

TRAVELLING WAVE SOLUTIONS OF A MATHEMATICAL MODEL FOR TUMOUR ENCAPSULATION

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Abstract

The formation of a capsule of dense, fibrous extracellular matrix around a solid tumour is a key prognostic indicator in a wide variety of cancers. However, the cellular mechanisms underlying capsule formation remain unclear. One hypothesised mechanism is the *expansive growth hypothesis*, which suggests that a capsule may form by rearrangement of existing extracellular matrix without new matrix production. A mathematical model was proposed to study the implications of this hypothesis by Perumpanani, Sherratt and Norbury in 1997. The model consists of conservation equations for tumour cells and extracellular matrix and exhibit travelling wave solutions in which a pulse of extracellular matrix, corresponding to a capsule, moves in parallel with the advancing front of the tumour. This project is based on the work done by Jonathan Sherratt in studying the expansive growth hypothesis. In this work the author presents a detailed study of travelling wave behaviour in the tumour model, the conditions for the existence of travelling waves and their key properties . The analytical work suggests that the traveling waves are stable and are a biologically relevant solution form for the model. Considering an improved model which includes a saturation in the extent of matrix rearrangement per cell, the analytical results show that rate of matrix movement and convection per cell will saturate at higher matrix densities.

Declaration

No portion of the work in this thesis has been submitted for another degree or qualification of this or any other university or another institution of learning.

Dedication

To my mother with love and to the millions of our fellow human beings who have died from cancer. It is my fervent hope that some day human endeavour will end the untold suffering produced by this disease.

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Chapter 1

Introduction and Literature Review

The World Health Organisation (WHO) predicts that global cancer rates of new cancers will increase by 50 percent from 10 million in 2000 to 15 million in 2020. Cancer is currently the second leading cause of death in developed countries and among the three top causes of death for those over 15 years of age in developing countries. Factors considered responsible for this trend include an aging population, world-wide trends in smoking prevalence, increasing adoption of unhealthy lifestyles (e.g., a western diet) particularly in developing countries, radiation, carcinogen infection in industries etc.

Cancer had been such a dark and fearful mystery because it takes so many forms. It can strike any organ, any tissue, anywhere in the body. Some examples of cancer are: lung cancer, breast cancer, brain cancer, cancer of the colon, cancer of the larynx, kidney cancer, skin cancers, cancers of the blood cells and the lymph glands. But despite this diversity, all cancers share certain characteristics. They are all diseases of individual cells, the basic building blocks of plants and animals. Most of these cells have the capacity for infinite multiplication and also for reversion to a more primitive and less specialised form (demonstrated by tissue culture). This capacity for repeated multiplication is continually operating in the perfectly healthy body, but always in a very carefully controlled manner. Cells of some kinds in the human body age and die and are constantly being replaced by fresh offspring but always

within the total ceiling of 10 to 12 trillion. Fault in this regulatory mechanism may lead to pathologically thin skins.

Cancer occurs when a cell and its descendants(or sometimes two/more cells of different kinds and their descendants) escape from this control, begin to behave in a renegade fashion and is able to bequeath its independence through every succeeding generation. More precisely, a tumour arises when one of the cells (or sometimes a few) proliferates more rapidly than its neighbours. This aggressive proliferation may be the result of a mutation which encourages division, or one that makes the cell deaf to the inhibitory growth signals from its neighbours.

In any case the result is a group of cells proliferatively outpacing the neighbouring cells and producing a localised growth called a benign tumour. The cancer cell exploits his new found freedom to the utmost. No longer need he stay in place, wait in a line for food, nor perform any function for the benefit of the whole organism. He can reproduce at will, building an immense clone of equally ruthless offspring. Suddenly he and his offspring can travel throughout the body, taking over new areas of territory and, leaping in and out of the circulatory systems, establish new colonies of equally ruthless aggressors in distant lands.

1.1 Key words

- tumour: a new growth usually in form of a lump or collections of abnormally growing cells. The term solid tumour is used to distinguish between a localised mass of tissue and leukemia. Leukemia is a type of tumour that takes on the fluid properties of the organ it affects-the blood. Some examples of solid tumours are sarcomas, carcinomas, lymphomas.
- extracellular matrix: it is the extracellular(outside the cell) substance of animal tissue

that usually provides structural support to the cells in addition to performing various other important functions.

- tumour encapsulation: formation of a capsule(dense band) of fibrous extracellular matrix around a solid tumour.

1.2 Tumour Encapsulation

The presence of a capsule around a solid tumour is the most significant gross morphological feature determining the clinical outcome. Solid tumours typically undergo an initial period of avascular growth, after which they become quiescent for a long period. The dormant state is ended by invasion into surrounding tissue and the onset of angiogenesis, the first steps in the metastatic cascade. A very significant feature of the quiescent phase is the presence, in some cases, of capsules of dense, fibrous extracellular matrix around the tumour. The presence of a capsule is a key prognostic indicator, and this is thought to be due to the capsule acting simply as a barrier to invasion and angiogenesis.

Tumours that are encapsulated (that is., having a dense band of surrounding extracellular matrix) have a favourable prognosis and only produce symptoms related to pressure effects on surrounding tissue. Such tumours are known as *benign* (usually not harmful). *Malignant* tumours are potentially lethal and may either arise *denovo* or in existing benign tumours which may be encapsulated. In the later case the cancerous cells have to disrupt the capsular barrier before spreading further.

Recent survival data comparisons for encapsulated and non-encapsulated tumours are available for a variety of cancers [1],[2]. For example, tumour encapsulation was identified as the only important favourable prognostic feature relating to disease-free survival in data for large hepatocellular carcinoma [1]. Despite this major clinical significance of tumour encapsulation, the mechanisms responsible for capsule formation remain unclear.

1.3 Theories of Tumour Encapsulation

There have been two schools of thought about the formation of a tumour capsule. According to the *expansive growth hypothesis*, a benign tumour becomes surrounded by a capsule when the adjoining extracellular matrix is passively convected by the expanding tumour and the cellular elements undergo pressure atrophy; the extracellular collagenous matrix becomes condensed into a circumferential capsule. Here it is argued that remodelling of existing extracellular matrix is responsible for the capsule formation.

It was observed that tumours growing within the lumen of a hollow organ, or on the surface of the body, do not become encapsulated, a finding that confirms the hypothesis that capsule can only be formed in situations where a tumour can exert pressure on surrounding tissue [3]. According to the expansive growth hypothesis, the appearance of a fibrous capsule is essentially a passive phenomenon, and the capsular collagen is derived from mature pre-existing collagen rather than being newly deposited. The aggregation of extracellular matrix represents the cumulative effect of a series of lower level interactions at the interface of the expanding tumour and the convected extracellular matrix.

Another school of thought about the mechanism of capsule formation is the *foreign – body hypothesis* where *denovo* cellular secretion of collagen plays an important role. This view is essentially of an active process where the body mounts a response akin to inflammation to create a fibrous barrier. The controlling influence of encapsulation suggest that the encapsulated tumours may thus be shielded from cellular attack [4].

However, evidence from various sources suggests that the foreign-body hypothesis is unlikely. For instance, none of the human tumours in which tumour-specific or tumour-associated antigens have been identified are associated with an encapsulated growth edge [5]. Hence, at best the foreign-body hypothesis has limited application [6].

In particular, it is debated whether remodelling of existing extracellular matrix alone is responsible for the capsule formation (the expansive growth hypothesis), or whether cellular secretion of collagen plays a key role (the foreign body hypothesis). Evidence on either side of this controversy comes primarily from pathological data. Hepatocellular carcinomas are encapsulated more frequently when the diameter is greater than 2 cm, which is taken to be evidence that the capsule forms by compression of adjacent extracellular matrix [7]. However, some research data showed no correlation between tumour size and either capsule incidence or thickness [2].

