Mathematical Model of Avascular Tumor Growth: Necrosis and Apoptosis

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Abstract. The first section of this paper reviews the research on the development of avascular tumours, which are tumours without a blood artery network to supply their cells with nutrients. The process of avascular tumours is then illustrated utilising classical PDE model, which is composed of an outer layer of actively dividing cells and an inner core of dead cells (referred to as necrotic cells) (called proliferating cells). The model takes into account both necrosis (a type of cell death brought on by changes in the cell's microenvironment) and apoptosis (a sort of programmed cell death that takes place when a cell reaches the end of its normal lifespan). We offer a modified, simplified model and study how the relative importance of these mechanisms shifts as the tumour enlarges using a mix of numerical and analytical methods.

1. Introduction

The avascular phase is the first stage of the growth of a solid tumour, when the tumour is tiny and has not yet developed a network of blood arteries to supply its cells with nutrients. During this stage, the tumour gets the nutrients and oxygen it needs to survive by diffusing from the nearby tissues. The second stage of tumour growth is the vascular phase. When solid tumours transition from the avascular to the vascular phase, a process known as angiogenesis takes place. The tumour triggers a new blood supply from adjacent blood arteries because of this procedure [Fol76]. Once the tumour becomes vascularized, its nutrient supply becomes effectively limitless, and it can grow rapidly, potentially leading to lethal growth.Moreover, angiogenesis is triggered by the release of tumour angiogenesis factor (TAF) into the surrounding tissue. TAF stimulates the growth of new blood vessels from existing ones, allowing the tumour to access a greater supply of nutrients and oxygen.

During the early stages of solid tumour growth, the size of the tumour colony is influenced by the balance between cell proliferation (the production of new cells) and cell death. If the rate of cell proliferation exceeds the rate of cell death, the tumour will grow. If the rate of cell death exceeds the rate of cell proliferation, the tumour will shrink. Two mechanisms that contribute to cell death in solid tumours are apoptosis and necrosis. Apoptosis is a type of programmed cell death that occurs when a cell reaches the end of its natural lifespan. Necrosis, on the other hand, is caused by changes in the cell's micro-environment and can occur, for example, in areas of the tumour with limited nutrients. Necrosis is a form of accidental cell death that is not controlled by the cell's internal machinery like apoptosis.

Mathematical models are used to represent and study the growth and behaviour of tumours called malignant cell systems. These models often depict the tumour as a spherical mass of cells that grows in response to the availability of nutrients from the surrounding tissue, and they often include a central region of dead cells, a layer of actively dividing cells, and possibly a third region of non-dividing cells. These models are used to understand the factors that influence MCS growth and identify potential targets for therapeutic intervention. Many of these models involve an ordinary differ- ential equation (ODE) and at least one reaction-diffusion equation (RDE) to describe the evolution of the tumour boundary and the distribution of nutrients and growth- inhibitory factors within the tumour.

The growth rate of a tumour is influenced by the balance between cell proliferation and cell loss. Nutrient availability plays a crucial role in maintaining the viability of tumour cells and supporting their capacity for division and growth. Previous studies have identified two mechanisms that contribute to cell loss in tumours: apoptosis and necrosis [Ker71], [KWH94]. Apoptosis is a form of programmed cell death that occurs as part of the normal functioning of a cell, while necrosis is an abnormal form of cell death induced by changes in the micro-environment of the cell. There is some debate in the literature regarding the precise distinction between these two mechanisms, but one commonly cited difference is that necrosis is triggered by external factors, while apoptosis is an intrinsic property of the cell. For example, a lack of nutrients in the centre of a tumour may cause cells to die due to necrosis, while cell death resulting from

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apoptosis may occur when a cell exceeds its natural lifespan. In situ labelling techniques have also facilitated the distinction between apoptosis and necrosis based on the presence or absence of DNA fragmentation. Apoptotic cells are characterized by DNA fragmentation that follows a specific pattern, while necrotic cells do not display DNA fragmentation until 24 hours after the onset of necrosis.

