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Steady-State Solutions of a Generic Model for the Formation of Capillary Networks

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Abstract—A steady-state analysis of solutions of a generic model for capillary network formation is discussed. Under certain circumstances such solutions represent incomplete network formation, and hence, are of importance in the study of tumour angiogenesis and antiangiogenesis.

Keywords—Global bifurcation, Singular perturbation, Angiogenesis, Tumour growth.

1. INTRODUCTION

Angiogenesis (the formation of a network of blood vessels from a preexisting vasculature) is essential for the growth and development of solid tumours. Without such a network, the tumour remains in a dormant avascular state. In [1,2], a possible mechanism to explain why capillary sprouts cease migrating towards the tumour is discussed. A model comprising random cell motility, chemotaxis, and haptotaxis terms for the distribution of endothelial tip cells (which form the network) is introduced and a steady-state analysis together with numerical experiments show that the model can produce solutions which represent the situation in which capillary sprouts fail to reach the tumour.

Here we consider a generic model (of which the model discussed above is a special case) for the formation of a vascular network in the presence of a solid tumour. Our model considers the effect that a variety of external chemical stimuli induced by the growth of a solid tumour and related processes has on an endothelial tip cell distribution. Moreover, we assume that these cells can proliferate (unlike [1,2]). Such effects can be summarised and represented by the single equation

$$\frac{\partial n}{\partial t} = D\frac{\partial}{\partial x}\left(\frac{\partial n}{\partial x} - nH\right) + \lambda n(1-n), \tag{1}$$

where $n(x,t)$ is the tip cell density, D and λ are the diffusion and cell proliferation coefficients, respectively, and $H = H(x)$ is the "taxis function" representing the response of the endothelial cells to the external chemical stimuli. Equation (1) is augmented by the no-flux boundary conditions: $\frac{\partial n}{\partial x} - nH = 0$, at $x = 0, 1$. It is assumed that an existing blood vessel is located

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at $x = 0$ and a solid tumour at $x = 1$. Hence, initially (at $t = 0$), all tip cells are assumed to be concentrated proximal to $x = 0$.

By setting $\lambda = 0$, (1) is reduced to a linear equation. For a particular choice of function $H(x)$, this equation is exactly of the type considered in [1]. A more general analysis of this equation (but still with $\lambda = 0$) is presented in [2].

In the following, we will consider steady-state solutions to (1) for values of $\lambda \geq 0$. We show that there exists a positive, nontrivial solution for each value of $\lambda \geq 0$ and obtain closed forms for these solutions in the cases λ sufficiently small and λ sufficiently large. Numerical solutions are presented in order to compare solutions of the steady-state problem with the asymptotic states of the initial value problem discussed above.

2. STEADY-STATE SOLUTIONS

Setting $\frac{\partial n}{\partial t} = 0$ reduces (1) to the following nonlinear boundary value problem:

$$\begin{aligned} -D\frac{d}{dx}\left(\frac{dn}{dx} - nH\right) &= \lambda n(1-n), \qquad && x \in (0,1), \\ \frac{dn}{dx} - nH &= 0, && \text{at } x = 0,\ 1. \end{aligned} \tag{2}$$

We wish to investigate the structure of the solution set of this boundary value problem as the proliferation parameter λ is varied. We assume that the function $H(x)$ is sufficiently differentiable. For all values of $\lambda \geq 0$, $n(x) \equiv 0$ is clearly a solution of (2). No other constant solution of (2) exists for all values of λ but we will show that $n(x) \equiv 1$ is in some sense an asymptotic solution for (2) as λ becomes very large. Of greater interest are solutions which are not spatially uniform in $[0,1]$. In [1], it is shown for the particular choice of $H(x)$ used there (and $\lambda = 0$) that a steady-state solution exists which has a single interior maximum, reducing to near zero at the boundaries $x = 0, 1$. In the following, we show that a spatially nonuniform solution of (2) exists for all values of $\lambda \geq 0$ (independent of the choice of $H(x)$).

