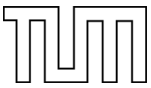

Technische Universität München

Department of Mathematics

Master's Thesis

Mathematical modelling of combined radiation and chemotherapy

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I hereby declare that this thesis is my own work and that no other sources have been used except those clearly indicated and referenced.

Garching,

Kurzdarstellung

Krebs ist keineswegs eine neue Krankheit. Sie ist schon seit Jahrhunderten bekannt, aber anders als damals werden die Menschen heutzutage um viele Jahre älter und da Krebs sich oftmals erst im hohen Alter zeigt, gibt es heute auch viel mehr an Krebs erkrankte Menschen als früher. Deshalb ist Krebs zu einem Hauptproblem in Gesundheitsfragen geworden und Krebsforschung extrem wichtig.
Das Ziel ist es natürlich, jeden Menschen, der an Krebs erkrankt ist, heilen zu können. Doch da es viele verschiedene Arten davon gibt, muss auch für jede spezielle Art eine eigene Therapie gefunden werden. Und dafür gibt es viele Möglichkeiten. Es gibt zahlreiche Chemotherapeutika, von denen man mit einer, oder auch mit mehreren therapieren kann. Zudem kann man mit Strahlentherapie behandeln, oder auch mit einer Kombination davon. Doch es gäbe noch viele weitere Methoden. Da das Thema dieser Arbeit die kombinierte Therapie ist, beginnt sie mit einem Überblick über den biologischen Hintergrund von Krebs, Chemo- und Radiotherapie. Dann wird mit der Behandlung von mathematischen Modellen begonnen, welche Tumorwachstum modellieren. Weiter geht es mit der Modellierung des Wachstums von Tumoren, welche mit Radiotherapie behandelt werden. Im nächsten Kapitel wird das Wachstum von Tumoren behandelt, die mit Chemotherapie behandelt wurden. Um einen allgemeinen Überblick über die Wechselwirkungen zwischen Körper und Chemotherapeutika zu bekommen, wird in diesem Kapitel mit einer Zusammenfassung der in der Pharmakokinetik und Pharmakodynamik verwendeten Modelle begonnen. Danach wird ein Zellpopulationsmodell und ein Zellzyklus-spezifisches Modell behandelt. Letztendlich werden die Modelle aus den beiden vorangegangen Kapiteln zusammengeführt und Modelle behandelt, die kombinierte Radio- und Chemotherapie beinhalten, wie das erweiterte LQ-Modell, ein Zellpopulationsmodell und ein räumliches Modell.
Zusätzlich gibt es am Ende jedes Kapitels einen Abschnitt, in dem die Modelle an Daten getestet werden. Gegebenfalls werden die Modelle auch angepasst, damit sie bestmöglich der Realität entsprechen. Doch man muss natürlich beachten, dass diese Modelle damit keine Allgemeingültigkeit haben, da sie sehr von den Versuchsbedingungen, der verwendeten Zelllinie, der Chemotherapeutika und vielem mehr abhängen.

Contents

1. Introduction

Cancer is far from being a new disease. It is well known since centuries, by the Egyptians for example. But since cancer is a disease which mainly shows up not until the latter decades of life only a small part of the people got ill in comparison to today. Today it is one major problem in health issues and thus cancer research is extremely important [KS05]. Specific research began when about 170 years ago Johannes Müller discovered that tumors are made up of cells. Scientists searched for the difference between a normal and a cancer cell. In the following a huge amount of information about the cancer cell has been collected [KS05].
Over the years many different therapies arose, but there is not the one and only therapy to treat cancer. As you can see in section 2.1 there are many different types of cancer and thus for every single one a particular therapy has to be found. And there are many ways to treat: with one or several of the diverse chemotherapeutic drugs, with radiotherapy or with both radio- and chemotherapy. Since the issue of this thesis is the combined therapy, chapter 2 gives a summary over cancer itself, over chemotherapy, especially over a drug called vinblastine and finally also over radiotherapy. The treatment schedule can be very important, too. This can be seen in section 5.4. Subsequent to the chapter about the biological background, chapter 3 gives an overview over mathematical models for tumor growth. Chapter 4 reviews a model for tumor growth including radiotherapy and chapter 5 covers different models for chemotherapy, beginning with a summary over the pharmacokinetics and pharmacodynamics, which describe how the body system and the drug interact. Chapter 5 continues with a cell population model and a cell cycle specific model. Finally in chapter 6 chemo- and radiotherapy are combined, first in the LQ-model, then in a cell population and finally in a spatial model.
At the end of every chapter, we fit the introduced models to data, which is provided by [AH14]. The idea is to test if the model can cover the reality and if it considers all effects of the therapy. If not, the model is adjusted, according to the data. But you have to keep in mind that the models are not universal, because they depend on the particular cell line, the drug and the general experimental setup.
In the last chapter some conclusions and an outlook for possible further research are shown.

2. Biological Background

2.1. Tumor Growth

To characterize cancer most simple, it arises when genes cause cells to malfunction and interact with the body in an abnormal, hyper-proliferative manner. Among a series of other mechanisms, this can happen by increased cell proliferation or reduced *apoptosis*, the programmed cell death [Mac10]. Cancer initiation, or *carcinogenesis*, is a complicate process that includes the malfunction of particular genes. The growth rate of normal tissue is regulated by growth promoting and growth inhibiting signals. Two types of genes are most relevant for these processes, the oncogenes and the tumor suppressor genes (TSGs). The oncogenes respond or create growth signals and support thereby cell cycle progression. Tumor suppressor genes on the other hand respond to inhibitory signals and retard or stop the cell cycle, in order to ensure correct cell repair. Under certain conditions they can also cause *apoptosis*. So the reason why carcinogenesis starts is a genetic mutation or an epigenetic alteration that causes a malfunction of one of these genes. This malfunction is either an over-expression of oncogenes or an under-expression of TSGs. It can happen in a small number of cells or even in one single cell. If this cell succeeds to avoid the DNA repair mechanisms and the numerous checkpoints, a whole colony of hyper-proliferative, damaged cells can arise. This can take years, but it can also be accelerated by external influences [Mac10, KS05].
Since differentiated cells can divide only a limited number of times before they reach a quiescent state or *apoptosis*, it has been proposed that cancer arises more likely from mutated somatic stem cells than from differentiated cells [Mac10]. But cancer cells do not necessarily divide faster than normal cells, they could also divide more often and thus over a longer period of time. A timespan after which a normal cell would be already quiescent or dead [Bri03].

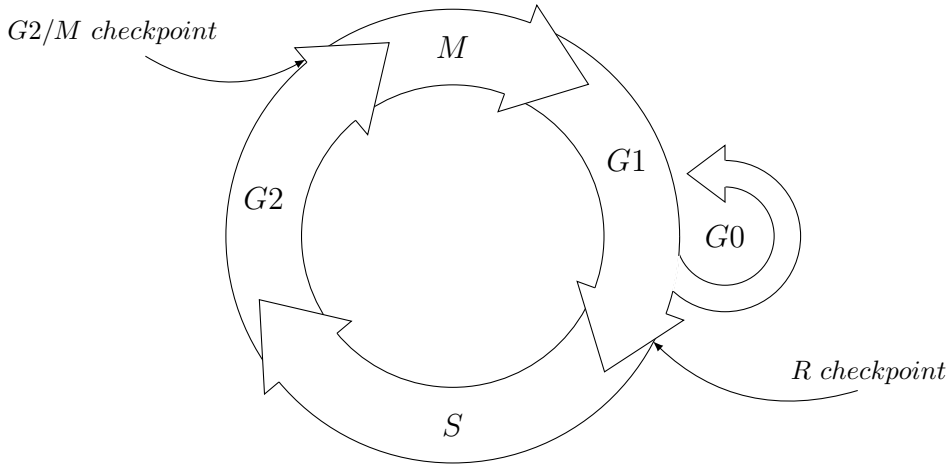


Figure 2.1: Cell cycle, based on a figure in [Mac10].