2. Literature review

The evolution of an avascular solid tumour in response to an exogenous nutrient is depicted using the mathematical model that will be provided. The model presupposes a continuum of cells in two states, living or dead, and, depending on the concentration of a general nutrient, the live cells may reproduce (causing the tumour to enlarge) or die (causing the tumour to contract) [CBK01]. Sherratt and Chaplain [SC01] create a new mathematical model based on the older one [WK99], which is described in terms of continuum densities of proliferating, dormant, and necrotic cells together with a general nutrient/growth factor. The mathematical model is modified in [CBK01] to describe the expansion of an avascular tumour spheroid implanted in a deformable medium (gel). Although historically the emphasis has been on studying these events through experimental and clinical observations, these efforts have been augmented by mathematical modelling and simulation that allow examination at various time and spatial scales.

3. Avascular tumour growth model

The mathematical model that is shown below illustrates how a multicellular spheroid changes over time in response to an exogenous nutrient like oxygen. Both proliferative and necrotic cells are thought to be present in the tumour, which is radially symmetric. The ratios of proliferative and necrotic cells may fluctuate over time as the tumour grows. This change in cell ratios may be impacted by a number of variables, including the availability of nutrients, the pace of cell division and death, and the effects of various therapeutic interventions on the tumour. The debate started by Byrne and Chaplain is built upon in this study as it considers a free boundary problem, modelling a spherically symmetric, nonnecrotic tumour growth with angiogenesis. [BC95b]

3.1 Assumptions and Derivation

Assign $R(t)$to the outer shell's radius and $r_{nec}(t)$ to the necrotic cell's radius. Recall that $r_{nec}(t)$ is zero if all the cells in the tumour are those that are reproducing. A reaction-diffusion equation (RDE) and an integral-differential equation make up the model. The integral-differential equation directs the progression of R, whereas the RDE defines the concentration of the nutrients $\big(\sigma(t)\big)$. When $r = r_{nec}(t)$, define nec as a particular value for the distribution of the nutrient (t). Cell proliferation begins when a region has sufficient nutrients. Necrosis loss happens in nutrient-depleted areas when $\sigma \leq \sigma_{nec}$. The model's derivation is fully described in [BC95c]. Instead of going into further detail, we'll focus on the analysis. The governing equations are presented in a more concise manner by writing them in dimensionless form, spherical polar coordinates, and radial symmetry. The equations listed below control the evolution of $\sigma(t)$ and $R(t)$:

$$\frac{\partial \sigma}{\partial t} = \frac{1}{r^2}\frac{\partial}{\partial r}\left(r^2 \frac{\partial \sigma}{\partial r}\right) - \Gamma H(r - r_{nec}) \quad (1)$$

$$R^2 \frac{dR}{dt} = \int_0^R (S(\sigma)H(r - r_{nec}) - N(\sigma)H(r_{nec} - r))r^2\, dr \quad (2)$$

This study set $\frac{\partial r}{\partial t} = 0$ in RDE (1) to have a quasi-steady approach. The nutrition intake term decreases to zero to describe the necrotic core, which only consists of dead cells. We'll use the Heaviside function H. $H(x) = 1$ for $x > 0$ and $H(x) = 0$ for $x < 0$. Scaling constants include. The second term in (1) illustrates how nutrients are absorbed by developing cells at a constant rate Γ.

$S(\sigma) = s(\sigma - \sigma\hat{}) N(\sigma) = 3s\lambda$ when $0 \leq r \leq$ $r$nec