Following Sleeman et al. [2], we employ the change of variable $n = u\phi$, where $\phi(x) = \exp(\int_0^x H(z)\,dz)$, thus finding a solution of (2) is equivalent to finding a solution u of

$$-D\,(\phi u')' = \lambda \phi u(1 - \phi u), \qquad x \in (0,1), \tag{3}$$

$$u' = 0, \qquad \text{at } x = 0, 1, \tag{4}$$

where $' \equiv \frac{d}{dx}$. Equation (3) is now of classical nonlinear Sturm-Liouville type (as ϕ is strictly positive and continuously differentiable by the definition of $H(x)$ given above). Clearly, $u = 0$ is a solution of (3),(4) for all values of $\lambda \geq 0$. Linearising (3) around $u = 0$ gives the equation

$$-D\,(\phi v')' = \lambda \phi v. \tag{5}$$

It is well known (see, for example, [3]) that the boundary value problem (5),(4) possesses an increasing sequence of simple eigenvalues (i.e., eigenvalues of algebraic multiplicity equal to one) given by $0 = \lambda_1 < \lambda_2 < \cdots < \lambda_j < \cdots$ with $\lambda_j \to \infty$ as $j \to \infty$. Any eigenfunction v_j corresponding to λ_j has exactly $j-1$ simple nodal zeros in $(0,1)$ (i.e., v_j has $j-1$ zeros in $(0,1)$ and at each of these points, v_j' is nonzero). Hence, for each j there is a branch of solutions of (5),(4) of the form $(\alpha v_j, \lambda_j)$, $\alpha \in \mathbb{R}$.

By Theorem 2.3 in [4], it follows that there exists a branch of nontrivial solutions to (3),(4) emanating from $(u, \lambda) = (0, \lambda_j)$ for each integer $j \geq 1$. On each of these branches, the solutions are locally of the form $(u, \lambda) = (\alpha v_j + o(|\alpha|), \lambda_j + o(1))$ for $\alpha \in \mathbb{R}$, $|\alpha|$ sufficiently small. Moreover, any solution on the branch containing the point $(0, \lambda_j)$ has exactly $j - 1$ simple nodal zeros. Hence, as we are interested in positive solutions, we concentrate on solutions contained within the first branch. Notice that $(u, \lambda) = (k, 0)$ for constants k, is a line of solutions to (3),(4) emanating from $(0,0)$ and this line of constant solutions is contained within this first branch. Any solution $u = k$, $k > 0$, on this line provides a positive solution $n = k\phi$ of (2). The existence of positive solutions for $\lambda > 0$ is obtained by looking for secondary bifurcations from the line of solutions $(k, 0)$. The details of this calculation are long and involved and the interested reader is directed to [5]. What follows is a statement of the main result. Let

$$X_r = \{v \in C^r[0,1] : v' = 0, \text{ at } x = 0, 1\}, \qquad Y = C[0,1], \qquad Z = Y \cap \left\{v : \int_0^1 v\,dx = 0\right\},$$

where $r = 1, 2$ and, e.g., C^2 denotes the space of twice differentiable functions as is standard. Next, decompose functions $u \in X_r$ into two orthogonal parts (where orthogonality is in the usual $L^2(0,1)$ sense), that is, let $u = k + \hat{u}$, where $k \in \mathbb{R}$ (in this context here and below, we identify $\mathbb{R}$ with the space of constant functions) and $\hat{u}$ satisfies $\int_0^1 \hat{u}\,dx = 0$. Define the operator $L : X_2 \to Z$ as follows: $L(k + \hat{u}) := -D(\phi(k + \hat{u})')' = -D(\phi\hat{u}')' = L\hat{u}$.

Applying a combination of local and global bifurcation results [6, Theorem 1.7; 7, Theorem 3.2] and an adaptation of a result by Dancer [8, Theorem 2], the following can be shown.

