A Continuous Model for Avascular Tumour Growth

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February 18, 2017

1 Introduction

Cancer continues to be one of the major causes of premature death in most countries of the northern hemisphere [AM04]. Understanding the growth of a tumour is essential to the development of new drugs that aim at inhibiting some of the underlying growth processes. A tumour can be defined as tissue that shows abnormal growth and forms 'a mass' [Coo92]. The tumour will usually start out as a small number of cells without their own blood supply [Byr12]. It will then grow until the nutrient concentrations in the center fall below certain levels, so that the inner cells either die (i.e. *necrosis*) or stop proliferating (i.e. they become *quiescent*). In this way, a steady state is attained. The tumour remains in this 'dormant state' until it is either destroyed by the immune system or it develops its own blood supply that allows nutrients to be transported into the tumour [Byr12]. The latter process is called *angiogenesis* and results in vascular tumours which are much more complex in their structure and behaviour [NHTM06]. This report will focus on the early stage of tumour development and describe avascular tumour growth.

Classification of the Problem at Hand Within the scope of this report, a tumour will be defined as a set of cells that can either proliferate, be quiescent or die. The cells will form a spherically symmetric shape. What kind of behaviour the cells exert will depend on the local concentration of a nutrient which might represent oxygen or another important nutrient [RCM07].

Mathematical Classification The tumour cells will be modelled by a continuous model, rather than an agent-based model. The growth of the tumour depends on the availability of the nutrient with concentration $\sigma(r, t)$, where r denotes distance from the origin and t denotes time. In reality, the cells will require various nutrients to survive, see Section 2.4 [Byr12]. The nutrient concentration will then be described by a reaction diffusion equation which is a certain type of partial differential equation (PDE). The model will be closed by specifying appropriate initial conditions and boundary conditions. In the given case, it turns out that the boundary is not fixed but moves with time as the tumour grows. Finding the boundary will therefore be part of the problem. Such problems are called 'moving boundary problems'.

Previous Research Much research has been conducted to describe the growth of avascular tumour growth using continuous mathematical models [Byr12], [AM04].

Moving Boundary Approach One of the earlier papers is by Greenspan and describes the growth in the above fashion, using a moving boundary approach [Gre72]. In this paper, the growth of the tumour is regulated through the availability of a nutrient with concentration σ as well as a chemical inhibitor with concentration β. The *nutrient equation* takes the form

$$\underbrace{\frac{\partial \sigma}{\partial t}}_{\text{Change in nutr. conc.}} = \underbrace{\nabla^2 \sigma}_{\text{Diffusion}} - \underbrace{\Gamma}_{\text{Consumption}} . \tag{1}$$

An analogous equation applies to β. The equation describing the evolution of the boundary (*boundary equation*) takes the form:

$$\underbrace{\frac{d}{dt}\left(\frac{4\pi R^3}{3}\right)}_{\text{Change in tumour vol.}} = \underbrace{\int_V S(\sigma, \beta)\, dV}_{\text{Cell proliferation}} - \underbrace{\int_V N(\sigma, \beta)\, dV}_{\text{Cell death}} . \tag{2}$$

In this equation, R denotes the outer tumour radius, S denotes the cell proliferation rate and N describes the rate at which cell death occurs, either due to natural cell death (*apoptosis*) or due to nutrient starvation (*necrosis*) [Gre72].

The chemical inhibitor β is assumed to either be a product of necrotic cells or of live cells [Gre72]. Both cases are investigated and modelled. The model suggests that there will be two or three different stages of tumour development. Initially, there will be exponential growth until either the concentration of the nutrient falls below a certain threshold or the concentration of the inhibitor increases above a certain threshold. In the next stage, there will be an outer rim or proliferating cell and an inner core of either necrotic or quiescent cells. Depending on the choice of model parameters such as the various thresholds, a steady state will either be achieved in this stage, or it will be achieved in stage three where there will be three distinct regions in the tumour: proliferating cells at the edge, followed by quiescent cells and necrotic cells in the center [Gre72]. The tumour will achieve a different steady state depending on how one assumes the production of the inhibitor. In this report, no such chemical inhibitor will further be explored.

Fisher's Equation for Brain Tumours An alternative approach was developed by Swanson, Bridge, Murray, Ellsworth and Alvord [SBMAJ03]. They describe brain tumours using a reaction diffusion equation similar to Fisher's equation but with exponential growth instead of logistic growth incorporated. To do so, they introduce

a 'tumour cell density c' and formulate the equation

$$\frac{\partial c}{\partial t} = \nabla \cdot (D \nabla c) + \rho c \,, \tag{3}$$

where D is the diffusivity and ρ is the net proliferation rate of the cells [SBMAJ03]. The major difference to the above approach is that they fix the boundary to represent the skull rather than using a moving boundary (see Section 1). They divide the brain into grey and white matter and use different diffusion coefficients D to describe them. Their model enables them to explain the classification of brain tumours into four different grades as developed by the WHO by considering the values of D and ρ [KBS93]. Also, they are able to incorporate the effects of chemotherapy and surgical resection on the shape and growth on the tumour. The focus of the paper is to compute a model prediction for survival time under various scenarios (surgery, chemotherapy, no therapy, etc.) and to compare this prediction to real patient outcomes [SBMAJ03]. In the following report, this approach will not be explored any further.

Outline of this Report This report will start out by describing and analysing a continuous, one dimensional, moving boundary approach to describe and model avascular tumour growth that only depends on the local concentration of one nutrient, following the work of Greenspan, Byrne and others [Gre72], [Byr12]. The analysis of the model will be split up into the three different stages of avascular tumour growth. This model will then be extended to include more realistic functional forms of the kinetic terms. Some properties of the model will be explored analytically. Furthermore, the resulting equations will be plotted and analysed numerically.

2 The Basic Model

In this section, a basic model for avascular tumour growth will be derived and analysed. The model will describe a moving boundary problem in one dimension that assumes spherical symmetry and only considers one single nutrient concentration given by $\sigma(r, t)$. No effects of a chemical inhibitor or medical treatment will be incorporated. Cells will be allowed three different behaviours: proliferation, quiescence or death, depending on the local nutrient concentration.

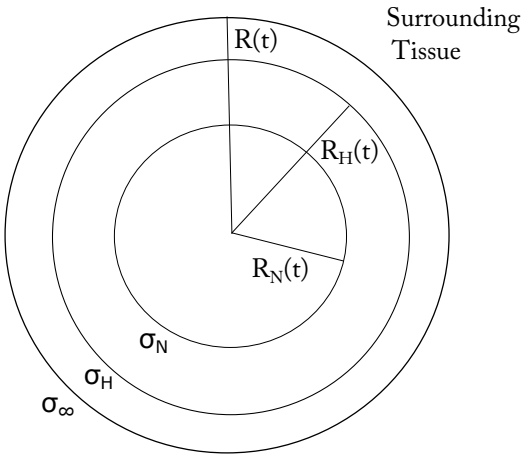

Figure 1: Sketch of the tumour in the last stage.