These contrasting results are hard to evaluate because of the difficulty of performing experimental tests. Among the most serious problems are the difficulty of reproducing experimental samples which frequently are obtained after complex surgery, the variety of phenotypes in any given patient, infection in human neoplasms which are in external or internal cavities, changes produced by anti-tumour therapy, and the presence of cells other than cancer cells. Moreover, in almost all human neoplasms there are large amounts of fibrous tissue, lymphocytes, and granulation tissue which are exceedingly difficult to separate from cancer cells. One of the few such tests showed that production of collagen by macrophages is responsible for the encapsulation of tumour implants in mice [8]. However, this may be different from the mechanisms involved in naturally arising tumours.

In a situation such as this, where experimental investigation is very difficult, mathematical modelling provides a convenient way of testing hypotheses. This approach is applied in this work to study the expansive growth hypothesis.

1.4 Objectives of the Project

- To provide a detailed background and analysis of the model of tumour encapsulation.
- To extend the analytical results to an improved model and finally discussing the biological implications of the model results.

1.5 Waves

One of the cornerstones in the study of nonlinear partial differential equations (and, for that matter, linear partial differential equations) is wave propagation. A *wave* is a recognisable signal that is transferred from one part of the medium to another part with a recognisable speed of propagation. Energy is often transferred as the wave propagates, but matter may not be. Wave propagation is of fundamental importance in the following areas: fluid mechanics(water waves, aerodynamics), acoustics(sound waves in air and liquids), biology(travelling waves), chemistry (combustion and detonation waves), elasticity(earthquakes, water waves), electromagnetic theory(optics, electromagnetic waves).

1.5.1 Travelling waves

The simplest form of a mathematical wave is a function of the form

$$u(x, t) = f(x - at) \tag{1.1}$$

The density u is the strength of the signal. At $t = 0$ the wave has the form $f(x)$, which is the initial wave profile. Then $f(x - at)$ represents the profile at time t , which is just the initial profile translated to the right at spatial units. The constant a therefore represents the speed of the wave. The form (1.1) represents a wave travelling to the right with speed a while $u(x, t) = f(x + at)$ represents a wave travelling to the left with speed a . These types of waves propagate undistorted along the straight lines $x - at = \text{constant}$ (or $x + at = \text{constant}$) in spacetime.

Time is usually regarded as varying from $-\infty$ to $+\infty$, so that the wave is assumed to have existed for all times. However, boundary conditions of the form

$$u(-\infty, t) = \text{constant} \quad u(+\infty, t) = \text{constant} \tag{1.2}$$

are usually imposed. A *wavefront type – solution* to a partial differential equation is a solution of the form $u(x, t) = f(x \pm at)$ subject to the boundary conditions (1.2) of constancy

at plus and minus infinity (not necessarily the same constant); the function f is assumed to have the requisite degree of smoothness defined by the partial differential equation (e.g., $C^1(R), C^2(R), \dots$). If u approaches the same constant at both plus and minus infinity, the wavefront solution is called a *pulse*.

1.6 Formulation of The Model

The model consists of conservation equations for the densities of tumour cells and extracellular matrix, denoted $u(x, t)$ and $c(x, t)$, respectively, where t and x denote time and space in a one-dimensional spatial domain [10], [11]. The equations in dimensionless variables are:

$$\begin{aligned}\frac{\partial u}{\partial t} &= f(u) + \frac{\partial}{\partial x} \left[h(c) \frac{\partial u}{\partial x} \right] \\ \frac{\partial c}{\partial t} &= k \frac{\partial}{\partial x} \left[ch(c) \frac{\partial u}{\partial x} \right]\end{aligned}\tag{1.3}$$

The assumptions are that $h(\cdot)$ and $f(\cdot)$ are continuously differentiable and satisfy the following conditions:

$$\begin{aligned}f(0) &= f(1) = 0 \text{ with } u > 0 \text{ for } u \in (0, 1) \\ f'(0) &> 0 \text{ and } f(u) < f'(0)u \text{ for } u \in (0, 1] \\ f(u) &\text{ has only one turning point on } (0, 1) \text{ at } u = u_m, \text{ say} \\ h(c) &\geq 0 \text{ and } h'(c) \leq 0 \text{ with } h(1) > 0\end{aligned}\tag{1.4}$$

The first and second conditions are standard assumptions for cell kinetic terms in the study of scalar reaction-diffusion equations. The third constraint facilitates the calculations in chapter 2, and is not at all restrictive from the viewpoint of applications.

The term $f(u)$ represents cell division and death; $f(0)$ must clearly be zero, and for simplicity we assume throughout that the cell density is rescaled so that $u = 1$ is the equilibrium level within the tumour, implying $f(1) = 0$. For simplicity we consider $f(u) = u(1 - u)$.

Random cell movement is assumed, and kinetics of extracellular matrix are neglected, in keeping with the expansive growth hypothesis, so that the extracellular matrix density only changes because of convection with the cells.

This convection does not imply large-scale movement of intact matrix by a cell; rather it is the net result of local matrix movement and remodelling during cell movement. This will increase with the local matrix density and is represented in the model as $k.c$. In practice, this term will saturate at high matrix densities, representing the limitation on matrix reorganisation per cell.

The function $h(c)$ is decreasing and is included in the model to represent the reduction in cell motility at high matrix densities. I will investigate the cases of constant $h(.)$ and non-constant $h(.)$, studying the existence and form of travelling wave solutions. Behaviour in the case of non-constant $h(.)$ depends on whether $h(\infty)$ is zero or nonzero.

Chapter 2

Analysis of the model

2.1 Solutions for constant $h(\cdot)$

The presentation here is based on the work of Sherratt [10], where the model consists of the following conservation equations

$$\begin{aligned}\frac{\partial u}{\partial t} &= f(u) + \frac{\partial}{\partial x} \left[h(c) \frac{\partial u}{\partial x} \right], \\ \frac{\partial c}{\partial t} &= k \frac{\partial}{\partial x} \left[ch(c) \frac{\partial u}{\partial x} \right],\end{aligned}\tag{2.1}$$

where $u(x, t)$ and $c(x, t)$ are the densities of tumour cells and extracellular matrix, respectively, and t and x denote time and space in one dimensional spatial domain. Here $f(u)$ represents cell division and death. When $h(\cdot)$ is constant, then the first equation of (2.1) is independent of c . In the context of tumour growth, one is concerned with the evolution of equations (2.1) from initial data corresponding to a localised population of of tumour cells,

and a uniform (nonzero) density of matrix, which I take to be $c \equiv 1$. We now have

$$\frac{\partial u}{\partial t} = f(u) + \frac{\partial}{\partial x} \left[h \frac{\partial u}{\partial x} \right], \quad (2.2)$$

$$\frac{\partial c}{\partial t} = k \frac{\partial}{\partial x} \left[h \frac{\partial u}{\partial x} \right],$$

where k is a parameter which reflects the strength of the extracellular matrix convection.