To understand this mechanisms better and since many treatments are brought into line with the cell cycle, it will be discussed in more detail. The cell cycle is a series of stages which regulate the cell division. There are five different stages: The $G1$, S, $G2$, M and the $G0$ phase, see figure 2.1. In the first phase, the $G1$ phase (gap 1) not much seems to happen, but the cell grows, synthesizes proteins, constructs new organelles and prepares for DNA replication. The next stage is the S phase (*synthesis*) in which the DNA is replicated and other cell components increase. In the $G2$ phase (gap 2) further preparations are made. This time in the cell nucleus, in preparation for cell division. In the M phase (*mitosis*), the final phase, the nuclear membrane breaks down, the two copies of the DNA are separated and integrated into two different nuclei (*mitosis*). Also all organelles and the cytoplasm are divided in order to put them with the nuclei in two daughter cells (*cytokinesis*). In the cell cycle there are also checkpoints to control the cycle progression. There it is possible to stop it, to check for DNA damage and to repair it. At the R checkpoint at the end of the $G1$ phase the cell can either continue the cycle or transition into the $G0$ phase (quiescent state). Here the cells have the same DNA content as in the $G1$ phase. Most of the normal, noncancerous cells are resting in this phase. There are further checkpoints in the $G2$ and the M phase. At this checkpoints the DNA is also checked for damage and repaired if necessary. If a repair should fail, *apoptosis* is induced [Mac10, KS05, Eis79, Kno88].
In the early stages of tumor growth the tumor has no own vasculature and thus no own blood supply. Hence the tumor has to get all needed substances like oxygen, nutrients or growth factors from the surrounding vascularized tissue. These "substrates" diffuse from the nearby tissue and create a substrate gradient from the external source to the tumor, the internal sink. Oxygen is extraordinary important here. After a diffusing distance of about $100 - 200\mu m$ the substrate concentration drops down to a level where metabolism is not possible anymore. Thus in this inner part of the tumor, the cells become hypoxic. Cells are hypoxic, if their oxygen supply is deficient. Further inside, the oxygen and glucose levels are so critically low that the cells start to die. Hence if the tumor is big enough, it has three layers. As you can see in figure 2.2 the outer one consists of proliferating cells, the next one of hypoxic cells and the inner layer consists of necrotic cells [Mac10]. It seems that the width of the outer rim which consists of proliferating cells tends to be constant. Nevertheless, an avascular tumor cannot grow indefinitely large [Bri03].
It was already said above that cells that are part of a proliferating cell populations are more likely to become cancerous than other cells. There are different types of cancer. Carcinomas are cancers of the epithelial cells, which form the surfaces and cavities throughout the body and add up to 90% of all cancers. Lymphomas are cancers of the immune system. The last one are Leukemias, which were known as cancers of the haematopoietic system, which is responsible for the blood cell production [Bri03]. But there are recent discussions about leukemia being a stem-cell disorder.
Of course there are further classifications of the different types of cancer, according to the location of the tumor. In figure 2.3 there are the 20 most common cancers in Ger-

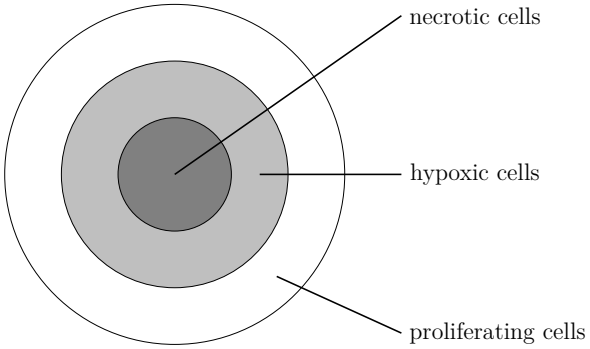


Figure 2.2: Three layer scheme, representing a slide of the tumor.

many. The data is from the International Agency for Research on Cancer [FSE+14]. As you can see, breast cancer is the most common type of cancer with 716 cases in the year 2012. Since the 1970s this number has increased. Among others this is due to the fact that the life expectation increased and the screening methods became more sensitive, which causes a better detection. So the number of cases increased, but fortunately the number of deaths decreased [AMA14].
There are many risk factors of cancer, which are classified as modifiable and non-modifiable risks. The modifiable risks of breast cancer are for example diet, alcohol consumption, body mass index, exogenous estrogen use, smoking, and physical inactivity. Non-modifiable risks of breast cancer are age, race/ethnicity, genetics/family history, and age at menarche. There are also potentially modifiable risks like the woman's age at the birth of her first child, her age at menopause, or her breast-feeding status. The mammographic breast density seems to correlate with the risk of getting breast cancer, too [AMA14].

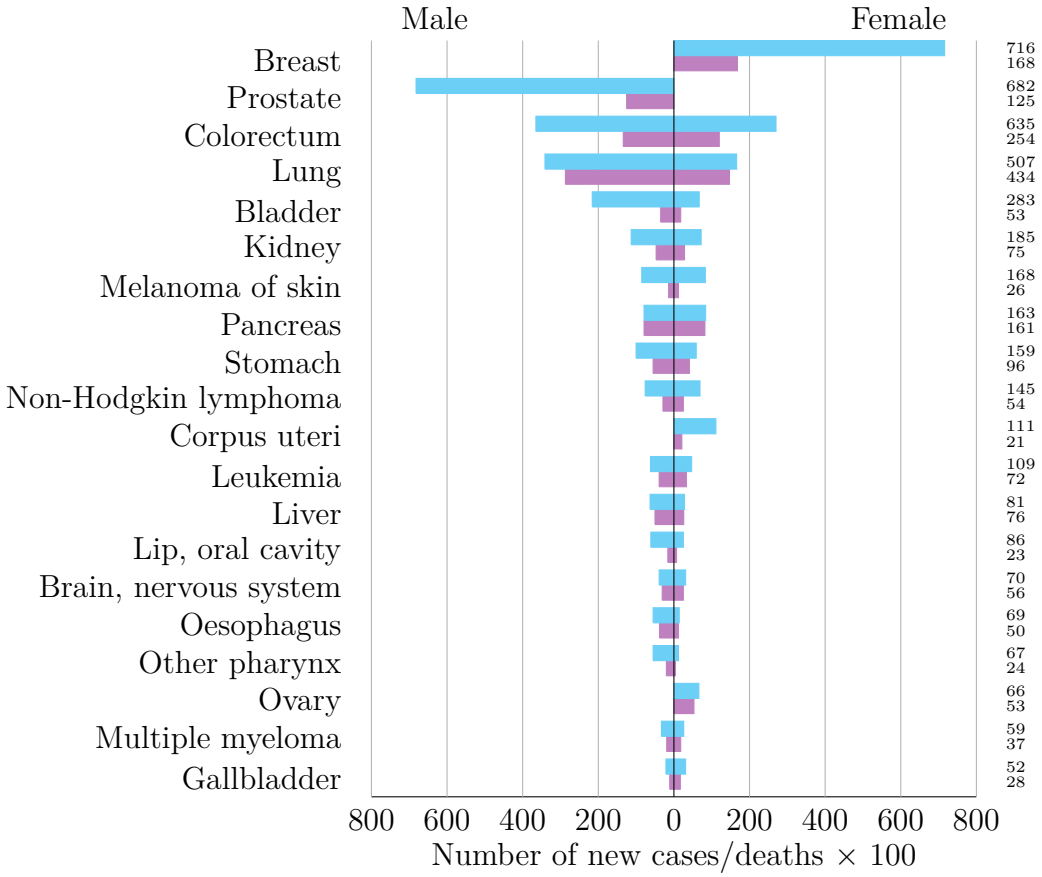


Figure 2.3: The 20 most common types of cancer in Germany in the year 2012. New cases are represented by the blue bars and the cases of death by the purple bars. Data from [FSE+14].

2.2. Chemotherapy

The broadest definition of chemotherapy covers any therapeutic intervention using chemicals and includes the use of any pharmaceutical compound. But in common it is the use of cytotoxic drugs to treat malignant diseases [KS05].
It is often heard that the origins of modern chemotherapy research were during World War II when the few survivors of an attack with mustard gas in 1943, which is named after its smell and was used in World War I chemical warfare, were examined. They showed a reduction of bone marrow cells and thus anemia. This reawakened the interest about the discovery which was originally made in 1919 [PV10, Wei07]. In 1942 research to the effects on mustard gas began at Yale University in Connecticut. They discovered that intravenous doses of mustard gas caused a temporarily regression of a lymphoma [Wei07]. Long before that, about 15 centuries ago, herbs and botanicals were used to treat tumors. Later also arsenical therapy was used systemically, which did not receive much attention, because it was considered dangerous. Then in 1865 the first instance of effective chemotherapy was found. Potassium arsenite was used to to treat chronic myelogenous leukemia. Even today arsenicals are still used to treat cancer [Pap01].
The focus of the research was to find new agents which kill neoplastic cells more likely than normal tissue or at least agents that only cause tolerable side effects. Indeed many more agents are found during the years, but still three basic questions are unanswered:

- How do the agents kill cancer cells?
- Why are cancer cells killed more likely than normal cells by these agents?
- How do cancer cells get resistant to agents that were effective in treating these tumors at the beginning?

These questions led to discovery of some of the more recent, molecularly designed agents [Wei07].
Despite the intention to find agents that affect the normal tissue as slightly as possible, all targets of the cytotoxic agents in the malignant dividing cell are also present in a normal dividing cell. Thus all fast dividing cells in the body, such as bone marrow, skin, hair follicle, and gastrointestinal mucosa are also impaired, nearly as much as the tumor itself. So the solution could be to adjust the treatment regime, since tumor cells often have no well-functioning DNA repair mechanisms. Thus the aim is to find a regime where the normal cells have enough time between two treatments to repair themselves, but the tumor cells cannot handle this. But also different normal tissues need different time spans to recover. White blood cells need for example only 1 - 3 days, but red blood cells in contrast need 120 days [KS05].
Another important aspect of chemotherapy are the various side effects. There are early side effects which can already occur after hours and late side effects which occur only after months, or even years, after the treatment has ended. Early side effects appear quite frequently and usually disappear again. There are for example nausea, alopecia and

myelosuppression, to mention just a few. Late side effects are very rare, but when they appear they are usually permanent and can even be disabling. Late side effects would be for example cardiotoxicity, premature menopause and pulmonary fibrosis [KS05].
Another "side effect" of the chemotherapeutic agents is that drug resistance develops sooner or later for all various agents and for all types of cancer. Thus whole colonies of drug resistant tumor cells develop and become bigger and bigger. Multi-drug protocols are the reaction to this. Often they apply combinations of drugs with distinct and complementary modes of cell killing. Thus the only chance for a tumor cell to survive this treatment is being resistant to all drugs that are used in this multi-drug protocol. But the probability of a cell to be resistant to all administered drugs is really very low, since the different surviving probabilities have to be multiplied [Wei07].
To test how the drugs are delivered with the maximum therapeutic effect, they were tested with the focus on the effects of the drugs on cultured tumor cells and on tumor xenografts (grown largely in laboratory mice). Thereby two different fields arose: The pharmacokinetics and the pharmacodynamics. The pharmacokinetics are dealing with the rates at which an administered drug is

(a) absorbed into the system,

(b) distributed in the various tissues,

(c) metabolized and

(d) excreted.

