Technische Universität München,
Department of Mathematics

Mathematical Models of Avascular Tumor Growth and Treatments

Bachelor's Thesis by Sophie Böhm

Supervisor : Prof. Dr. Christina Kuttler

Advisor : Dr. Judith Pérez-Velázquez

Submission date : 03.08.2011

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Abstract

This thesis treats different models for the growth of heterogeneous, avascular cancer tumors. On the one hand we discuss and variate a model just for the pure number of cancer cells. We especially detail to the treatments chemotherapy and radiotherapy. We analyze the trivial equilibria of the models. In this way it is possible to determine the dose of chemotherapy or ionizing radiation necessary to dispose the tumor. The results of some of these models are tested with the help of experimental data and MATLAB.
The second part dedicates to the creation and simplification of a model including the spatial structure of an avascular cancer tumor. We analyze this model in parts at its limits.

Zusammenfassung

Diese Bachelorarbeit behandelt verschiedene Modelle zur Darstellung des Wachstums heterogener, avaskulärer Krebstumoren. Zum einen diskutiert und variiert die Arbeit ein Modell über die reine Anzahl an Krebszellen. Hierbei wird im Speziellen eingegangen auf die Behandlungsmöglichkeiten Chemotherapie sowie Radiotherapie. Im Fokus steht auch die Analyse der trivialen Gleichgewichtspunkte der Modelle. Auf diese Art lässt sich bestimmen, welche Dosis an Chemotherapeutika bzw. ionisierender Strahlung nötig sind, um den Tumor abzutöten. Die Ergebnisse einzelner Modelle werden anhand von empirischen Daten mit Hilfe von MATLAB überprüft.
Der zweite Teil widmet sich vollkommen der Aufstellung und Vereinfachung eines Modelles über Krebszellen, welches sich auch mit der räumlichen Struktur eine avaskulären Tumors beschäftigt. Dieses Modell wird im Anschluss in Auszügen an deren Grenzen analysiert.

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The errors, idiocies and inconsistencies remain my own.

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1 Introduction

Currently in Germany every fourth person's dead can be traced back to cancer [9]. In this country the risk to develop cancer during your lifetime is about 40% [9]. Thus we tend to view cancer as a contemporary disease, caused by our unhealthy way of life caused by smoking, drugs, lack of physical activity and pollution. however, already the physician Hippocrates (born 460 B.C.) [7] described a disease called 'carzinos' (*gr.: crab*, as the veins surrounding an outer tumor look like the arms of a crab), appearing, among others, on breast, stomach and uterus and corresponding to today's cancer [12]. Some scientists do actually think it can be traced back to the early years of the human being, more than one million years ago [12].

1.1 Tumor Growth

Today the developing process of cancer is already quite well-known. We differentiate three stages of solid tumor growth (the information for the following is provided by [2, 14, 5, 15, 16]).
The tumor arises by a mutating cell, a cell which gentic material is defect, originating from bad DNA given over by the parents or changes in the DNA caused by external effects (e.g. inhalation of toxic, as smoking). By the division of this mutated cell the defect DNA is transfered and so the mass of cancer cells form a tissue, called the avascular tumor.

In this stage the supply necessary for growth is guaranteed by nutrients as oxygen and glucose diffusing from the surrounding vascular tissue to the center of the tumor. Because of the size the cells in the center suffer a shortage of nutrients, they stop growing and finally die. The well-developed avascular tumor finally consists of the so-called necrotic core, an annulus of hypoxic (quiescent) and an outer layer of proliferating cells. The tumor stops growing when a balance of cell death and cell proliferation is reached. So avascular tumors are still rather small and harmless.

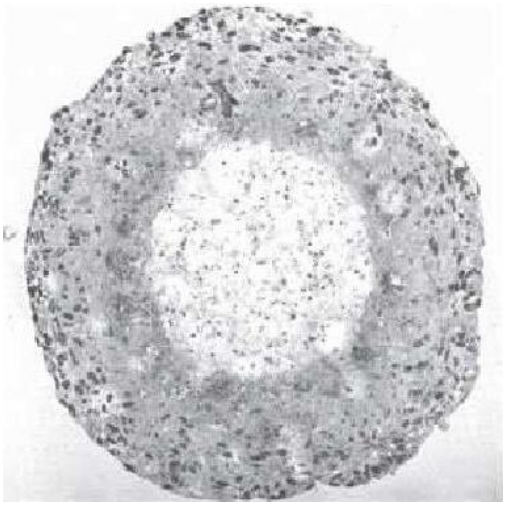


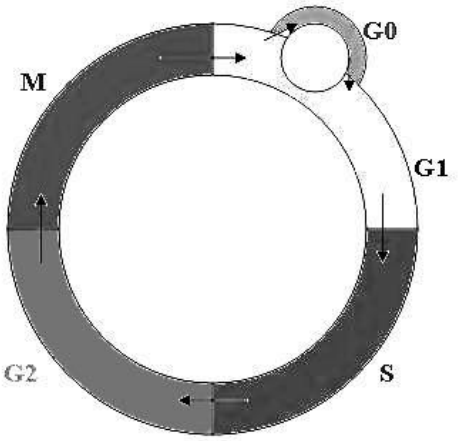
Figure 1: Avascular Tumor Layers [15]

In the next stage, angiogenesis, the tumor cells emit angiogenic growth factors activating blood vessels of the surrounding tissue to spread there. The vascular tumor forms.
The good supply with nutrients through the blood vessels provides an exceeding

growth of the vascular tumor up to lifethreatening sizes in the last stage. Thus it displaces the surrounding tissue, reducing its functioning, invades into blood vessels or lymph nodes and so cancer cells can spread to the whole body. The tumor settles down at other locations and develop metastases, further growth centers.
During the growth the cells continue mutating and so different subpopulations can arise, so we normally have a heterogeneuos cell population in a tumor.

1.2 Cell Cycle

For the understanding of tumor growth it is important to have basic information about the cell cycle.
During this cycle a proliferating cell undergoes four phases. The information about the cell cycle stages is provided by [2, 5, 8, 15, 16].



In the first one, the gap phase (G1), the cell grows up to a certain size, then enters the next phase (S), where it duplicates its DNA. The following gap phase (G2) serves for last preparations for the division in the last phase (M): Mitosis and cytokinesis occur, the divisions of the nucleus and of the cell. So an identical copy of the mother cell arises.

Figure 2: Cell Cycle

During the stages (G1), (S) and (G2)occurs the synthesis of RNA and protein, which is necessary for the mitosis phase. An additional stage has been introduced by the scientists, the resting phase (G0), where the cells remain quiescent. It is possible for a cell which is remaining in the (G0)-phase to return into the cycle, entering (G1). The cell-cycle-control-system is responsible for the functioning of the whole cycle, initiating the steps. Also, the cell has to pass several checkpoints. There the progress can be stopped if some errors are identificated. If there is no ability to repair them, apoptosis (organized cell death, by comparison with necrosis, the uncontrolled cell death) is induced to avoid spreading of the damage. In the cycle of mutated cancer cells apoptosis can e.g. be supressed by mutations, so the damaged cells divide regardless, loosing control over cell division and proliferation.

In the following we will deal with models for avascular solid tumors, focusing on homogeneous ones. Firstly we neglect the spatial structure of the tumor, only re-

garding the total number of cells. We variate the resulting model to illustrate the influence of treatment with a chemotherapeutic drug or radiotherapy. Furthermore we try to compare the models as our predictions to real data.
In the second part of the thesis we do mind the spatial arrangement inside the tumor, which means we introduce layers of necrotic, hypoxic and proliferating cells. The model includes the influence of a diffusing chemical on the tumor, which can be nutrient or cell-growth limiting.

2 Structure-Neglecting Model for Homogeneous Tumors

2.1 Growth Model

First, we want to develop a model for the growth of a homogeneous avscular tumor, we assume the tumor only consists of one type of cells. We want to constitute an equation presenting the number of cells $N(t)$ at moment t. In this regard we consider the following equation [3]

$$\frac{dN(t)}{dt} = \frac{k}{\alpha} N(t) \left(1 - \left(\frac{N(t)}{\Theta}\right)^{\alpha}\right) \tag{2.1}$$

$$N(t=0) = N_0$$

Remark. This is a generalized version of the logistic growth law (for $\alpha = 1$ we get the original logistic equation). The exponential growth is of the factor $k/\alpha > 0$, which describes the proliferation rate. $\Theta > 0$ is the cell capacity of the tumor; we introduce it to model the fact, that the expansion of the tumor is accompanied by a growing competition for nutrient as the tumor is avascular. $\alpha > 0$ is a parameter indicating how fast the carrying capacity is reached, so it adjustes the point of inflection. The smaller α, the steeper is the function. N_0, the initial population size, can be figured out through clinical observation.

The **solution** of the equation (2.1) is given through separation of variables. The explicit solution is constructed as follows:

$$\int_{N_0}^{N(t)} \frac{1}{N - \frac{N^{\alpha+1}}{\Theta^{\alpha}}} dN = \int_0^t \frac{k}{\alpha} dt$$

Via partial fraction decomposition the left side of the expression can be rewritten:

$$\int_{N_0}^{N(t)} \frac{1}{N - \frac{N^{\alpha+1}}{\Theta^{\alpha}}} dN = \int_{N_0}^{N(t)} \frac{1}{N} - \frac{N^{\alpha-1}}{N^{\alpha} - \Theta^{\alpha}} dN = \left[ln(N) - \frac{1}{\alpha} ln(\Theta^{\alpha} - N^{\alpha}) \right]_{N_0}^{N(t)}$$

The absolute value bars in the ln-function can be neglected, we can assume the real positivity of the values in the brackets (otherwise the solution will be $N(t) \equiv 0$ or

$N(t) \equiv \Theta$). So we get

$$\frac{1}{\alpha} \cdot ln\left(\frac{N(t)^\alpha \cdot (\Theta^\alpha - N_0^\alpha)}{N_0^\alpha \cdot (\Theta^\alpha - N(t)^\alpha)}\right) = t \cdot \frac{k}{\alpha}$$
$$\Rightarrow N(t) = \frac{\Theta N_0}{(N_0^\alpha + (\Theta^\alpha - N_0^\alpha)e^{-kt})^{1/\alpha}} \tag{2.2}$$

The equation (2.1) possesses two **steady states**:

$$\frac{dN}{dt} = 0 \Leftrightarrow N^* = 0 \text{ and } N^* = \Theta.$$

For $N_0 = 0$ we never have cancer cells. For $N_0 > \Theta$ it is $\frac{dN}{dt} < 0$ and thus the cells die until $N(t) = \Theta$, as there is not enough space/ too much competition for so many tumor cells. If we start in a point different to zero and $\leq \Theta$, it holds $N(t) \to \Theta$ for $t \to \infty$ as $\frac{dN}{dt} > 0$.
We call the steady state $N^* = \Theta$ asymptotically stable, $N^* = 0$ is unstable.

2.2 Data Comparison

Now we want to evaluate the model, using the data [19].
The source measures and registers the growing number of cell units of different cells 2,3,4,5 and 6 days after a sowing of 0.1 cell units.
The experiment is performed twelve times parallel for each cell line to get more suitable results. For our needs we calculate the mean value of the conductions of one cell type at the current timepoint, meaning we sum up the values of the different implementations at a certain day and divide by 12. We plot this average values $N_{data}(t)$ of the data in MATLAB and, for comparison, also chart the number $N_{model}(t)$ of cell units according to our model (2.2) at the given timepoints. We minimize $\sum_i N_{model}(i) - N_{data}(i)$ at day $i = 0, 2, 3, 4, 5, 6$ and search for the best-fitting parameter values for k, Θ and α.

As an example, we now present the results applied to two cell lines. Firstly, we introduce the plot for the MOS 62 cells (fig. 3). Following the experiment, we have $N_0 = 0.1$. The capacity Θ is evaluated to 3.9. Simplifying, for the first step we assume $N_{data}(i) = e^{\frac{k}{\alpha}i} N_0$ and using $N_{data}(2) \approx 2.587 \cdot N_0$ we choose $k/alpha = 0.5 \cdot ln(2.587) \approx 0.5$ as a first guess. We see the point of inflection is shifted to the right in comparison to the traditional logistic equation and thus we know $\alpha > 1$. Starting from this, we vary k and α to fit them even better to the data. This way we receive $k = 13.5$ and $\alpha = 19$, thus we have a total growth factor (= proliferation rate = $\frac{k}{\alpha}$) of 0.7105.
The fitting of the model to the data is already quite good, as the sum of the differences as above described is 0.6543.