Taking $f(u) = u(1 - u)$, the first equation of (2.2) becomes

$$u_t - hu_{xx} = u(1 - u) \quad (2.3)$$

This equation is the much studied Fisher equation. It is convenient to introduce non-dimensional quantities x^*, t^*, u^* defined by

$$x^* = (1/h)^{1/2}x, \quad t^* = t, \quad u^* = u \quad (2.4)$$

Using (2.4) and dropping the asterisks, equation (2.3) takes the non-dimensional form

$$u_t - u_{xx} = u(1 - u), \quad x \in \mathbb{R}, \quad t > 0 \quad (2.5)$$

In the spatially homogeneous problem, the stationary states are $u = 0$ and $u = 1$ which are unstable and stable equilibrium solutions, respectively. It is then appropriate to look for travelling wave solutions of (2.5) for which $0 \leq u \leq 1$. Since we assumed that the cell density is rescaled so that $u \equiv 1$ is the equilibrium level within the tumour, we seek solutions of (2.5) subject to

$$0 \leq u(x, 0) \leq 1, \quad x \in \mathbb{R} \quad (2.6)$$

such that all derivatives of u vanish as $|x| \rightarrow \infty$, and

$$\lim_{x \rightarrow -\infty} u(x, t) = 1, \text{ and } \lim_{x \rightarrow +\infty} u(x, t) = 0, \quad t \geq 0. \quad (2.7)$$

Physically the first condition implies that the density of the tumour cell has its maximum as $|x| \rightarrow -\infty$ and the second condition represents zero population as $|x| \rightarrow +\infty$. For all initial data of the type $0 \leq u(x, 0) \leq 1, x \in \mathbb{R}$, the solution of the type (2.5) is also bounded

by the same constants, i.e., $0 \leq u(x, t) \leq 1, x \in \mathbb{R}, t > 0$ [12]. We note that equation (2.5) is invariant under the transformation $x \rightarrow -x$. So, that is why it is sufficient to consider waves propagating to the right only. We seek a travelling wave solution of (2.5) in the form

$$u(x, t) = u(z), z = x - at \quad (2.8)$$

where the wave speed a is to be determined and the waveform $u(z)$ satisfies the boundary data (2.7). We substitute (2.8) into (2.5) to obtain the nonlinear ordinary differential equation

$$u''(z) + au'(z) + u(z) - u^2(z) = 0 \quad (2.9)$$

Writing $\frac{du}{dz} = v$, equation (2.9) gives two first order equations.

$$\frac{du}{dz} = 0.u + v, \quad \frac{dv}{dz} = u(u - 1) - av, \quad (2.10)$$

implying that

$$\frac{dv}{du} = \frac{u(u - 1) - av}{v} \quad (2.11)$$

The system (2.10) has a simple interpretation in the Poincare phase plane. The singular points of this system are the solutions of the equations

$v = 0, u(u - 1) - av = 0$. Thus two singular points: $(u, v) = (0, 0)$ and $(1, 0)$ which represent the steady states. We follow the standard phase plane analysis to examine the nature of the nonlinear autonomous system given by

$$\frac{du}{dz} = p(u, v), \quad \frac{dv}{dz} = q(u, v)$$

The matrix associated with this system at the critical point (u_0, v_0) is

$$\mathbf{A} = \begin{bmatrix} p_u(u_0, v_0) & p_v(u_0, v_0) \\ q_u(u_0, v_0) & q_v(u_0, v_0) \end{bmatrix}$$

In the present problem, the matrix A at $(0, 0)$ is

$$\mathbf{A}_{(0,0)} = \begin{bmatrix} 0 & 1 \\ -1 & -a \end{bmatrix}$$

The matrix at $(1, 0)$ is

$$\mathbf{A}_{(1,0)} = \begin{bmatrix} 0 & 1 \\ 1 & -a \end{bmatrix}$$

The eigenvalues λ of the matrix at $(0, 0)$ are given by

$$\lambda = -\frac{1}{2}[a \mp \sqrt{a^2 - 4}] \quad (2.12)$$

The eigenvalues are real, distinct and of the same sign if the discriminant $D = a^2 - 4 > 0$. According to the theory of dynamical systems, the origin is a stable node for $a \geq a_{min} = 2$, and, when $a = a_{min} = 2$, it is a degenerate node. If $a^2 < 4$, eigenvalues are complex with a negative real part.

The eigenvalues of the matrix A at $(1, 0)$ are

$$\lambda = \frac{1}{2}[-a \pm \sqrt{a^2 + 4}]. \quad (2.13)$$

Here, $\lambda_- = \frac{1}{2}[-a - \sqrt{a^2 + 4}] < 0$ and $\lambda_+ = \frac{1}{2}[-a + \sqrt{a^2 + 4}] > 0$. Hence the equilibrium point $(1, 0)$ is a saddle point. Thus in this case, there is exactly one expanding and one contracting direction. Both equilibrium points are hyperbolic since both the eigenvalues have nonzero real part. The phase plane trajectories of the equation (2.9) for the travelling wavefront solution for $a \geq 2$ shows that there is a unique separatrix joining the stable node $(0, 0)$ with the saddle point $(1, 0)$ i.e., the global qualitative behaviour is obtained from the local behaviour of the phase trajectories at the neighbourhood of each critical point. The

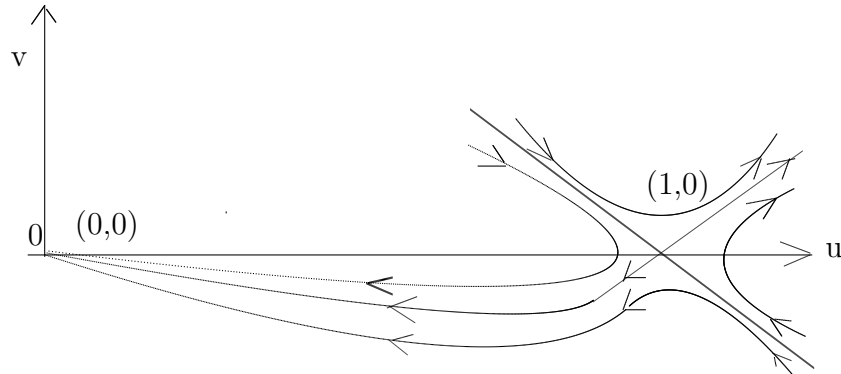


Figure 2.1: Phase plane trajectories for $a \geq 2$

travelling wave solution $u(z)$ of (2.5) for $a \geq 2$, satisfying the boundary conditions (2.7), as

$z \rightarrow \mp\infty$ corresponds to the separatrix joining the singular points $(1, 0)$ and $(0, 0)$, as shown in Figure 2.1 and is a monotonically decreasing function of z when its first derivatives vanish as $z \rightarrow \mp\infty$. A typical travelling wave solution (cline) $u(z)$ for $a \geq 2$ is shown on Figure 2.2. We consider the stability of the travelling wave solutions of (2.5) in the form $u(x, t) = u(z)$, $z = x - at$ where a is the wave speed. Such solution is said to be asymptotically stable if a small perturbation imposed on the system at time $t = 0$ decays to zero, as $t \rightarrow \infty$.

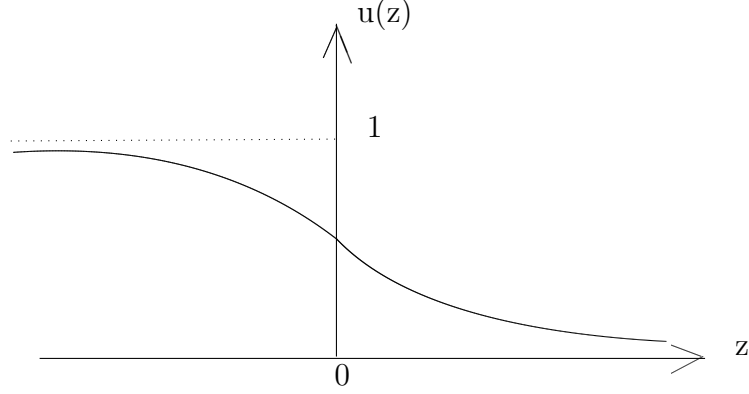


Figure 2.2: Traveling wave solution for $a \geq 2$

Introducing a coordinate frame moving with the wave speed a , that is, $z = x - at$, equation (2.5) reduces to the form

$$u_t - au_z = u_{zz} + u(1 - u) \quad (2.14)$$

We look for a perturbed solution of (2.5) in the form

$$u(z, t) = U(z) + \epsilon v(z, t) \quad (2.15)$$

where $\epsilon(0 < \epsilon \ll 1)$ is a small parameter and the second term represents a small perturbation from the given basic solution $U(z)$. The perturbed state $v(z, t)$ is assumed to have compact support in the moving frame, that is, $v(z, t) = 0$ for $|z| \geq d$ for some finite $d > 0$. Substituting (2.15) into (2.14) gives the equation for the perturbed quantity, to order ϵ ,

$$v_t - av_{zz} = v_{zz} + (1 - 2U)v. \quad (2.16)$$

Now, we seek solutions of this equation in the form

$$v(z, t) = V(z) \exp(-\lambda t). \quad (2.17)$$

Substituting this solution into (2.16) gives the following linear eigenvalue problem

$$V''(z) + aV'(z) + (\lambda + 1 - 2U)V = 0, \quad (2.18)$$

where the growth factor λ is an eigenvalue. Since the original perturbed state has a compact support, we may take the boundary condition on $V(z)$ as $V(\pm a) = 0$. According to the general theory of eigenvalue problems [22], the perturbation will grow in time if the eigenvalues λ are negative, and hence the system will become unstable. On the other hand, if the eigenvalues λ are positive, then the perturbation will decay to zero, as $t \rightarrow \infty$, and hence the system is asymptotically stable.

