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Mathematical Modelling of Vascular Tumour Growth
and Implications for Therapy

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Summary. In this chapter we briefly discuss the results of a mathematical model formulated in [22] that incorporates many processes associated with tumour growth. The deterministic model, a system of coupled non-linear partial differential equations, is a combination of two previous models that describe the tumour-host interactions in the initial stages of growth [11] and the tumour angiogenic process [6]. Combining these models enables us to investigate combination therapies that target different aspects of tumour growth. Numerical simulations show that the model captures both the avascular and vascular growth phases. Furthermore, we recover a number of characteristic features of vascular tumour growth such as the rate of growth of the tumour and invasion speed. We also show how our model can be used to investigate the effect of different anti-cancer therapies.

Key words: Vascular tumours, angiogenesis, hypoxia, anti-cancer therapy.

18.1 Introduction

Tumour growth is a complex process that involves a sequence of well-orchestrated events. These characterise the initial avascular phase of growth, the angiogenesis that enables the tumour to become vascularised and the vascular phase of growth. During the early stages of growth, oxygen is delivered to the tumour cells via diffusion from nearby blood vessels and the tumour cells proliferate rapidly and consume more oxygen than the host cells [7]. Due to the diffusion-limited supply of oxygen such growth is limited in size [31]. To grow larger the tumour must undergo a cascade of processes that include the secretion of tumour angiogenic factors, such as vascular endothelial growth factor (VEGF). VEGF stimulates the formation of a tumour-specific vascular network from the host vessels. Upon successful vascularisation oxygen is rapidly supplied to the tumour and it can grow larger.
Within the last three decades a number of mathematical models for tumour growth have been developed as part of the quest to understand tumour growth dynamics. Most of these models focus on one particular aspect, for example, avascular growth (e.g., [27,32]), tissue-tissue interactions (e.g., [11,28]), angiogenesis (e.g., [1,6,21]) or vascular tumour growth (e.g., [4,5,14,18]). However, if we wish to compare and contrast the effectiveness of different treatment protocols via mathematical modelling, we need a model that integrates several key processes that occur during tumour growth.

A first attempt at deriving such a model was made by de Angelis and Preziosi [8]. They developed a model to describe the evolution of tumour growth from the avascular stage to the vascular stage through the angiogenic process. The model was able to predict the formation of necrotic regions, the control of mitosis by the presence of an inhibitory factor, the angiogenesis process with proliferation of capillaries just outside the tumour surface and the regression of the tumour and the angiogenic capillaries when angiogenesis was controlled or inhibited. Here we briefly describe an extended model to the one in [8] including the density of the healthy host cells in the system, and we also model two distinct components of the vasculature, distinguishing between capillary tips and blood vessels. We refer the reader to [22] for full details. In Section 18.2, we present the model equations. In Section 18.3 we illustrate the types of behaviour that the model yields when formulated on a one-dimensional spatial domain. The potential use of our model for testing anti-tumour drug protocols is illustrated in Section 18.4. We present our conclusions and comment on future research directions in Section 18.5.

18.2 Model Formulation

The model we develop comprises a system of non-linear partial differential equations and aims to reproduce the animal chamber experiments of Gimbrone et al. [12] and Muthukkaruppan et al. [17]. Thus we consider a small solid tumour implanted in the cornea of a test animal close to the limbal vessels. Angiogenesis is quick (14–21 days) and tumour growth evolves continuously from the avascular phase, through angiogenesis to the vascular phase.

A novel feature of our model, compared to previous models, is that tumour-host interactions are active in the region while the new capillary network is forming during angiogenesis. This enables us to investigate how the coupling of tumour-host dynamics and angiogenesis influences tumour growth. To our knowledge this has not been considered in existing models, which have tended to focus on a single specific aspect of tumour development.

Tumour growth, via invasion of the surrounding host cells, and angiogenesis are multidimensional processes. By averaging the dependent variables in a plane perpendicular to the direction of motion of the vascular front it is possible to restrict attention to one spatial dimension. This direction is chosen to be parallel to the line connecting the limbus, situated at \( x = 0 \) and where the nearest host blood vessels are found, to the tumour centre at \( x = 1 \) (in dimensionless terms). We introduce independent variables \( t \) and \( x \) representing, respectively, time and spatial position in a direction parallel to that of tip growth.