But for the MOS 1189 cells we obtain an even better matching of the cell number. Using the same methods as above we use parameter values $N_0 = 0.1, \Theta = 1.34, k = 2$

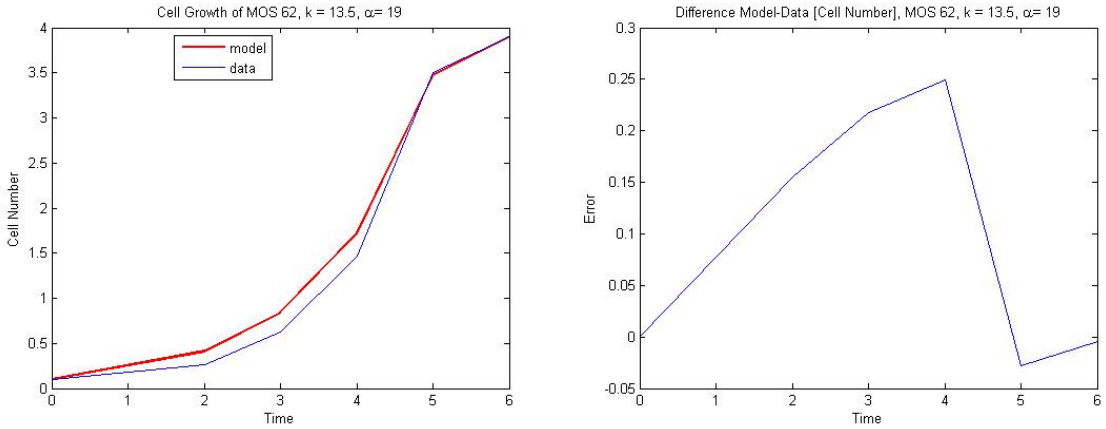


Figure 3: Growth Curves of MOS 62 cells (Data vs. Model, using MATLAB [21])

and $\alpha = 3.9$, see fig. 4. This means an overall growth factor of 0.5128. The sum of the differences only is 0.0449, just 3.35% of the biggest value that is nearly Θ.

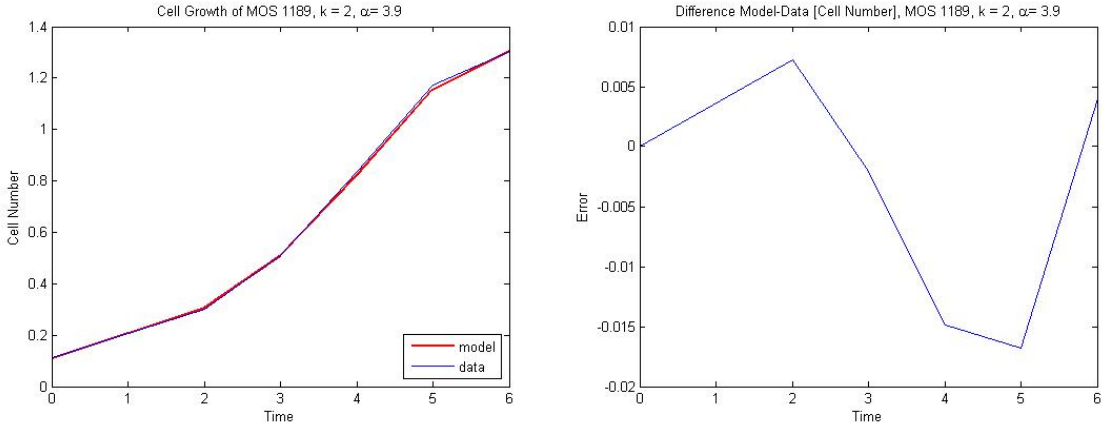


Figure 4: Growth Curves of MOS 1189 cells (Data vs. Model, using MATLAB [21])

Additionally we can observe in both of the cases that for almost every value of $N_0 < \Theta$ the number of cells converges to the carrying capacity Θ. The solitary exception is for $N_0 = 0$, because if there are no cancer cells in the beginning, there will never be such cells and thus $N_{model}(t) = 0 \quad \forall t \geq 0$.
This confirms the results of the stability analysis above.

It is easy to show that if we had chosen exponential growth ($\frac{dN(t)}{dt} = kN(t)$), the model would fit much worse to the data. We try to fit this model for exponential growing cells (and with an infinite carrying capacity) to the data and see immediately (compare fig. 5) it doesn't work as well as the generalized logistic growth. It is that the cells compete for nutrient and space and thus there is a maximum limit for the cell number in a tumor.

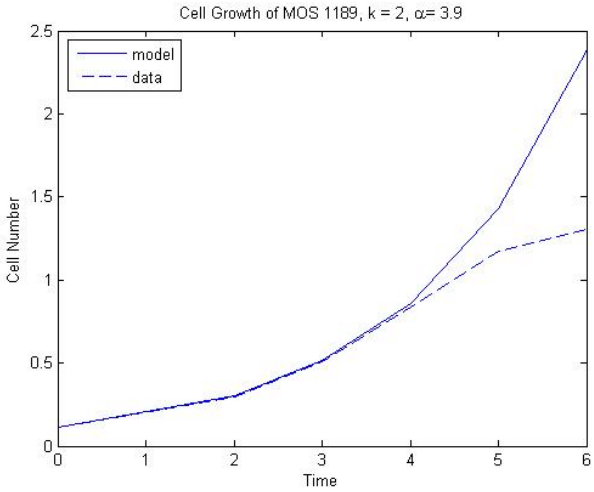


Figure 5: Growth Curves of MOS 1189 cells (Data vs. Model, using MATLAB [21])

2.3 Chemotherapeutic Treatment

There are several therapies to treat cancer [14]. The intuitive one is to remove the tumor by surgery, but e.g. when the tumor is too big or metastases already settled down it is very difficult to eliminate the whole tumor. Chemotherapy can also be used, here the cancer patient gets injections of a special drug. We consider substances which attack the cells and cause their death, called cytotoxic. Unfortunately they do not just attack tumor cells, also healthy cells can be injured, so it is important not to overdose the drug. Furthermore, the cytotoxins also have a cancer-causing effect and the mutating cancer cells generate resistence against them [14].

In this section we want to develop a model which describes the influence of a chemotherapeutic drug on the growth of our tumor. We consider a non-cycle-specific drug which causes the cells to die instantly. A view of a model for phase-specific drugs can be seen in [10].

We assume logisic growth of N, so the above model (2.1) with the parameter $\alpha = 1$. The model we include for the number of cells $N(t)$ and the concentration of the cytotoxic drug in the tumor $A(t)$ is the following [3]:

$$\begin{aligned} \frac{dN}{dt} &= kN\left(1 - \frac{N}{\Theta}\right) - \mu AN = f_1(N, A) \\ \frac{dA}{dt} &= a(t) - \lambda_1 A - \lambda_2 AN = f_2(N, A) \end{aligned} \tag{2.3}$$

$$N(t = 0) = N_0, \qquad A(t = 0) = A_0$$

Remark. k, Θ as above; $\mu > 0$ signifies how much the drug damages the cells, thus how many cells are killed. $a(t) \geq 0$ is the infusion quantity of the chemotherapeutic at moment t. The parameters $\lambda_1 > 0$ and $\lambda_2 > 0$ decribe the decline of the drug as λ_1 is the rate of decay, whilst λ_2 is the rate of consumption at contact of cell and

chemotherapeutic substance.

It makes sense to look for the **equilibria**, more specifically the points for which the concentration of the drug and the number of cells are balanced. This means the number of cells or the concentration input to the system equals the number of cells dying or the decline of the drug.
In mathematical language: We request

$$\frac{dN}{dt} = 0, \qquad \frac{dA}{dt} = 0$$

The obvious solution is

$$(N^*, A^*) = \left(0, \frac{a(t)}{\lambda_1}\right)$$

and for the second equilibrium we need

$$\begin{aligned} 0 &= (N^*)^2 + N^*\left(\Theta - \frac{\lambda_1}{\lambda_2}\right) + \frac{\Theta}{\lambda_2}\left(a(t)\frac{\mu}{k} - \lambda_1\right) \\ \Rightarrow N^*_{1,2} &= \frac{1}{2}\left(\Theta - \frac{\lambda_1}{\lambda_2} \pm \sqrt{\left(\Theta - \frac{\lambda_1}{\lambda_2}\right)^2 - 4\frac{\Theta}{\lambda_2}\left(\frac{\mu}{k}a(t) - \lambda_1\right)}\right), \\ A^* &= \frac{k}{\mu}\left(1 - \frac{N^*}{\Theta}\right). \end{aligned}$$

Now we want to figure out the drug dose we have to inject to stop the growth of a tumor or even to eradicate it. So we fix the parameters $k, \Theta, \mu, \lambda_1$ und λ_2, as the tumor is given and we already decided which drug to take, and vary the injection $a(t)$.
Sure, we only take the real (positive) solution for N. This is the case if the discriminant is nonnegative, so for

$$a(t) \le a_{max} := \frac{k\lambda_1}{4\mu}\left(2 + \frac{1}{\Theta\lambda_2} + \frac{\Theta\lambda_2}{\lambda_1}\right).$$

For $a(t) > a_{max}$ the only realistic equilibrium is the case $N(t) = 0$, which means that no tumor exists. Depending on the parameters we obtain up to three sensible solutions for $0 \le a(t) \le a_{max}$.

Case 1: $\frac{\Theta\lambda_2}{\lambda_1} > 1$
We obtain at least one nontrivial steady state. If

- $a^* < \frac{\lambda_1 k}{\mu} : N_2^* < 0$, we only have two steady states,
- $a_{max} \ge a^* > \frac{\lambda_1 k}{\mu}$: we obtain a third equilibrium.

Case 2: $\frac{\Theta\lambda_2}{\lambda_1} < 1$
We have at most one nontrivial steady state. If

- $a^* < \frac{\lambda_1 k}{\mu} : N_1^* < 0$, we get two steady states,
- $a_{max} \ge a^* > \frac{\lambda_1 k}{\mu} : N_1^*, N_2^* < 0$, we only have the trivial fixed point.

2.3.1 Continuous Injection

We first want to have a look at our model's behaviour if we inject the drug continiously in a constant dose to the patient. So we set (according to [3])

$$a(t) = a^* \quad \forall t \geq 0.$$

To perform the stability analysis for this case we first have to **linearize** about the steady states (N^*, A^*) (for justification see [11] and especially Hartmann-Grobmann theorem). We develop the Taylor polynomial after a transformation

$$\begin{pmatrix} f_1(N,A) \\ f_2(N,A) \end{pmatrix} = 0 + \begin{pmatrix} \frac{\partial f_1}{\partial N}(N^*,A^*) & \frac{\partial f_1}{\partial A}(N^*,A^*) \\ \frac{\partial f_2}{\partial N}(N^*,A^*) & \frac{\partial f_2}{\partial A}(N^*,A^*) \end{pmatrix} \cdot \begin{pmatrix} N(t) - N^* \\ A(t) - A^* \end{pmatrix} \tag{2.4}$$

including

$$\begin{pmatrix} f_1(N,A) \\ f_2(N,A) \end{pmatrix} = \begin{pmatrix} \dot{N} \\ \dot{A} \end{pmatrix} = \begin{pmatrix} \dot{N(t)} - N^* \\ \dot{A(t)} - A^* \end{pmatrix}.$$

2.3.1.1 Trivial Equilibrium For $\bar{N} = N(t) - N^*, \bar{A} = A(t) - A^*$ and the trivial steady state $(N^*, A^*) = (0, a^*/\lambda_1)$ we obtain the differential equations

$$\begin{pmatrix} \dot{\bar{N}} \\ \dot{\bar{A}} \end{pmatrix} = \begin{pmatrix} (k - \frac{\mu a^*}{\lambda_1})\bar{N} \\ -\lambda_1 \bar{A} - \frac{\lambda_2 a^*}{\lambda_1}\bar{N} \end{pmatrix}.$$

Their unique solution is

$$\bar{N}(t) = \bar{N}(0)e^{(k-\mu a^*/\lambda_1)t}$$

and (via the variation of constants method)

$$\bar{A}(t) = \left(\bar{A}(0) + \frac{\lambda_2 a^* \bar{N}(0)}{\lambda_1^2 + k\lambda_1 - \mu a^*}\right)e^{-\lambda_1 t} - \frac{\lambda_2 a^* \bar{N}(0)}{\lambda_1^2 + k\lambda_1 - \mu a^*}e^{(k-\mu a^*/\lambda_1)t}.$$

We know that the steady state is asymptotically stable if all the eigenvalues of the Hessian in (2.4) have negative real parts and unstable for real eigenvalues and at least one positive real part [RL]. As they are $(k - \mu\frac{a^*}{\lambda_1})$ and $(-\lambda_1)$ in this case, we have asymptotic stability for $a^* > \frac{k\lambda_1}{\mu}$ and instability for $a^* < \frac{k\lambda_1}{\mu}$.
This means for $a^* > \frac{k\lambda_1}{\mu}$:

$$A(t) \to \frac{a^*}{\lambda_1}, \quad N(t) \to 0,$$

so the tumor dies.
As the stability properties change for a^*, we call it bifurcation parameter and $a^* = \frac{k\lambda_1}{\mu}$ bifurcation point.