But this cannot tell us how the cells really respond to the drug. For this purpose there is the second field, the pharmacodynamics [Wei07]. Thus the pharmacokinetics deal with the question what the body does to the drug while the pharmacodynamics deal with the question what the drug does to the body [PV10].
At the end of this subsection we want to go into a particular chemotherapeutic drug called vinblastine. Its molecular structure can be seen in figure 2.4 [Fva10]. It is produced naturally from a plant called *Vinca rosea*, a periwinkle plant which grows in Madagascar [Wei07, CCK07]. Thus it belongs to a class called Vinca alkaloids [MHM$^+$06, CCK07]. The reason why vinblastine is affective against cancer is its functionality. It belongs to a class of antimetabolites which affects the normal cell function by inhibiting the microtubule assembly [Wei07, CCK07]. It binds to tubulin, a structural protein. Since it is the basic block of the microtubule, vinblastine inhibits its accumulation. Microtubule themselves are hollow cylindrical protein structures and thus structural components of cells. An important purpose of them is to form the mitotic spindle. Since this spindle is responsible for the separation of the chromosomes during cell division, the cell division is stopped at the metaphase stage of the cell cycle by vinblastine [CCK07]. To understand better what is happening, see figure 2.5. It shows the different stages of the meta- or M-Phase. It is quite obvious that without the microtubule, the chromosomes cannot divide and thus no cell division is possible anymore.

Vinca alkaloids are used in lymphomas, lung cancers, breast cancers and head-and-neck squamous cell carcinomas [Wei07, CCK07]. In particular vinblastine is used in Hodgkin's disease and testicular neoplasms [SSS84].

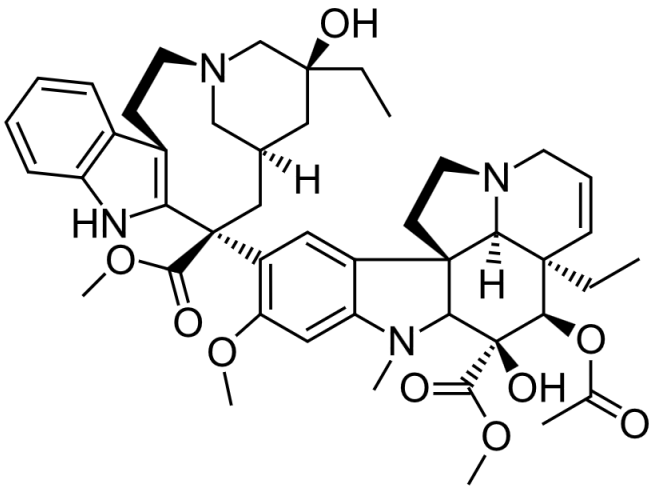


Figure 2.4: Molecular structure of vinblastine. Figure from [Fva10].

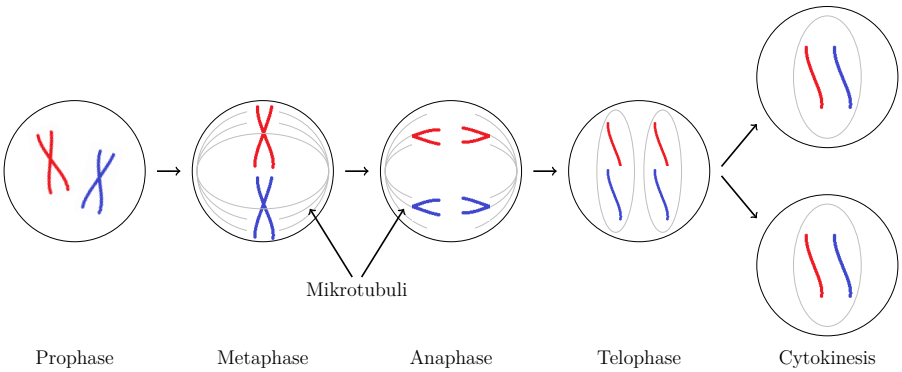


Figure 2.5: M-Phase.

2.3. Radiotherapy

The foundation of the radiation oncology was laid in 1895 when Röntgen discovered X-rays. Soon it was discovered that the X-rays in form of electromagnetic radiation cause damage of the normal tissue in the form of burn, and even tissue necrosis [Wei07]. The first cure of cancer which was caused by radiotherapy was in 1899 [CHN09], but radiation was not really used until the end of World War II when they figured out how to direct the rays in relatively narrow fields. Further problems were the little knowledge about the effects of the radiation and the inability to control the doses of the administered X-rays properly [CHN09]. By directing the rays they were able to focus the diagnosed tumor. By treating the tissue which is adjacent to the tumor after a surgery with radiation the post-surgical relapse could be reduced. Thus adjacent radiation therapy has become an important clinical tool [Wei07, CHN09]. Since 90% of tumor recurrence arises in the tissue adjacent to the tumor, it is very important to focus on this. This adjacent tissue is defined as a $10mm$ margin which contains actual or potential cancer cells [EAC+05]. Thus in the case of breast cancer one would concentrate on this area instead of treating the whole breast.
One of the central issues of radiobiology is to understand which factors influence radiosensitivity. Radiosensitivity is the response of the cells to a particular radiation dose. These radiation doses are measured in Gray, where 1 Gray = 1 Gy = 1 Joule / Kg. The main effect of radiation is that it causes molecular excitation and the ejection of fast electrons from the atoms of the cell, which is called ionization. Molecular excitation is degraded as heat, which is quite harmless, but in the ionization process free radicals are produced. Radicals have an unpaired valence electron or an open electron shell. Thus they are very unstable and reactive towards other substances which can cause reversible and irreversible changes to the cell nucleus. This again can involve DNA lesions, including single and double DNA strand breaks [CHN09].
The reason why radiotherapy is working on cancer is more or less the same as the one for chemotherapy. Normal cells have the ability to repair DNA damage in the majority of cases. If not, cell *apoptosis* is induced. Tumor cells however often show absence of this ability. So the damage on the tumor cells is bigger than the damage on the normal cells. The extend of this damage depends on the radiosensitivity of the tumor cells which is influenced by many factors. First of all proliferating cells are more radiosensitive than resting cells, i.e. cells in the $G0$ phase. Second a low oxygen concentration, called hypoxia, decreases radiosensitivity. Thus the tumor cells which lie internally are damaged much less than the proliferating cells in the outer shell.
But of course, also radiotherapy has its side effects. If the DNA damage of a normal cell is repaired incorrect and also *apoptosis* fails, the cell keeps on living with the DNA damage. If this cell splits into two new cells, the DNA damage is transferred to both daughter cells. The two daughter cells can transfer the damaged DNA again and so on. Thus genomic instability and subsequent carcinogenesis can arise [CHN09].
There are different radiotherapies used. The first one is the external beam radiotherapy

(EBRT) which is the standard therapy. It is delivered in, for example, 25 fractions of 2 Gray, given in a timespan of 4 to 6 weeks. In the time between two fractions, the healthy cells have time to repair the damage caused by the radiotherapy. Another, newer treatment is the targeted intraoperative radiotherapy (TARGIT) where a single high dose of radiation is delivered directly into the tumor bed. This happens during the surgery, while the patient is still sedated [ECAV06].
The most influential processes in tumor radiotherapy are known as the 5 R's [CHN09]. These five R's of radiobiology are

- Radiosensitivity,
- Repair,
- Redistribution over the cell cycle,
- Reoxygenation and
- Repopulation.

3. Modelling Tumor Growth

This section deals with some important models for tumor growth. These models are based on the assumption that the tumor cells are homogeneous and form a solid avascular tumor. Since the nutrient supply is diffusion limited, the tumor cannot grow indefinitely. Thus an avascular tumor stays so small that it cannot be seen in vivo [Bri03]. The critical tumor size is defined by the avascular threshold, which is about $10^5 - 10^6$ cells [BW02, Fol95]. Anyway an avascular tumor is not defined by its size. We also assume that the tumor is growing continuously. Here and also in the whole thesis only deterministic models and no stochastic models are considered.