$S(\sigma)$ denotes necrosis cell growth, while $N(\sigma)$ denotes necrosis cell death in integral-differential equation (2). While necrosis cell loss takes place in the nutrient-deficient area where $\sigma < \sigma_{nec}$, necrosis cell proliferation is only present in the area where $r_{nec} < r < R$. This study will focus on the case in which and the proliferation rate are linearly connected. Both s and $\sigma\hat{}$ are scaling constants, where s indicates the rate of proliferating cells and s represents the rate of apoptotic cell death. Assume that necrosis causes the necrotic core to continually lose volume A constant is. As a result, the study makes the following adjustments by substituting above equations into (2) [MFS86] The equation can be denoted according to corresponding boundary conditions as:

$$R^2 \frac{dR}{dt} = -\mathrm{s}\lambda r^3{}_{nec} + s\int_{r_{nec}}^{R} (\sigma - \hat{\sigma})r^2 dr \quad (3)$$

that is relevant to

$$\frac{\partial \sigma}{\partial r} = 0, \text{ on } r = o \quad (4)$$

$$\sigma = \sigma_\infty, \text{ on r = R(t)} \quad (5)$$

$$\sigma(r_{nec}, t) = \sigma_{nec} \quad (6)$$

$$R(r, 0) = R_0 \quad (7)$$

$\sigma, \frac{\partial \sigma}{\partial r}$ continuous at r_{nec}. (8)

Initial and boundary conditions are necessary for the system to be closed. (4) demonstrates the tumor's assumed symmetry. Outside of the tumour, the nutritional concentration is constant, suggesting the constant, as seen in (5). While (7) specifies an initial-boundary radius, (6) automatically provides the definition for at r_{nec} . The premise stated above is summarised here. This analysis

also assumes that, as shown in, is continuous across the boundary (8). The parameters that showed up in this model and its unique constants, respectively, are listed in the two tables below.

Table 1. Summary of variables

	Parameters
$R(t)$	radius of the outer shell
$r_{nec}(t)$	radius of necrotic cell
$r(t)$	radius of the cell
$\sigma(t)$	concentration of the nutrients
$S(\sigma)$	cell proliferation
$N\ (\sigma)$	cell loss due to necrosis

Table 2. Table of constants

	Constants
σ_∞	external nutrients concentration rate (cell proliferating rate)
$\sigma\hat{}$	cell loss rate due to apoptotic
σ_{nec}	cell loss rate due to necrosis (con- centration at cell loss rate due to necrosis (con- centration at rnec)
Γ	proliferating cells nutrient consumption rate
λ	scaling the necrosis volume loss within necrotic core
R_0	initial radius at $t\ =\ 0$

Simplified model

It can be concluded from (1) based on $\frac{\partial \sigma}{\partial r} = \mathbf{0}$ that,

$$0 = \begin{cases} \frac{\partial^2\sigma}{\partial r^2} + \frac{2}{r} * \frac{\partial \sigma}{\partial r}, & when\ 0 < r < r_{nec} \\ \frac{\partial^2\sigma}{\partial r^2} + \frac{2}{r} * \frac{\partial \sigma}{\partial r} - \Gamma, & when\ r_{nec} \le r \le R \end{cases} \quad (9)$$

The second-order ODE (9) can be derived with boundary conditions and initial conditions (4)-(8) to obtain:

$$\sigma(r,t) = \begin{cases} \sigma_{nec}, & for\ \ 0 < r < r_{nec} \\ \sigma_{nec} + \frac{\Gamma r^2}{6}\left(1 + \frac{2r_{nec}^3}{r^3} - \frac{3r_{nec}^2}{r^2}\right), & for\ \ r_{nec} \le r \le R \end{cases} \quad (10)$$

When $r\ =\ R(t)$, we get $\sigma(r,t) = \sigma_\infty$ and the rate of apoptotic cell death is represented as $\sigma\hat{}$. The connection between R(t) and rnec(t) may thus be (10).

$$\sigma_\infty - \hat{\sigma} = \frac{\Gamma R^2}{6}\left(1 + \frac{2r_{nec}^3}{R^3} - \frac{3r_{nec}^2}{R^2}\right) \quad (11)$$

Substitute (11) into (4) :

$$\frac{R^2}{s}\frac{dR}{dt} = \frac{(\sigma_{nec} - \hat{\sigma})}{3}(R^3 - r_{nec}^3) - \lambda r^3{}_{nec} + \frac{\Gamma}{6}\left(\frac{1}{5}\left[R^5 - r_{nec}^5\right] - R^2 r_{nec}^2 (R - r_{nec})\right] \quad (12)$$