Within our modelling framework we consider two types of dependent variables: those that contribute to the tumour volume and those of negligible volume. In the former category we include the healthy (host) cell density \( n_1(x,t) \), the tumour cell density \( n_2(x,t) \) and two components for the vasculature, namely the capillary tip density \( n_3(x,t) \) and the density of the blood vessels \( b(x,t) \). The nutrient, which in our case is oxygen, concentration \( a(x,t) \) and TAF, which in our model is VEGF, concentration \( c(x,t) \) are assumed to be of negligible volume. To formulate the model equations we combine models by Byrne and Chaplain [6] and Gatenby and Gawlinski [11]. Following [6], the deterministic modelling of the vasculature-TAF interactions is based on the fungal growth model of [9], the two processes sharing many common features, including branching, anastomosis and migration [12,17]. Based on experimental results by Sholley et al. [29], we assume that migration of the capillary tips up the gradient of VEGF concentration is the key mechanism during angiogenesis and that proliferation of the cells at the capillary tip stimulated by VEGF is secondary, and as a result, less significant. This makes our model assumptions biologically different from the modelling assumptions from [6].

Following [11] we model the tumour-host interactions via non-linear reaction-diffusion equations for the cell density. However, we assume that the normal tissue is immobile and neglect its random motion coefficient. As in [11] we assume that the tumour is unable to spread unless the surrounding healthy tissue has been diminished from its carrying capacity by, for example, increased acidity leading to death of normal cells. Thus we consider the expansion of the tumour into the adjacent tissue to depend on its composition and we model the random motion coefficient for the tumour cell density to be dependent on the density of the surrounding normal cells. Unlike [11] the equations we use for the tumour and the host cell density are coupled via the oxygen equation, rather than hydrogen ion density \( H^+ \) as a measure of the pH and acidity of the region. Oxygen is blood-borne and it controls cell proliferation and oxygen-deprived (hypoxic) death. These assumptions are based on experimental observations of tumour-host interactions in the presence and absence of oxygen [7]. The novel aspect of our model is the coupling of the equations for the cell densities and oxygen concentration with equations for the vasculature-TAF interactions. We explore the fact that when oxygen concentration in the region lowers, tumour cells (and to a lesser extent normal cells) secrete VEGF [13]. We incorporate this by assuming that VEGF is produced by the tumour and the normal cells under hypoxia. This coupling distinguishes our model from [11], from [6] and from previous models such as [8].

Combining the above ideas we arrive at the following non-dimensionalised system of equations (see [22] for details):

\[
\frac{\partial n_1}{\partial t} = \frac{r_1 n_1^a}{1 + \rho a} - \frac{r_2 n_1}{1 + \rho a} - \frac{R_1 n_1}{c_1 n_1 n_2} \quad \text{(18.1)}
\]

...
18.3 Model Simulations

We investigate, using numerical computation, the behaviour of the model in various parameter regimes. We use the NAG library routine D03PCF which discretises the system of equations using finite differences and solves the resulting system of ordinary differential equations using backward differentiation [26]. We find that, by changing parameter values, the model can simulate a growing tumour before and after vascularisation, as well as the clearance of the tumour due to interactions with the host tissue. Qualitatively we can capture avascular tumour growth with invasion of the host cells, the migration of the neovasculature during the angiogenic process and also vascular tumour growth characterised by the tumour growing larger and invading the host cells more rapidly than its avascular counterpart.

In Fig. 18.1(a)(e) we present numerical solutions of the equations (18.1)-(18.10) for different parameter values. We observe avascular tumour growth and invasion of the host cells (see Fig. 18.1(a)); successful angiogenesis and tumour invasion of the host cells (see Fig. 18.1(b)); avascular tumour growth and tumour coexistence with the host cells (see Fig. 18.1(c)); successful angiogenesis and tumour-host coexistence (see Fig. 18.1(d)); and tumour regression during avascular growth only (see Fig. 18.1(e)). We note that changes in key model parameters (competition parameters $c_1$, $c_2$ and oxygen consumption $\lambda_2$ as well as the chemotactic parameters $\eta$, $\psi$) allow us to switch from one type of behaviour to another. We illustrate this in the bifurcation diagrams in Fig. 18.2(a)(c) where parameter space is divided into distinct regions depending on the outcomes of the simulations.