3.1. Homogeneous Tumor Growth Models

Exponential Growth Equation The easiest model of tumor growth is the exponential growth equation. Here the only further assumption is, that the tumor cells grow exponentially. With $N(t)$ being the number of tumor cells at time t the model reads as

$$\frac{dN}{dt} = rN \tag{3.1a}$$

$$N(0) = N_0, \tag{3.1b}$$

with the solution

$$N(t) = N_0 e^{rt}, \tag{3.2}$$

where N_0 is the initial number of tumor cells at time $t = 0$ and the term $r > 0$ is the net rate at which the cells proliferate [Pre03]. Here all nutrients and other vital growth factors are available unrestrictedly. Thus according to equation (3.2) the number of tumor cells would grow without a limit. But since in vivo there are restrictions another model is needed.

Logistic Growth Equation There is not unlimited space and there are also not unlimited nutrients. Thus at a certain point the number of cells stop growing and converge to a limit $K > 0$, the carrying capacity [Bri03, Pre03, All07]. Including this fact in the exponential growth equation yields

$$\frac{dN}{dt} = rN\left(1 - \frac{N}{K}\right) \quad \text{with } r, K > 0 \tag{3.3a}$$

$$N(0) = N_0, \tag{3.3b}$$

with the solution

$$N(t) = \frac{N_0 K}{N_0 + e^{-rt}(K - N_0)}. \tag{3.4}$$

If one is interested in the way of finding the solutions of the differential equations, please have a look at [Web13], where the analytical solutions are found with the aid of substitution and bernoulli equations. This model is still not perfect, since it is not very flexible. The maximum growth rate is always at $K/2$ which does not always correspond to the reality. Thus another, more flexible model is needed.

Generalized Logistic Growth Equation With the aim to vary the equation's maximum we introduce a new parameter α. It allows a better control of the tumor growth. If $\alpha < 1$ the model reaches the saturation faster and if $\alpha > 1$ it reaches the saturation slower than the logistic growth equation [Web13].

$$\frac{dN}{dt} = \frac{r}{\alpha} N \left(1 - \left(\frac{N}{K}\right)^{\alpha}\right) \quad \text{with } \alpha > 0 \tag{3.5a}$$

$$N(0) = N_0. \tag{3.5b}$$

One can see easily that if $\alpha = 1$, equation (3.5a) is identical to the logistic growth equation. The solution of (3.5) reads as

$$N(t) = \frac{N_0 K}{(N_0^{\alpha} + e^{-rt}(K^{\alpha} - N_0^{\alpha}))^{\frac{1}{\alpha}}}, \tag{3.6}$$

[Pre03]. To see the difference between the three discussed models better, please have a look at figure 3.1.

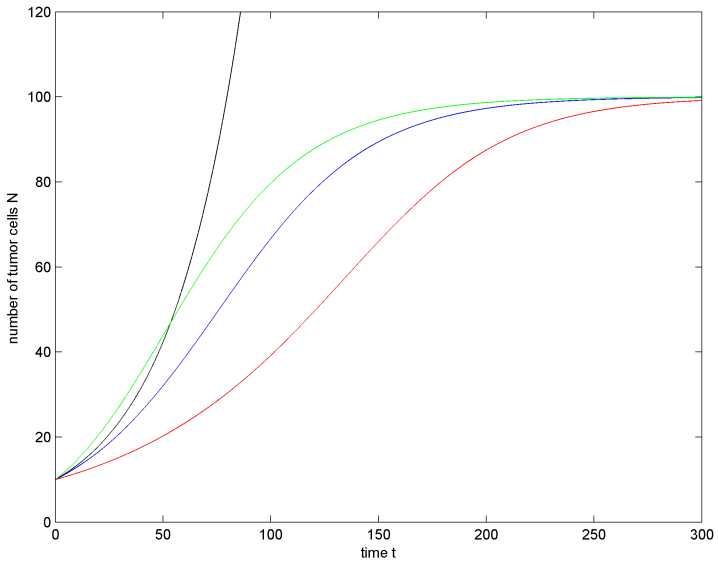


Figure 3.1: Different tumor growth models: The exponential growth equation is represented by the black line, the logistic growth equation by the blue line and the generalized logistic growth equation is depicted by the green line for $\alpha = 0.5$ and by the red line for $\alpha = 2$. Further parameters are $r = 0.0289\frac{1}{h}$, $K = 100$ cells and $N_0 = 10$ cells. The curves are obtained by the corresponding analytical solutions (3.2), (3.4) and (3.6).

3.2. Fitting the model to data

Now we want to apply the generalized logistic growth model to the data. This data was measured in the Institute of Radiobiology at the Helmholtz Zentrum München. In this experiment breast cancer cells from the cell line T47D were put in a 96-well plate and let grow in a hanging drop for three days. After these three days the resulting spheroid was put in a gravity plate where it stayed for another day. The time t was set to zero and the area of the spheroid was measured for the first time. There were control tumors and tumors which were treated with radiation or chemotherapy or both. First the radiation was administered once and after that the chemotherapeutic drug, called vinblastine, was administered. The drug stayed in the nutrient solution for six days before it was washed away. The area of the spheroid was measured again on the days 3, 6, 9 and 12. More details to this process follow in the next sections. In this section we focus on the tumor growth without treatment.
Since the generalized logistic growth model returns the number of cells and the dataset only includes the mean image region area, we need to convert the data. For this purpose we take the formula and the parameters from [Web13], since in that thesis also cell counts were available. In that thesis equation (3.6) was used with the parameters $\alpha = 0.325$, $K = 0.069$ cells, $N_0 = 0.001$ cells and $r = 0.000013\frac{1}{\mu m^2}$. The correlation between the mean area and the cell number per μm^2 can be seen in figure 3.2.

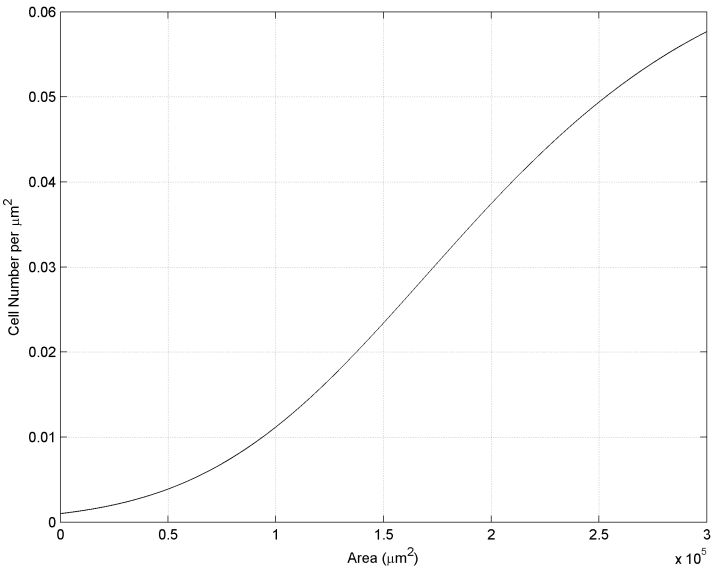


Figure 3.2: Coherence of the mean area and the cell number per μm^2. The used formula is the solution of the generalized logistic growth equation (3.6) and the parameters are chosen as follows: $\alpha = 0.325$, $K = 0.069$ cells, $N_0 = 0.001$ cells and $r = 0.000013\frac{1}{\mu m^2}$. Formula and parameters are taken from [Web13].

Days	0	3	6	9	12
Area (μm^2)	79312.42	131492.7	194451.8	222105.0	233064.7
Number of cells	596.3	2424.5	6986.6	9581.6	10659

Table 1: Mean area measured over a period of 12 days and number of cells. Data taken from [AH14].

Knowing these correlation, it is easy to calculate the needed data which can be seen in table 1. So now we can compare the data with the generalized logistic growth model. In order to get appropriate parameters for the model, we use algorithm 1. The idea behind this algorithm is to get a minimal error between the data points and the model curve. For calculating the error, we use the weighted sum of squares which reads

$$\text{error} = \sum_{i=1}^{n} \left(\frac{\text{Data}_i - \text{Model}_i}{\text{Model}_i} \right)^2, \tag{3.7}$$

where Model_i is the i-th point which is calculated with the model equation and Data_i is the corresponding i-th point of the dataset [Web13]. To find the best fit, we use algorithm 1 and set $N_0 = 596.3$ cells, according to the data. Additionally we can set $r = \frac{\ln 2}{60h} = 0.0116\frac{1}{h}$, since this parameter is known for the cell line T47D [Web13]. The algorithm returns $\alpha = 0.2030$ and $K = 13380$ cells with an error of 0.0297. Figure 3.3 shows the model curve with the found parameters and the data points. This and all further simulations in the next chapters are made with the technical computing language MATLAB from MathWorks®. The codes for the simulations and algorithm are attached in the appendix.