2.3.1.2 Nontrivial Equilibrium For the nontrivial equilibrium (N^*, A^*) we proceed analogically. So we obtain the following system of differential equations.

$$\begin{pmatrix} \dot{\bar{N}} \\ \dot{\bar{A}} \end{pmatrix} = \begin{pmatrix} \left(k - \frac{2kN^*}{\Theta} - \mu a^*\right) & -\mu N^* \\ -\lambda_2 A^* & -(\lambda_1 + \lambda_2 N^*) \end{pmatrix} \begin{pmatrix} \bar{N} \\ \bar{A} \end{pmatrix} =: D \cdot \begin{pmatrix} \bar{N} \\ \bar{A} \end{pmatrix}$$

Its unique solution is $(\bar{N}, \bar{A})^T = (\bar{N}(0), \bar{A}(0))e^{Dt}$ which can be computed via the Jordan canonical form of D [11].

We again obtain asymptotic stability if the eigenvalues $\epsilon_{1,2}$ of D satisfy $Re(\epsilon_{1,2}) < 0$ and instability for $Re(\epsilon_i) > 0$, $i = 1$ or 2. It is

$$\epsilon_{1,2} = \frac{1}{2}\left[\left(\frac{\partial f_1}{\partial N} + \frac{\partial f_2}{\partial A}\right)(N^*, A^*) \pm \sqrt{\left(\left(\frac{\partial f_1}{\partial N} + \frac{\partial f_2}{\partial N}\right)^2 - 4\left(\frac{\partial f_1}{\partial N}\frac{\partial f_2}{\partial A} + \frac{\partial f_1}{\partial A}\frac{\partial f_2}{\partial N}\right)\right)(N^*, A^*)}\right].$$

Thus, for

$$\left(\frac{\partial f_1}{\partial N} + \frac{\partial f_2}{\partial A}\right)(N^*, A^*) < 0 < \left(\frac{\partial f_1}{\partial N}\frac{\partial f_2}{\partial A} - \frac{\partial f_1}{\partial A}\frac{\partial f_2}{\partial N}\right)(N^*, A^*) \tag{2.5}$$

the fixed point (N^*, A^*) is asymptotically stable.

Remark. For $\left(\frac{\partial f_1}{\partial N} + \frac{\partial f_2}{\partial A}\right)(N^*, A^*) > 0$ or $\left(\frac{\partial f_1}{\partial N}\frac{\partial f_2}{\partial A} - \frac{\partial f_1}{\partial A}\frac{\partial f_2}{\partial N}\right)(N^*, A^*) < 0$ we have at least one real positive eigenvalue.
If $\left(\frac{\partial f_1}{\partial N}\frac{\partial f_2}{\partial A} - \frac{\partial f_1}{\partial A}\frac{\partial f_2}{\partial N}\right)(N^*, A^*) = 0$ one eigenvalue equals zero, thus we cannot make any declaration.
If $\left(\frac{\partial f_1}{\partial N} + \frac{\partial f_2}{\partial A}\right)(N^*, A^*) = 0$ we obtain either one positive or one complex eigenvalue, which means the real part is zero and we do not know the behaviour.
Further analysis of the last two cases is topic of the Center Manifold Theory (see [18]) as the Theorem of Hartman-Grobman cannot be applied for non-hyperbolic steady states.

The equation (2.5) holds if and only if

$$\begin{aligned} &\left(\frac{\partial f_1}{\partial N} + \frac{\partial f_2}{\partial A}\right)(N^*, A^*) < 0 \\ &\Leftrightarrow N^*\left(\frac{2k}{\Theta} + \lambda_2\right) + \mu A^* + \lambda_1 - k > 0 \\ &\Leftrightarrow N^*\left(\frac{k}{\Theta} + \lambda_2\right) + \lambda_1 > 0 \end{aligned}$$

which is always satisfied, and

$$\begin{aligned} &\left(\frac{\partial f_1}{\partial N}\frac{\partial f_2}{\partial A} - \frac{\partial f_1}{\partial A}\frac{\partial f_2}{\partial N}\right)(N^*, A^*) > 0 \\ &\Leftrightarrow \left(-k + \frac{2kN^*}{\Theta} + \mu A^*\right)(\lambda_1 + \lambda_2 N^*) > \mu N^* \lambda_2 A^* \\ &\Leftrightarrow N^* > \frac{1}{2}\left(\Theta - \frac{\lambda_1}{\lambda_2}\right). \end{aligned}$$

If there is at most one nontrivial steady state, also the latter requirement is fulfilled, which means that the equilibrium is asymptotically stable. If we have two nontrivial ones, the bigger one is stable as it fulfills the condition above, whilst the smaller one is unstable.

Summing Up For $a^* < \frac{\lambda_1 k}{\mu}$ we always have an unstable trivial fixed point and one asymptotically stable nontrivial steady state.
This means the dose of the chemotherapeutic is too small and the tumor goes on growing up to the size in the nontrivial fixed point.
For $a^* > \frac{\lambda_1 k}{\mu}$ we have an asymptotically stable trivial fixed point. If $\frac{\Theta\lambda_2}{\lambda_1} < 1$ or $a^* > a_{max}$ we only have this equilibrium. For $\frac{\Theta\lambda_2}{\lambda_1} > 1$, $a^* \leq a_{max}$ (we obtain 2 nontrivial equilibria), the bigger nontrivial steady state is stable, the smaller one unstable and separatrix (separating the points converging to the trivial and to the nontrivial stable node).
That is if the dose exceeds the value above (meaning, the growth rate k and the decay rate λ_1 of the chemotherapeutic are big enough and the killing rate μ small), the tumor dies. For the case $\frac{\Theta\lambda_2}{\lambda_1} > 1$ this only works if the extent of the tumor is not too big yet, more precisely smaller than the separatrix.

2.3.2 Periodic Infusion

As also normal cells are attacked by the infusion of a chemotherapeutic drug, it makes sense to consider periodic injection, as the cells get the posibility to recover (unfortunately this is also the case for tumor cells). This proceeding of injecting a drug periodically is the type of chemotherapy used most in practice.
According to [3]

$$a(t) = \begin{cases} a^*, & n < t < n + \tau \\ 0, & n + \tau < t < n + 1 \end{cases}$$

Remark. $0 < \tau < 1$ corresponds to the proportional duration of the infusion, n is the number of injections.

Applying the same techniques as above, we again consider the linearized system for the trivial equilibrium $(N^*, A^*) = (0, \frac{a(t)}{\lambda_1})$

$$\begin{pmatrix} \dot{\bar{N}} \\ \dot{\bar{A}} \end{pmatrix} = \begin{pmatrix} (k - \frac{\mu a(t)}{\lambda_1})\bar{N} \\ -\lambda_1 \bar{A} - \frac{\lambda_2 a(t)}{\lambda_1}\bar{N} \end{pmatrix} = \begin{cases} \begin{pmatrix} k & 0 \\ 0 & -\lambda_1 \end{pmatrix}\begin{pmatrix} \bar{N} \\ \bar{A} \end{pmatrix}, & n < t < n + \tau \\ \begin{pmatrix} (k - \frac{\mu a^*}{\lambda_1}) & 0 \\ -\frac{\lambda_2 a^*}{\lambda_1} & -\lambda_1 \end{pmatrix}\begin{pmatrix} \bar{N} \\ \bar{A} \end{pmatrix}, & n + \tau < t < n + 1 \end{cases}$$

The intuitive way is to make stabilty analysis as above.

Case 1: $n < t < n + \tau$
This case was already dealt with in chapter 2.2.1, so we know $(0, \frac{a^*}{\lambda_1})$ is asymptotically stable in this case if $a^* > \frac{k\lambda_1}{\mu}$ and unstable for $a^* < \frac{k\lambda_1}{\mu}$.

Case 2: $n + \tau < t < n + 1$
As the eigenvalues of the representing matrix of the linearized system are $\epsilon_1 = -\lambda_1 < 0$ and $\epsilon_2 = k > 0$ we know that $(0, 0)$ is a unstable saddle point. This corresponds to the fact that while the number of cell increases (because there is no injection), the concentration of the drug in the tumor falls as the chemotherapeutic still underlies decay and consumption by the cells.

PROBLEM: We know now that if $a^* < \frac{k\lambda_1}{\mu}$ the number of cells increases both during injection and also after, which means the tumor keeps growing up. For the case that $a^* > \frac{k\lambda_1}{\mu}$ the number of cells decreases during the infusion and in the regeneration time it increases. So, we have to figure out for which values of a^* the decline of cell number in the injection-phase overbalances the growth of the tumor in the regeneration period.
In the following we are only interested in the stability analysis of the cell number N and the steady state $N^* = 0$ as it is the important one.

The solution of the linearized system for $n < t < n + \tau$ is

$$\bar{N}(t) = \bar{N}(n)e^{(k-\mu\frac{a^*}{\lambda_1})(t-n)}, \tag{2.6}$$

here again we see the decline of $\bar{N}$ for $a^* > \frac{k\lambda_1}{\mu}$.

The solution of the linearized system for $n + \tau < t < n + 1$ is

$$\bar{N}(t) = \bar{N}(n + \tau)e^{k(t-n-\tau)}.$$

Now we can express $\bar{N}(n + \tau)$ through (2.6) on the assumption that $\bar{N}$ is continous at time $t = n + \tau$. We get

$$\bar{N}(n + \tau) = \bar{N}(n)e^{(k-\mu\frac{a^*}{\lambda_1})\tau}$$

and thus in the regeneration phase we have

$$\bar{N}(t) = \bar{N}(n)e^{k(t-n)-\mu\frac{a^*}{\lambda_1}\tau}.$$

Obviously for $a^* > \frac{k\lambda_1}{\mu}\frac{1}{\tau} > \frac{k\lambda_1}{\mu}$ and $t^* \to n + 1$ it holds that

$$\bar{N}(t^*) < \bar{N}(n) \quad \forall n$$

and thus the tumor is steadily declining, which means the state for which $N^* = 0$ is stable and the tumor vanishes.
For $a^* < \frac{k\lambda_1}{\mu}\frac{1}{\tau}, \quad t^* \to n + 1$ it is $\bar{N}(t^*) > \bar{N}(n) \quad \forall n$, so the equilibrium with $N^* = 0$ is unstable; the tumor remains alive.

Summing Up For the extinction of a cancer tumor through periodic infusion we need a dose exceeding a value depending, as in the case of continuous infusion, of growth rate k, drug decay rate λ_1 and death rate μ, but additionally of the factor τ, which represents the duration of one injection. This value is $\frac{k\lambda_1}{\mu}\frac{1}{\tau}$. This means the bigger the injection rate τ, the smaller the dose we need (for $\tau = 1$ we get the continuous case). Thus, periodic infusion requires a bigger injection dose than continuous one, as the cancer cells get the posibility to regenerate.