2.1 Definitions

We assume that outside the tumour of outer radius $R(t)$, the nutrient is available at a constant rate, $\sigma = \sigma_\infty$. The nutrient will then diffuse into the tumour where it is consumed by live cells. If σ falls below the threshold value σ_H, the cells stay alive but stop proliferating, they become quiescent. The transition between proliferating and quiescent cells is marked by the radius $R_H(t)$. If the nutrient concentration further decreases to fall below a second threshold, $\sigma = \sigma_N$, then the cells die of nutrient shortage. The transition between the quiescent region and the necrotic region is given by the radius $R_N(t)$ [Byr12]. In Figure 1, the different radii and nutrient concentrations are shown.

2.2 Model Derivation

Assuming that cells consume the nutrient at a constant rate Γ as long as they are alive, one can write the equation for the nutrient consumption $\Gamma(\sigma)$ as follows [Byr12]

$$\Gamma(\sigma) = H(\sigma - \sigma_N)\,\Gamma\,. \tag{4}$$

Here, H denotes the *Heaviside function*.

The Nutrient Equation Given this definition, one can write down the nutrient consumption as a reaction-diffusion equation [Byr12]:

$$\frac{\partial \sigma(r,t)}{\partial t} = D\,\nabla^2 \sigma(r,t) - \Gamma(\sigma)\,, \quad r \in [0, R(t)]\,, \tag{5}$$

where D denotes the diffusion coefficient which will be assumed to be constant throughout the tumour. Equation (5) states that σ diffuses through the tumour and is consumed at a rate Γ. Since the problem is assumed to be spherically symmetric, polar coordinates will be used and Equation (5) becomes

$$\frac{\partial \sigma(r,t)}{\partial t} = \frac{D}{r^2}\frac{\partial}{\partial r}\left(r^2 \frac{\partial \sigma(r,t)}{\partial r}\right) - \Gamma(\sigma)\,, \quad r \in [0, R(t)]\,, \tag{6}$$

where the Laplace-Operator in polar coordinates was written employed, keeping in mind that the angular derivatives are zero, which makes the problem one-dimensional in space.

The Boundary Equation In order to derive an equation for the outer boundary $R(t)$, the principle of mass balance will be used [Gre72]:

[Rate at which volume changes] = [Proliferation throughout the tumour]
−[Cell death throughout the tumour].

This can be translated into mathematics as follows [Byr12]:

$$\frac{d}{dt}\left(\frac{4\pi R(t)^3}{3}\right) = \int_{V(R)} P(\sigma) dV - \int_{V(R)} N(\sigma) dV\,, \tag{7}$$

where P denotes the proliferation rate and can be written as follows [Byr12]:

$$P(\sigma) = p\sigma\, H(\sigma - \sigma_H)\,. \tag{8}$$

Here, it is assumed that proliferation depends linearly on the nutrient concentration. The constant of proportionality is denoted by p. More general forms of the proliferation rate will be explored in Section 3.

For cell death, two causes will be considered: natural cell death at a rate λ_A as well as death due to necrosis at a rate λ_N. With this choice, one can write

$$N(\sigma) = \lambda_A + \lambda_N\, H(\sigma_N - \sigma)\,. \tag{9}$$

It follows [Gre72]:

$$\frac{d}{dt}\left(\frac{4\pi R(t)^3}{3}\right) = 4\pi \int_{R_H(t)}^{R(t)} p\sigma r^2 dr - \frac{4}{3}\pi R(t)^3 \lambda_A - \frac{4}{3}\pi R_N(t)^3 \lambda_N\,. \tag{10}$$

This can be rearranged to give:

$$3\, R^2 \frac{dR}{dt} = 3 \int_{R_H(t)}^{R(t)} p\sigma r^2 dr - R^3 \lambda_A - R_N^3 \lambda_N\,. \tag{11}$$

Once $\sigma(r,t)$ is known, a solution for $R(t)$ can in principle be found. Depending on the form of $\sigma(r,t)$, this might require numerical methods.

Boundary Conditions In order to close the model, boundary (BCs) and initial conditions (ICs) need to be specified. In principle, one initial condition and two boundary conditions are required for the nutrient Equation (5). However, it will become apparent later (see Section 2.2) that in fact, no initial condition is needed for the nutrient concentration because a diffusive equilibrium will be assumed [Byr12]. Mathematically, that corresponds to setting the time derivatives equal to zero. This will be justified later. However, one initial condition for $R(t)$ is needed. The following conditions will be used:

$$\text{Symmetry} \qquad \frac{\partial \sigma}{\partial r} = 0 \qquad \text{at } r = 0\,, \tag{12}$$

$$\text{BC for } \sigma \qquad \sigma(r,t) = \sigma_\infty \qquad \text{at } r = R(t)\,, \tag{13}$$

$$\text{IC for R} \qquad R(t) = R_0 \qquad \text{at } t = 0\,. \tag{14}$$

Additionally, it will be required that σ and $\frac{\partial \sigma}{\partial r}$ are continuous across R_H and R_N [Gre72].

Nondimensionalisation In order to analyse the model and to compute results, it is convenient to nondimensionalise. This will be done using the following definitions:

$$r = \hat{r}\, R_0\,, \quad t = \hat{t}\, T\,, \quad \sigma = \hat{\sigma}\, \sigma_\infty\,, \quad R = \hat{R}\, R_0\,, \quad R_H = \hat{R}_H\, R_0\,, \quad R_N = \hat{R}_N\, R_0. \tag{15}$$

For the length scale, the initial radius R_0 was chosen while for the nutrient scale, the outer nutrient concentration σ_∞ was employed. For the time scale, there are two possible choices: either the diffusive time scale, $T_D = \frac{R_0^2}{D}$ or the cell proliferation time scale, $T_P = \frac{1}{p\sigma_\infty}$. The diffusion time scale will be of the order of minutes, while the proliferation time scale will be of the order of days [Gre72]. Since this model aims at investigating the growth of the tumour, the proliferation time scale T_P will be chosen. This yields for the nutrient equation

$$\frac{\sigma_\infty}{T_P}\frac{\partial \hat{\sigma}}{\partial \hat{t}} = D\,\frac{\sigma_\infty}{R_0^2}\nabla^2\hat{\sigma} - \Gamma H(\hat{\sigma}\sigma_\infty - \hat{\sigma}_N\sigma_\infty)\,, \tag{16}$$

or equivalently

$$\frac{R_0^2}{D}\frac{1}{T_P}\frac{\partial \hat{\sigma}}{\partial \hat{t}} = \nabla^2\hat{\sigma} - \frac{\Gamma R_0^2}{D\sigma_\infty}H(\hat{\sigma} - \hat{\sigma}_N)\,. \tag{17}$$