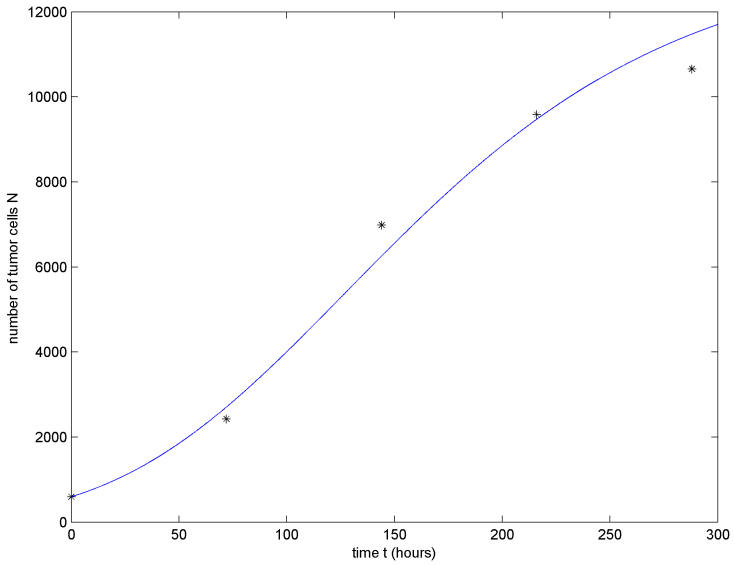


Figure 3.3: Generalized logistic growth model versus data. Used parameters for the model curve: $r = 0.0116\frac{1}{h}$, $N_0 = 596.3$ cells, $\alpha = 0.2030$ and $K = 13380$ cells, which were put in equation (3.6). Data points taken from [AH14].

4. Modeling Radiotherapy

This section recapitulates the basic model of tumor growth including radiotherapy, which is described in detail in [Web13] and based on a model in [Pre03]. Once again the tumor is assumed to be solid, homogeneous and in an avascular state.

4.1. Mathematical Model

To model the tumor growth, the generalized logistic growth model (3.5) is used. To include radiation, we need an additional term. The model reads as follows

$$\frac{dN}{dt} = \frac{r}{\alpha} N \left(1 - \left(\frac{N}{K}\right)^{\alpha}\right) - \mu A N \text{ with } \mu > 0 \tag{4.1a}$$

$$N(0) = N_0, \tag{4.1b}$$

where A is the amount of radiation which is administered in Gray. Since the treatment is continuous it holds that $A = a \ \forall \ t \geq 0$. If $a = 0$ no radiation is administered and the system of equations (4.1) is reduced to the generalized logistic growth model. The parameter μ describes how much the cells are damaged by radiation per Gray.
The solution of (4.1) is given by

$$N(t) = \frac{N_0 K}{\left(\frac{N_0^{\alpha} r}{r - \alpha\mu A} + e^{-rt + \alpha\mu A t}\left(K^{\alpha} - \frac{N_0^{\alpha} r}{r - \alpha\mu A}\right)\right)^{\frac{1}{\alpha}}}. \tag{4.2}$$

For the detailed calculation please have a look at [Web13].
Equation (4.1) has two equilibria. An equilibrium is clarified by the following definition:

Definition 1. *Let (X, Φ) a dynamical system. Then $x_e \in X$ is an equilibrium (state point) of this system, if and only if*

$$\Phi(t, x_e) = x_e \quad \forall t \in \mathbb{R}(\mathbb{Z}).$$

[Sch13]. Thus the trivial equilibria is

$$\hat{N}_1 = 0$$

and the nontrivial one is

$$\hat{N}_2 = K\left(1 - \frac{\alpha\mu A}{r}\right)^{\frac{1}{\alpha}}.$$

For the following we need another definition:

Definition 2. *Let $(X, d(\cdot,\cdot))$ be a metric space.*

- *The equilibrium $x_e \in X$ of (X, Φ) is called stable (in the sense of Lyapunov) if* $\forall \epsilon > 0 \ \exists \ \delta > 0 :$ $d(x_0, x_e) < \delta \Rightarrow d(x_e, \Phi(t, x_o)) < \epsilon \ \forall \ t \geq 0.$

- *Otherwise x_e is called unstable.*
- *$x_e \in X$ is called asymptotically stable if it is stable and there is $b > 0$, such that $d(x_0, x_e) < b \Rightarrow \lim_{t\to\infty} d(\Phi(t, x_0), x_e) = 0$.*

[Sch13]. $\hat{N}_1$ is asymptotically stable if $A > \frac{r}{\alpha\mu}$ and unstable if $A < \frac{r}{\alpha\mu}$. Analogously $\hat{N}_2$ is asymptotically stable if $A < \frac{r}{\alpha\mu}$ and unstable if $A > \frac{r}{\alpha\mu}$. Thus A is our bifurcation parameter and if $A > \frac{r}{\alpha\mu}$ the number of tumor cells converges to zero as $t \to \infty$, which means that the tumor can be eradicated. Figure 4.1 shows tumor growth without radiation and two times with different dosages of radiation. With $A = 0.25Gy$ the tumor tends to the trivial equilibrium $\hat{N}_1 = 0$ cells, but the radiation dosage $A = 0.05Gy$ is not sufficient and thus the tumor tends to the nontrivial equilibrium.

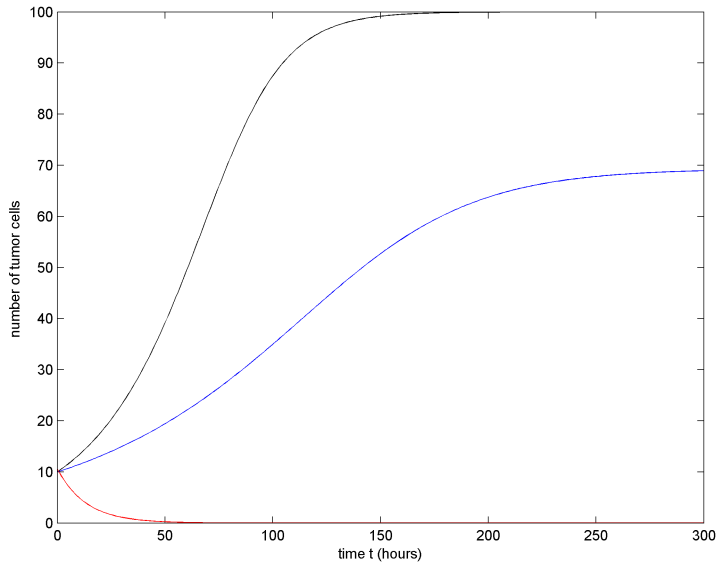


Figure 4.1: Continuous Radiation: The black line represents tumor growth without radiation, the blue line depicts tumor growth including radiation with $A = 0.05Gy$ and the red line with $A = 0.25Gy$. The remaining parameters are $N_0 = 10$ cells, $K = 100$ cells, $\alpha = 2$ and $r = 0.0578\frac{1}{h}$. The curves are made with the analytical solutions (3.6) and (4.2)

4.2. Fitting the model to data

Again the T47D cell line was used to measure the area of the tumor after 0, 3, 6, 9 and 12 days. The experiment was performed in the same way as it is described in section 3.2. The only difference is that the cells were treated with radiotherapy this time. In the beginning of day zero they were radiated with a dosage of 2, 4, 6 and 8 Gray respectively, where 1 Gray was administered in 2 minutes. The radiation source was

^{127}Cs, which emits γ-rays. Algorithm 2 finds the best approximation by varying μ in equation (4.2). We expect μ to be comparable small, since the cell line T47D is known to be radioresistant. The error is calculated like before with equation (3.7). The other parameters are chosen according to the previous section: $K = 13380$ cells, $\alpha = 0.2030$ and $r = 0.0116\frac{1}{h}$. Table 2 shows the normalized data we want to approximate.

Number of cells	**Days**				
Radiation (Gy)	0	3	6	9	12
2	596.3	2048.9	4636.0	5681.7	7167.2
4	596.3	1801.4	3063.3	3950.6	4194.8
6	596.3	2145.8	3130.3	2819.0	4072.0
8	596.3	1968.3	2319.7	1939.2	2944.5

Table 2: Number of cells treated with radiotherapy over a period of 12 days. Data taken from [AH14].

We get the best fit with the following parameters: For $A = 2Gy$ the algorithm returns $\mu = 0.0024\frac{1}{Gy \cdot h}$ with an error of 0.0154, for $A = 4Gy$ the algorithm returns $\mu = 0.0023\frac{1}{Gy \cdot h}$ with an error of 0.0284, for $A = 6Gy$ the algorithm returns $\mu = 0.0015\frac{1}{Gy \cdot h}$ with an error of 0.2196 and for $A = 8Gy$ the algorithm returns $\mu = 0.0015\frac{1}{Gy \cdot h}$ with an error of 0.3343. Figure 4.2 shows the resulting curves. The values of μ fit in with the assumption that the death rate by radiotherapy are dose dependent insofar, that there are different ones for dosages of more than 5 Gray and for dosages of less than 5 Gray [EAC+05, ECAV06].
In the cases $A = 6Gy$ and $A = 8Gy$ the errors a quite big, but a look at figure 4.2 gives a possible explanation. In these two cases the data points spread quite far away. After day 6 many of the cells die, but after day 9 the population recovers quite fast. The question is, if this depends on the treatment or if another reason causes this behavior. We will return to this question in the next section, since we do not have any explanation right now.

