32}$$

$$\frac{dR(t)}{dt} = u(R(t),t), \tag{3.33}$$

with initial conditions

$$p(r,0) = p_0(r), \quad 0 < r < R(0), \tag{3.34}$$

where $R(0)$ is given.

7. Models with only Proliferating Cells

In this subsection, we shall further simplify the model (M_2) by assuming that all the cells are proliferating and assume radially symmetric nutrient concentration, c. Therefore we let,

$$K_Q \equiv 0,\ K_D \equiv 0,\ P \equiv const;$$

When dealing with this simplified case, we usually replace (3.22) with the more general diffusion equation (3.9). Thus, this system takes the following form:

$$\epsilon_0 \frac{\partial c}{\partial t} = \nabla^2 c - \lambda c \text{ in } \Omega(t), \tag{3.35}$$

$$c = \overline{c} \text{ on } \partial\Omega(t), \tag{3.36}$$

$$\nabla^2 c = \mu(c - \widetilde{c}) \text{ in } \Omega(t) \tag{3.37}$$

ecall that $\epsilon_0 = \frac{T_{diffusion}}{T_{growth}}$ = ratio of nutrient diffusion time scale to tumor doubling time scale. Typically $T_{diffusion} \cong 1$ minute and $T_{growth} \cong 1$ day so that $\epsilon \ll 1$.

Also, where $\mu(c - \widetilde{c})$ is the proliferation rate or more precisely, μc = birth rate and $\mu\tilde{c}$ = death rate. In addition,

$$\sigma = \gamma\kappa \text{ on } \partial\Omega(t), \tag{3.38}$$

$$\frac{\partial \sigma}{\partial r} = V_n \text{ on } \partial\Omega(t), \tag{3.39}$$

$$c|_{t=0} = c_0(x),\ x \in \Omega(0) \tag{3.40}$$

where $\Omega(0)$ is given. since $c = c(r)$ and $\nabla^2 = \partial_r^2 + \frac{2}{r}\partial_r$ in spherical coordinates, we have

$$\epsilon_0 \frac{\partial c}{\partial t} = c_{rr} + \frac{2}{r} c_r - \lambda c, \quad 0 < r < R(t) \tag{3.41}$$

$$c_r(0,t) = 0, \quad c(R(t),t) = \overline{c} \tag{3.42}$$

$$c(r,0) = c_0(r), \quad 0 < r < R(t) \tag{3.43}$$

$$\dot{R}(t) = \frac{1}{R^2(t)} \int_0^{R(t)} \mu(c(r,t) - \tilde{c}) r^2 dr. \tag{3.44}$$

CHAPTER 4

Mathematical Results for a Spherically Symmetric Cancer Model

In this section, we solve a spherically symmetric case for mixed models M_2 with only proliferating cells, i.e., we solve equations (3.41) to (3.44) from Chapter 3.

Our main result is as follows:

THEOREM 4.1. *Consider system (3.41)-(3.44)*

(i) *(Existence) If* $\frac{\tilde{c}}{\bar{c}} < 1$, *then there exists a stationary solution* $(\tilde{c}(r), \tilde{R})$.

(ii) *(Uniqueness) For any initial data* $(c_0(r), R(0))$, *there exists a unique solution* $(c(r,t), R(t))$.

(iii) *(Stability) For* $\epsilon_0 > 0$ *sufficiently small in (ii), then*

$$R(t) \longrightarrow \tilde{R}$$

exponentially fast as $t \to \infty$ *, where* $\tilde{R}$ *is the stationary radius in (i).*

This theorem is proven in [2], and we will explore the proof of parts (i) $\to$ (iii) for the rest of this section.

Remarks

(i) Ratio $\frac{\tilde{c}}{\bar{c}}$ = death rate over concentration at the boundary has the be smaller than a fixed constant < 1 for a stationary solution to exist.

(i) and (ii) Show that if the tumor appears, tumor persists for all time. In fact, you can show $\lim_{t\to\infty}$ inf $R(t) > 0$ i.e., radius of tumor is always positive for all time

(iii) shows that tumor will grow/shrink to a fixed radial size $\tilde{R}$ = const. exponentially fast if ϵ_0 is small enough (recall $\epsilon_0 = \frac{T_{diffusion}}{T_{growth}} \ll 1$).