Growth of tumour: R* = R

Equation using an algebraic simplification to predict the tumour development velocity when R = R (18) based on [BC95b]

$$\frac{dR}{dt} = \frac{s}{15R^*}(3\sigma_\infty - 5\hat{\sigma} + 2\sigma_{nec}) \equiv \mathbb{Q} \quad (13)$$

If Q is greater than zero, the tumor's radius is changing at a positive rate. The tumor's core endures as it continues to enlarge. If Q is greater than 0, the tumour begins to contract and the core vanishes.

3.1.1Proliferation Rate: S(σ)

When the linear proliferation rate is replaced by a logistic term, it becomes clear how the choice of $S(\sigma)$ impacts the tumor's growth characteristics. A new version of the $S(\sigma)$ expression can be introduced [BC95a].

$$S(\sigma) = s\sigma\left(1 - \frac{\sigma}{\tilde{\sigma}}\right) = s\sigma - \frac{s\sigma\hat{}2}{\tilde{\sigma}} \quad (14)$$

3.1.2Asymptotic Decay Rate ($\tilde{\sigma}$)

According to mathematical findings from [BC95a], when time approaches infinity, the tumour radius either stabilises at a certain value or shrinks to zero. $\tilde{\sigma}$, $\sigma_\propto$ and σ_{nec} determine which condition the tumour will be in (concentration of cell loss caused by apoptosis, cell proliferation and cell loss caused by necrosis accordingly). The strength of a tumor's apoptotic degradation rate determines how quickly it will grow. The tumour will eventually shrink and vanish if the rate is high. The tumour will swell and eventually die if the rate is low. The final result of the tumor's growth depends on its initial size R for intermediate rates $R(0)$. The tumour will eventually shrink and vanish if its starting size, $R(0)$, is negligible enough. However, if the tumor's original size is greater, it will eventually turn necrotic (dead tissue). To effectively forecast the growth features of a tumour, it is critical to comprehend the proliferation rate. In [BC98], this is depicted. Understanding the proliferation rate precisely is crucial because of the differences in the steady-state shape of the tumour that are dependent on the choice of the apoptotic decay rate. [BC95a]

3.2 Numerical Simulations

In mathematical modelling, numerical analysis is a crucial tool since it enables us to approximatively solve challenging issues. The model equations can be numerically simulated to predict that the cancer will eventually behave as shown below as time approaches infinity. Below, representative illustrations of various behaviors will be covered.

3.2.1Cases regarding the existence of necrotic core

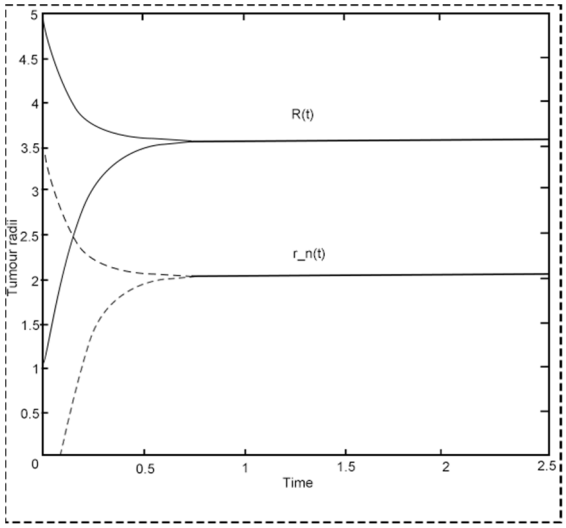

Figure 1. Necrotic core exists [BC98].