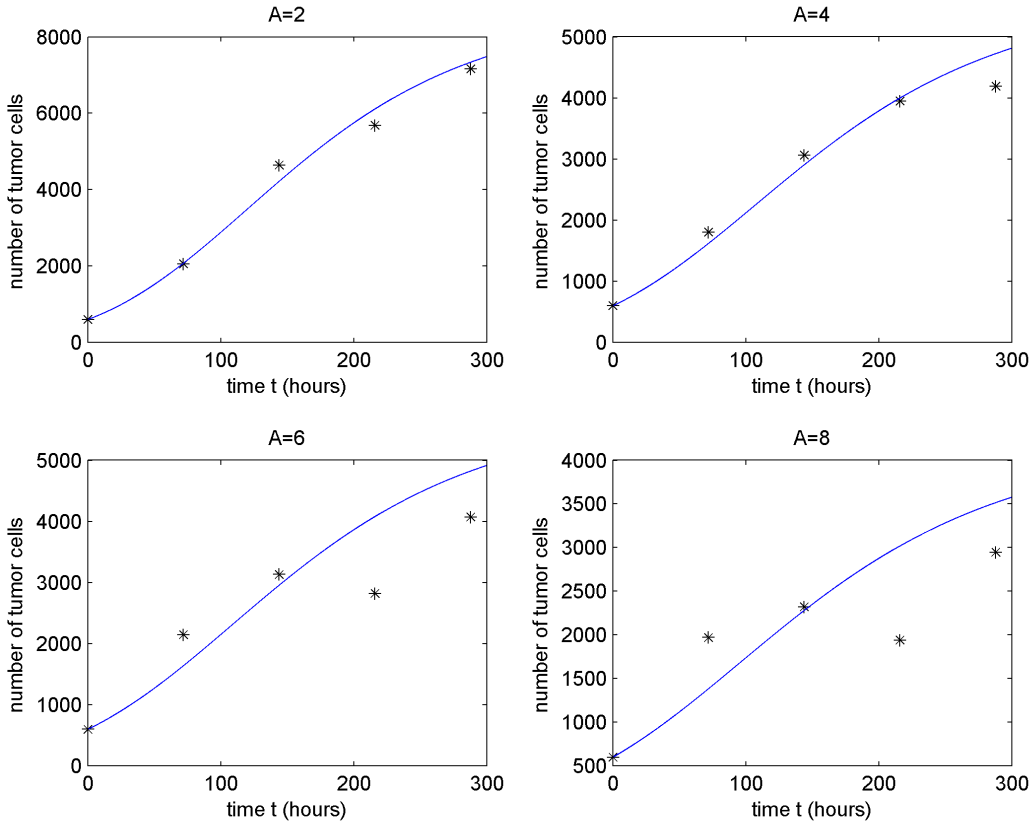


Figure 4.2: Model of tumor growth including radiation versus data points. Used parameters: $r = 0.0116\frac{1}{h}$, $N_0 = 596.3$ cells, $K = 13380$ cells and $\alpha = 0.2030$. Additional parameters: $\mu = 0.0024\frac{1}{Gy \cdot h}$ for $A = 2Gy$, $\mu = 0.0023\frac{1}{Gy \cdot h}$ for $A = 4Gy$, $\mu = 0.0015\frac{1}{Gy \cdot h}$ for $A = 6Gy$ and $\mu = 0.0015\frac{1}{Gy \cdot h}$ for $A = 8Gy$. Used equation: (4.2). Data points from [AH14].

5. Modeling Chemotherapy

This chapter covers the treatment of a tumor with a chemotherapeutic drug. Among other things also here a cell population model will be considered. Already decades ago the influence of chemotherapeutic drugs on tumor cells was modeled mathematically. The log-kill hypothesis was stated very early, which claims that a specific amount of a therapeutic drug kills the same percentage of a cell population rather than always the same number of cells [Ski64].
Like before we assume the tumor in this section to be avascular, i.e. in an early stage of growth. We assume also that the tumor has no structure. Since the tumor has no vasculature the problem arises that the drug has to diffuse through the solid tumor to reach all tumor cells. These diffusion gradients can considerably limit the medication access [FEF+09].
This chapter begins with two sections about pharmacokinetics and pharmacodynamics to give a general summary how the system of the body and the drug interact. The next section covers a continuous cell population model. The last model which is discussed in this chapter is a cell cycle specific model. This model shows how important the treatment schedule is, if more than one drug is used.

5.1. Pharmacokinetics

This section will give a general overview about pharmacokinetics. Pharmacokinetics started in the 1920s and 1930s with papers about the disposition of ethyl ether, the elimination of ethyl alcohol and the mathematics associated with pharmacokinetic modeling [WB94]. It includes absorption, distribution, metabolism and excretion, also known as ADME. The goal is to be able to estimate the time course of the drugs and the effects on the body properly. The effectiveness of a given dosage of a particular drug is determined by the concentration of this drug in the body [DK06]. Since the plasma concentration time profile of many drugs is not a straight line, a one compartment model is not sufficient here. Thus we use a two compartment model to model these processes in the body, as in figure 5.1.

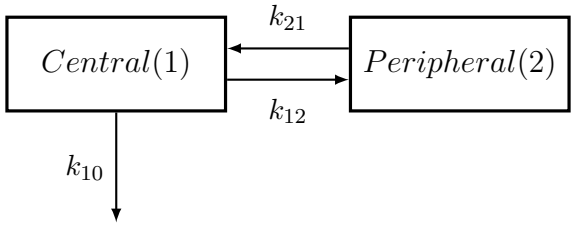


Figure 5.1: Generalized open two-compartment pharmacokinetic model.

The drug is distributed in the central compartment and also eliminated from there. It also distributes in other regions (peripheral compartment), but with different rates. The distribution rate into the peripheral compartment is defined by the microconstant k_{12} and the distribution back in the central compartment by k_{21}. The two distribution rate constants are significantly slower than k_{10} and are consequently the rate limiting factors [Riv11, RP13]. The concentration of the drug can be represented by the following biexponential equation:

$$c(t) = Ae^{-\alpha t} + Be^{-\beta t}, \tag{5.1}$$

with the two slopes α and β and the corresponding intercepts A and B [SSS84]. We denote $c_0 := c(0) = A + B$.

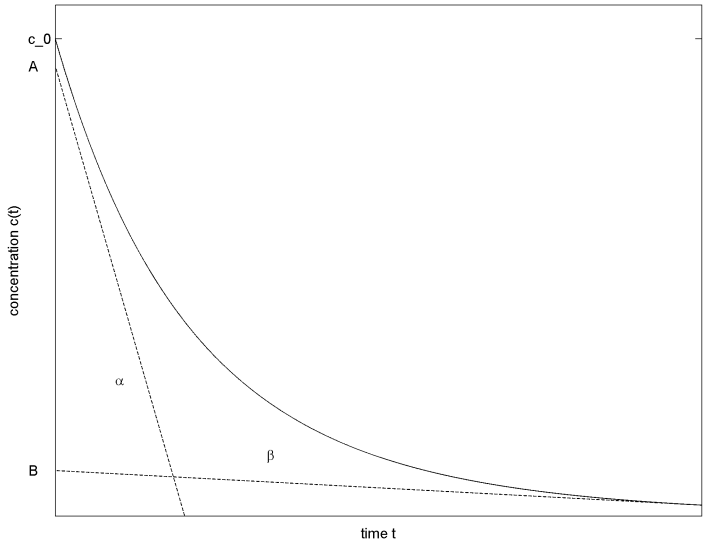


Figure 5.2: Biexponential Function. Based on figures in [Riv11] and [RP13].

If $\alpha = \beta$ the equation would represent a one compartment model. By definition $\alpha \gg \beta$ and β is accordingly the terminal slope. Following this, the rate of drug disposition reads as

$$\frac{dc_1}{dt} = -(k_{12} + k_{10})c_1 + k_{21}c_2, \tag{5.2}$$

where c_1 and c_2 are the concentrations of the compound in the central and peripheral compartment, respectively. The slopes, the corresponding intersects and the microconstants are related to each other in the following way:

$$\begin{aligned} k_{21} &= (A \cdot \alpha + B \cdot \beta)/(A + B), \\ k_{10} &= (\alpha \cdot \beta)/k_{21}, \\ k_{12} &= \alpha + \beta - k_{21} - k_{10}. \end{aligned}$$

Furthermore each slope has a corresponding half life $T_{1/2}$. The half life is the time which is needed for a quantity to drop down to the half of its value. It can be calculated as

$$\begin{aligned} T_{1/2}(\alpha) &= \ln 2/\alpha \qquad \text{Distribution,} \\ T_{1/2}(\beta) &= \ln 2/\beta \qquad \text{Elimination,} \end{aligned}$$

[Riv11, RP13]. There are different volumes of distribution, like the volume of the central compartment V_c, the volume of the peripheral compartment V_p and $V_t := V_c + V_p$. The volume of the central compartment for example is calculated as

$$V_c = \frac{D}{c_0} = \frac{D}{A+B}, \tag{5.3}$$

where D is the administered dosage [Riv11, RP13]. Another volume is the apparent volume of distribution V_d, which is often used when clinical dosage regiments are constructed. It reads as

$$V_d = \frac{D}{\mathrm{AUC}\,\beta}, \tag{5.4}$$

where AUC is called area under the curve and can be calculated with the following equation:

$$\mathrm{AUC} = \int_{\infty}^{0} c(t)\,\mathrm{d}\,t = \frac{A}{\alpha} + \frac{B}{\beta}. \tag{5.5}$$

The last important thing here is the systemic or plasma clearance CL:

$$\mathrm{CL} = k_{10}V_c = \beta V_d = \frac{D}{\mathrm{AUC}}, \tag{5.6}$$

[Riv11, RP13, SSS84].