THEOREM 1. *The boundary value problem (2) has a positive, bounded solution for all values of $\lambda \geq 0$. These solutions lie on a continuum $\mathcal{C} \subset X_2 \times \mathbb{R}$ emanating from the secondary bifurcation point $(n, \lambda) = (\hat{k}\phi, 0)$, where*

$$\hat{k} := \frac{\int_0^1 \phi\,dx}{\int_0^1 \phi^2\,dx}.$$

Moreover, for λ sufficiently small and positive, all positive solutions of the boundary value problem (2) lie on the continuum $\mathcal{C}$ and have the form

$$n = \hat{k}\phi + s\phi L^{-1}\hat{k}\phi\left(1 - \hat{k}\phi\right) + o(|s|), \qquad \lambda = s + o(|s|), \tag{6}$$

for $s \in \mathbb{R}$, with $|s|$ sufficiently small.

The proof can be found in [5].

We now turn attention to the case when λ is large. In this case, (2) may be rewritten as

$$\begin{aligned} -\epsilon\frac{d^2n}{dx^2} + \epsilon\frac{d(nH)}{dx} &= n(1-n), \qquad && x \in (0,1), \\ \frac{dn}{dx} - nH &= 0, && \text{at } x = 0,\ 1, \end{aligned} \tag{7}$$

where $\epsilon = D/\lambda \ll 1$. Clearly, if $\epsilon = 0$, then $n \equiv 1$ solves the first equation in (7). However, this solution does not satisfy the boundary conditions, and hence, it is anticipated that for each fixed ϵ, with $0 < \epsilon \ll 1$, solutions of (7) undergo a rapid change in value in a small neighbourhood of the boundaries.

Using standard singular perturbation theory, we now construct a uniformly valid asymptotic expression for the solution of (7). We first construct a more detailed outer solution of (7) by seeking a solution of the form $n_{\text{out}} = n_0(x) + \epsilon n_1(x) + \cdots$, as $\epsilon \to 0$. By substituting and equating coefficients, if follows that

$$n_{\text{out}} = 1 - \epsilon\frac{dH}{dx} + o(\epsilon).$$

Next, we construct inner solutions which are valid close to the boundaries $x = 0$ and $x = 1$. Consider first the boundary $x = 0$ and let $y = x/\epsilon^\alpha$, where $\alpha > 0$. Then it follows that in a small region close to $x = 0$, the behaviour of the solutions of (7) can be investigated by studying solutions of the following system:

$$\begin{aligned} -\epsilon^{1-2\alpha}\frac{d^2 n}{dy^2} + \epsilon^{1-\alpha}\frac{d\left(nH\left(\epsilon^{\alpha} y\right)\right)}{dy} &= n(1-n), \qquad && y \in (0,\infty), \\ \frac{dn}{dy} - \epsilon^{\alpha} nH\left(\epsilon^{\alpha} y\right) &= 0, && \text{at } y = 0. \end{aligned} \tag{8}$$

Notice that $H(x)$ is a given function of x, and therefore, in terms of the stretched coordinate, $H \equiv H(\epsilon^{\alpha} y)$. A balance between the highest-order derivative and other terms in (8) is obtained by choosing $\alpha = 1/2$. Also, we may write the term $H(\epsilon^{1/2} y)$ as a Taylor series, $H(\epsilon^{1/2} y) = H(0) + \epsilon^{1/2} y H'(0) + \cdots$, where the prime denotes differentiation with respect to $\epsilon^{1/2} y = x$. After some calculation, it can be shown that the inner solution at the boundary $x = 0$, n^0_{in} is of the form

$$n^0_{\text{in}}(y) = n^0_0(y) + \epsilon^{1/2} n^0_1(y) + \epsilon n^0_2(y) + \cdots, \tag{9}$$

where

$$n^0_0(y) \equiv 1 \qquad \text{and} \qquad n^0_1(y) = Ae^{y} + Be^{-y},$$

with A and B constants. To determine these constants, we apply the standard matching condition (see, e.g., [9, Chapter 7]), i.e.,

$$\lim_{\epsilon\to 0} n^0_{\text{in}}\left(\frac{\gamma(\epsilon)}{\epsilon^{1/2}}\eta\right) = \lim_{\epsilon\to 0} n_{\text{out}}(\gamma(\epsilon)\eta),$$

where $\eta = x/\gamma(\epsilon)$ is considered fixed for some function γ such that $\gamma(\epsilon) \to 0$, $\gamma(\epsilon)/\epsilon^{1/2} \to \infty$, as $\epsilon \to 0$. Using these conditions, it can be shown that $A = 0$ and $B = -H(0)$.