The factor on the left is equivalent to $\frac{T_D}{T_P}$, which is very small because the diffusion time scale is much shorter than the proliferation time scale [Gre72]. Using the definition

$\hat{\Gamma} = \frac{\Gamma}{\Gamma_0}$, where $\Gamma_0 = \frac{D\sigma_\infty}{R_0^2}$, and assuming diffusive equilibrium ($T_D/T_p \approx 0$), this transforms into

$$0 = \nabla^2 \hat{\sigma} - \hat{\Gamma} H(\hat{\sigma} - \hat{\sigma}_N)\,. \tag{18}$$

One can check that the definition for $\hat{\Gamma}$ makes sense by considering units. The unit of Γ is $\frac{[\sigma]}{\mathrm{s}}$, therefore one needs to make sure Γ_0 has the same units:

$$[\Gamma_0] = \frac{[D\sigma_\infty]}{[R_0^2]} = \frac{\mathrm{m}^2}{\mathrm{s}\,\mathrm{m}^2} \cdot [\sigma] = \frac{[\sigma]}{\mathrm{s}}\,, \tag{19}$$

which proves that the definition for $\hat{\Gamma}$ is correct as far as units go. For the boundary equation, one finds

$$3\,\frac{R_0^3}{T_P}\,\hat{R}^2 \frac{d\hat{R}}{d\hat{t}} = 3\int_{\hat{R_H}}^{\hat{R}} p\sigma_\infty \hat{\sigma}\hat{r}^2 R_0^3 d\hat{r} - R_0^3 \hat{R}^3 \lambda_A - R_0^3 \hat{R}_N^2 \lambda_N\,, \tag{20}$$

or equivalently

$$3\,\hat{R}^2 \frac{d\hat{R}}{d\hat{t}} = 3\,p\,\sigma_\infty T_P \int_{\hat{R}_H}^{\hat{R}} \hat{\sigma}\hat{r}^2 d\hat{r} - T_P \lambda_A \hat{R}^3 - T_P \lambda_N \hat{R}_N^3\,. \tag{21}$$

Using the definition of $T_P = \frac{1}{\sigma_\infty p}$ and defining $\hat{\lambda}_A = T_P\,\lambda_A$, $\hat{\lambda}_N = T_p\,\lambda_N$, the equation for the boundary becomes:

$$3\,\hat{R}^2 \frac{d\hat{R}}{d\hat{t}} = 3\int_{\hat{R}_H}^{\hat{R}} \hat{\sigma}\hat{r}^2 d\hat{r} - \hat{\lambda}_A \hat{R}^3 - \hat{\lambda}_N \hat{R}_N^3\,. \tag{22}$$

Implicit Definition of the Internal Boundaries So far, the internal boundaries $\hat{R_H}$ and $\hat{R_N}$ have not yet been defined. Define:

$$\hat{R}_H = 0 \text{ if } \hat{\sigma}(0,\hat{t}) > \hat{\sigma}_H \text{ , otherwise } \hat{\sigma}\left(\hat{R}_H, \hat{t}\right) = \hat{\sigma}_H \tag{23}$$

$$\hat{R}_N = 0 \text{ if } \hat{\sigma}(0,\hat{t}) > \hat{\sigma}_N \text{ , otherwise } \hat{\sigma}\left(\hat{R}_N, \hat{t}\right) = \hat{\sigma}_N\,. \tag{24}$$

Those definitions ensure that the radii only take values greater than zero if the process they describe (cell death, quiescence) occurs in the tumour [Gre72].

The Nondimensional Model Having nondimendionalised the nutrient equation and the boundary equation, one still has to nondimensionalise the boundary and initial conditions. Once this is done, the model can be written in the following form,

omitting the hats:

$$\text{Nutrient Equation:} \qquad 0 = \nabla^2\sigma - \Gamma H(\sigma - \sigma_N)\,, \tag{25}$$

$$\text{Boundary Equation:} \qquad 3\,R^2\frac{dR}{dt} = 3\int_{R_H}^{R} \sigma r^2 dr - \lambda_A R^3 - \lambda_N R_N^3\,, \tag{26}$$

$$\text{Boundary Conditions:} \qquad \frac{\partial\sigma}{\partial r}\Big|_{r=0} = 0\,, \tag{27}$$

$$\sigma(R(t),t) = 1\,, \tag{28}$$

$$\text{Initial Condtion:} \qquad R(0) = 1\,. \tag{29}$$

Those equations, together with the requirement of continuity at the internal boundaries in σ and $\frac{\partial\sigma}{\partial r}$ and the implicit definitions given by Equation (23) & Equation (24), specify the nondimensional model.

2.3 Model Results

In this section, the model will be explored and results for the tumour growth with respect to time will be presented. The section will be subdivided into the three different stages of tumour growth. The results will be discussed towards the end of the section (see Section 2.4).

The Three Stages of Avascular Tumour Growth The tumour will start out as a small number of cells that are going to proliferate until the nutrient concentration at the origin falls below σ_H. This will mark the transition from stage one to two. There will then be an outer rim of proliferating cells and an inner kernel of quiescent cells. This stage will end when the nutrient concentration at the centre falls below σ_N, at which point the cells in the center are going to die from necrosis [Gre72] at a rate λ_N. This marks the transition from stage two to stage three. Stage three will result in a steady state. It is not at all clear that all three stages will be encountered, for a given set of initial parameters, the steady state might well form earlier, as will be shown in the following [Byr12].

Stage One: Exponential Growth Initially, $R_H = R_N = 0$. The nutrient equation reads

$$\frac{1}{r^2}\frac{\partial}{\partial r}\left(r^2\frac{\partial\sigma}{\partial r}\right) = \Gamma\,. \tag{30}$$

This has a solution

$$\sigma(r,t) = \frac{r^2}{6}\Gamma - \frac{C_1}{r} + C_2\,, \tag{31}$$

where C_1 and C_2 are constants that have to be determined from the boundary conditions. The requirement that $\frac{\partial \sigma}{\partial r}$ shall vanish at the origin means that $C_1 = 0$. For C_2, one can use Equation (28) to find:

$$\sigma(r,t) = 1 - \frac{\Gamma}{6}\left(R^2(t) - r^2\right) , \tag{32}$$

where the t dependence is through $R(t)$. The boundary Equation (26) becomes:

$$3\,R^2\frac{dR}{dt} = 3\int_0^R r^2\left(1 - \frac{\Gamma}{6}\left(R^2 - r^2\right)\right)dr - \lambda_A R^3\,. \tag{33}$$

This gives

$$\frac{dR}{dt} = \frac{R}{3}\left(1 - \lambda_A - \frac{\Gamma}{15}R^2\right) . \tag{34}$$

This can be rearranged to give t as a first integral of R. Stage one will last until either a steady state is attained or the nutrient concentration at the centre falls below σ_H. Both possibilities will be explored.