Our results suggest that the success of the angiogenic process depends on the strength of tumour-host competition: only when the tumour can compete with the host cells will angiogenesis be complete (regions M and P in Fig. 18.2(a)(b)). Thus we predict that angiogenesis must follow invasive avascular tumour growth and it is not possible for a tumour that initially regresses to then undergo angiogenesis and invade the host cells. This occurs because in our model the tumour cells are the main source of VEGF. Hence when the normal cells are dominant the tumour recedes and VEGF secretion decreases (see Fig. 18.1(c)). Tumour vascularisation is quicker when the tumour consumes larger amounts of oxygen (i.e., as $\lambda_2$ increases; see Fig. 18.3(a)). Equally, increasing $\lambda_2$, and making the region hypoxic, in Fig. 18.2(a)(b), increases the size of the region P thus making it more likely for the tumour to invade the host cells. This suggests that tumour invasion is stronger in hypoxic conditions and this is a new prediction of our model. Combining these results we predict that hypoxic conditions, brought about by large oxygen consumption by the tumour cells, render the tumour more invasive and able to vascularise more quickly.

Successful angiogenesis, in Fig. 18.4(c)(d), is characterised by vascular profiles that propagate from the limbal vessels towards the tumour, with increasing speed and increasing maximum density (see Fig. 18.4(c)). In addition the capillary tip profiles precede the vessel profiles (compare Figs. 18.4(c) and 18.4(d)). These features are of what is called the brush-border effect associated with successful tumour vascularisation in the experiments by Muthukkaruppan [17]. By tracking the position of a point in the wave front over time, we estimate the speed of propagation of the tips to be
Fig. 18.1. Series of plots illustrating the types of behaviour that emerge from equations (18.1)–(18.10). The normal $n_1$ (–) and the tumour cell density $n_2$ (—) propagate as waves of normal cell regression and tumour invasion before and after successful vascularisation (a)–(d); or when the normal cells are better competitors the tumour density regresses (e) in which case angiogenesis is unsuccessful. Following successful vascularisation the tumour grows larger ((b) and (d)). During avascular tumour invasion in (a) and (c) the capillary tips $n_3$ (—) propagate from the limbus towards the tumour with increasing speed and increased maximum density. Post angiogenesis tip profiles propagate with constant speed and either increase to a maximum value within the tumour mass (b) or decrease towards the tumour centre (d). The results are shown at dimensionless $t = 5, 10, 15$ in (a), (c) and (e) and $t = 20, 25$ and $30$ in (b) and (d). Parameter values: $r_1 = 4, r_2 = 8, R_1 = 1, r_2 = 10, ho_2 = 15, R_2 = 2, d_{n_2} = 0.0007, h = 10, l_1 = 0.1, r_1 = 0.1, r_4 = 10, p_1 = 10, d_e = 0.28, v = 1, d_{n_3} = 0.0001, \psi = 0.8, l_1 = 1, p_2 = 50, p_1 = 10, l_1 = 0.25, k = 30, p_3 = 10, c_2 = 250, a_2 = 0.9, c_3 = c_4 = c_5 = 250, c_2 = 4 = 0$ and (a) $c_1 = 10, c_2 = 7, c_2 = 50$; (b) $c_1 = 1, c_2 = 5, c_2 = 50$; (c) $c_1 = 1, c_2 = 25, c_2 = 50$.

The maximum density of the capillary tips either reaches a maximum value within the tumour mass (see Fig. 18.1(b)) or decreases towards the tumour centre once the tips have penetrated the tumour (see Fig. 18.1(d)). The former case occurs when the tumour is a better competitor than the host cells, whereas the latter case occurs when the tumour cells coexist with the host cells. Therefore we predict that the outcome of