1. Stationary Solution

In this section, we prove Theorem 4.1 (i), i.e., we prove the existence of a stationary solution to equation (3.41). Note that the stationary solution ($\frac{\partial c}{\partial t} = 0$) to (3.41) satisfies

$$\frac{\partial^2 c}{\partial r^2} + \frac{2}{r}\frac{\partial c}{\partial r} - \lambda c = 0, \quad 0 \ < \ r \ < \tilde{R} \tag{4.1}$$

PROPOSITION 4.2. *There exists a solution to (4.1) of the form*

$$c_s(r) = \overline{\sigma}\frac{\tilde{R}}{sinh(\sqrt{\lambda}R)}\frac{sinh(\sqrt{\lambda r})}{r} \tag{4.2}$$

where $c_s(r)$ denotes the stationary concentration solution.

PROOF. □

Now, we complete the proof of Theorem 4.1 (i). The constraint (3.10) (from Chapter 3) becomes:

$$\frac{1}{3}\tilde{c}(\tilde{R})^3 = \int_0^{\tilde{R}} c_s(r)r^2dr. \tag{4.3}$$

Substituting, (4.2) into (4.3), we obtain

$$\tanh(\eta) = \frac{\eta}{1+\Lambda(\eta)^2}, \text{ where } \eta = \sqrt{\lambda}\tilde{R}, \tag{4.4}$$

where

$$\Lambda = \frac{1}{3}\frac{\tilde{c}}{\overline{c}}. \tag{4.5}$$

Using the fact that

$$\overline{c} \ > \ \tilde{c} \ > \ \lambda, \tag{4.6}$$

then

$$0 \ < \ \Lambda \ < \ \frac{1}{3}. \tag{4.7}$$

PROOF. We claim there exists a unique solution to (4.4), and hence, there exists a unique stationary solution to (3.7) $\rightarrow$ (3.10).

Indeed, we need to prove that the function

$$g(\eta) = 1 + \Lambda(\eta)^2 - \eta\coth(\eta) \quad 0 \ < \ \Lambda \ < \frac{1}{3} \tag{4.8}$$

has a unique zero $\eta,\ \eta > 0$.

First, we claim

$$\lim_{\eta\to 0} \frac{1}{\eta^2} - \frac{\coth(\eta)}{\eta^2} = -\frac{1}{3} \tag{4.9}$$

PROOF.

$$\begin{aligned}
\lim_{\eta\to 0} \eta\coth(\eta) &= \lim_{\eta\to 0} \frac{\eta}{\tanh(\eta)} \\
&= \lim_{\eta\to 0} \frac{1}{\operatorname{sec}^2 h(\eta)} \\
&= \frac{1}{1} \\
&= 1
\end{aligned}$$

So,

$$\lim_{\eta\to 0} \frac{1-\eta\coth(\eta)}{\eta^2} = \lim_{\eta\to 0} -\frac{[\coth(\eta)+\eta(-\operatorname{csch}^2 x)]}{2\eta}$$

Now,

$$\begin{aligned}
-\coth(\eta)+\eta\operatorname{csch}^2\eta &= \frac{-\cosh(\eta)}{\sinh(\eta)} + \frac{\eta}{(\sinh^2\eta)} \\
&= -\frac{\cosh(\eta)\sinh(\eta)+\eta}{\sinh^2(\eta)}
\end{aligned}$$

and

$$\begin{aligned}
\lim_{\eta\to 0}\big[-\coth(\eta)+\eta\operatorname{csch}^2\eta\big] &= \lim_{\eta\to 0} -\frac{\cosh(\eta)\sinh(\eta)+\eta}{\sinh^2(\eta)} \\
&= \lim_{\eta\to 0} -\left[\frac{\cosh^2(\eta)-\sinh^2(\eta)+1}{2\sinh(\eta)\cosh(\eta)}\right] \\
&= \lim_{\eta\to 0} \frac{-4\cosh(\eta)\sinh(\eta)}{2(\cosh^2(\eta)+\sinh^2(\eta)} \\
&= 0
\end{aligned}$$

Therefore

$$\begin{aligned}
\lim_{\eta\to 0} -\frac{\coth(\eta)+\eta\operatorname{csch}^2(\eta)}{2\eta} &= \lim_{\eta\to 0} \frac{\operatorname{csch}^2(\eta)+\operatorname{csch}^2(\eta)+\eta-\Big[2\operatorname{csch}^2(\eta)[-\coth(\eta)]\Big]}{2} \\
&= \lim_{\eta\to 0} \frac{2\operatorname{csch}^2(\eta)[1-\eta\coth(\eta)}{2}
\end{aligned}$$