Steady State In order for the tumour to attain a steady state in stage one, it is required that $\frac{dR}{dt} = 0$. This has two solutions: either $R = 0$ (no tumour) or R positive, with solution

$$R = \sqrt{\frac{15}{\Gamma}\left(1 - \lambda_A\right)}\,, \tag{35}$$

which exists for $\lambda_A < 1$. Denoting the right-hand-side of Equation (34) by $f(R)$, one can calculate

$$3\,\frac{df(R)}{dR} = \left(1 - \lambda_A - \frac{\Gamma}{15}R^2\right) + R\left(-2R\frac{\Gamma}{15}\right) . \tag{36}$$

For a stable steady state, one needs $\frac{df}{dR} = f' < 0$. For the trivial solution $R = 0$, one finds $f' = (1 - \lambda_A)/\,3$. If a non-trivial steady state exists, i.e. if $\lambda_A < 1$, the trivial steady state is unstable, otherwise if $\lambda_A > 1$, it is stable. For the non-trivial steady state, one finds $f' = -2/3\,(1 - \lambda_A)$. For this steady state to exist, one needs $\lambda_A < 1$, so this steady state is stable [Byr12]. However, this steady state can only be attained if the model does not break down before it is reached. Therefore, it is important to consider when σ falls below σ_H.

Model Breakdown - Transition to the Second Stage The tumour evolves from stage one to stage two when σ falls below σ_H. The aim here is to establish the

condition that must hold such that the model can attain the above steady state, i.e. finding the condition such that at the time the non-trivial steady state is reached, $\sigma > \sigma_H$ at the centre. We see that

$$\sigma(0,t) > \sigma_H\,, \tag{37}$$

which holds whenever

$$1 - \frac{\Gamma}{6}R^2 > \sigma_H\,. \tag{38}$$

For R, one can now substitute in the value at which the non-trivial steady-state is attained so that we require

$$1 - \frac{\Gamma}{6}\frac{15}{\Gamma}\left(1-\lambda_A\right) > \sigma_H\,, \tag{39}$$

or equivalently

$$3 < 5\lambda_A - 2\sigma_H\,. \tag{40}$$

If this condition holds, i.e. if $5\lambda_A > 2\sigma_H + 3$, then a stable, non-trivial steady state is attained already in the first stage (see Figure 3 in the appendix for an example). Physically, this means that the cells proliferate at a rate that is slow enough for it to be counteracted by natural cell death. If Equation (39) does not hold, then the tumour will move to stage two. The value of the outer radius R at which the transition will occur can be computed easily by solving Equation (37) (with equality) for R, which yields $R = \sqrt{\frac{6}{\Gamma}\left(1-\sigma_H\right)}$.

Stage Two: Central Region of Quiescence In the second stage of avascular tumour growth, the tumour consists of an outer rim of proliferating cells and an inner core of quiescent cells. There is no necrotic core, so $R_N = 0$. The nutrient equation therefore stays unchanged:

$$\frac{1}{r^2}\frac{\partial}{\partial r}\left(r^2\frac{\partial\sigma}{\partial r}\right) = \Gamma\,, \tag{41}$$

so using the same arguments as in Section 2.3, one finds:

$$\sigma(r,t) = 1 - \frac{\Gamma}{6}\left(R^2(t) - r^2\right). \tag{42}$$

The boundary equation stays almost unchanged, only the limits of integration have to be adjusted to account for the fact the R_H is no longer zero, giving

$$\begin{aligned} R^2\frac{dR}{dt} &= \int_{R_H}^{R} r^2\left(1 - \frac{\Gamma}{6}\left(R^2 - r^2\right)\right)dr - \frac{\lambda_A R^3}{3} \\ &= \frac{R^3 - R_H^3}{3} - \frac{\Gamma}{6}\left(R^2\frac{R^3 - R_H^3}{3} - \frac{R^5 - R_H^5}{5}\right) - \frac{\lambda_A R^3}{3}\,. \end{aligned}$$

This can be rearranged to give

$$\frac{dR}{dt} = \frac{R}{3}(1-\lambda_A) - \frac{R_H^3}{3\,R^2} - \frac{\Gamma}{6}\left(\frac{2R^5 - 5R^2R_H^3 + 3R_H^5}{15R^2}\right) . \tag{43}$$

The inner radius R_H is now defined as follows (using Equation (23)):

$$\sigma_H = 1 - \frac{\Gamma}{6}\left(R^2 - R_H^2\right) , \tag{44}$$

or equivalently

$$R_H^2 = R^2 + \frac{6}{\Gamma}(\sigma_H - 1) . \tag{45}$$

In principle, the expression for R_H can now be substituted into Equation (43) and a numerical solution for $R(t)$ can be calculated. The interesting question is again whether a steady state can be achieved in this stage (which would terminate tumour growth before reaching stage three). For an equilibrium to exist, one needs $\sigma(r,t) > \sigma_N$ for all r. Since the lowest point is always found at the origin, it is sufficient to require:

$$\sigma(0,t) > \sigma_N . \tag{46}$$

If this conditions holds, then a steady state could exist in this stage. Numerical results will show whether this steady state exists in practice. For an example of a situation where the steady state is attained in this stage, see Figure 4 in the appendix. In case Equation (46) does not hold, the tumour will evolve to stage three when a narcotic core starts forming. The outer radius at which this happens can be found by considering

$$\sigma(0,t) = \sigma_N , \tag{47}$$

which means

$$1 - \frac{\Gamma}{6}R^2 = \sigma_N \tag{48}$$

and therefore

$$R = \sqrt{\frac{6}{\Gamma}\,(1-\sigma_N)} \tag{49}$$

A steady state in stage two is physically realistic if the value for the outer radius at which it is attained is less that this value of R. In general, in stage two, the values of R will be bounded by:

$$\sqrt{\frac{6}{\Gamma}\,(1-\sigma_H)} < R < \sqrt{\frac{6}{\Gamma}\,(1-\sigma_N)} . \tag{50}$$

Stage Three: Proliferation, Quiescene and Necrosis In stage three, all three allowed cell behaviours will occur. There will be an outer rim of proliferating cells, followed by an intermediate rim of quiescent cells and an inner core of necrotic cells. In this case, one has to solve the nutrient equation in two distinct regions and impose continuity

$$\frac{1}{r^2}\frac{\partial}{\partial r}\left(r^2\frac{\partial \sigma}{\partial r}\right) = 0 \qquad \text{for } \sigma \in [0, \sigma_N]\,, \tag{51}$$

$$\frac{1}{r^2}\frac{\partial}{\partial r}\left(r^2\frac{\partial \sigma}{\partial r}\right) = \Gamma \qquad \text{for } \sigma \in (\sigma_N, 1] \tag{52}$$