2.3.3 Discussion

To show the functioning and thus the relation to practice of the performed analysis we again use MATLAB ([21]).

Continuous Injection For testing the analysis of the continuous infusion we include the equation (2.3) with $a(t) = a^*$ into MATLAB and plot the solution of the ODE at time period $[0, 500]$.

We choose the parameter values $k = 0.5, \Theta = 1, \mu = 0.5, \lambda_1 = 0.5, \lambda_2 = 0.3, N_0 = 0.01$. So we know $\frac{\Theta\lambda_2}{\lambda_1} = 0.6 < 1$ and thus either one asymptotically stable trivial equilibrium for big $a^* > \frac{\lambda_1 k}{\mu} = 0.5$ or a stable nontrivial steady state for $a^* < 0.5$.
For $a^* = 0.49$ (fig. 6) we here see a growing tumor. We observe, the number of cells at the left plot and the drug concentration at the right one converge to the nontrivial equilibrium $(0.047, 0.953)$. The drug concentration converges top down as it decreases also because of the existing (and thus consuming) cells, but the cell number is too low during the first time span to affect the drug.
For $a^* = 0.51$ (fig. 7) we see a tumor that becomes extinct. This is because of the convergence towards the trivial equilibrium $(0, 1.020)$.

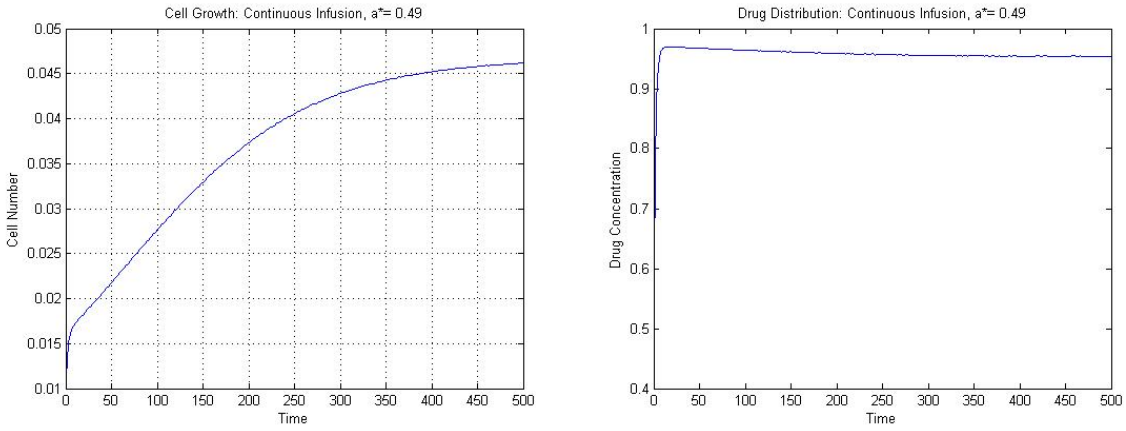


Figure 6: Model results: The tumor grows (via MATLAB [21], $a^* = 0.49$)

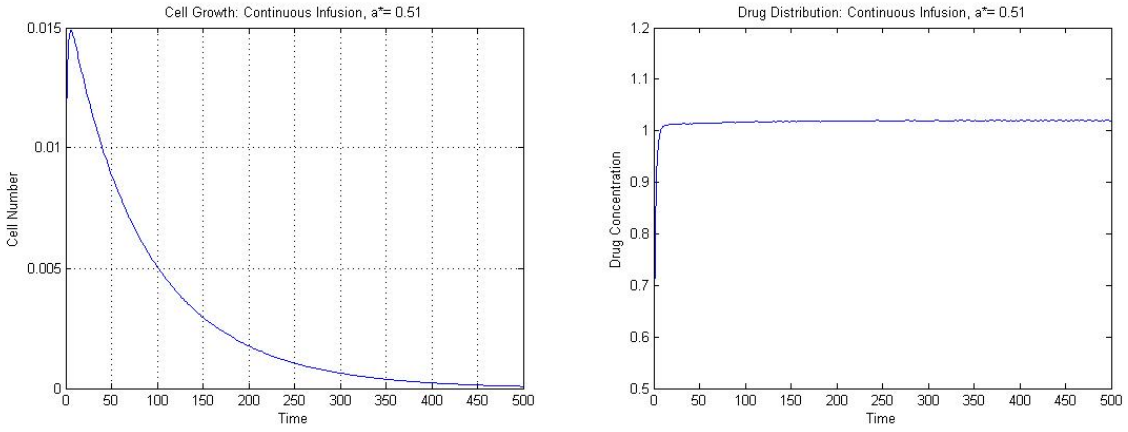


Figure 7: Model results: The tumor dies (via MATLAB [21], $a^* = 0.51$)

We now use the parameters $k = 0.5, \Theta = 1, \mu = 0.5, \lambda_1 = 0.3, \lambda_2 = 0.5, N_0 = 0.01$. So we know $\frac{\Theta\lambda_2}{\lambda_1} = 1.667 > 1$ and thus we have for small $a^* < \frac{\lambda_1 k}{\mu} = 0.3$ (e.g. $a^* = 0.29$, fig. 8) one asymptotically stable nontrivial fixed point $(0.445, 0.555)$.

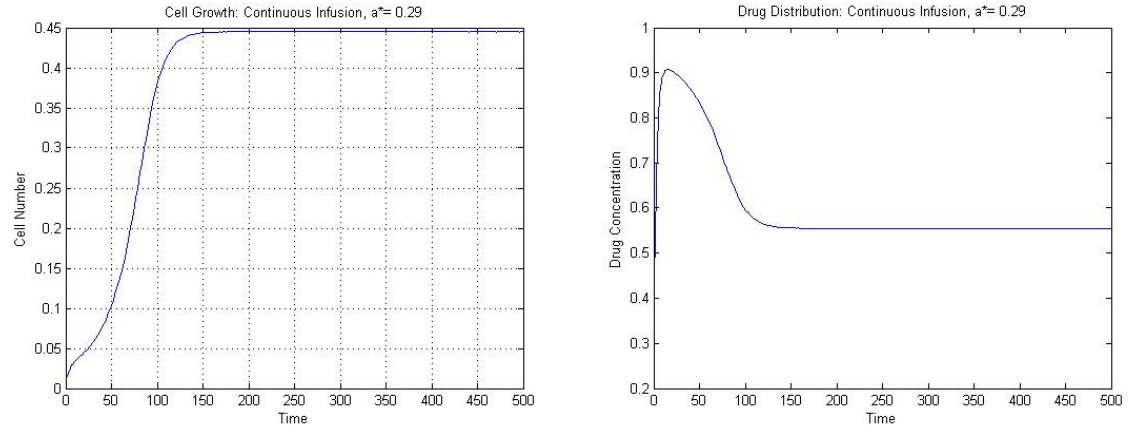


Figure 8: Model results: The tumor remains (via MATLAB [21], $a^* = 0.29$)

If $a^* = 0.31$ we have an asymptotically stable trivial steady state $(0, 1.033)$ and an asymptotically stable nontrivial equilibrium $(0.341, 0.659)$. We converge to one of the two, depending of our initial value (if it is bigger or smaller than the second nontrivial fixed point $(0.059, 0.941)$).
So, for $N_0 = 0.01$ (fig. 9) we have convergence to $(0, 1.033)$ and for $N_0 = 0.06$ (fig. 10) we have convergence to $(0.341, 0.659)$.

MATLAB only displays a numerical solution, therefore the plots are not always precise for values a^* very close to $\frac{\lambda_1 k}{\mu}$. However, this allows to confirm our analysis. As the stabiliy analysis is not globally, we have to choose N_0 close to zero if we want to show the trivial equilibrium is asymptotically stable.

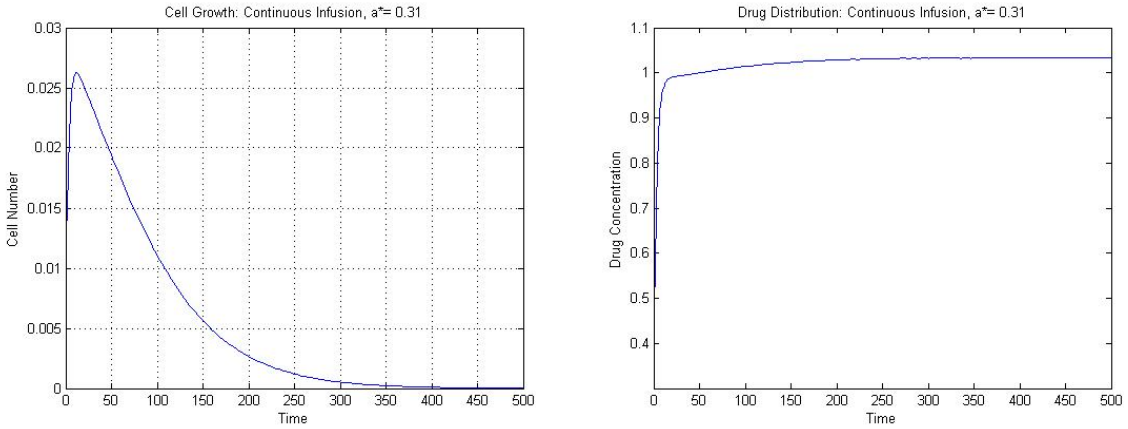


Figure 9: Model results: The tumor dies off (via MATLAB [21], $a^* = 0.31$, $N_0 = 0.01$)

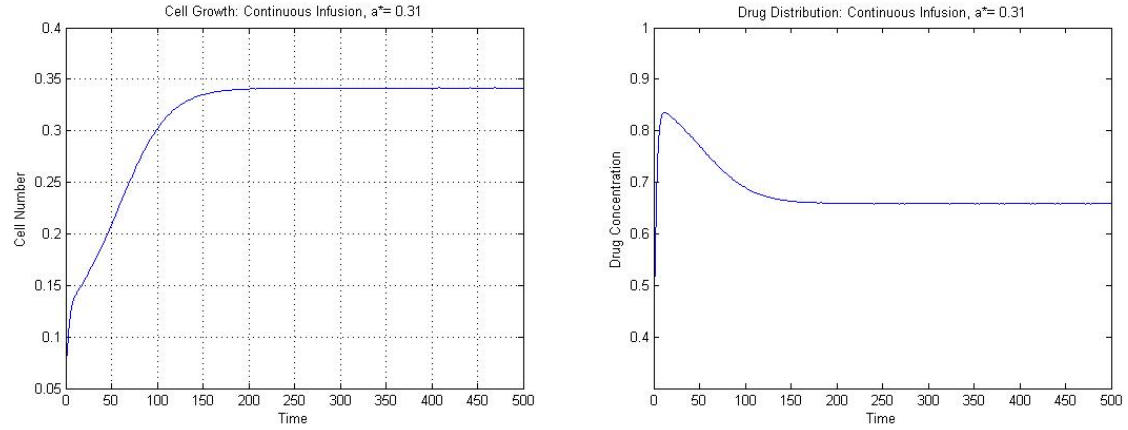


Figure 10: Model results: The tumor remains (via MATLAB [21], $a^* = 0.31$, $N_0 = 0.06$)

Periodic Injection For the periodic infusion we once again solve the equation (2.3) with MATLAB, this time with $a(t) = a^*$ for $n < t < n+\tau$ and $a(t) = 0$ for $n+\tau < t < n$. Again we plot its numerical solution for the time period $[0, 500]$.

As in the case of continuous infusion we choose $k = 0.5, \Theta = 1, \mu = 0.5, \lambda_1 = 0.5, \lambda_2 = 0.3$ and $N_0 = 0.01$. For simulating a steady change between the phase of exposure to the chemotherapeutic and the phase of regeneration, we further define $\tau = 0.5$. For this parameters the bifurcation point for the injection a^* is $\frac{k\lambda_1}{\mu}\frac{1}{\tau} = 1$.

Therefore, for $a^* = 0.9$ (fig. 11) the tumor remains alive as too much cells recover during the regenartion phase. But as $\frac{\Theta\lambda_2}{\lambda_1} < 1$ and $\frac{\lambda_1 k}{\mu} = 0.5 < 0.9 = a^*$ we have no steady state during the infusion $(n < t < n + \tau)$ except of the trivial one. During the recovering phase $(n + \tau < t < n + 1,\ a(t) = 0)$ we have a nontrivial fixed point $N(t) = 1$.
We do not have a more precise declaration for the nontrivial equilibrium.