Fig. 18.3. (a) Numerically calculated decrease in the time when the tumour becomes vascularised as a function of the parameter $l_2$ that controls oxygen consumption by the tumour cells. (b)–(c) Diagrams illustrating how the $(l_2, l_2)$ and $(l_2, l_2)$ parameter spaces can be decomposed into distinct regions depending on the effectiveness of an anti-proliferative therapy. In (b) in the long term, only tumour cells are killed (II), only normal cells are killed (IV), both cell types are killed (III) by the therapy, or it has no effect on tumour growth (I). In (c) the therapy is not effective in region $N$; the tumour regresses and is removed in region $R$ and the tumour reaches saturated growth in region $S$. 
18.4 Applications of the Model

The model (18.1)–(18.10) can be used to investigate the effect of different anti-cancer treatments. We now extend our model to include an equation for a blood-borne drug with different modes of action. For example, model simulations suggest that a tumour which in the absence of therapy invades the adjacent host tissue, when treated continuously with an anti-proliferative drug can saturate in growth or can regress. The effect of the drug in our simulations is thus similar to the effect of chemotherapeutic drugs such as doxorubicin [3] which target rapidly proliferating cells. In Fig. 18.3(b)–(c) we depict the bifurcation diagrams for the parameters that control the effectiveness of the anti-proliferative therapy: \( \Delta_1 \) and \( \Delta_2 \) associated with the potency of the drug on the healthy and the tumour cells and \( \beta_2 \) representing the rate of drug uptake by the tumour cells. We predict that the therapy is most effective when the potency on the tumour cells and the uptake of the drug by the tumour cells are large, whereas the potency on the normal cells is small.

Alternatively we study administration of a drug that destroys the vascular network. Such a drug may fall into two categories: one that targets the angiogenic stimuli (e.g., VEGF) via inhibitors such as endostatin [19] or angiosstatin [20]; or a drug such as cabozantinib (CABP) [33] that directly targets the immature blood vessels. Within our model we are able to incorporate these different modes of action of the anti-vascular drug and compare the outcomes. Qualitatively the results are the same. Our simulations predict that upon administration of the anti-vascular drug tumour vascularisation can be prevented but tumour invasion of the host cells continues in this case. The tumour density resembles an avascular mass that invades with a constant speed. This is unrealistic, as we know that avascular tumours cannot grow indefinitely, and occurs because the model [11] does not properly include necrosis. Recently, an extension of the model in [11] has been proposed and shown to exhibit growth saturation [30]. A future extension of the present integrated model would be to include this new model.

When a combination of anti-proliferative and anti-vascular therapy is introduced into our model, the qualitative outcome is similar to that when only anti-proliferative therapy is applied. Tumour invasion into the host cells can either be halted and the tumour reaches a saturated growth, or tumour invasion is reversed and the tumour regresses. For more details of these and other therapeutic applications see [22] and [24].

18.5 Conclusions

We believe that the mathematical model presented here enables us to better understand the complex interactions that govern tumour growth. The continuum approach adopted in [22] allows us to make analytical predictions, for example, of wavespeed of invasion. Recently many cellular automata (CA) approaches have been developed to describe different aspects of tumour growth (see [16]). CA allows one to consider properties of individual cells but there is little in the way of mathematical theory developed for such models. Our model was the first deterministic model to study how tumour cells,
host cells and host blood vessels interact. With our results we can capture avascular followed by vascular tumour growth, as well as tumour elimination due to interactions with the host tissue. We can confirm that a vascular tumour is more aggressive and grows larger than its avascular counterpart. This agrees with in vivo observations of tumour growth and the modelling results presented in [4]. Furthermore we predict that it is not possible for a tumour that initially regresses to undergo angiogenesis and then invade the host cells. This may be a consequence of the fact that we do not allow for genetic mutations of the tumour cells. Our simulations also suggest that, during vascular growth, the maximum density of immature vessels within the tumour mass stays constant or decreases towards the tumour centre. In practice the situation which arises depends on the nature of the tumour-host interactions.

In terms of novel therapies, our numerical results suggest that targeting a vascular tumour with a highly potent anti-proliferative drug in combination with reducing the VEGF influence in the region (and thus preventing angiogenesis) is the most effective treatment. When the therapy only destroys the vascular network, we predict that angiogenesis can be prevented but tumour invasion will continue unaffected. We note that in our model there is continuous infusion of the drug. Questions remain as to whether such a therapy is feasible and, of course, our modelling framework does not account for the issue of side effects. A full critique of this modelling approach together with possibilities for further research are presented in [24].

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