To reduce the problem to standard form, we introduce the transformation [17], [22]

$$v(z) = p(z) \exp\left(-\frac{1}{2}az\right) \quad (2.19)$$

so that the eigenvalue problem (2.18) reduces to the form

$$p'' + [\lambda - n(z)]p = 0 \quad (2.20)$$

$$p(-l) = p(l) = 0, \quad (2.21)$$

where

$$n(z) = \frac{a^2}{2} - (1 - 2U) \geq 2U(z) > 0 \text{ for } a \geq 2. \quad (2.22)$$

This is a standard eigenvalue problem, and all its eigenvalues are real and positive provided $a \geq 2$ [22], [31]. This means that small perturbations of the form (2.17) decay exponentially to zero, as $t \rightarrow \infty$. We conclude that the travelling wave solution of (2.5) is asymptotically stable.

2.1.1 c - wave solution for constant $h(\cdot)$

The case $h(\cdot)$ is constant is made as a simplifying assumption. In reality, rates of cell movement are significantly affected by local extracellular matrix. If $h \equiv 1$, then the changes in extracellular matrix density have no effect on cell motility. This case is relevant during the early stages of tumour growth, in which extracellular matrix accretion on the surface of the tumour is too low to significantly restrain its expansion. Thus, the study of the case $h(\cdot)$ constant is done to obtain important mathematical insights into the behaviour of more general forms of $h(c)$.

The study of this case of constant $h(\cdot)$ is done analytically with two key objectives:

- to determine the value of k at which the c -wave changes form, and
- to determine the rate at which the peak of c increases when k is above this value.

The main goal of the study of dynamical systems is to understand the long term behaviour of states in a system for which there is a deterministic rule for how a state evolves. To fulfill this goal let us rewrite the second equation of (2.1), in terms of coordinates $\tau = t$ and $z = x - at$.

$$\frac{\partial c}{\partial \tau} + \left[k \frac{\partial u}{\partial z} - a \right] \frac{\partial c}{\partial z} = -k \frac{\partial^2 u}{\partial z^2} c \quad (2.23)$$

where $\frac{\partial u}{\partial z}$ is the flux of the tumour cells [9]. Consequently, by letting $u(x, t) = u(z)$ where $z = x - at$, we have a function that satisfy our partial differential equation (2.23). The plan is to find a solution of our partial differential equation by constructing an integral surface as a union of characteristic curves.

This first order partial differential equation can be solved using Lagrange method of characteristics. We will use this method to determine the qualitative form of the solution $c(z, \tau)$. We note that $\frac{\partial u}{\partial z} \geq 0 \quad \forall z$, with $\frac{\partial u}{\partial z} \rightarrow 0$ as $z \rightarrow \pm\infty$, and $\frac{\partial^2 u}{\partial z^2}$ nonzero except at the unique

local maximum, at which the flux is maximum i.e., $\frac{\partial u}{\partial z} = \left(\frac{\partial u}{\partial z}\right)_{max}$, say. This follows from the shape of the travelling wave in the Fisher equation. The characteristic equations of (2.23) are:

$$\frac{d\tau}{1} = \frac{dz}{k\left(\frac{\partial u}{\partial z}\right) - a} = \frac{-dc}{k\frac{\partial^2 u}{\partial z^2}c}.$$

In effect, by introducing these characteristic equations, we have reduced our partial differential equation (2.23) to a system of ordinary differential equations. We can then use ordinary differential equation theory to solve the characteristic equations, then piece together these characteristic curves to form a surface. Such a surface will provide us with a solution to our partial differential equation (2.23). By the theory of ordinary differential equations, this system of characteristic equations has a unique solution which satisfies the initial conditions. Two characteristic functions are obtained from the above characteristic equations.

$$p_1(\tau, z) = \tau - G(z) \quad \text{and} \quad p_2(c, z) = \frac{c}{c_{tw}(z)}$$

where $c_{tw}(z) = \frac{1}{a - k\frac{\partial u}{\partial z}}$ and $G(z) = -\int c_{tw}(z)dz$. A solution of c is given by substituting a suitable choice of constant $h(\cdot)$ into the following:

$$\frac{c}{c_{tw}(z)} = \frac{c_0(h(\cdot))}{c_{tw}(h(\cdot))} \quad \text{and} \quad G(z) - \tau = G(h(\cdot)) \quad (2.24)$$

where $c_0(x) \equiv c(x, t = 0)$. Recall that the parameter k represents the strength of the extracellular matrix. Meanwhile, $\frac{\partial u}{\partial z}$ represents the flux of the tumour cells. Thus $k\frac{\partial u}{\partial z}$ is the velocity at which extracellular matrix is being convected, while a is the speed of the tumour wave.

The key determinant of the form of this solution is the sign of $k\left(\frac{\partial u}{\partial z}\right)_{max} - a$. If this expression is negative, then $p_2(c, z)$ is finite for all z so that a possible travelling wave solution for c is $c(z, \tau) = c_{tw}(z)$, independent of τ . When $a > k\left(\frac{\partial u}{\partial z}\right)_{max}$, i.e., the velocity of the extracellular matrix is slower than that of the tumour cell wave, only a fleeting ripple is produced in the solution for c .

However when $k \left(\frac{\partial u}{\partial z} \right)_{max} > a$ at some points, the extracellular matrix at these points is actually convected faster than the speed at which the tumour cell wave moves, causing a build up of extracellular matrix. This shows that the qualitative behaviour depends crucially on whether k is above or below the critical value $\frac{a}{\max_{-\infty < z < \infty} [-h(\cdot) \frac{\partial u}{\partial z}]}$. For k below this value, c also evolves to a permanent form travelling wave solution. The wave form is in fact given by the simple expression $c_{tw}(z) = \frac{a}{[a + kh(\cdot) \frac{\partial u}{\partial z}]}$.

If c is above the critical value, then the solution for c again has a wave form but in this case not of constant shape. Rather, the height of the peak in this wave front grows, without limit, as time increases. Such growth is entirely consistent with the assumption of no matrix production. The peak becomes thinner as it grows, so that the total density of matrix within it is constant.

The assumption that $h(\cdot)$ is constant is mathematically very convenient, but biologically it is unrealistic, since in practice rates of cell movement are significantly affected by local extracellular matrix. In the next two sections, we consider travelling wave behaviour in the more general case, studying separately the cases of $h(\infty)$ zero and nonzero. The results depend on the assumption that $h(\cdot)$ and $f(\cdot)$ are continuously differentiable and satisfy the conditions (1.4).

2.2 Travelling waves when $h(\infty) = 0$

We now see if tumour invasion may be represented by travelling waves of the model (2.1) when $h(\infty) = 0$. Thus, we look for solutions which have a constant shape given by

$$u(x, t) = U(z), \quad c(x, t) = C(z), \quad z = x - at,$$

and move in space at a constant speed a . Substituting these into the system (2.1) gives

$$f(U) + aU' + [U'h(C)]' = 0, \tag{2.25}$$

$$aC' + k[CU'h(C)]' = 0,$$

where prime denotes d/dz . The wave speed a enters the equation as a parameter, taken $a > 0$ without loss of generality. We solve this model in the context of tumour growth on the infinite x domain with boundary conditions

$$U \rightarrow 0, \quad C \rightarrow 1 \text{ as } z \rightarrow \infty, \text{ and } U \rightarrow 1, \quad C \rightarrow 1 \text{ as } z \rightarrow -\infty$$

with $U \geq 0$ for all z .