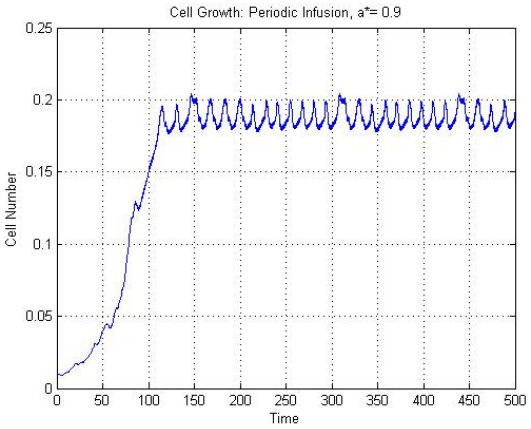


Figure 11: Model results: The tumor remains (via MATLAB [21], $a^* = 0.9$)

For $a^* = 1.1$ (fig. 12) not enough cancer cells regenerate for balancing the big number of dying cells and thus the tumor dies off.
For the drug concentration A we have no exact information in both of the cases. But we know the drug concentration converges to $A^* = \frac{a(t)}{\lambda_1}$ for $a^* = 1.1 > \frac{k\lambda_1}{\mu}\frac{1}{\tau}$, and as $a(t)$ switches between zero and a^* we get an oscillation for $A(t)$.

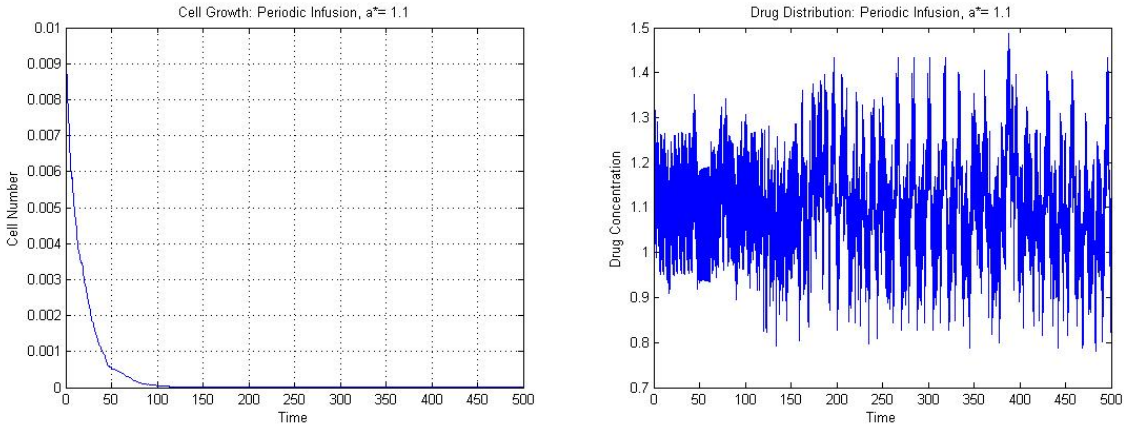


Figure 12: Model results: The tumor dies off (via MATLAB [21], $a^* = 1.1$)

Also in the case of periodic infusion we have some inaccuracies because of solving the ode numerically. But we can see well how the cells and the drug behave in general.

2.4 Radiotherapeutic Treatment

Another posibility for medical treatment of cancer tumors is radiotherapy, also called radiation therapy and often applied post-operative (meaning after surgery). Here,

the tumor gets penetrated with high-energy radiation, damaging the DNA of the cancer cells. This radiation can i.e. consist of γ-, electron- or proton-rays ([4]).
This rays have an ionizing effect, meaning they break up the chemical compounds of the energetic neutral tumor cells. The positively charged restovers of them remain, while free radicals are split off. Radicals are atoms or molecules with at least one unpaired electron and thus they are very reactive.
The ionization directly damages the cancer cells. Furthermore, the free radicals attack amongst others the genetic material of surrounding, nearby cancer cells leading (if there is no possibility to repair or if they are misrepaired) to their death. Induced through this secondary damage, a chain reaction starts(compare [13]).
The unit of measurement for the energy dose which is released while irradiation is one Gray ($1Gy = 1\frac{Joule}{kg}$).
Radiation, as chemotherapy, damages also normal cells, in addition the cancer cells mutate and develop resistence against the rays. So the aim again is to minimize the deaths of the normal cells and to maximize the ones of the cancer cells, as to avoid too large doses.
For this reason, in the following we do only consider models for fractioning of the radiation dose, giving the cells time to recover (again, unfortunately also for the cancer cells).

2.4.1 Classical Model

The most widely used model for radiotherapy is the linear-quadratic (LQ) model.We define the surviving fraction N_{SF}, the fraction of cells surviving one dose $D[Gy]$ of radiation. It holds (see [1, 6, 17])

$$N_{SF} = \frac{N_{before}}{N_{after}} = e^{-\alpha D - \beta D^2}.$$

Remark. $\alpha\left[\frac{1}{Gy}\right]$, $\beta\left[\frac{1}{Gy^2}\right]$ are radio-biological parameters. Simplified, αD represents the cell kill due to double strand breaks of the cell's double helix while βD^2 arises from cell kill through single strand breaks of the helix that require an encounter of two cells.
$\frac{\alpha}{\beta}[Gy]$ is called the sensivity- or α-β-ratio. This is the dose for which the contribution to N_{SF} from the two terms is equal. It indicates how fast the cancer cells reproduce themselves between treatments (the higher, the faster the reproduce). That also means α is big if the effect of the radiation arises early and β is relatively big if the effect occurs late.
It is also possible to include the growth of the tumor between the radiation doses.

Although the model seems to correnspond well with reality, it is quite difficult to determine the parameters α and β. So we try another model in the following chapter.

2.4.2 Adapted Model

A big difference between chemotherapy and radiotherapy from the mathematical point of view is, that many of the cells do not die instantly. The checkpoints realize the cell is damaged and try to repair it. Only if the cell cannot be repaired, it is eliminated. Sometimes cells are misrepaired but not separated, so this ones again divide and pass over their damage to the daughter cells. Thus, the effect of the rays on the cell number is not just linear, but also depends on how fast the cells proliferate.
Another difference is that the cells do not consume radiation, meaning the only thing conteracting the growth of the radiation concentration is decay at a constant rate.
For the growth of the cells in the radiation model we use the generalized logistic law (2.1).
So we obtain a model similar but not identical to the model for chemotherapeutic treatment.

$$\begin{aligned}\frac{dN}{dt}(t) &= \frac{k}{\alpha}N(t)\left(1-\left(\frac{N(t)}{\Theta}\right)^{\alpha}\right) - N(t)A(t)(\mu_1+\mu_2\frac{k}{\alpha}N(t)\left(1-\left(\frac{N(t)}{\Theta}\right)^{\alpha}\right)\\ \frac{dA}{dt}(t) &= a(t)-\lambda A(t)\end{aligned} \tag{2.7}$$

$$N(t=0)=N_0, \qquad A(t=0)=A_0$$

As we want to analyze periodic infusion, we use again

$$a(t)=\begin{cases} a^*, & n<t<n+\tau \\ 0, & n+\tau<t<n+1\end{cases}$$

Remark. $\mu_1 >$ is the linear part of the rate of cells kills when the tumor is hit by radiation. μ_2 is the rate weighting the influence of the cell growth on the cell deaths. The parameters Θ, k and α are as above and thus indicate the carrying capacity, the proliferation rate and how fast the capacity is reached, whilst λ is the decay rate of the radiation. $a(t)$ accordingly is the administered radiation at time t, $0<\tau<1$ is the duration of the irratiation and n the number of doses that have already been given.

Again we are only interested in the stability of the trivial equilibrium. Therefore we linearize around the fixed point $(N^*, A^*) = (0, \frac{a(t)}{\lambda})$.

$$\begin{pmatrix}\dot{\bar{N}}\\ \dot{\bar{A}}\end{pmatrix} = \begin{pmatrix}(k-\frac{\mu a(t)}{\lambda_1})\bar{N}\\ -\lambda_1\bar{A}-\frac{\lambda_2 a(t)}{\lambda_1}\bar{N}\end{pmatrix} = \begin{cases}\begin{pmatrix}\frac{k}{\alpha} & 0\\ 0 & -\lambda\end{pmatrix}\begin{pmatrix}\bar{N}\\ \bar{A}\end{pmatrix}, & n<t<n+\tau\\ \begin{pmatrix}(\frac{k}{\alpha}-\frac{\mu_1 a^*}{\lambda}) & 0\\ 0 & -\lambda\end{pmatrix}\begin{pmatrix}\bar{N}\\ \bar{A}\end{pmatrix}, & n+\tau<t<n+1\end{cases}$$

The solution of this linearized system is

$$\begin{aligned} N(t) &= N(n)e^{\frac{k}{\alpha}(t-n)-\frac{a^*}{\lambda}(t-n)} && \text{for } n<t<n-\tau,\\ N(t) &= N(n+\tau)e^{\frac{k}{\alpha}} && \text{for } n+\tau<t<n+1.\end{aligned}$$

As above we want $N(n+\tau)$ which is, as $N(t)$ again is supposed to be stable, $N(n+\tau) = N(n)e^{\frac{k}{\alpha}\tau - \frac{a^*}{\lambda}\mu_1\tau}$.
It follows $N(t) = N(n)e^{\frac{k}{\alpha}(t-n) - \frac{a^*}{\lambda}\mu_1\tau}$ for $n+\tau < t < n+1$, and therefore

$$N(n+1) = N(n)e^{\frac{k}{\alpha} - \frac{a^*}{\lambda}\mu_1\tau}.$$

So we have $N(n+1) < N(n) \forall n$ and thus stability of the trivial fixed point for $a^* > \frac{k\lambda}{\alpha\mu_1}\frac{1}{\tau}$ and $N(n+1) > N(n) \forall n$, meaning instability, for $a^* < \frac{k\lambda}{\alpha\mu_1}\frac{1}{\tau}$.
The biological interpretation again is: For big radiation doses a^* we achieve the necrosis of the tumor, but if the dose is too small, the tumor stays alive.

2.4.3 Discussion

As we have the data provided by [20], we want to use it for the verification of the established model.
The experiment that revealed the information about the cell number in a tumor is performed the following way (according to [13]).
Cells of a certain line are placed on a plate and consecutively put into and taken out of a γ-radiation field (thus $\tau := 0.5$). In the field prevails a constant γ-irradiation.
The cellular response is measured in Cell Index values with the xCELLigence System, a real-time cell analyzer monitoring cell proliferation and cytotoxic effects. The Cell Index is a designed unit, which is zero if no cells do exist. If the number of cells expand, the CI grows accordingly.

We choose the data series for T47D cells (human ductal breast epithelial tumor cells). The Cell Index is measured and registered, one after another, for radiation doses of 0, 2.5, 5 and 7.5 Gy, each time over a time period of nearly 142 hours.
We again use MATLAB [21] to plot numerically the solution of the equation (2.7) for suitable parameters, setting $a^* = 0, 2.5, 5$ or $a^* = 7.5$ and compare the resulting charts to the four data graphs.
We equate the parameters of (2.7) to $\alpha = 0.05, k = 0.001, \Theta = 4.8, \mu_1 = 0.000007, \mu_2 = 0.05, \lambda = 1$ and $N_0 = 0.01$.
This way, we receive the presented plots, every one of them showing the model for one given a^* in comparison to the data.
We see also this model fits well. The only bigger error already arises in the growth curve without radiation (ca. between hour 10 and 40) and thus is maintained throughout the calculation. It arises because of the experimental equipment.

For both of the treatments it holds: The models (2.3) and (2.7) are quite simplified. This is their biggest benefit but also their biggest disadvantage. They are easy to handle, so also the professional categories working on the models in the end (such as biologists or physicians) can understand it well. On the other hand, not all of the assumptions are realistic. So it is problematic to apply the models generally.