Solving this in the two regions yields:

$$\sigma(r,t) = -\frac{C_1}{r} + C_2 \qquad \text{for } \sigma \in [0, \sigma_N]\,, \tag{53}$$

$$\sigma(r,t) = \frac{r^2}{6}\Gamma - \frac{D_1}{r} + D_2 \qquad \text{for } \sigma \in (\sigma_N, 1]\,. \tag{54}$$

For $\frac{\partial \sigma}{\partial r}$ to vanish at the origin, one requires $C_1 = 0$. The continuity condition at R_N then requires $C_2 = \sigma_N$. This agrees with the intuition that the nutrient concentration should not vary in the necrotic core since no nutrients are consumed there. Using the boundary condition and the continuity of σ at the boundary $r = R_N(t)$, one finds the two equations

$$\frac{R^2}{6}\Gamma - \frac{D_1}{R} + D_2 = 1\,, \tag{55}$$

$$\frac{R_N^2}{6}\Gamma - \frac{D_1}{R_N} + D_2 = \sigma_N\,. \tag{56}$$

Solving those equations for D_1 and D_2 yields:

$$D_1 = \frac{RR_N}{R - R_N}\left(1 - \sigma_N + \frac{\Gamma}{6}\left(R_N^2 - R^2\right)\right) \tag{57}$$

$$D_2 = \frac{RR_N}{R - R_N}\left(\frac{1}{R_N} - \frac{\sigma_N}{R} + \frac{\Gamma}{6}\left(\frac{R_N^2}{R} - \frac{R^2}{R_N}\right)\right)\,, \tag{58}$$

and substituting into Equation (54), one finds for the outer region

$$\begin{aligned}\sigma_{\text{out.}}(r,t) &= r^2\frac{\Gamma}{6} - \frac{D_1}{r} + D_2 \\ &= r^2\frac{\Gamma}{6} - \frac{RR_N}{R - R_N}\left(\frac{r - R_N}{rR_N} + \sigma_N\left(\frac{R - r}{rR}\right) + \frac{\Gamma}{6}\left(\frac{R_N^3 - R^3}{RR_N} + \frac{R^2 - R_N^2}{r}\right)\right)\end{aligned}$$

This fulfils the boundary and continuity conditions: $\sigma_{\text{out.}}(R_N, t) = \sigma_N$ and $\sigma_{\text{out.}}(R, t) = 1$. To summarise, the solution for the nutrient equation in stage three is:

$$\sigma(r,t) = \begin{cases} \sigma_N, & \text{for } r \in [0, R_N] \\ r^2\frac{\Gamma}{6} - \frac{D_1}{r} + D_2, & \text{for } r \in (R_N, R] \end{cases} \tag{59}$$

For the boundary equation, this yields

$$R^2 \frac{dR}{dt} = \int_{R_H}^{R} r^2 \sigma_{\text{out.}}(r,t)\, dr - \frac{\lambda_A R^3}{3} - \frac{\lambda_N R_N^3}{3}$$

which can be evaluated and rearranged to give the change in the outer radius as a function h, that depends on a number of arguments:

$$\frac{dR}{dt} = h(R, R_H, R_N, \Gamma, \sigma_N, \lambda_A, \lambda_N).$$

In this ordinary differential equation $\Gamma, \sigma_N, \lambda_A, \lambda_N$ are all known constants. For the radius R_H, one can use

$$\sigma_{\text{out.}}(R_H, t) - \sigma_H = 0\,. \tag{60}$$

In order to find R_N, one can use the continuity condition for the derivative at the necrotic boundary: $\frac{\partial \sigma}{\partial r}\Big|_{r=R_N} = 0$, which gives:

$$\frac{R_N}{3}\Gamma + \frac{D_1}{R_N^2} = 0\,, \tag{61}$$

where D_1 is as defined in Equation (57). If one uses $\frac{dR}{dt} = h(R, R_N, R_H)$, numerical results for the growth of the tumour can be computed in the following manner:

1. use values for R and t from stage two as initial values,
2. compute R_N by finding the roots of Equation (61),
3. compute R_H by finding the roots of Equation (60) (use new R_N),
4. compute new value for R using explicit euler: $R_{\text{New}} = \Delta T h(R_{\text{Old}}, R_N, R_H)$,
5. repeat steps 2 - 4 until a steady state is attained.

An example of a situation where the steady state is attained in stage three is shown in Figure 5 in the appendix.

2.4 Discussion

The model presented above is a basic approach towards describing avascular tumour growth, yet it captures some of the important features of the problem at hand, such as the formation of different regions in the tumour, which has been observed in experiments [RCM07]. In this model, the tumour was assumed to be spherically

symmetric, oxygen (or another important nutrient) diffused into the tumour from the outside where it was consumed by the cells if they were alive. The model predicts that, depending on the parameter values chosen, a steady state will be reached in stage one, two or three of tumour development. In the numerical calculations presented in the appendix (Figures 3, 4 and 5), the time and the stage where the steady state was attained changed depending on the the natural cell death rate λ_A. The first two stages are easy to calculate analytically, the third stage is easy in principle but gets complicated due to the increased number of terms.

Theory and Experiment If the parameters values are chosen the right way, e.g. $1-\sigma_H \ll 1$ and $\lambda_A+\lambda_N \ll 1$, then the model predicts a thin outer rim of proliferating cells (see Figure 6 in the appendix), which agrees with experimental observations carried out in vitro [Byr12]. If one wanted to find those parameter values by means of an experiment, one would have to introduce an objective function that describes the agreement between a model prediction (e.g. for $R(t)$) and what is observed in the lab. This objective function would then have to be maximised with respect to the model parameters. To do this, one would first have to establish whether all parameters in the model are identifiable [RSB+13]. Another interesting model prediction is that the distance between $R_H(t)$ and $R_N(t)$ will be almost constant once the third stage is reached, see Figure 8 in the appendix. This is in agreement with experimental observations [Gre72].

Possible Extensions The model presented above is in principle the model developed by Greenspan [Gre72], with some elements taken from Byrne [Byr12]. Many extensions to this model are possible. The number of nutrients consumed by the cells could be increased to be more realistic. More general, the biological and chemical processes in the tumour could be included to account for multiple chemical species inside the tumour, their interaction and movement. Multiple authors have done this, one example is the paper by Casciari, Sotirchos & Sutherland [CSS92]. Another possible extension is to drop the assumption of spherical symmetry, thereby going from a one dimensional model to a two or three dimensional model. This has for example been performed by Byrne and Chaplain with the aim to investigate the stability of the radially symmetric steady state subject to asymmetric perturbations [BC97]. Furthermore, it is possible to consider the abundance of a chemical inhibitor in the tumour that inhibits cell growth [Gre72]. This chemical inhibitor could either be supplied externally and represent a drug, or it could be supplied internally and represent

a side by-product of live or death cells. This has for instance been investigated by Greenspan [Gre72]. Another possible extension is to treat dead and live cells differently to account for their different physical properties. This leads to the introduction of multiphase models for avascular tumour growth. There are many different approaches in this field, one of the earliest ones was developed by Please, Pettet and McElwain [PPM98].