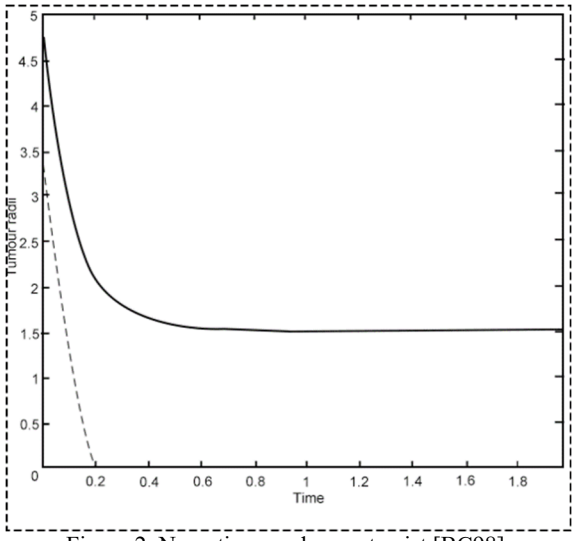

Figure 2. Necrotic core does not exist [BC98].

The final figure contains an inner portion of the necrotic area when a necrotic core is present. Figure 1 from [BC98] depicts the development of the tumor's outer radius R and the necrotic r_{nec}'s radius as t increases from 0 to 2.5 seconds. Starting values of $R(t)$ converge to 2.42 with the particular set of parameter analytic values, but initial values of rnec(t) converge to 0.63. This implies that both tumour size and necrotic core size have upper bounds. These numbers are used:

σ_∞= 0.8, σ_{nec} = 0.4, $\sigma\hat{}$ = 0.5, Γ = 25, s = 100.

In the absence of a necrotic core, r_{nec} equals 0. $\sigma\hat{}$ becomes a little bit larger in comparison to the first case. When the cell loss rate through apoptosis, $\sigma\hat{}$ is then 0.7, Figure 2 shows the progression of $R(t)$ and $r_{nec}(t)$. Other parameter values are $s = 100$, σ_{nec} = 0.4, $\sigma\hat{}$ = 0.7, λ = 0.1, σ_∞= 0.8, and Γ = 25. R's starting values converge to 1.51 when r_{nec} is set to 0.

3.2.2Disappearance of tumours

The value of increases more than in the previous two phases in the event of tumour disappearance. Apoptosis-related cell death is set to occur at a rate of 0.9. The tumour shrinks until it has a radius of zero before going away. Figure 3 depicts the motion of R(t) and rnec(t) for various cell death rate owing to apoptosis values. With = 0.9 and the following parameter values: σ_∞= 0.8, σ_{nec}= 0.4, $\sigma\hat{}$ = 0.7, λ = 0.1, and s = 100. A simple solution is reached since the initial values for R and r_{nec} converge to 0.

3.2.3Steady state

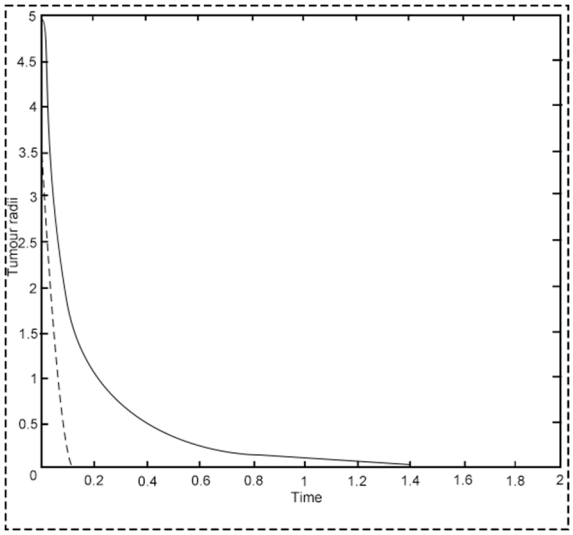

Figure 3. Tumour free [BC98].