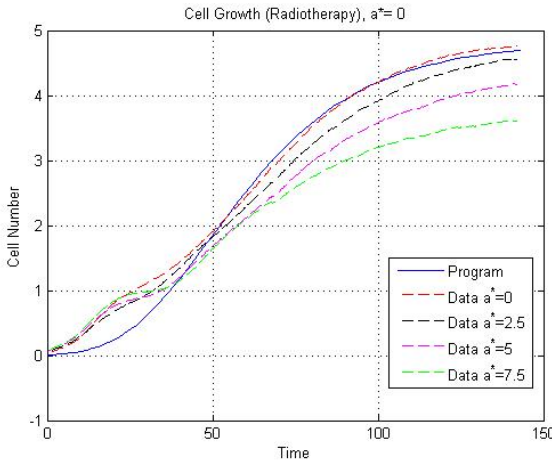


Figure 13: Cell Growth: Model vs. Data, using MATLAB [21], $a^* = 0$

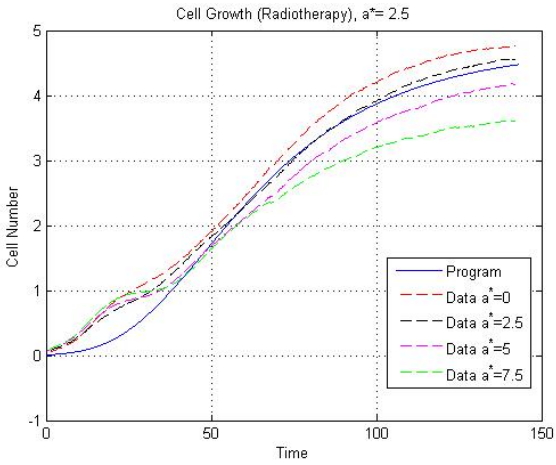


Figure 14: Cell Growth: Model vs. Data, using MATLAB [21], $a^* = 2.5$

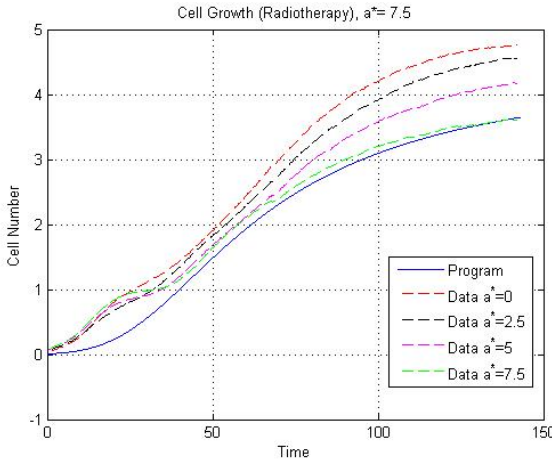


Figure 15: Cell Growth: Model vs. Data, using MATLAB [21], $a^* = 7.5$

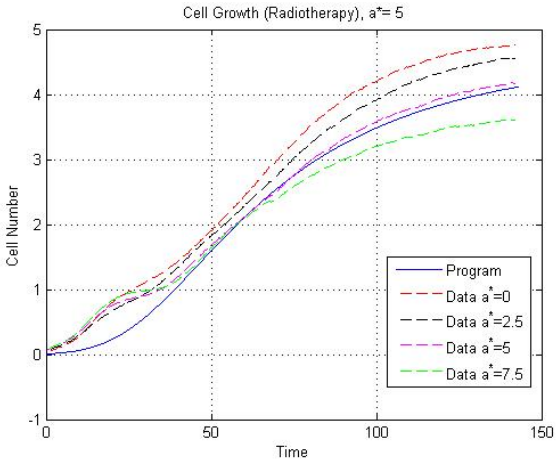


Figure 16: Cell Growth: Model vs. Data, using MATLAB [21], $a^* = 5$

3 Structure-Regarding Model of Avascular Tumors

As we know, the well-developed avascular tumor has three layers: the inner necrotic core, a ring of quiescent cells and an outer tier of proliferating cells. We want to introduce a model which includes this statement.

3.1 The Model

Again we assume that the avascular tumor consists of only one type of cells, so we have a homogeneous tumor (it is possible to vary the model to have a model for

heterogeneous tumors; the three layers are layers of cells with different proliferation rates which react differently to environmental influences, so they can be interpreted correspondingly as layers of different cells).

Additionally we assume the avascular tumor and its extension is radially-symmetric and furthermore the growth is one-dimensional. We observe the volume of the tumor under the influence of a diffusible chemical, entering the tumor from the surrounding tissue. Assume this chemical is nutrient for the cells (e.g. oxygen), but this model (after variation) serves also for growth-repressing chemicals.

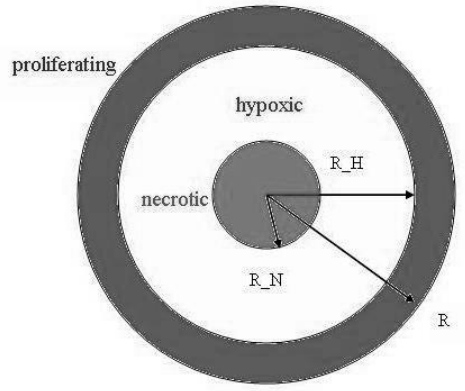


Figure 17: Three Layers of the Tumor

We consider the following model for the concentration $c(r,t)$ of the observed chemical at distance r from the core and time t, and the volume of the tumor if it has an outer radius $R(t) > 0$. As R changes in time, this is a moving boundary problem. We took the model from [3], but it was firstly introduced by Greenspan.

$$\frac{\partial c}{\partial t} = D\frac{1}{r^2}\cdot\frac{\partial}{\partial r}\left(r^2\frac{\partial c}{\partial r}\right) - \Gamma(c,R,R_H,R_N) \tag{3.1}$$

$$\frac{d}{dt}(\frac{1}{3}R^3) = \int_0^R P(c,R,R_H,R_N)\cdot r^2 dr - \int_0^R N(c,R,R_H,R_N)\cdot r^2 dr \tag{3.2}$$

for

$$\Gamma(c,R,R_H,R_N) = \gamma H(r-R_H),$$
$$P(c,R,R_H,R_N) = pcH(r-R_H),$$
$$N(c,R,R_H,R_N) = p\delta_A + p\delta_N H(R_N - r)$$

and Heaviside-function

$$H(r) = \begin{cases} 1, & r > 0 \\ 0, & r \le 0 \end{cases}$$

Remark. R_H is the distance from the core (radius) the proliferating and hypoxic cells are separated at, and R_N the distance of isolation of hypoxic and quiescent cells. Both radii can be obtained through observation.
Equation (3.1) describes the change of the concentration of the chemical, this is raised by the flux caused by diffusion under constant diffusion D (according to Fick's law), and lowered by the consumption of the nutrient by the cells. The latter

is described through the function Γ, we assume the proliferating just as the quiescent cells consume oxygen at a constant rate γ. Necrotic cells do not consume oxygen any more.
(3.2) is an equation identifying the change of the tumor volume with the difference of cell proliferation rate $P(c, R, R_H, R_N)$ and cell deaths $N(c, R, R_H, R_N)$. Proliferation occurs only for $r > R_H$, depending of the nutrient concentration $c(r,t)$, so we have the growth rate $p \cdot c(r,t)$. All cells die due to apoptosis at constant rate $p \cdot \delta_A$ and the inner cells additionally because of necrosis also at constant rate $p \cdot \delta_N$ (for $p, \delta_A, \delta_N \geq 0$ constants), but only if $r < R_N$.

Inserting the equations for P and N into (3.2) we obtain

$$\frac{d}{dt}(\frac{1}{3}R^3) = p\int_{R_H}^{R} c(r,t)r^2dr - p\frac{1}{3}(\delta_A R^3 + \delta_N R_N^3). \tag{3.3}$$

We add following initial and boundary conditions to close our problem (3.1),(3.3)

$$\begin{aligned}
&\frac{\partial c}{\partial r}(0,t) = 0\\
&c(R(t),t) = c^*\\
&c(r,0) = c_0(r)\\
&R(0) = R_0,
\end{aligned}$$

and assume that $c(r,t)$, $\frac{\partial c}{\partial r}(r,t)$ are continuous.
Further we define $c_H = c(R_H(t),t)$ as the nutrient concentration which is necessary for proliferation and $c_N = c(R_N(t),t)$, the concentration for which necrosis occurs.
So our problem is the following: We vary the nutrient inflow c^* and observe the effect on the concentration in the tumor and the radius.

3.1.1 Nondimensionalization

For further analysis we want to simplificate our model. Thus we perform nondimensionalization.
So we firstly set ([3])

$$\begin{aligned}
&C{:=}\text{typical unit for nutrient concentrations}\\
&T{:=}\text{typical unit for time}\\
&X{:=}\text{typical unit for length}
\end{aligned}$$

and accordingly define

$$\bar{c} = \frac{c}{C}, \quad \bar{t} = \frac{t}{T}, \quad \bar{r} = \frac{r}{X}, \quad \bar{R} = \frac{R}{X}, \quad \bar{R_H} = \frac{R_H}{X}, \quad \bar{R_N} = \frac{R_N}{X}.$$

For our calculations it is not necessary to specify the units more precisely.
We insert this variables, which hence are dimensionless, into (3.1) and (3.2).

$$\begin{aligned}&\frac{d}{d\bar{t}}(\frac{1}{3}\bar{R}^3) = \bar{R}^2\frac{\partial\bar{R}}{\partial\bar{t}} = \bar{R}^2\frac{T}{X}\frac{\partial R}{\partial t}\\ &= \frac{\bar{R}^2\cdot T}{X\cdot\bar{R}^2X^2}\left[\int_0^{\bar{R}X} sC\bar{c}H(\bar{r}-\bar{R_H})\bar{r}^2X^2 - \int_0^{\bar{R}X} s\lambda_A + s\lambda_N H(\bar{R_N}-\bar{r})\bar{r}^2X^2\right]\end{aligned}$$

and via substitution we receive

$$\frac{d}{d\bar{t}}(\frac{1}{3}\bar{R}^3) = \int_0^{\bar{R}}\left[sCT\bar{c}H(\bar{r}-\bar{R_H}) - sT\lambda_A - sT\lambda_N H(\bar{R_N}-\bar{r})\right]\bar{r}^2d\bar{r}. \tag{3.4}$$

Further:

$$\frac{\partial\bar{c}}{\partial\bar{t}} = \frac{\partial}{\partial\bar{t}}\frac{c(\bar{t}\cdot T)}{C} = \frac{TD}{X^2}\frac{1}{\bar{r}^2}\cdot\frac{\partial}{\partial\bar{r}}\left(\bar{r}^2\frac{\partial\bar{c}}{\partial\bar{r}}\right) - \frac{\gamma}{C}TH(\bar{r}-\bar{R_N}). \tag{3.5}$$

There are three parameter sets including the timescale in this equations: $\frac{TD}{X^2}$, $\frac{\gamma}{C}T$ and sCT. We want to set T s.t. at least one parameter vanishes. We choose $T = \frac{1}{sC}$. Furthermore, experiments revealed that $\frac{X^2}{D} << \frac{1}{sC}$ and we assume $\mathcal{O}(\gamma) = \mathcal{O}\left(\frac{D}{X^2}\right) >> \mathcal{O}\left(\frac{1}{T}\right)$.
Multiplying (3.5) by $\frac{X^2}{TD}$ and defining $\bar{\gamma} := \frac{\gamma X^2}{CD}$, $\bar{\lambda_A} := sT\lambda_A$ $\bar{\lambda_N} := sT\lambda_N$ we get our **nondimensionalized problem**

$$0 = \frac{1}{\bar{r}^2}\cdot\frac{\partial}{\partial\bar{r}}\left(\bar{r}^2\frac{\partial\bar{c}}{\partial\bar{r}}\right) - \bar{\gamma}H(\bar{r}-\bar{R_N}) \tag{3.6}$$

$$\frac{d}{d\bar{t}}(\frac{1}{3}\bar{R}^3) = \int_0^{\bar{R}}\left[\bar{c}H(\bar{r}-\bar{R_H}) - \bar{\lambda_A} - \bar{\lambda_N}H(\bar{R_N}-\bar{r})\right]\bar{r}^2d\bar{r}. \tag{3.7}$$

The boundary and initial conditions change accordingly

$$\begin{aligned}&\frac{\partial\bar{c}}{\partial\bar{r}}(0,\bar{t}) = 0\\ &\bar{c}(\bar{R}(\bar{t}),\bar{t}) = \bar{c^*}\\ &\bar{c}(\bar{r},0) = \bar{c_0}(r)\\ &\bar{R}(0) = \bar{R_0}\\ \bar{c}(\bar{R_H},\bar{t}) = \bar{c_H},\quad &\bar{c} > \bar{c_H}\quad \forall r\in(0,\bar{R}) \Rightarrow R_H = \bar{R}_N = 0\\ \bar{c}(\bar{R_N},\bar{t}) = \bar{c_N},\quad &\bar{c} > \bar{c_N}\quad \forall r\in(0,\bar{R}) \Rightarrow \bar{R_N} = 0,\end{aligned}$$

$$\text{where}\quad \bar{c^*} = \frac{c^*}{C},\quad \bar{c_H} = \frac{c_H}{C},\quad \bar{c_N} = \frac{c_N}{C}.$$

We also still want the continuity of $\bar{c}(r,t)$ and $\frac{\partial\bar{c}}{\partial r}(r,t)$.