The third coefficient in n^0_{in} can, therefore, be found by equating coefficients of ϵ in (8) and after some algebra is given by

$$n^0_2(y) = -\frac{1}{6}H^2(0)e^{-y} + \frac{1}{3}H^2(0)e^{-2y} - \frac{1}{2}H^2(0)ye^{-y} - H'(0).$$

In a similar manner, an inner solution at $x = 1$ can be derived. In this case, the stretched variable required is $z = (1-x)/\epsilon^{1/2}$. Using similar techniques to those outlined above, it can be shown that an inner solution of the form

$$n^1_{\text{in}}(z) = n^1_0(z) + \epsilon^{1/2} n^1_1(z) + \epsilon n^1_2(z) + \cdots$$

can be found where

$$n^1_0(z) \equiv 1, \qquad n^1_1(z) = H(1), \qquad n^1_2(z) = -\frac{1}{6}H^2(1)e^{-z} + \frac{1}{3}H^2(1)e^{-2z} - \frac{1}{2}H^2(1)ze^{-z} + H'(1).$$

A uniformly valid asymptotic expression for the solution of (7) is, therefore,

$$n_{\text{unif}}(x) = n_{\text{out}}(x) + n^0_{\text{in}}\left(\frac{x}{\epsilon^{1/2}}\right) + n^1_{\text{in}}\left(\frac{1-x}{\epsilon^{1/2}}\right) - 2\lim_{\epsilon\to 0} n_{\text{out}}(x) + o(\epsilon), \tag{10}$$

for $x \in [0,1]$ and ϵ sufficiently small with, as is clear, $\lim_{\epsilon\to 0} n_{\text{out}}(x) = 1$.

The above results for small and large λ can be summarised as shown in Figure 1. Here, we have used the functional form for $H(x)$ and the parameter values (the value of λ excepted) suggested

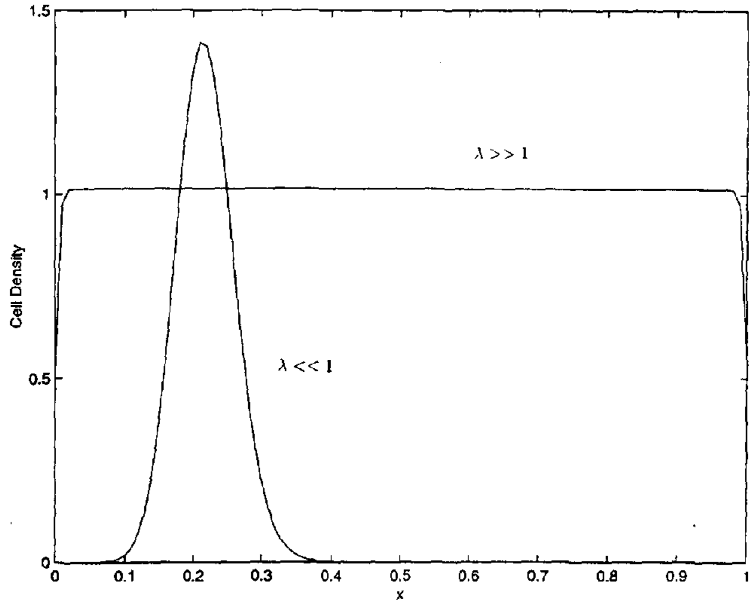

Figure 1. Steady-state tip cell distribution as given by (6) and (10) to first order with $\epsilon = 2 \times 10^{-5}$ ($\lambda = 50$). The function $H(x) = (\chi(c)\frac{\partial c}{\partial x} + \rho\frac{\partial f}{\partial x})/D$, where $c(x) = \exp(-(1-x)^2/\gamma)$, $f(x) = \exp(-x^2/\gamma)$, and $\chi(c) = \chi_0/(1+\alpha c(x))$ with parameter values $\alpha = 0.6$, $\gamma = 0.45$, $D = 0.001$, $\chi_0 = 0.38$, and $\rho = 0.34$.