A solution of this type is illustrated in Figure 2.2 where the wave corresponds to the advancing front of the tumour edge.

Proposition 2.1 *When $h(\infty) = 0$, and with $f(\cdot)$ and $h(\cdot)$ satisfying conditions (1.4), equations (2.25) have a solution of the type shown in Figure 2.2 if and only if $a \geq 2[\sqrt{f'(0)h(1)}]$.*

Proof

Integrating the second equation of (2.25) gives

$$U'h(C) = \frac{a}{k} \left(\frac{1}{C} - 1 \right), \tag{2.26}$$

since $U' \rightarrow 0$, $C \rightarrow 1$ as $z \rightarrow \pm\infty$.

Recall that $h(C)$ is a decreasing function. This implies that $1/h(C)$ is an increasing function of C . Our tumour model assumes that the density of the extracellular matrix is strictly increasing, hence $1/C$ is a strictly decreasing function of C . Consequently $1 - \frac{1}{C}$ is a strictly increasing function of C .

Therefore equation (2.26) implies that U' is a strictly decreasing function of C .

Also note that,

$U' = \infty$ in the absence of extracellular matrix ($C = 0$) whilst $U' = 0$ when $C = 1$. When $h(\infty)$ is zero and $C = \infty$ we have $U' = -\infty$ as shown in Figure 2.3(a, b).

Figure 2.3c illustrates the inverse of the statement that U' is a strictly decreasing function of C i.e., C is a strictly decreasing function of U' and hence $(1/C - 1).a/k \equiv U'h(C)$ is a strictly increasing function of U' , denoted by $\phi(U')$. This is shown in Figure 2.3d. The choice of $h(C)$ determines the form of $\phi(\cdot)$. However, in all cases we have following:

$\phi(-\infty) = -a/k$, $\phi(0) = 0$ and $\phi(\infty) = \infty$.

Substituting the expression $U'h(C) = \phi(U')$ into the first equation of the system (2.25) gives

$$f(U) + aU' + \phi'(U')U'' = 0. \quad (2.27)$$

Differentiating equation (2.26) with respect to U' gives

$$\begin{aligned} h(C) + U'h'(C)\frac{\partial C}{\partial U'} &= \frac{-a}{k} \frac{\partial C}{\partial U'} \frac{1}{C^2} \\ \Rightarrow \frac{\partial C}{\partial U'} &= \frac{-kC^2h(C)}{kC^2U'h'(C) + a} \\ &= \frac{-kC^2(h(C))^2}{ah(C) + aC(1 - C)h'(C)} \quad \text{using equation (2.26).} \end{aligned}$$

Recall that

$$\begin{aligned} \phi(U') &= U'h(C) \\ &= \frac{a}{k} \left(\frac{1}{C} - 1 \right) \end{aligned}$$

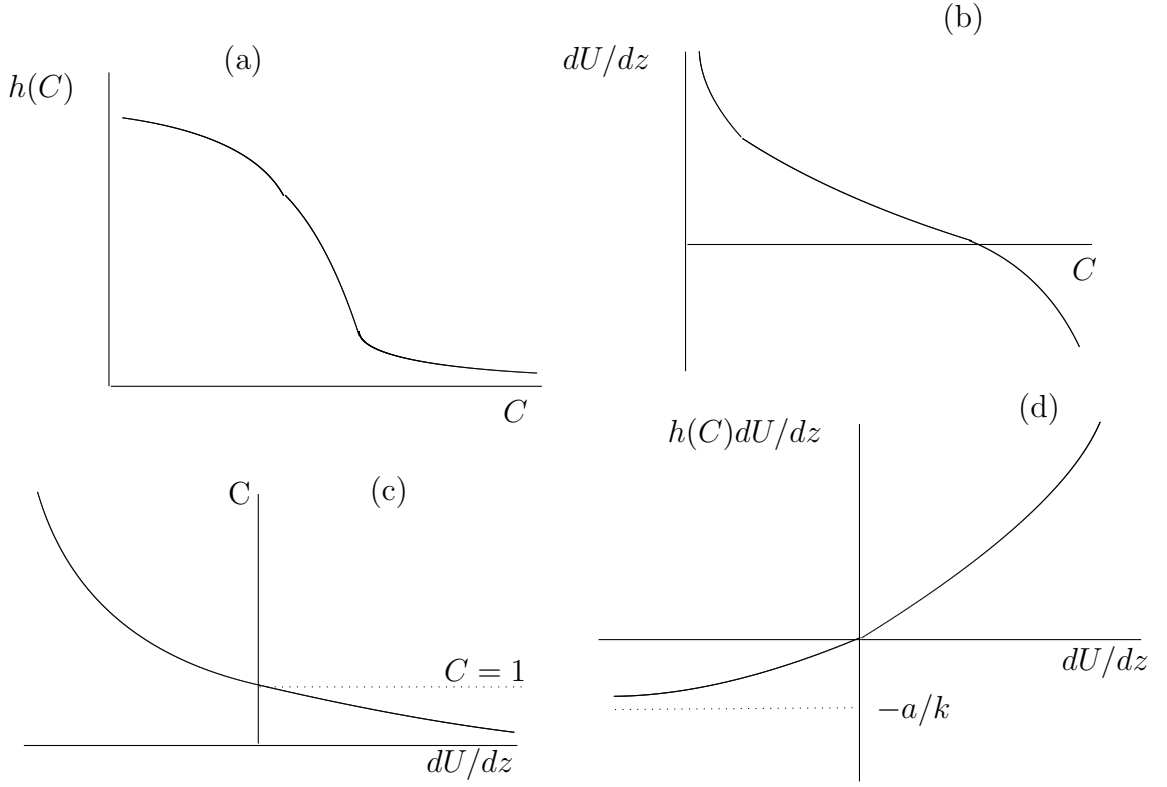


Figure 2.3: Schematic illustration of the derivation of the form of U' , from (2.26), when $h(\infty) = 0$. (a) The form of $h(C)$ as a function of C . (b) The form of $U'h(C) \equiv (\frac{1}{C} - 1)\frac{a}{k}$ as a function of C . (c) The form of C as a function of U' . (d) The form of $\phi(U') \equiv U'h(C) \equiv (\frac{1}{C} - 1)\frac{a}{k}$ as a function of U' .

Therefore

$$\begin{aligned}
 \phi'(U') &= \frac{\partial}{\partial U'} \left[\frac{a}{k} \left(\frac{1}{C} - 1 \right) \right] \\
 &= \frac{-a}{kC^2} \left(\frac{\partial C}{\partial U'} \right) \\
 &= \left\{ \frac{1}{h(C)} + \frac{C(1-C)h'(C)}{(h(C))^2} \right\}^{-1}, \tag{2.28}
 \end{aligned}$$

where

$$C = \frac{1}{1 + \frac{k}{a}U'h(C)}$$

and C has the qualitative form illustrated in Figure 2.3c.

In particular, note that $\phi'(0) = h(1)$.

Let us now study equation (2.27) in a phase plane to complete the proof of the existence of a positive travelling wave solution. Here, we make use of methods developed by Kolmogorov, Petrovskii and Piscounov for studying travelling wave solutions of Fisher's equation.

It is often useful to rewrite an n^{th} -order differential equation as a system of first order equations, and to recall the geometric interpretation of a differential equation as a vector field. To this end, consider the change of variable $U' = \frac{W}{k}$ so that equation (2.27) becomes:

$$U' = \frac{W}{k}, \quad W' = -\gamma(W)[kf(U) + aW], \quad (2.29)$$

where $\gamma(W) = 1/\phi'(W/k)$ and the dependence on the parameter k is clearer.