Parametrisation A general challenge that is discussed e.g. by Roose, Chapman & Maini is to find the right parameter values experimentally [RCM07]. As the model becomes more complex, it requires knowledge about more and more parameters which might in practice be very hard to establish [RCM07]. Interesting here might be the work of Raue et al. who have dealt extensively with parameter inference in dynamical settings, especially in case of complicated ODE models that feature non-identifiable parameters by using a profile likelihood approach [RSB+13].

3 Model Extensions

Another possible extension is to replace the nutrient consumption rate Γ and the natural cell death rate λ_A by functions of σ, or to modify the nutrient dependence of the cell proliferation rate P. This would allow for a more realistic description of real processes in the cell. In practice, one could use functions that were determined by some sort of data-fitting [Byr12]. In this section, the σ dependence of the nutrient consumption rate will be varied as an example of varying the functional dependence of kinetic terms in the model.

3.1 Model Derivation

For simplicity, only the first stage of tumour growth will be considered. The other stages could be extended to account for the new consumption rate as well, but it would not provide much more insight. The computations will be done numerically to allow for an arbitrary functional dependence. The equations introduced in Section 2.2 stay the same except for Equation (26), which will be replaced by:

$$\text{Boundary Equation:} \qquad R^2 \frac{dR}{dt} = \int_0^R f(\sigma) r^2 dr - \frac{\lambda_A R^3}{3}\,, \tag{62}$$

where $f(\sigma)$ now describes the nutrient consumption by live cells. R_H and R_N are zero in this first stage.

Numerical Computations The numerical scheme employed was the following:

1. initialise by $R_0 = 1$, $t_0 = 0$,
2. determine the value of the integral by numerical integration,
3. compute the new outer radius using the RHS of Equation (62) and explicit Euler,
4. repeat steps 2 & 3 until either steady state is attained or model breaks down.

Functional Forms Two different functional forms of the proliferation rate were explored. Physical constraints were taken into account: the proliferation rate should be strictly positive on [0, 1] and monotonically increasing with the nutrient concentration σ. Realistically, the proliferation rate should tend to zero as σ tends to σ_H and attain some maximum as σ tends to one. The following two functions were investigated:

$$f_1(\sigma) = 1 - e^{-3\,(\sigma - \sigma_H)}\,, \tag{63}$$

$$f_2(\sigma) = 0.75\ (\mathrm{e}^{(\sigma-\sigma_H)/1.1} - 1)\,. \tag{64}$$

Motivation to use those Functions The two functions are plotted in Figure 7 in the appendix. Both functions are positive on [0, 1] and monotonically increasing with σ. Furthermore, they are zero when $\sigma = \sigma_H$ and they tend to a similar value for $\sigma \to 1$. The function on the left, $f_1(\sigma)$, describes cells whose proliferation rate attains a plateau when σ goes to one and a steep decrease when σ approaches σ_H. The function on the right, $f_2(\sigma)$ describes cells with the opposite behaviour. The average proliferation rate will be much higher in case of $f_1(\sigma)$, so one expects the steady state to be attained later in that case. Also, one would expect the final outer radius $R(t)$ to be bigger using $f_1(\sigma)$. The other parameter values were chosen such that a steady state is attained in the first stage.

3.2 Model Results

The results are plotted in Figure 2. The results are in accordance with the expectations as the final steady state is attained later using $f_1(\sigma)$ and the outer radius $R(t)$ is bigger in that case.

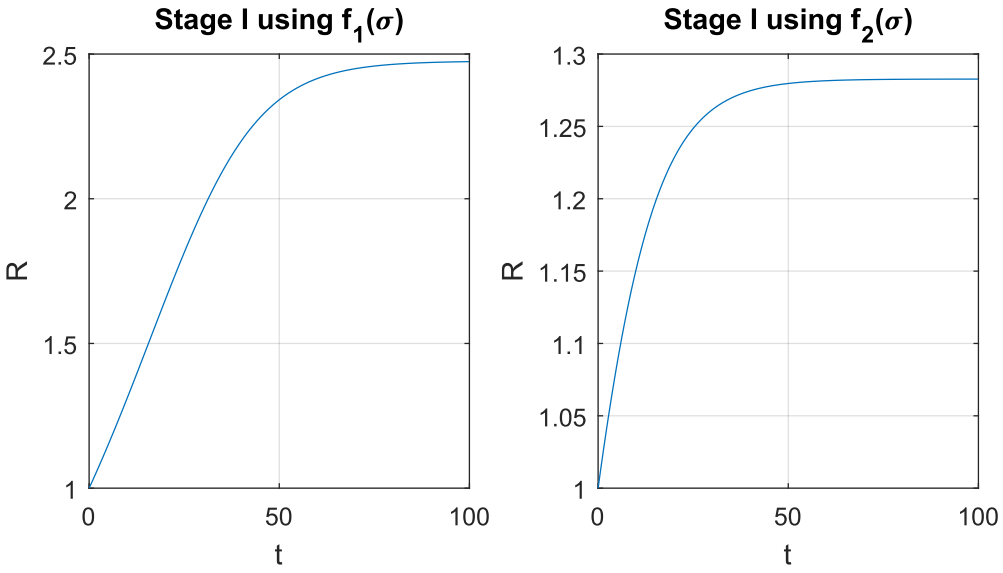

Figure 2: Comparison of the dynamical behaviour of $R(t)$, using different functions for the cell proliferation rate. On the left, the average proliferation rate is higher, which results in a bigger radius for the steady state. Moreover, the steady state is attained later, in accordance with expectations. Parameters were $\lambda_A = 0.9$, $\Gamma = 0.3$, $\sigma_H = 0.1$.

3.3 Discussion

The results demonstrate how more realistic forms of the kinetic terms can be incorporated. The obtained graphs were in accordance with the formulated expectations. The logical next step would be to extend this approach to cover the other kinetic terms, as well as stage two and three of avascular tumour growth. The respective form of functional dependence should be derived from biological of chemical considerations and the parameter values in those new functions should be specified such that the agreement between model prediction and observation is maximised. This will result in a higher number of parameters which will make it difficult to specify them all by experiments. It is likely that some of the new parameters will be non-identifiable or will at least require measuring quantities other than $R(t)$.