5.2. Pharmacodynamics

This section gives a summary of the basic models of pharmacodynamics, which are based on the receptor theory. Most drugs work by interacting with receptors. This leads to a change in the receptor and therefore to a signal or stimulus. The stimulus in turn leads to other possible actions and finally to a biological response, see figure 5.3. This response is assumed to correlate with the number of receptors occupied by the drug. The law of mass action describes the receptor occupancy in the following way:

$$C \;+\; R \underset{k_{off}}{\overset{k_{on}}{\rightleftharpoons}} \; RC, \tag{5.7}$$

where C is the molar concentration of the drug, R the molar concentration of the unoccupied receptors and RC the molar concentration of the drug's receptor complex.

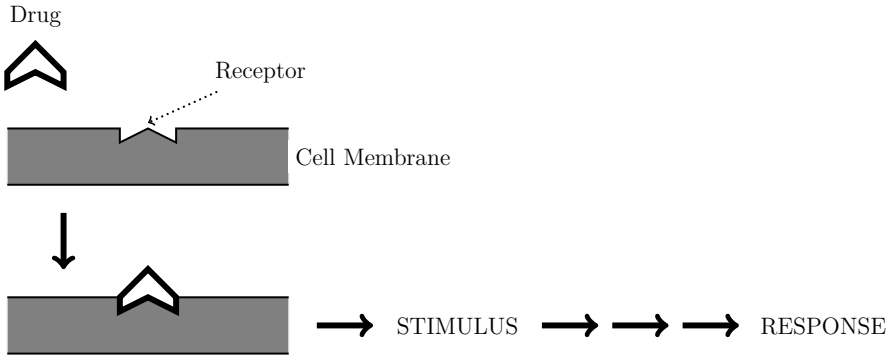


Figure 5.3: Sketch of the drug-receptor interaction. Based on a figure in [Ros12].

k_{on} and k_{off} are the rate constants for the forward and backward process, respectively [Ros12]. In an equilibrium the rates for the forward and backward process are equal and thus in an equilibrium it holds that

$$(R_T - RC) \cdot C \cdot k_{on} = RC \cdot k_{off}, \tag{5.8}$$

where R_T is the total molar concentration of receptors [Ros12]. Using the drug's dissociation constant $K_d = \frac{k_{off}}{k_{on}}$, equation (5.8) is equivalent to

$$\begin{aligned} RC &= \frac{R_T \cdot C}{K_d + C} \\ \Leftrightarrow \frac{RC}{R_T} &= \frac{C}{K_d + C}. \end{aligned} \tag{5.9}$$

K_d is equal to the drug concentration when the half of all receptors are occupied, see figure 5.4. It is also an inverse measure of the drug's affinity for the receptors. The number of occupied receptors RC is limited by the total number of receptors in a system. Thus the relationship between the occupancy and the concentration has a hyperbolic shape, see figure 5.4 [Ros12, D'A04].
Since the response to a drug is also assumed to correlate with the number or fraction of occupied receptors, the relationship between the drug concentration and the response can also be represented by a hyperbolic shape. Thus the fraction of maximum response $\frac{E}{E_{max}}$ is defined by

$$\frac{E}{E_{max}} = \alpha \cdot \frac{RC}{R_T}, \tag{5.10}$$

where E is the response, E_{max} the systems maximum possible response and $0 < \alpha < 1$ an efficacy term, called the intrinsic activity. The value of the stimulus is denoted by S and can be expressed as

$$S = e \cdot \frac{RC}{R_T}, \tag{5.11}$$

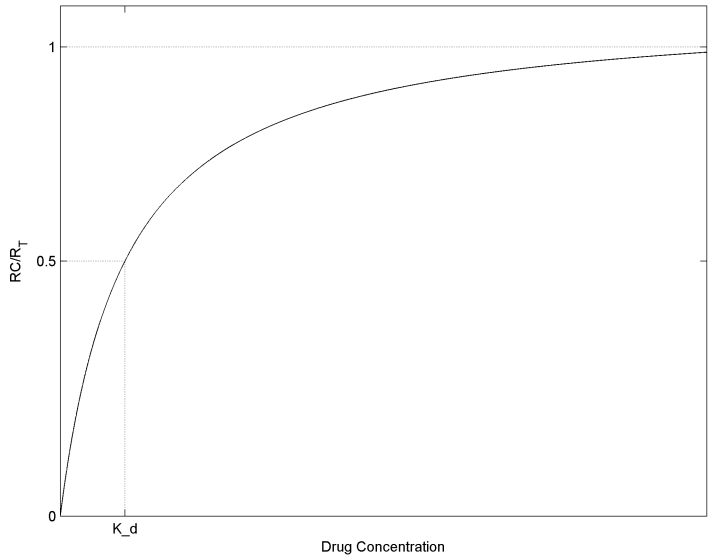


Figure 5.4: Correlation between fraction of receptors occupied (RC/R_T) and drug concentration C. Based on a figure in [Ros12].

where $e > 0$ is the efficacy. Since the stimulus does not represent the fraction of maximum response, e can be also greater than 1, compared with α [Ros12, D'A04]. The system converts this stimulus into a biological response. This can be expressed as

$$\frac{E}{E_{max}} = f(S), \tag{5.12}$$

where f is a hyperbolic function, in order to represent the capacity-limited characteristics of the relationship between the drug response and drug concentration. A possible hyperbolic function would be

$$f(S) = \frac{S}{1+S}.$$

The next and last parameter which is used in this model is the intrinsic efficacy χ, which is defined by

$$\chi = \frac{e}{R_T}, \tag{5.13}$$

[Ros12].

5.3. Cell Population Model

This section begins with a simple model for the delivery of drugs. Infusion is a realistic case since sometimes the drug cannot be given orally and thus they have to be injected

directly. One way to do this is with serial injections, the other one is continuous infusion [EK05]. In the model the number of tumor cells at time t is represented by $N(t)$ and the number of drug units in circulation is represented by $c(t)$. So the model reads as

$$\frac{dN}{dt} = \begin{matrix}\text{growth rate}\\ \text{of cells}\end{matrix} - \begin{matrix}\text{drug-induced}\\ \text{death rate}\end{matrix} \tag{5.14a}$$

$$\frac{dc}{dt} = \begin{matrix}\text{rate drug}\\ \text{infused}\end{matrix} - \begin{matrix}\text{rate of uptake}\\ \text{by cells}\end{matrix} - \begin{matrix}\text{rate of removal by}\\ \text{the circulation}\end{matrix}, \tag{5.14b}$$

[EK05]. So the next step is to find appropriate terms for the different rates. For the growth rate of the tumor cells the logistic growth model (3.3) can be used [Web13, Pre03]:

$$\begin{aligned}\frac{dN}{dt} &= rN\left(1-\frac{N}{K}\right)\\ N(0) &= N_0.\end{aligned}$$

To model the drug induced death rate the most common term reads as

$$\begin{matrix}\text{drug-induced}\\ \text{death rate}\end{matrix} = \nu c N,$$

where ν is the drug-induced death rate, see for example [PKS+07, BW02, EC13]. Thus equation (5.14a) reads in mathematical terms as

$$\begin{aligned}\frac{dN}{dt} &= rN\left(1-\frac{N}{K}\right) - \nu c N\\ N(0) &= N_0.\end{aligned} \tag{5.15}$$

Now the change of the drug concentration has to be modeled in the same way. There is a model in [KGR13] which is quite complicated since the change of the drug concentration is modeled very exactly:

$$\begin{aligned}\frac{dc}{dt} = &\underbrace{\underbrace{\kappa|_{\text{at region}}}_{\text{supply, release, activation}}}_{\text{DRUG PRODUCTION}} + \underbrace{\underbrace{D\Delta c}_{\text{diffusion}} - \underbrace{u\cdot\nabla c}_{\text{advection}}}_{\text{DRUG TRANSPORT}} - \underbrace{\underbrace{\alpha c}_{\text{decay, deactivation}} - \underbrace{\beta c|_{\text{at cell}}}_{\text{cellular uptake}}}_{\text{DRUG ELIMINATION}}\\ c(0) &= c_0,\end{aligned} \tag{5.16}$$

where κ is a constant rate of drug supply, release or activation that takes place in a part of the domain which may be a blood vessel (supply), nanoparticle (release), or low oxygen area (activation). D is a constant diffusion coefficient, u is the velocity of the interstitial fluid, α is a decay or deactivation rate constant and β is a rate constant of drug uptake by the cell [KGR13].