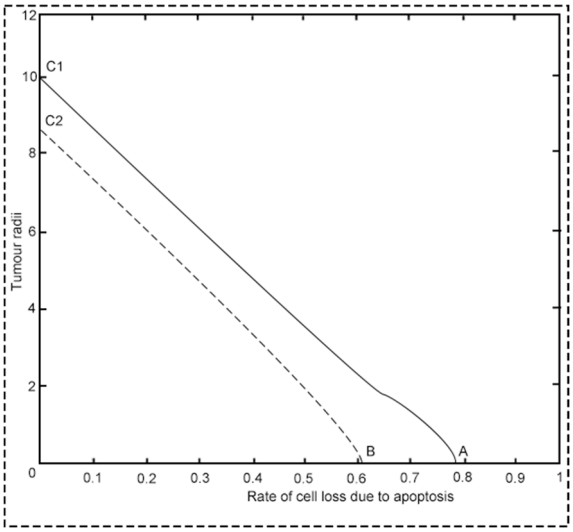

Figure 4. Tumour free [BC98].

The steady state motion is described by the ODE when $\frac{dR}{dT}$= 0. Figure 4 illustrates the relationship between the steady-state tumour size R(t) and necrotic core size r_{nec} (t) and the rate of cell death brought on by apoptosis. A finite analytical range of variables restricts the existence of a necrotic tumour given parameter values, σ_∞= 0.8, σ_{nec}= 0.4, λ = 0.1, Γ = 25, and s = 100. The non-trivial solution is only present when the rate of cell death by apoptosis is

less than 0.8, as may noticed (at point A). That corresponds to the value of σ_∞.

4. Conclusion

The formation of an avascular tumour made up of proliferating and necrotic cells is illustrated mathematically in this work. The concept assumes that the existence of an external nutrition source allows these cells to multiply. Both necrosis and apoptosis are described as distinct cell-death mechanisms that function to stop the development and growth of the tumour. "Cell loss due to necrosis" describes the nutrient-starved cell death that takes place in the tumor's core. Apoptosis, in contrast, is a natural cell death process that can take place when a cell reaches the end of its lifecycle. It is important to note that compared to necrosis, apoptosis is less typically included in models of the evolution of avascular tumours. The paper's primary objectives were to create experimental hypotheses and to demonstrate how, as a tumour grows, the relative relevance of the two cell loss pathways shifts utilising asymptotic techniques. Numerical analysis has been left out due to space restrictions. If numerical results support the concept in this work, more research can be done to determine this.

Asymptotic techniques were used to study the model at three distinct stages of the cancer evolution because numerical simulations usually make it difficult to understand how the different physical processes interact. A simplified model is created at each level under specific presumptions. There has been discussion and research on the relative effects of cell proliferation, cell death from necrosis, and cell death from apoptosis. These findings could lead to a range of model predictions, some of which have already been supported by earlier research and experimental evidence. The main summaries of this project are as follows.

Small tumour analysis (r_{nec}= 0)

The trivial solution is stable and free of tumours if $\sigma\hat{} > \sigma\infty$,. If not, the equation finds a non-trivial steady-state solution.

Beginning of the necrosis

The radius of the tumour is defined as $R* = \left(\frac{6(\sigma_\infty - \sigma_{nec})}{\Gamma}\right)^{\frac{1}{2}}$

While the necrotic volume rapidly expands, the overall tumour volume remains essentially constant.

If $5\sigma\hat{} \leq 3\sigma_\infty = +2\sigma_{nec}$, then$\frac{dR.}{dT}$is greater than zero. When the tumour reaches equilibrium, a necrotic core will form.

Proliferating Rim

If $\sigma_\infty$and σ_{nec}, are very close (σ_∞- $\sigma_{nec} \ll 1$), then the width of the proliferating rim at equilibrium is expressed as $\frac{2(\sigma_\infty - \sigma_{nec})^{\frac{1}{2}}}{\Gamma}$

The asymptotic methods employed in this study have the benefit of being transferrable to other models with more accurate, nonlinear expressions for parameters like cell growth, cell death due to apoptosis, and nutrient consumption. There are numerous ways to expand the mathematical model. Consider looking at more intricate expressions for S(σ) and N(σ). In addition to nonlinearities, these phrases may also contain time delays. These delays are an accurate reflection of how long cell division takes.

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