4 Summary

In this report, an approach towards modelling avascular tumour growth was presented. The model that was derived and analysed was first developed by Greenspan

and extended by Byrne and others [Gre72], [Byr12]. The model allowed for the formation of three distinct regions within the tumour, depending on the local abundance of one nutrient. The parameters values determined when and in which stage a steady state was attained.

Outlook One of the major challenges is to develop models that capture all of the important physical, biological and chemical properties of the tumour, while incorporating not too many parameters and complex relationships such that it is still possible to experimentally determine good parameters values and to understand the general behaviour of the model. The task of modelling tumour growth becomes even more challenging when the vascular phase of tumour growth is to be described. The tumour will then be highly non-symmetric and the process of acquiring a blood supply will have to be taken into account.

Usefulness of Mathematical Models in Tumour Modelling A precise description of tumour growth across the different stages and phases in terms of mathematics is difficult. Yet, by focusing on certain aspects of the problem, valuable expertise can be gained. Even simple models with few parameters might be able to describe the general behaviour and to give an insight into the underlying principles [AM04]. The strength of mathematical models is their ability to formulate theoretical knowledge in a systematic manner, so that it can be tested against experimental observations.

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Appendix

Stage I Tumour Growth

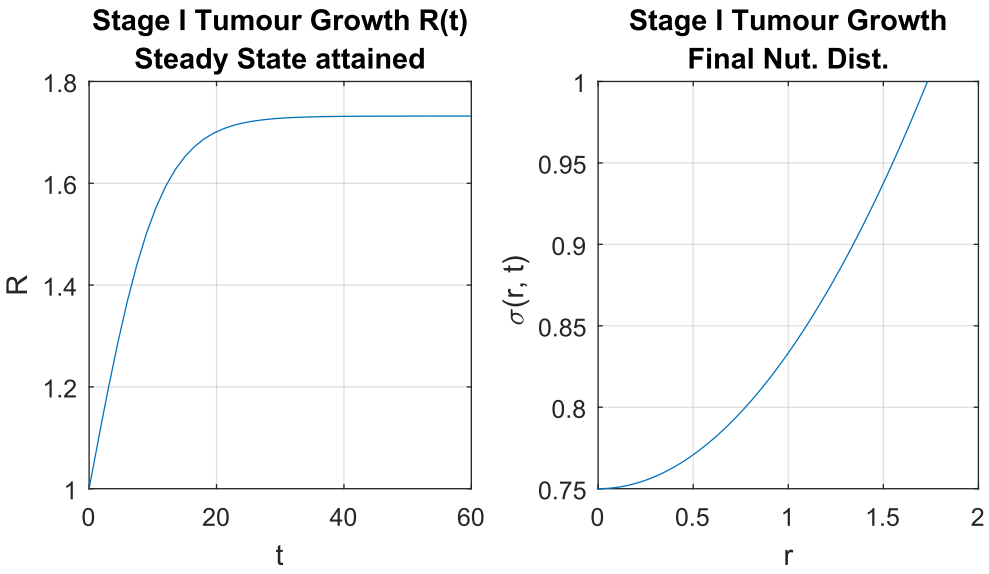

Figure 3: Stage one tumour growth. On the left, the outer radius R is plotted as a function of time. On the right, the final nutrient distribution is plotted. Parameters are chosen such that a steady state is attained in this stage. Parameters: $\lambda_A = 0.9$, $\Gamma = 0.5$, $\sigma_H = 0.6$.

Stage I and II Tumour Growth

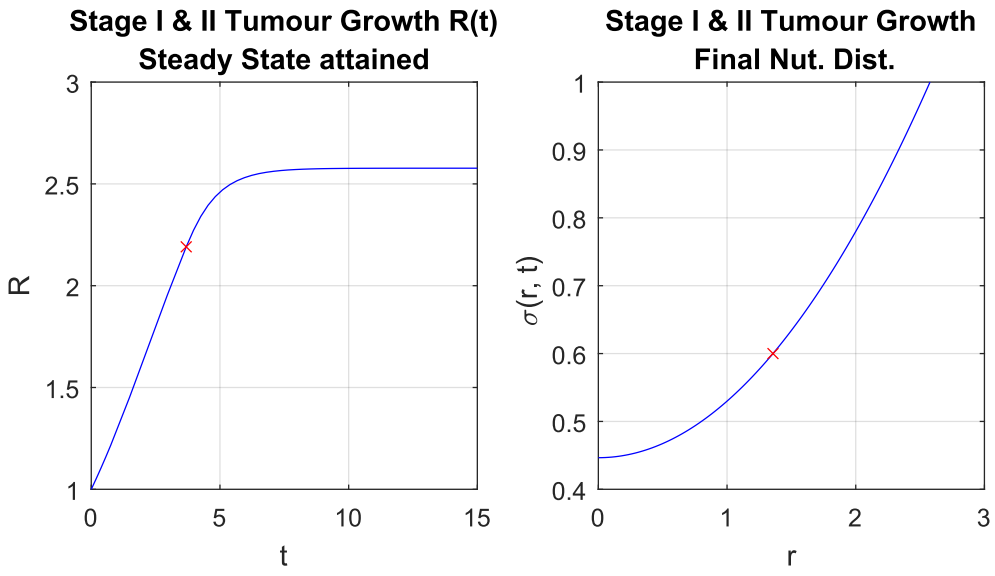

Figure 4: Stage I and II tumour growth. The red cross in the left graph denotes the transition from stage one to stage two. The red cross in the right graph denotes the value of σ_H. Parameters are chosen such that a steady state is attained in this stage. Parameters: $\lambda_A = 0.7$, $\Gamma = 0.5$, $\sigma_H = 0.6$, $\sigma_N = 0.3$.