Let us denote the global solution (the collection of all integral curves) to system (2.29) by the flow or trajectory τ . We need to show that for functions $f(\cdot)$ satisfying conditions (1.4), and equations (2.29) has two equilibrium points: $(1, 0)$ which is a saddle point, and $(0, 0)$, which is a stable node if $a \geq 2[f'(0)/\gamma(0)]^{1/2} = 2[f'(0)h(1)]^{1/2}$, and a stable focus otherwise.

The travelling waves under consideration correspond to connections between the two equilibrium points and thus to the trajectory τ . Thus there exist at most one wave for any given a , with the wave existing if and only if τ terminates at $(0, 0)$. If $U \geq 0$ and $(0, 0)$ is a spiral then this is not possible.

There are three possible ways in which τ can leave the lower right quadrant ($U > 0, W < 0$) when $a \geq 2[f'(0)h(1)]^{1/2}$ namely:

- τ can pass through the positive U -axis. However, at the point of crossing we have $U > 0, W = 0$, and $W' > 0$, which contradicts equations (2.29).
- τ can leave the lower right quadrant through the negative W -axis. In this case, τ must first cross the line $W = \lambda kU$, where λ is one of the eigenvalues at $(0, 0)$, which are real and negative for a above the critical value. Using boundary conditions (1.4) and

recalling that $W = \lambda k U$ we see that at the point of this crossing

$$\begin{aligned}
\frac{dW}{dU} &= -ak\gamma(W) - k^2 f(U)\gamma(W)/W \\
&< -ak\gamma(W) - k^2 U f'(0)\gamma(W)/W \\
&= -ak\gamma(W) - k\gamma(W)f'(0)/\lambda \\
&= \lambda k\gamma(W)/\gamma(0)
\end{aligned}$$

using the eigenvalue equation $\lambda^2 + a\gamma(0)\lambda + \gamma(0)f'(0) = 0$.

Considering the relationship between C and U' when $W < 0$, we conclude that $C > 1$.

When $C > 1$ and since $h'(C) \leq 0$, equation (2.28) shows that

$$\begin{aligned}
\gamma(W) &\geq 1/h(C) \\
&\geq 1/h(1) \\
&= \gamma(0).
\end{aligned}$$

Therefore when τ crosses the line $W = \lambda k U$ we see that

$dW/dU < \lambda k$ ($\lambda < 0$), which is a contradiction.

- The third possibility is that whenever $a \geq 2[f'(0)h(1)]^{1/2}$, τ leaves the region $U > 0, W < 0$ by terminating at $(0, 0)$. This corresponds to a monotonically decreasing travelling wave solution for $U(z)$.

The corresponding solution for $C(z)$ is determined by its relationship with $U'(z)$, which is illustrated in Figure 2.3c where $C(z)$ is a pulse wave form.

2.3 Travelling waves when $h(\infty) > 0$

Recall that $h(c)$ is a nonnegative decreasing function representing the reduction in cell motility at high extracellular matrix density. In this section we assume that this reduction in cell motility is positive at high matrix densities and that there is a limit of h as $c \rightarrow \infty$. In this case of $h(\infty) > 0$, many of the arguments of the previous sections continue to hold. More importantly, there still exist heteroclinic connections in the system (2.29) which correspond to travelling wave solutions. Also the proof that such connections exist whenever $a \geq 2[\sqrt{f'(0)h(1)}]$ is still valid.

Most significantly, U' and C are now related differently from the qualitative form illustrated in Figure 2.3c. Here, $1/h(C)$ approaches a finite asymptote as $C \rightarrow \infty$. Thus, U' is a strictly decreasing function of C , approaching $-\frac{a}{kh(\infty)}$ as $C \rightarrow \infty$ as illustrated in Figure 4(a, b). Inversely, C is a strictly decreasing function of U' that is defined only for $U' > -\frac{a}{kh(\infty)}$ as evidenced by Figure 2.4c. Depending on the form of $h(C)$ as $C \rightarrow \infty$, γ may either approach a finite positive value or $+\infty$ as $U' \rightarrow -\frac{a}{(kh(\infty))^+}$.

The trajectory τ in the $U - W$ phase plane only gives a solution of (2.25) when $h(\infty) > 0$ and it lies entirely above the line $W = -\frac{a}{h(\infty)}$. To demonstrate this, the following propositions are proved:

Proposition 2.2

- (i) τ has a unique minimum in the $U - W$ plane, at the point (U_{min}, W_{min}) , say.
- (ii) W_{min} (< 0) is a strictly decreasing function of k .
- (iii) $W_{min} \rightarrow 0$ as $k \rightarrow 0$, and $W_{min} \rightarrow -\infty$ as $k \rightarrow \infty$.

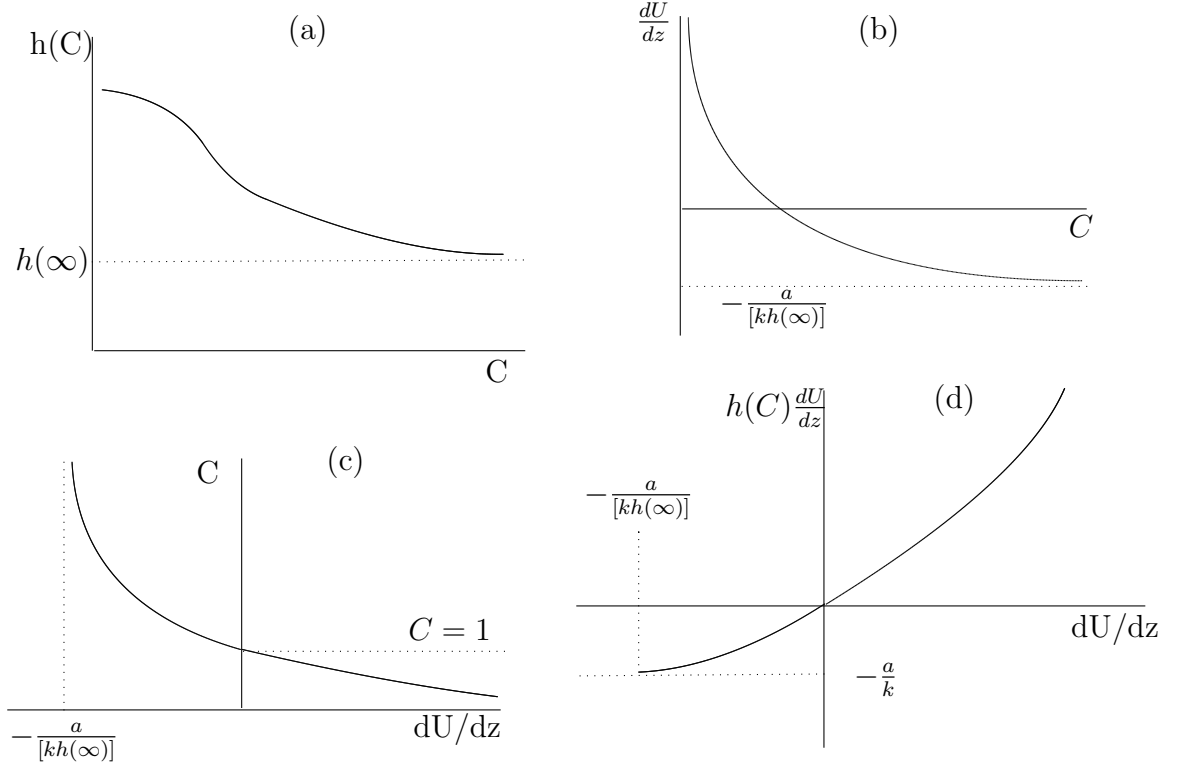


Figure 2.4: Schematic illustration of the derivation of the form of U' , from (2.26), when $h(\infty) > 0$. (a) The form of $h(C)$ as a function of C . (b) The form of $U'h(C) \equiv (\frac{1}{C} - 1)\frac{a}{k}$ as a function of C . (c) The form of C as a function of U' . (d) The form of $\phi(U') \equiv U'h(C) \equiv (\frac{1}{C} - 1)\frac{a}{k}$ as a function of U' .