3.1.2 Further Simplification

Starting from now we neglect the bars and work directly on the nondimensionalized model (3.6), (3.7).
The goal is to express the nutrient concentration $c(r,t)$ in terms of R, R_H, R_N and to find equations for R_H and R_N in terms of R ([3]).

We solve equation (3.6) directly and for this purpose differentiate two cases.

Case 1: $r \le R_N$ (within the necrotic core)
The equation we want to solve is $\frac{\partial}{\partial r}\left(r^2 \frac{\partial c}{\partial r}\right) = 0$, which general solution is $c(r,t) = v_1 - \frac{v_2}{r}$.
We use following conditions to specify the (at the moment unknown) v_1 and v_2:

- $c(R_N,t) = c_N \quad \Rightarrow v_1 = c_N$
- $\frac{\partial c}{\partial r}(0,t) = 0 \quad \Rightarrow v_2 = 0$, so we get

$$c(r,t) \equiv c_N,$$

which means the necrotic cells suffer a constant nutrient concentration equal to the boundary limit c_N.

Case 2: $r > R_N$ (within the outer rims)
We search for solutions of $\frac{\partial}{\partial r}\left(r^2 \frac{\partial c}{\partial r}\right) = \gamma r^2$, which are of the type $c(r,t) = \frac{1}{6}\gamma r^2 + v_1 - \frac{v_2}{r}$.
Additionally we want

- $c(R,t) = c^* \quad \Rightarrow v_1 = c^* - \frac{1}{6}\gamma R^2 + \frac{v_2}{R}$
- $\lim_{r \to R_N} c(r,t) = c_N \quad \Rightarrow v_1 = c_N - \frac{1}{6}\gamma R_N^2 + \frac{v_2}{R_N}$.

We finally get the solution

$$c(r,t) = c_N + \frac{\gamma}{6r}\left[r^3 + R_N^2(R-r) + RR_N(R-r) - R^2 r\right] + \frac{R}{r}\frac{c_N - c^*}{R_N - R}(r - R_N).$$

As we'll see that for different sizes of R we get different equations for c, R, R_H and R_N, we distinguish three cases.

a) $\mathbf{0 < R^2 < \frac{6}{\gamma}(c^* - c_H)}$ For all $R_N < r < R$ and $0 < R < \frac{6}{\gamma}(c^* - c_H)$ we want $c \ge c_N$, which means that cells in the hypoxic or proliferating rim require more nutrient than the ones in the necrotic core. More precisely:

$$r^3 + R_N^2 R - R_N^2 r + R^2 R_N - RR_N r - R^2 r + \frac{6R}{\gamma}\frac{r - R_N}{R - R_N}(c^* - c_N) \ge 0.$$

This is now fulfilled for $R_N = 0$, and consequently we get

$$c(r,t) = c^* + \frac{\gamma}{6}(r^2 - R^2).$$

Additionally we require $c > c_H \quad \forall R_H < r < R, 0 < R < \frac{6}{\gamma}(c^* - c_H)$. For $r < R_N$ we want $c(r,t) = c_N \leq c_H$.
We choose R smaller but close to $\frac{6}{\gamma}(c^* - c_H)$: $\quad c(r,t) \searrow c^* + \frac{\gamma}{6}r^2 - c^* + c_H$,
so $c(r,t) \searrow c_H$ for $r \searrow 0 = R_N$; therefore it is

$$R_H = R_N = 0.$$

We receive following equation for $R(t)$.

$$\begin{aligned}\frac{dR}{dt} &= \frac{1}{R^2}\int_0^R c^* r^2 + \frac{1}{6}\gamma r^4 - \frac{1}{6}\gamma R^2 r^2 dr - \frac{1}{3}R^3\lambda_A - 0 \\ &= \frac{R}{3}\left(c^* - \lambda_A - \frac{\gamma R^2}{15}\right) \end{aligned} \tag{3.8}$$

Summarizing, for small tumor radii we have neither necrotic nor hypoxic cells but only proliferating ones.

b) $\frac{6}{\gamma}(c^* - c_H) < R^2 < \frac{6}{\gamma}(c^* - c_N)$ Analogously to case a) we get for $c(r,t)$

$$c(r,t) = c^* + \frac{\gamma}{6}(r^2 - R^2), \quad R_N = 0.$$

Now picking R close to $\frac{6}{\gamma}(c^* - c_N)$ we have: $\quad c(r,t) \searrow c^* + \frac{\gamma}{6}r^2 - c^* + c_N$,
so $c(r,t) \searrow c_N$ for $r \searrow 0 = R_N$
and $c(r,t) \searrow c_N + \frac{\gamma}{6}R_H^2$ for $r \searrow R_H$.
This means $\exists r \in [R_N, R_H]: \quad c_N < c(r,t) \leq c_H$

$$\Rightarrow 0 = R_N < R_H.$$

We hence want to determine the equation for R_H.

$$\begin{aligned} c(R_H,t) = c_H &\Leftrightarrow -(c^* - c_H)\frac{6}{\gamma} + R^2 = R_H^2 \\ \Rightarrow R_H &= \sqrt{R^2 - \frac{6}{\gamma}c^* + \frac{6}{\gamma}c_H} \end{aligned} \tag{3.9}$$

For $R(t)$ we operate the following way.

$$\begin{aligned}\frac{dR}{dt} &= \frac{1}{R^2}\int_{R_H}^R c^* r^2 + \frac{1}{6}\gamma r^4 - \frac{1}{6}\gamma R^2 r^2 dr - \frac{1}{3}R^3\lambda_A - 0 \\ &= \frac{R}{3}\left[\left(c^* - \frac{\gamma R^2}{6}\right)\left(1 - \frac{R_H^3}{R^3}\right) + \frac{\gamma R^2}{10}\left(1 - \frac{R_H^5}{R^5}\right) - \lambda_A\right] \end{aligned} \tag{3.10}$$

This means for a radius in this range of values the tumor contains not only proliferating but already hypoxic cells. Once again there exists no necrotic core.

c) $\frac{6}{\gamma}(c^* - c_N) < R^2$ If the radius of the tumor exceeds the value $\sqrt{\frac{6}{\gamma}(c^* - c_N)}$ the tumor possesses a necrotic core, and of course also a hypoxic and a proliferating layer. Therefore it is fully developed.
This is because under the assumption $R_N = 0$ it holds
$c = c^* + \frac{\gamma}{6}(r^2 - R^2) < c_N$, which stands in contradiction to the above supposition and thus $R_N \neq 0$.

The boundary values $c(R_N, t) = c_N, c(R, t) = c^*$ are satisfied without further requirements.
Also, we want $c(R_H, t) = c_H$ to be valid. For this we need additional conditions, so we firstly inlude

$$\frac{6}{\gamma R^2}(c^* - c_N) = \left(1 - \frac{R_N}{R}\right)^2 \left(1 + \frac{2R_N}{R}\right) \tag{3.11}$$

and rewrite $c(R_H, t)$ into
$c(R_H, t) = c_N + \frac{\gamma}{6}R_H^2 + \frac{\gamma}{6R_H}\left[R_N^2(R - R_H) + R^2(R_N - R_H) - RR_NR_H\right.$
$\left. + (R_N - R)(R_N - R_H)(R + 2R_N)\right]$ to get a second one:

$$\frac{6}{\gamma R_H^2}(c_H - c_N) = \left(1 - \frac{R_N}{R_H}\right)^2 \left(1 + \frac{2R_N}{R_H}\right).$$

Under this two conditions the wanted requirement $c(R_H, t) = c_H$ is fulfilled.

Including them into the equation for $c(r, t), r > R_N$ we receive

$$c(r,t) = \begin{cases} c_N, & 0 \le r \le R_N \\ c_N + \frac{\gamma}{6r}(r - R_N)^2(r + 2R_N), & R_N < r \le R. \end{cases}$$

For $R(t)$ we proceed accordingly:

$$\begin{aligned} \frac{dR}{dt} =& \frac{1}{R^2}\int_{R_H}^{R} c(r,t)r^2 dr - \frac{1}{3}R^3\lambda_A - \frac{1}{3}R_N^3\lambda_N \\ =& \frac{R}{3}\left[c_N\left(1 - \frac{R_H^3}{R^3}\right) - \lambda_A - \lambda_N\frac{R_N^3}{R^3}\right] \\ &+ \frac{\gamma}{6}R^3\left[\frac{1}{5}\left(1 - \frac{R_H^5}{R^5}\right) - \frac{R_N^2}{R^2}\left(1 - \frac{R_H^3}{R^3}\right) + \frac{R_N^3}{R^3}\left(1 - \frac{R_H^2}{R^2}\right)\right] \end{aligned} \tag{3.12}$$

3.2 Model Behaviour

Finally, we obtained a model we can work with. We have three different cases: Small tumors, which only contain proliferating cells. The larger ones, where some of the cells have not enough nutrient to grow further. And tumors so big, including quiescents and where the inner cells die of hunger. For the different sizes we have

got different equations for $c(r,t), R(t), R_H(t)$ and $R_N(t)$.
As a complete analysis of the model would exceed the dimension of the thesis and often requires an complex numerical analysis, we confine ourselves to three special cases.

3.2.1 Small Tumor: $0 < R < \frac{6}{\gamma}(c^* - c_H)$

For small tumors (case a)) we do have two steady states $R^*_{1,2}$ of the outer tumor radius (3.8), as
$\frac{R^*}{3}\left(c^* - \lambda_A - \frac{\gamma R^{*2}}{15}\right) = 0 \Leftrightarrow R_1^{*2} = \frac{15}{\gamma}(c^* - \lambda_A)$ or $R_2^{*2} = 0$.
Further we know

- $\frac{dR}{dt} < 0 \Leftrightarrow R^2 > R_1^{*2}$
- $\frac{dR}{dt} > 0 \Leftrightarrow R^2 < R_1^{*2}$

R_1^* is a valid solution ($R_1^{*2} < \frac{6}{\gamma}(c^* - c_H)$) if and only if

$$\frac{5}{2}(c^* - \lambda_A) < c^* - c_H \qquad (\Leftrightarrow c > c_H \quad \forall r) \tag{3.13}$$

Under this condition the tumor stays in the state of just having proliferating cells. If (3.13) does not hold, the tumor grows up into the next stage, developing a quiescent rim, as $\frac{dR}{dt}(t) > 0 \quad \forall t$ then.
We can conclude, that if the nontrivial steady state R_1^* exists ($c^* > \lambda_A$) and (3.13) holds it is asymptotically stable and R_2^* is unstable. For the case $c^* < \lambda_A$, the nontrivial fixed point does not exist in a biologically sensible way as it is negative, so the only equilibrium we consider is $R_1^* = 0$ and this one now is asymptotically stable. Descriptively, this means if the external nutrient concentration is small enough ($c^* < \lambda_A$), the tumor dies as the nutrient supply is too bad. But if $c^* > \lambda_A$ the tumor levels out at radius $R_2^* < \frac{6}{\gamma}(c^* - c_H)$ or, if (3.13) is not valid (so if the outer nutrient c^* falls below a value depending on the apoptosis rate λ_A and on the nutrient concentration necessary for proliferation c_H,) , exceeds to the next stage (existence of hypoxic rim).