However,

$$\begin{aligned}
\lim_{\eta\to 0} 2\,\mathrm{csch}^2(\eta)[1-\eta\coth(\eta)] &= \lim_{\eta\to 0}\frac{2}{\sinh^2(\eta)}\Big[1-\frac{\eta\cosh(\eta)}{\sinh(\eta)}\Big] \\
&= \lim_{\eta\to 0}\frac{2[\sinh(\eta)-\eta\cosh(\eta)]}{\sinh^3(\eta)} \\
&= \lim_{\eta\to 0}\frac{2[\cosh(\eta)-\cosh(\eta)-\eta\sinh(\eta)]}{3\sinh^2(\eta)\cosh(\eta)} \\
&= \lim_{\eta\to 0}-\frac{2\eta\sinh(\eta)}{3\sinh^2(\eta)\cosh(eta)} = -\frac{2\eta}{3\sinh(\eta)\cosh(\eta)} \\
&= \lim_{\eta\to 0}-\frac{2}{3[\cosh^2(\eta)+\sinh^2(\eta)]} \\
&= -\frac{2}{3}
\end{aligned}$$

So

$$\lim_{\eta\to 0}\frac{2\,\mathrm{csch}^2(\eta)[1-\eta\coth(\eta)]}{2} = \frac{-\frac{2}{3}}{2} = -\frac{1}{3}$$

□

Therefore, from equation 4.9, we have:

$$\frac{g(\eta)}{\eta^2} \to \Lambda - \frac{1}{3} \;<\; 0 \text{ if } \eta \to 0,$$

(since $\Lambda < \frac{1}{3}$)

$$\frac{g(\eta)}{\eta^2} \to \Lambda \text{ if } \eta \to \infty.$$

Hence it suffices to show that the function

$$h(\eta) = \frac{g(\eta)}{\eta^2} \text{ is strictly monotone increasing.} \tag{4.10}$$

We have

$$h'(\eta) = \frac{\eta\cosh\eta\cdot\sinh\eta - 2(\sinh\eta)^2 + \eta^2}{\eta^3(\sinh\eta)^2}$$

Denoting the numerator by $k(\eta)$, it suffices to show that $k(\eta) > 0$. But a straightforward calculation shows that

$$k^{(4)}(\eta) = 16\eta\cosh\eta\cdot\sinh\eta \;>\; 0,$$

whereas $k^{(j)}(0) = 0$ for $0 \leqq j \leqq 3$, so that indeed $k(\eta)$ is a positive function.

□

2. Local Existence and Uniqueness

In this section, we prove Theorem 4.1 (ii), i.e., there exists a unique solution to (3.41) → (3.44). For the rest of this project, we assume

$$0 \leq c_0(r) \ < \ \overline{c} \text{ for } 0 \leq r \leq R(0) \text{ and } c_0(r) \text{ is a continuous function} \tag{4.11}$$

PROPOSITION 4.3. *The system (3.41) → (3.44) has a unique solution $c(r,t), R(t)$ and satisfies*

$$0 < c(r,t) < \overline{c} \qquad \text{if} \quad 0 < r < R(t), \quad t > 0, \tag{4.12}$$

$$R(0)e^{-\tilde{c}t} \leq R(t) \leq R(0)e^{\overline{c}-\tilde{c}t}, \quad t > 0, \tag{4.13}$$

$$-\tilde{c}\ R(t) \leq R(t) \leq (\overline{c} - \tilde{c})R(t), \quad t > 0. \tag{4.14}$$

PROOF. Local existence and uniqueness of system (3.41) → (3.44) can be proven by standard arguments for the Stefan problem both wth free boundary condition

$$\frac{1}{3}R^2(t)\frac{dR}{dt} = \int_0^{R(t)} (c(r,t) - \tilde{c})r^2 dr,$$

replacing the Stefan condition $\tilde{R} = -c_x$ (see [4], Chapter 8). Since I ran out of time, I will not explore this proof in this thesis.

To prove estimates (4.11) to (4.13), we first need the following Maximum principle.