In order for the trajectory τ to exist we assume that $a \geq 2[\sqrt{f'(0)h(1)}]$. An important result of this proposition is that the travelling pulse solution for C has a unique maximum, whose height increases strictly with k , tending to ∞ as $k \rightarrow k_{crit}^-$.

Proof 2.2(i)

Let us denote the curve $W = -kf(U)/a$ by D_1 . We note that $dW/dU > 0$ if and only if W lies above the curve D_1 . Also, the eigenvector along which τ leaves $(1, 0)$ has a slope equal to the product of k and the corresponding eigenvalue which is equal to

$$\begin{aligned} \frac{k}{a} \left[-\frac{1}{2}a^2\gamma(0) + \sqrt{\frac{1}{4}a^4\gamma(0)^2 - a^2\gamma(0)f'(1)} \right] &< \frac{k}{a} \left(-\frac{1}{2}a^2\gamma(0) + \sqrt{\frac{1}{2}a^2\gamma(0) - f'(1)^2} \right) \\ &= -\frac{kf'(1)}{a}, \end{aligned}$$

and this is the slope of D_1 at $(1, 0)$. Thus when U is close to 1, the trajectory τ lies above the curve D_1 . τ will have a turning point when it crosses D_1 , and at such a point, τ will be horizontal in the $U - W$ plane. Thus, our inference suggests that the first turning point must occur when the slope of D_1 is negative, that is, when $U < u_{min}$. Here, we must recall from conditions (1.4) that the function $f(U)$ is assumed to have a unique local maximum at $U = u_{min}$, say. Consequently, τ must have at least one first turning point, and we denote it by (U_{min}, W_{min}) . We would require τ to cross D_1 horizontally so that we have another turning point. Here, $U_{min} < u_m$ so that the slope of D_1 is positive for $U < U_{min}$. However, this is impossible since U decreases monotonically along τ . Hence there is a unique turning point, as required.

Proof 2.2(ii)

We need to show that W_{min} is a decreasing function of k i.e., for any two values of k ($k_1 < k_2$), say, we must have $W_{min}(k_1) < W_{min}(k_2)$. Differentiating dW/dU (from equation (2.29)) with respect to k gives

$$\frac{\partial}{\partial k} \left[\frac{dW}{dU} \right] = -\gamma(W)[a + 2kf(U)/W],$$

which is positive if and only if W lies between the U -axis and the curve $W = -2kf(U)/a$, which we refer to as D_2 . It is clear that the value of W on D_2 is exactly twice that on D_1 for each U . Let us now consider any two values of k , k_3 , and k_4 , say, satisfying $k_3 < k_4 < 2k_3$. Let us denote the curves D_1 and D_2 (or D_2 and D_1) corresponding to k_3 and k_4 (or k_4 and k_3) by $D_{1_{k_3}}$ and $D_{2_{k_4}}$ (or $D_{2_{k_3}}$ and $D_{1_{k_4}}$) respectively. Similarly, let us represent the trajectories corresponding to k_3 and k_4 by τ_{k_3} and τ_{k_4} respectively.

Then the minimum of τ_{k_4} lies on the curve $D_{1_{k_4}}$, which lies between the U -axis and the curve $D_{2_{k_3}}$, since $k_4 < 2k_3$. Thus the portions of the trajectories τ_{k_3} and τ_{k_4} between $(1, 0)$ and their

respective minimum both lie in a region of the phase plane within which $\frac{\partial}{\partial k}(dW/dU) > 0$ for $k \in [k_3, k_4]$. This implies that this portion of τ_{k_3} lies strictly between the U -axis and the corresponding portion of τ_{k_4} , so that $W_{min}(k_4) < W_{min}(k_3)$ as required. The required monotonicity is satisfied since k_3 and k_4 are arbitrary within the specified restrictions.

Proof 2.2(iii)

Let us consider the equation for the nature (or shape) of the trajectories defined by

$$\frac{dW}{dU} = \lambda k \gamma(W) / \gamma(0)$$

We see that $dW/dU \rightarrow \infty$ as $k \rightarrow \infty$. Also, $dW/dU \rightarrow 0$ as $k \rightarrow 0$ for all $U \in (0, 1)$ and $W > 0$. Thus, the proof is completed.

Chapter 3

Saturation in matrix remodelling rate

In keeping with the expansive growth hypothesis, random cell movement is assumed, and kinetics of extracellular matrix are neglected so that the extracellular matrix density only changes because of convection with the cells. This convection will increase with the local extracellular matrix density and is represented in model (1.3) as $k.c$.

In practice, this term will saturate at high extracellular matrix densities, representing the limitation on matrix reorganisation per cell. In this chapter saturation is included, by replacing the constant k in (1.3) by $k.\theta(c)$, where $\theta(c)$ is a continuously differentiable decreasing function of c , with $\theta(1) = 1$.

This result in the following model:

$$\begin{aligned}\frac{\partial u}{\partial t} &= f(u) + \frac{\partial}{\partial x} \left[h(c) \frac{\partial u}{\partial x} \right] \\ \frac{\partial c}{\partial t} &= k \frac{\partial}{\partial x} \left[ch(c)\theta(c) \frac{\partial u}{\partial x} \right]\end{aligned}\tag{3.1}$$

The results in sections 2.2 and 2.3 can be easily extended to these equations also. Travelling

wave solutions of (3.1) have the form

$u(x, t) = U(z)$, $c(x, t) = C(z)$, $z = x - at$ where a is the wave speed, and thus satisfy the ordinary differential equations

$$f(U) + aU' + [U'h(C)]' = 0 \quad (3.2)$$

$$aC + kCh(C)\theta(C)U' = a,$$

using notation as in section 2.2. Our approach is based on the prediction that the early growth of a tumour has the form of a travelling wave moving outwards from an initial size of disease into the surrounding normal tissue [9]. Following the work in section 2.2 i.e., integrating the second equation of (3.2) and letting $\tilde{\phi}(\cdot) \equiv U'h(C)$, we get

$$f(U) + aU' + \tilde{\phi}'(U')U'' = 0, \quad (3.3)$$

The notation of writing with a tilde the amended forms of the various functions in sections 2.2 and 2.3 is adopted in this chapter.

Therefore

$$\begin{aligned} \tilde{\phi}'(U') &= \frac{\partial}{\partial U'} \left[\frac{a}{k} \left(\frac{1}{C} - 1 \right) \frac{1}{\theta(C)} \right] \\ &= \frac{-a}{kC^2\theta(C)} \frac{\partial C}{\partial U'} \left[1 + C(1 - C) \frac{\theta'(C)}{\theta(C)} \right] \\ &= \frac{h(C)^2\theta(C)[1 + \theta'(C)C(1 - C)/\theta(C)]}{h(C)\theta(C) + [h(C)\theta'(C) + h'(C)\theta(C)]C(1 - C)} \\ &= \left(\frac{1}{h(C)} + \frac{C(1 - C)h'(C)}{(h(C))^2[1 + C(1 - C)\theta'(C)/\theta(C)]} \right)^{-1} \end{aligned} \quad (3.4)$$

Here $\frac{\partial C}{\partial U'}$ has been calculated using the second equation of (3.2) in a manner directly analogous to that used in section 2.2. Writing $W = kU'$ then gives a coupled system of ordinary differential equations analogous to equations (2.29):

$$U' = W/k, \quad W' = -\tilde{\gamma}(W)[kf(U) + aW], \quad (3.5)$$

where $\tilde{\gamma}(W) = 1/\tilde{\phi}'(W/k)$. The function $\tilde{\gamma}(\cdot)$ inherits the qualitative form of $\gamma(\cdot)$. In addition, when $W < 0$, the function $\tilde{\gamma}(\cdot)$ satisfies the key inequality $\tilde{\gamma}(W) \geq \tilde{\gamma}(0)$. Therefore, there exists heteroclinic connection between $(1, 0)$ and $(0, 0)$ in the $U - W$ phase plane for this amended system, as is proved in Proposition 2.1 in section 2.2.