We also can show an equivalence to the model in section 2.1. If we use equation (3.8) and substitute $V(t) = \frac{4}{3}\pi R(t)^3$ we obtain such an equilvalent version, showing how the pure cell number is connected to the tumor volume:

$$\begin{aligned}
\frac{dV}{dt}(t) &= V(t)\left(c^* - \lambda_A - \left(\frac{\gamma}{15}\frac{3}{4\pi}V(t)\right)^{\frac{3}{2}}\right) \\
&= \frac{2/3(c^* - \lambda_A)}{2/3}V(t)\left(1 - \left(\frac{V}{4\pi/3 \cdot [15/\gamma \cdot (c^* - \lambda_A)]^{3/2}}\right)^{2/3}\right) \\
&=: \frac{k}{\alpha}V(t)\left(1 - \left(\frac{V(t)}{\Theta}\right)^{\alpha}\right)
\end{aligned}$$

3.2.2 Tumor With Quiescent Region: $\frac{6}{\gamma}(c^* - c_H) < R^2 < \frac{6}{\gamma}(c^* - c_N)$

We consider a tumor (case b)) with a quiescent rim but without necrotic core, therefor $R_N = 0$. We already know (3.9) and conclude $\frac{dR_H}{dt} = \frac{R}{R_H}\frac{dR}{dt}$.
As $R > R_H$ it follows $\frac{dR_H}{dt} > \frac{dR}{dt}$,([3])
which means that when the tumor grows so does the radius of the hypoxic region, and even faster than the radius of the entire tumor.

3.2.3 Tumor With Small Necrotic Core: $0 < R_N = R_H << R \sim \mathcal{O}(1)$

The tumor we want to work on now is a big one wich possesses a necrotic core (case c))([3]). We further assume the shift from quiescence to necrosis is very quick and smooth, meaning $R_N = R_H, c_N = c_H$. The intention is to analyse the behaviour around that moment when the necrotic nucleus arises. For that, suppose

$$R(t) \sim R_0(t) + \epsilon R_1(t) + \epsilon^2 R_2(t), \quad R_N(t) \sim \epsilon R_{N1}(t) \quad \text{for } \epsilon \text{ small.}$$

Inserting this polynomial into (3.11) and making comparison of coefficients of $\mathcal{O}(\epsilon)$ implies

$$R_0 = \sqrt{\frac{6}{\gamma}(c^* - c_N)}, \quad R_1 = 0, \quad R_2(t) = \frac{3R_{N1}^2(t)}{2R_0}.$$

Substituting with the equations for R_N and R_2 in (3.12) results in a differential equation for R_2. Addtitionally icluding $\tau = \frac{t}{\epsilon^2}$ we receive

$$R_2(\tau) = R_2(\tau = 0) + R_0\left(\frac{1}{5}(c^* - c_N) - \frac{1}{3}(\lambda_a - c_N)\right)\tau.$$

Define τ^*, the time when necrosis initiates/ceases. It follows $R_2(\tau^*) = 0$, as then it holds $R^2(\tau^*) = \frac{6}{\gamma}(c^* - c_N)$.
It is $R_2(\tau^*) = 0 \Leftrightarrow \tau^* = -\frac{R_2(\tau=0)}{R_0\left[\frac{1}{5}(c^*-c_N)-\frac{1}{3}(\lambda_A-c_N)\right]}$ for $c^* < c_N + \frac{5}{3}(\lambda_A - c_N)$ (otherwise $\tau^* < 0$).
That is, if the outer nutrient concentration falls below this value, the tumor contracts and the necrotic core vanishes.
If (and only if) $c^* > c_N + \frac{5}{3}(\lambda_A - c_N)$ the necrotic core persists, $R(t) > \frac{6}{\gamma}(c^* - c_N) \quad \forall t$.

Considering $\frac{dR}{dt} = \epsilon^2\frac{dR_2}{dt} = 3\frac{R_N}{R_0}\frac{dR_N}{dt}$ we see:
As $R_N << R$ it follows $R_N << R_0$ and thus $\frac{dR_N}{dt} > \frac{dR}{dt}$,
meaning that growth of the tumor always leads to an enlargement of the necrotic core, as the growth of the radius of the inner nucleus is always bigger than the growth of the entire tumor.

3.3 Discussion

So, as we see, we can use this model to determine the spatial structure and size such as the stability of a tumor. We have seen that the spatial structure especially depends on the entire tumor Radius $R(t)$, itself affected by the outer nutrient

concentration c^* (that we vary in this thesis), the minimal nutrient necessary for proliferating c_H and the maximum nutrient concentration necrosis can occur at (c_N). Furthermore, $R(t)$ depends on the rate γ that indicates how much nutrient the cells consume.
We got equations denoting the sizes of c, R, R_H and R_N. And we can figure out, under which conditions for c^* we obtain which spatial structure (e.g. see 'Small Tumor Analysis'; the tumor remains small (or extinguishes) if (3.13) holds).

As the model is only one-dimensional it is not entirely realistic. Also the assumption of radially-symmetric tumor expansion is not totally correct especially for vascular tumors, but for avascular ones it is justifiable as the nutrient only diffuse from the surrounding tissue.

4 Outlook

So, we have got two quite different basic models and worked on some modfications of them. We received conditions for the eradication of a cancerous tumor through different types of treatment such as conditions under which it attains a certain spatial structure.
The above models can be extended and variated in many different ways, every resulting model having some special cases it serves good at.

Modification of the Structure-Neglecting Model One possible modification of the treatment-models is simply to change the growth model, e.g. to include α as in the beginning of the thesis (see equation (2.1)). This could look like this (for the continuos injection of a chemotherapeutic)

$$\frac{dN}{dt} = \frac{k}{\alpha} N \left(1 - \left(\frac{N}{\Theta}\right)^{\alpha}\right) - \mu A N$$
$$\frac{dA}{dt} = a^* - \lambda_1 A - \lambda_2 A N.$$

We can e.g. show the stability of the trivial equilibrium is similar as above. It is, for $a^* > \frac{k\lambda_1}{\alpha\mu}$ the fixed point $(0, \frac{a^*}{\lambda_1})$ is stable, and for $a^* < \frac{k\lambda_1}{\alpha\mu}$ unstable.

We also could change the equation for $A(t)$, i.e. λ_1, as the decay rate often depends linearly from environmental factors such as temperature or pressure. Also the consumption rate λ_2 can be modified by including saturation. This might describe better reality. And of course it is possible to inject the drug e.g. linearly or periodicallly but with different doses, meaning ($2n$ =number of doses, $2\tau + \epsilon \leq 1$,

$\tau, \epsilon \geq 0$)

$$a(t) = \begin{cases} a_1^*, & n < t < n + \tau \\ 0, & n + \tau < t < n + \tau + \epsilon \\ a_2^*, & n + \tau + \epsilon < t < n + 1 - \tau \\ 0, & n + 1 - \tau < t < n + 1 \end{cases}$$

to see what is the better/best way to inject a chemotherapeuthic.
Also we could analyze a model prescribing the combination of radiotherapy and chemotherapy, as this is done sometimes in practice. This is done quite precisely in paper [1].

A good extension would be to treat on a tumor consisting of cells susceptible to chemotherapeutica and additionally of those that are not. This corresponds to the adding of another equation for the non-susceptibles (which just grow logistically). The infusion of the drug is continuous, it is consumed also by the not susceptibles.

$$\begin{aligned} \frac{dN_1}{dt} &= k_1 N_1 \left(1 - \left(\frac{N_1 + N_2}{\Theta}\right)\right) - \mu A N_1 \\ \frac{dN_2}{dt} &= k_2 N_2 \left(1 - \left(\frac{N_1 + N_2}{\Theta}\right)\right) \\ \frac{dA}{dt} &= a^* - \lambda_1 A - \lambda_2 A N_1 N_2 \end{aligned}$$

It is thus possible to determine for which relation of k_1 and k_2 and under which conditions for a^* the tumor extinguishes.

To model radiotherapy, the LQ-model often is a good choice. Additionally to the surviving fraction, inclusion of growth between two doses is possible.
As the cells need time to react to the radiation therapy, it also makes sense to include delay to the model. A possible way to do this is

$$\begin{aligned} \frac{dN}{dt}(t) &= \frac{k}{\alpha} N(t) \left(1 - \left(\frac{N(t)}{\Theta}\right)^{\alpha}\right) - \mu A(t - \delta) N(t) \\ \frac{dA}{dt}(t) &= a(t) - \lambda_1 A(t) - \lambda_2 A(t) N(t) \end{aligned}$$

for delay δ.

Modification of the Spatial Model One way to modificate the model for a radially symmetric tumor and diffusion from the surrounding tissue is to replace the nutrient by a chemotherapeutic. The biggest difference is, instead of being necessary für the growth of cancer cells, the drug reduces their proliferation. So we can keep the equation for the concentration of the diffusing chemical (3.1), just introduce a third equation for the dose n(r,t) of the chemotherapeutic and change equation (3.2) for

the outer tumor radius $R(t)$. We describe the drug also according to Fick's Law.

$$\frac{\partial c}{\partial t} = D_c \frac{1}{r^2} \cdot \frac{\partial}{\partial r}\left(r^2 \frac{\partial c}{\partial r}\right) - \Gamma_c(c, R, R_H, R_N)$$
$$\frac{\partial n}{\partial t} = D_n \frac{1}{r^2} \cdot \frac{\partial}{\partial r}\left(r^2 \frac{\partial n}{\partial r}\right) - \Gamma_n(n, R, R_H, R_N)$$
$$\frac{d}{dt}(\frac{1}{3}R^3) = \int_0^R P(c, R, R_H, R_N) \cdot r^2 dr - \int_0^R N(n, R, R_H, R_N) \cdot r^2 dr$$

for

$\Gamma_c(c, R, R_H, R_N) = \gamma_c H(r - R_H)$,
$\Gamma_n(n, R, R_H, R_N) = \gamma_n H(r - R_N)$,
(the drug is consumed at a constant rate by the proliferating and hypoxic cells)
$P(c, R, R_H, R_N) = pc(r, t)H(r - R_H)$,
$N(n, R, R_H, R_N) = p\delta_A + p\delta_N n(r, t)$,
(the necrosis rate now depends on the drug concentration
and occurs overall the tumor)

A varification to model radiotherapy for a radially-symmetric, one-dimensional tumor is similar to the chemotherapetic. Let κ be the ionizing radiation. We assume there is no consumption of the radiation, and it follows Fick's Law.

$$\frac{\partial c}{\partial t} = D_c \frac{1}{r^2} \cdot \frac{\partial}{\partial r}\left(r^2 \frac{\partial c}{\partial r}\right) - \Gamma_c(c, R, R_H, R_N)$$
$$\frac{\partial \kappa}{\partial t} = D_\kappa \frac{1}{r^2} \cdot \frac{\partial}{\partial \kappa}\left(r^2 \frac{\partial \kappa}{\partial r}\right)$$
$$\frac{d}{dt}(\frac{1}{3}R^3) = \int_0^R P(c, R, R_H, R_N) \cdot r^2 dr - \int_0^R N(\kappa, R, R_H, R_N) \cdot r^2 dr$$

for

$\Gamma_c(c, R, R_H, R_N) = \gamma_c H(r - R_H)$,
$P(c, R, R_H, R_N) = pc(r, t)H(r - R_H)$,
$N(c, R, R_H, R_N) = p\delta_A + p\delta_N \int_0^R \kappa(r, t) dr.$

The necrosis rate now depends on the radiation allover the tumor as the cells ionize themselves and activate a chain reaction.

For all of the modifications it makes sense to do some stability analysis, depending on a^* as in this thesis. But furthermore, choosing other bifurcation parameters can be of biological interest. For example, if we variate the proliferation rate k or the dependence factor μ in equation (2.3), we can compare how a given drug influences varying cells. In reverse, a shift of λ_1 or λ_2 (or again μ) corresponds to the injection of different drugs into a given tumor. Accordingly we can change the bifurcation parameter in equation (3.1), (3.2).

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