THEOREM 4.4. *Maximum Principle (for Parabolic PDEs)*

Consider the operator

$$Lu = \sum_{i,j=1}^{n} a_{ij}(x,t)\frac{\partial^2 u}{\partial x_i \partial x_j} + \sum_{i=1}^{n} b_i(x,t)\frac{\partial u}{\partial x_i} + c(x,t)u - \frac{\partial u}{\partial t}$$

in $\Omega_\infty = \Omega \times (0,\infty)$, and $\Omega \subseteq \mathbb{R}^n$, open and bounded. Suppose the coefficients of C are bounded functions in Ω_∞ and that the coefficients $a_{ij}(x,t)\xi_i\xi_j > \lambda|\xi|^2$ for some $\lambda > 0$ and for every $(x,t) \in \Omega_\infty$, and for any real vector $\xi \neq 0$. Then $u = u(x,t)$ only attains its maximum and minimum on the boundary of Ω_∞.

We prove (4.11) first. It can be easily seen that (3.41) is a parabolic PDE, and hence, by maximum principle, and the assumption in (4.11) made earlier, $c(r,t)$ cannot take a non-positive minimum in the set $\{r < R(t)\}$, so that $c(r,t) > 0$ if $0 < r < s(t)$. Similarly, $c(r,t)$ cannot obtain a maximum larger than or equal to $\overline{c}$ in the set $\{r < R(t)\}$. Hence, (4.11) is proven.

Now, we prove (4.13). By the operator for the maximum principle, we have

$$\begin{aligned} \dot{R}(t) &= \frac{3}{R^2(t)} \int_0^{R(t)} (c(r,t) - \tilde{c}) r^2 dr \\ &= \frac{3}{R^2(t)} \int_0^{R(t)} c(r,t) r^2 dr - \tilde{c} R(t) \end{aligned}$$

Since the first term on the right hand side is ≥ 0, then clearly $\dot{R}(t) \geq -\tilde{c}R(t)$.

Now, since $c(r,t) < \overline{c}$ by (4.11). then the above equation implies that

$$\begin{aligned} \dot{R}(t) &\leq \frac{3}{R^2(t)} \int_0^{R(t)} (\overline{c} - \tilde{c}) r^2 dt \\ &= (\overline{c} - \tilde{c}) R(t), \end{aligned}$$

which proves the other inequality in (4.13).

To prove, (4.12), we obtain from (4.13):

$$-\tilde{c} \leq \frac{\dot{R}(t)}{R(t)} \leq (\overline{c} - \tilde{c})$$

$$\Longrightarrow$$

$$\int_0^t (-\tilde{c}) d\tau \leq \int_0^t \frac{\dot{R}(t)}{R(t)} d\tau \leq \int_0^t (\overline{c} - \tilde{c}) d\tau$$

$$\Longrightarrow$$

$$-\tilde{c}t \leq Lu\Big(\frac{R(t)}{R(0)}\Big) \leq (\overline{c} - \tilde{c})t$$

$$\Longrightarrow$$

$$R(0)e^{-\tilde{c}t} \leq \Omega(t) \leq R(0)e^{(\overline{c}-\tilde{c})t},$$

which ends the proof of (4.12), and the proof of Proposition 4.3, and the proof of theorem 4.1(ii).

□

3. Stability

In this section, we prove Theorem 4.1 (iii), i.e., we prove stability of the solutions found in Theorem 4.1 (ii). Due to time constraints, we were not able to investigate the proof of Theorem 4.1 (iii) using formal two scale asymptotic analysis.

CHAPTER 5

Closing Remarks

In this section, we describe the biological implications of Theorem 4.1 proven in Chapter 4.

(i) Theorem 4.1 (i) and (ii) show that

$$\lim_{t\to\infty} R(t) \; > \; 0,$$

i.e., once engendered, tumors persist in time.

(ii) Theorem 4.1 (iii) says that if c is sufficiently small, then $R(t) \to \tilde{R}$ exponentially fast. This implies that the tumors radius will converge to some fixed (non-growing) $\tilde{R} \; > \; 0$, i.e., the tumor will grow/shrink exponentially fast to some fixed size, and hence, becomes a benign/dormant tumor (if nutrient concentration is quite small).

(iii) There exists a constant $\gamma \; > \; 0$ such that

(a) if the concentation c is not "sufficiently small" but smaller than γ, then

$$\lim_{t\to\infty} \sup R(t) \; < \; \infty,$$

i.e., the size of the tumor stays a finite size for all time.

(b) if concentation $c \; > \; \gamma$, then

$$R(t) \to \infty \text{ exponentially fast, as } t \to \infty,$$

i.e., this is a maligant tumor.

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