In particular, for functions satisfying conditions (1.4), the system (3.5) has two equilibrium points: $(1, 0)$ which is a saddle point and $(0, 0)$ which is a stable node if $a \geq 2[\sqrt{f'(0)/\gamma(0)}]$, and a stable focus otherwise. The minimum wave speed is not affected by the change in the model since $\tilde{\gamma}(0)$ is independent of $\theta(\cdot)$. Thus, for wave speeds greater than or equal to this minimum value, a travelling wave solution of (3.1) exists for all values of k when $h(\cdot)$ and $\theta(\cdot)$ are such that $h(\infty)\theta(\infty) = 0$.

Conversely, when both $h(\infty)$ and $\theta(\infty)$ are nonzero, a travelling wave solution exists for k below a unique, critical value.

3.1 Comparing the original and the amended model

Recall that the change made to the model in this chapter corresponds to limiting the extent of matrix convection. We therefore, expect the peak in the C wave form for the original model to be higher than for the amended model (with saturation) for given functions $h(\cdot)$ and $f(\cdot)$, and a given value of k for which travelling waves exist for both models. Thus, we need to show that this intuitive expectation is correct.

The assumption that $\theta(\cdot)$ is a continuously differentiable and decreasing function implies that $\theta'(C) \leq 0$ for all C . Comparing equations (2.28) and (3.4) shows that $[1/\phi'(C)] > [1/\tilde{\phi}'(C)]$ for a given value of $C > 1$. However, we cannot extend the corresponding inequality to $\gamma(W)$ and $\tilde{\gamma}(W)$ since these are not necessarily monotonic functions. Thus, the comparison of trajectories in the $U - W$ plane is made difficult.

Therefore, we choose to work in the $U - C$ phase plane which makes comparison of wave forms

easier although it is a more difficult system to work with when considering the existence of travelling waves [10]. The equations follow directly from the two systems of equations (2.25) and (3.2) from the original and the amended model respectively:

$$U' = \frac{-a(1 - 1/C)}{kh(C)}, \quad (3.6)$$

$$C' = \frac{kC^2 f(U)}{a} - \frac{aC(C - 1)}{h(C)}$$

for the original model, and

$$U' = \frac{-a(1 - 1/C)}{k\theta(C)h(C)}, \quad (3.7)$$

$$C' = \frac{\frac{k\theta(C)C^2 f(U)}{a} - \frac{aC(C-1)}{h(C)}}{[1 + \frac{C(1-C)\theta'(C)}{\theta(C)}]}$$

for the amended model.

In this system of ordinary differential equations, a travelling wave solution corresponds to a heteroclinic connection between the equilibrium points $(0, 1)$ and $(1, 1)$. The existence of such a connection has important implications regarding the dynamics of both models. As mentioned earlier, our goal is to compare these solutions for given functions $h(\cdot)$, $f(\cdot)$, a , and k such that both systems have a travelling wave solution.

Let us denote the corresponding trajectories in the $U - C$ plane by τ for the original model (1.1) and $\tilde{\tau}$ for the amended model (3.1). Likewise, we represent the points on these trajectories at which the extracellular matrix wave i.e., C - wave has its unique local maximum as U_{min} and $\tilde{U}_{min}$, respectively.

Considering the portion $U \in (\tilde{U}_{min}, 1)$ of the trajectory $\tilde{\tau}$, and making use of equations (3.7), it follows that along $\tilde{\tau}$,

$$\frac{dC}{dU} < 0 \Rightarrow \frac{k\theta(C)Cf(U)}{a} > \frac{a(C - 1)}{h(C)}$$

$$\Rightarrow \frac{a(C-1)}{h(C)} - \frac{kCf(U)}{a} < \frac{a(C-1)}{h(C)} - \frac{k\theta(C)Cf(U)}{a} < 0 \quad (3.8)$$

Now, considering the original model, equations (3.6) imply that along τ we have

$$\frac{dC}{dU} = \frac{kC^2h(C)}{a(C-1)} \left[\frac{a(C-1)}{h(C)} - \frac{kCf(U)}{a} \right].$$

Applying the conditions $\theta(C) \leq 1$, $C > 1$, and $\theta'(C) \leq 0$ along the portion $U \in (\tilde{U}_{min}, 1)$ of the curve $\tilde{\tau}$ we find the slope of $\tilde{\tau}$ using equations (3.8) as

$$\begin{aligned} \frac{dC}{dU} &< \frac{kC^2h(C)}{a(C-1)} \left[\frac{a(C-1)}{h(C)} - \frac{kC\theta(C)f(U)}{a} \right] \\ &\leq \frac{\theta(C)kC^2h(C)}{a(C-1)} \left[\frac{\frac{a(C-1)}{h(C)} - \frac{kC\theta(C)f(U)}{a}}{[1+C(1-C)\theta'(C)/\theta(C)]} \right], \end{aligned} \quad (3.9)$$

Therefore in the system (3.6), all trajectories pass through the portion $U \in (\tilde{U}_{min}, 1)$ of the curve $\tilde{\tau}$ in the direction of increasing C . Here, the trajectories can be analysed along two lines namely:

- along the line $U = \tilde{U}_{min}$, $C > 1$, where the main technical result is that $U' < 0$.
- along $C = 1$, $U \in (0, 1)$, where the second equation of (3.6) implies that $C' = kf(U)/a > 0$.

Therefore, all trajectories leave the portion of the phase plane between $\tilde{\tau}$, $C = 1$, and $U = \tilde{U}_{min}$. At the equilibrium point $(1, 0)$, both slopes of τ and $\tilde{\tau}$ are the same at $(1, 0)$ since the eigenvector is independent of $\theta(\cdot)$.

However, for U close to 1, τ lies outside the portion of the phase plane between $\tilde{\tau}$, $C = 1$, and $U = \tilde{U}_{min}$.

Hence, τ must remain outside the portion $\tilde{\tau}$, $C = 1$, and $U = \tilde{U}_{min}$ for $U \in (\tilde{U}_{min}, 1)$ and

thus the extracellular matrix wave of the original model must reach a value that is at least as large as the value of the amended model. Thus the travelling wave in the original model, corresponding to τ , has a maximum value of C at least as large as that for the amended model, corresponding to $\tilde{\tau}$. Interestingly, we have shown that our intuitive expectation at the beginning of this section is indeed correct.

Chapter 4

Discussions

In this work, we have studied the expansive growth hypothesis which suggests that a dense fibrous capsule forms by remodelling of existing extracellular matrix, without any new matrix production. The model solutions all have the form of a pulse of extracellular matrix moving ahead of the growing tumour, corresponding to a fibrous capsule. The predicted density of the matrix in the capsule correlates directly with the parameter k , which represents the rate of local matrix movement and remodelling per cell.

Most importantly, this implies that the capsule density is not correlated with either the speed at which the tumour grows (which is independent of k) or its size. This explains the wide discrepancies between studies attempting to correlate tumour size and capsule incidence or thickness. It also contradicts the conventional intuition that these should be correlated if the capsule forms without matrix production. Thus a challenge for future work is to study the correlation between capsule density and some measure of the parameter k .

When saturation in the extent of matrix rearrangement per cell is included, the results show that rate of matrix movement and convection per cell will saturate at higher matrix densities. Analysis of the case when there is both new matrix secretion and remodelling occur, would enable investigation of tumour encapsulation in a broader context, thus is a

significant challenge for future work.

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