Stage I, II, and III Tumour Growth

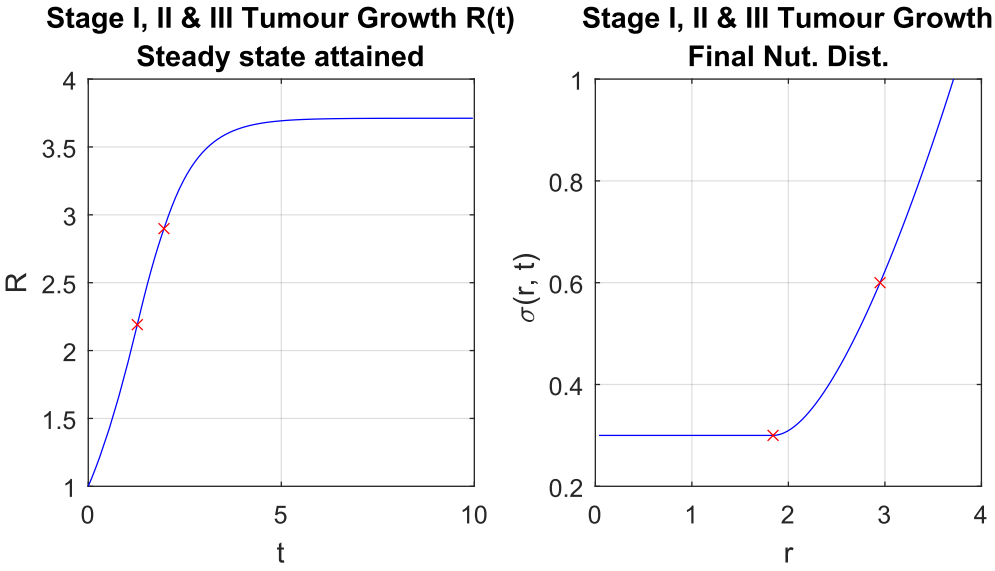

Figure 5: Stage I, II and III tumour growth. The red crosses in the left graph cross denote the transition from stage one to stage two and three, respectively. The red crosses in the right graph denote the value of σ_N and σ_H, respectively. Parameters are chosen such that a steady state is attained in this stage. Parameters: $\lambda_A = 0.3$, $\lambda_N = 0.8$ $\Gamma = 0.5$, $\sigma_H = 0.6$, $\sigma_N = 0.3$.

Stage I, II, and III Tumour Growth

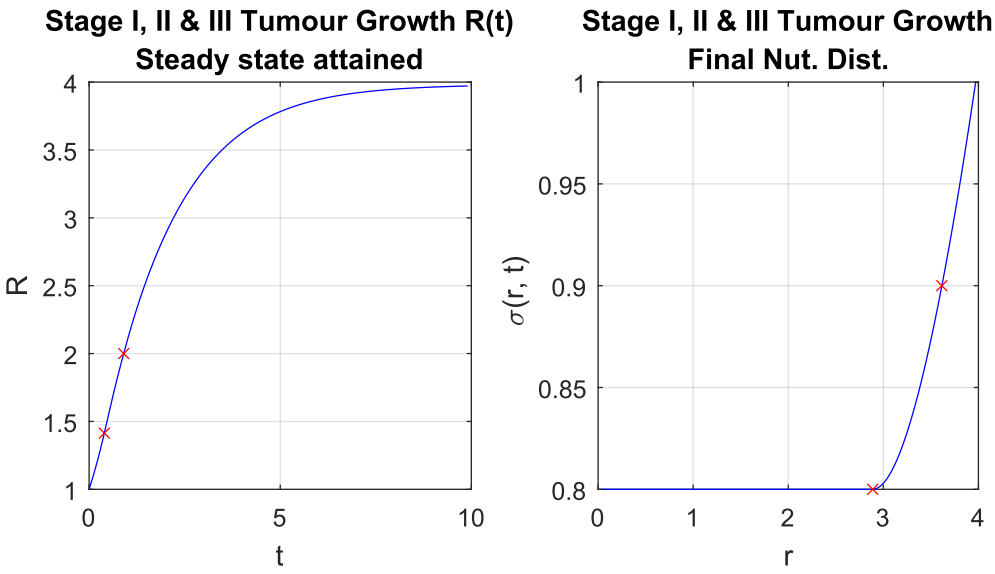

Figure 6: Stage I, II, and III tumour growth with realistic parameter values. Parameters values are chosen such that the model prediction agrees with experimental observations. The steady state is attained at an outer radius of about 4. At this point, the width of the proliferating rim is only about 0.5 in non-dimensional units. Parameters values: $\lambda_A = 0.1$, $\lambda_N = 0.2$ $\Gamma = 0.3$, $\sigma_H = 0.9$, $\sigma_N = 0.8$

The Functional Form of the Cell Proliferation Rate

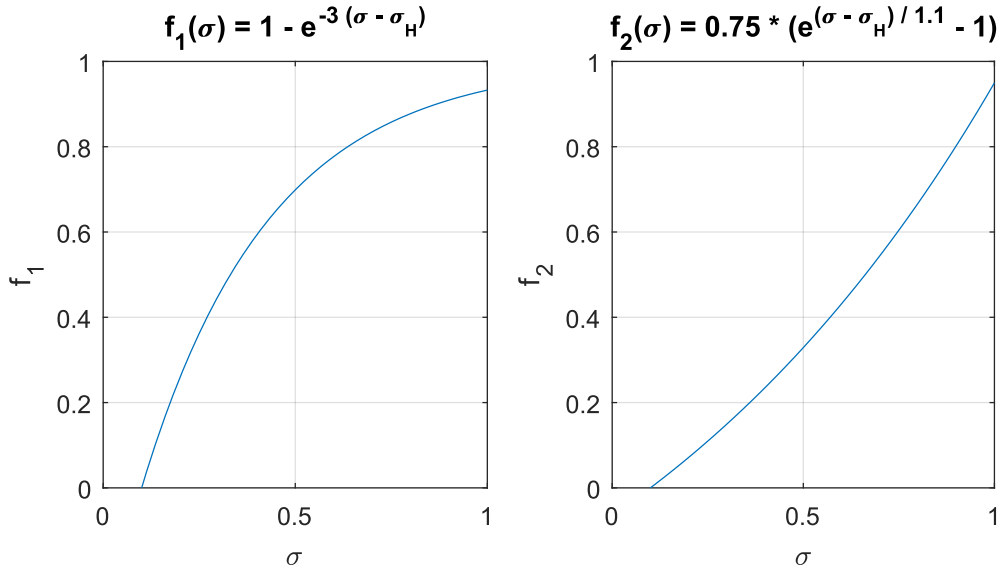

Figure 7: Two functions used to describe the proliferating rate.

The Distance between $R_H(t)$ and $R_N(t)$

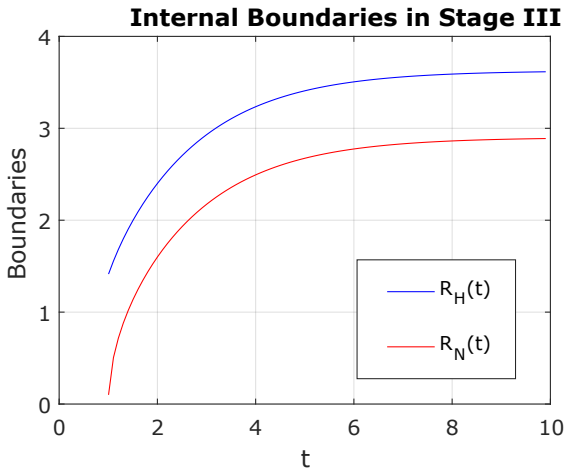

Figure 8: Internal boundaries in stage three of avascular tumour growth. Parameter values: $\lambda_A = 0.1$, $\lambda_N = 0.2$ $\Gamma = 0.3$, $\sigma_H = 0.9$, $\sigma_N = 0.8$.