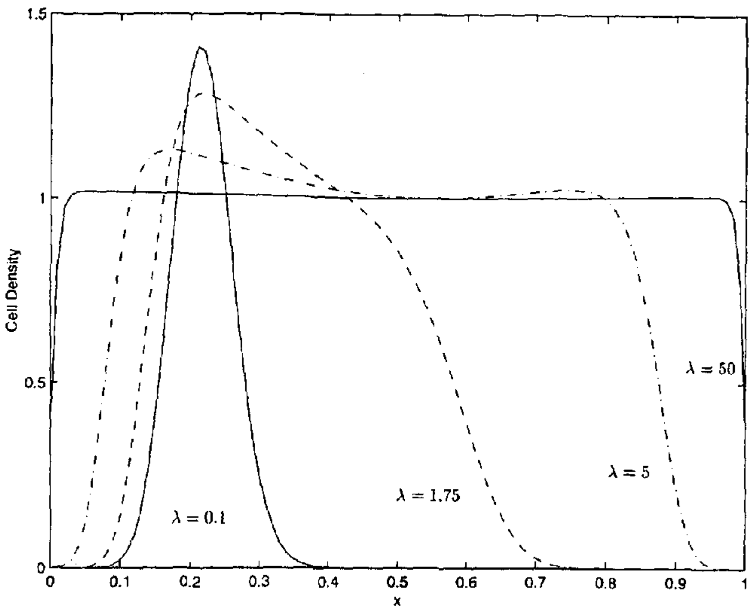

Figure 2. Steady-state tip cell distributions of the initial value problem discussed in Section 1 for $\lambda = 0.1, 1.75, 5, 50$. The function $H(x)$ and parameter values are as in Figure 1. The initial data used is referred to in Section 1 and is identical to that described in [1].

in [1]. The solution as given by (6) and the uniformly valid asymptotic solution given in (10) are shown to first order.

In Figure 2, numerical simulations of the initial value problem discussed in Section 1 are shown in order to compare these solutions with those obtained analytically and shown in Figure 1. Here, we again use the functional form for $H(x)$ suggested in [1] and also use the parameter values and initial data described there. The dependence of the solution on λ is clear; for small values, a steady state of similar form to that from (6) is obtained. As λ is increased, the central peak becomes wider until the whole interval $[0, 1]$ is covered by a significant cell density. As λ becomes very large, the solution tends to the uniform state $n \equiv 1$ and is in good agreement with the asymptotic solution obtained from (10). Notice, however, that even for fairly large values of λ, a nontrivial solution is obtained which reduces in size to near zero close to the boundary $x = 1$.

There is close agreement between the steady-state solutions obtained analytically (Figure 1) and the numerically calculated steady states of the initial value problem (Figure 2) providing strong evidence that the steady states discussed in this paper are stable asymptotic states of the initial value problem.

3. CONCLUSIONS

In the formulation of the initial value problem discussed in Section 1, it is assumed that the tumour is situated at the right-hand boundary. For the choice of taxis function used in the numerical calculations discussed above, it is shown that for a large range of values of λ, significant concentrations of tip cells do not reach this right-hand boundary, representing the situation where vascularisation of the tumour does not occur. This result is not unique to the choice of $H(x)$ used here; for other appropriate functional forms, see, e.g., [2]. (A necessary condition for appropriate functions is that $H(x)$ changes sign in $[0,1]$ and that $H'(x)$ is not nonnegative in all of $[0,1]$.) It seems, then, that for a sizable range of cell proliferation rates, the form of the taxis function is of greater importance with respect to the existence of such steady states. The generic structure of the problem studied here allows for the consideration of many possible mechanisms which may induce retardation of capillary network development, and hence, the above analysis has impact on the study of angiogenesis modelling for both primary and secondary tumours. In the former, retardation of capillary network development is thought to occur as a result of interactions between endothelial cells and extracellular matrix macromolecules such as fibronectin, laminin, and collagen [1] and in the latter to occur due to the release of antiangiogenic factors such as angiostatin and endostatin [10].

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