To examine the model better, a simpler model for the change of drug concentration is used here. The whole model reads as

$$\frac{dN}{dt} = rN\left(1 - \frac{N}{K}\right) - \nu cN =: f(N) \tag{5.17a}$$

$$\frac{dc}{dt} = C(t) - \lambda c - \gamma cN =: f(c) \tag{5.17b}$$

$$N(0) = N_0$$

$$c(0) = c_0,$$

where ν is the rate at which the tumor cells are killed by the drug, λ is the drugs half-life (or decay rate), γ denotes the rate at which the drug becomes ineffective as a result of cell kill, and $C(t)$ represents the rate at which the drug is delivered to the tumor. For all parameters we assume: ν, λ, $\gamma > 0$ [Pre03]. There are two ways to deliver the chemotherapeutic drug: continuous and periodic. This is modeled in the following way:

$$\text{Continuous Infusion: } C(t) = \quad c_\infty \quad \forall t \geq 0 \tag{5.18a}$$

$$\text{Periodic Infusion: } C(t) = \begin{cases} c_\infty & n < t < n + \tau \\ 0 & n + \tau < t < n + 1 \end{cases}. \tag{5.18b}$$

If $C(t) = 0$ equation (5.17a) becomes the logistic growth equation and thus $N \to K$ as $t \to \infty$.
If the drug is administered continuously to the tumor, then $N(t)$ as well as $c(t)$ will converge to an equilibrium [Pre03]. To obtain these equilibria, it is necessary to set $\frac{d}{dt} = 0$ in equations (5.17a) and (5.17b). We get

$$rN\left(1 - \frac{N}{K}\right) - \nu cN = 0$$

$$\Leftrightarrow rN\left(1 - \frac{N}{K} - \frac{\nu}{r}c\right) = 0 \text{ and} \tag{5.19}$$

$$c_\infty - \lambda c - \gamma cN = 0. \tag{5.20}$$

The first equilibrium is quite simple to see. It reads as

$$(\hat{N}_1, \hat{c}_1) = (0, \frac{c_\infty}{\lambda}). \tag{5.21}$$

The second equilibrium is not that simple to see. If $N \neq 0$ equation (5.19) yields that

$$\left(1 - \frac{N}{K} - \frac{\nu}{r}c\right) \stackrel{!}{=} 0 \tag{5.22}$$

and thus

$$c = \frac{r}{\nu}\left(1 - \frac{N}{K}\right). \tag{5.23}$$

So after inserting (5.23) in equation (5.20) we get

$$\begin{aligned} 0 =& c_\infty - \frac{\lambda r}{\nu}\left(1-\frac{N}{K}\right) - \frac{\gamma r N}{\nu}\left(1-\frac{N}{K}\right) \\ =& N^2 \frac{\gamma r}{\nu K} - N\left(\frac{\gamma r}{\nu} - \frac{\lambda r}{\nu K}\right) + c_\infty - \frac{\lambda r}{\nu} \\ =& N^2 + \frac{\lambda}{\gamma}\left(1-\frac{K\gamma}{\lambda}\right)N - \frac{\lambda K}{\gamma}\left(\frac{c_\infty \nu}{\lambda r} - 1\right). \end{aligned} \tag{5.24}$$

Hence the second equilibrium is represented by the equations (5.23) and (5.24). Since equation (5.24) is not very meaningful about the value of N, it will be examined further. The roots of N are

$$N_\pm = \frac{-\frac{\lambda}{\gamma}\left(1-\frac{\gamma K}{\lambda}\right) \pm \sqrt{\frac{\lambda^2}{\gamma^2}\left(1-\frac{\gamma K}{\lambda}\right)^2 - 4\frac{\lambda K}{\gamma}\left(\frac{c_\infty \nu}{\lambda r} - 1\right)}}{2}. \tag{5.25}$$

So to get two real roots it has to hold that

$$\frac{\lambda^2}{\gamma^2}\left(1-\frac{\gamma K}{\lambda}\right)^2 - 4\frac{\lambda K}{\gamma}\left(\frac{c_\infty \nu}{\lambda r} - 1\right) > 0. \tag{5.26}$$

If the tumor and the drug are already determined, the parameters λ, γ and ν are fixed. Thus c_∞ will be our bifurcation parameter. To get the bifurcation point the following equation has to be solved for c_∞^{max}:

$$\begin{aligned} & \frac{\lambda^2}{\gamma^2}\left(1-\frac{\gamma K}{\lambda}\right)^2 - 4\frac{\lambda K}{\gamma}\left(\frac{c_\infty^{max} \nu}{\lambda r} - 1\right) = 0 \\ \Leftrightarrow \quad & \frac{c_\infty^{max} \nu}{\lambda r} - 1 = \frac{\gamma}{4\lambda K}\frac{\lambda^2}{\gamma^2}\left(1-\frac{\gamma K}{\lambda}\right)^2 \\ \Leftrightarrow \quad & c_\infty^{max} = \frac{\lambda r}{\nu}\left(\frac{\lambda}{4K\gamma}\left(1-\frac{\gamma K}{\lambda}\right)^2 + 1\right). \end{aligned} \tag{5.27}$$

So there are no real roots for N if

$$c_\infty > c_\infty^{max} = \frac{\lambda r}{\nu}\left(\frac{\lambda}{4K\gamma}\left(1-\frac{\gamma K}{\lambda}\right)^2 + 1\right), \tag{5.28}$$

and thus only the equilibrium $\hat{N}_1 = 0$ exist which means that the number of tumor cells tends to zero as $t \to \infty$. So if the administered dose of the drug is high enough, the tumor will vanish. In a real case you also have to keep in mind the consequences of the drug for the normal tissue. So the question remains: To which equilibria will N and c converge if the drug dose is not high enough to allow only one equilibrium, i.e. if $c_\infty < c_\infty^{max}$?
To answer this question we need another definition:

Definition 3. *Lyapunov's indirect method*
For ODE-systems in $\mathbb{R}^n$: Let v be a C^1 vector field in $\mathbb{R}^n$ and x_e an equilibrium point of the dynamical system generated by v. Consider the Jacobian (matrix) $Jv(x_e) \in \mathbb{R}^{n\times n}$:

- *$Re\lambda < 0 \ \forall$ eigenvalues λ of $Jv(x_e)$*
  $\Rightarrow x_e$ is asymptotically stable
- *$Re\lambda > 0$ for (at least) one eigenvalue λ of $Jv(x_e)$*
  $\Rightarrow x_e$ is unstable

[Sch13]. According to this definition, the Jacobian matrix of $f(N)$ and $f(c)$, given in (5.17a) and (5.17b) respectively, will be computed:

$$J(N,c) = \begin{pmatrix} \frac{df(N)}{dN} & \frac{df(N)}{dc} \\ \frac{df(c)}{dN} & \frac{df(c)}{dc} \end{pmatrix} = \begin{pmatrix} r\left(1-2\frac{N}{K}\right) - \nu c & -\nu N \\ -\gamma c & -\lambda - \gamma N \end{pmatrix}. \tag{5.29}$$

The stationary point from (5.21) is inserted to see if it is stable or not:

$$J(0, \frac{c_\infty}{\lambda}) = \begin{pmatrix} r - \nu\frac{c_\infty}{\lambda} & 0 \\ -\frac{\gamma c_\infty}{\lambda} & -\lambda \end{pmatrix}. \tag{5.30}$$

Since it is a lower triangular matrix, the diagonal yields the eigenvalues x_1 and x_2 immediately:

$$x_1 = -\lambda < 0 \tag{5.31}$$

$$x_2 = r - \frac{\nu c_\infty}{\lambda} < 0 \text{ if } c_\infty > \frac{r\lambda}{\nu}. \tag{5.32}$$

Thus for $c_\infty > \frac{r\lambda}{\nu}$ the stationary point $(\hat{N}_1, \hat{c}_1)$ from (5.21) is asymptotically stable and for $c_\infty < \frac{r\lambda}{\nu}$ it is unstable.
Next the nontrivial stationary points will be examined. Since the term $\left(1 - \frac{\gamma K}{\lambda}\right)$ switches its sign depending on whether $\frac{\gamma K}{\lambda} < 1$ or $\frac{\gamma K}{\lambda} > 1$ there are two cases.
In the case $\frac{\gamma K}{\lambda} > 1$ there are two physically realistic solutions for N if $\frac{\lambda r}{\nu} < c_\infty < c_\infty^{max}$. For $c_\infty = \frac{\lambda r}{\nu}$ one root of N is zero which is the trivial equilibrium and if $c_\infty < \frac{\lambda r}{\nu}$ one root of N is smaller than zero which would be unrealistic. Thus for $0 \leq c_\infty \leq \frac{\lambda r}{\nu}$ there is only one nontrivial realistic solution [Pre03].
In the case $\frac{\gamma K}{\lambda} < 1$ the sign of the term $\left(1 - \frac{\gamma K}{\lambda}\right)$ switches and thus we have one nontrivial, realistic solution for $0 \leq c_\infty \leq \frac{\lambda r}{\nu}$ and for $\frac{\lambda r}{\nu} < c_\infty < c_\infty^{max}$ we have no nontrivial solution, since both roots of N are negative [Pre03], see figure 5.5.
But this tells nothing about the stability of the nontrivial equilibria. Thus the Jacobian is needed again. The stability of the stationary points is analyzed different as in [Pre03]. Let j_1, j_2, j_3 and j_4 be the entries of the matrix J, i.e.

$$J = \begin{pmatrix} j_1 & j_2 \\ j_3 & j_4 \end{pmatrix}.$$

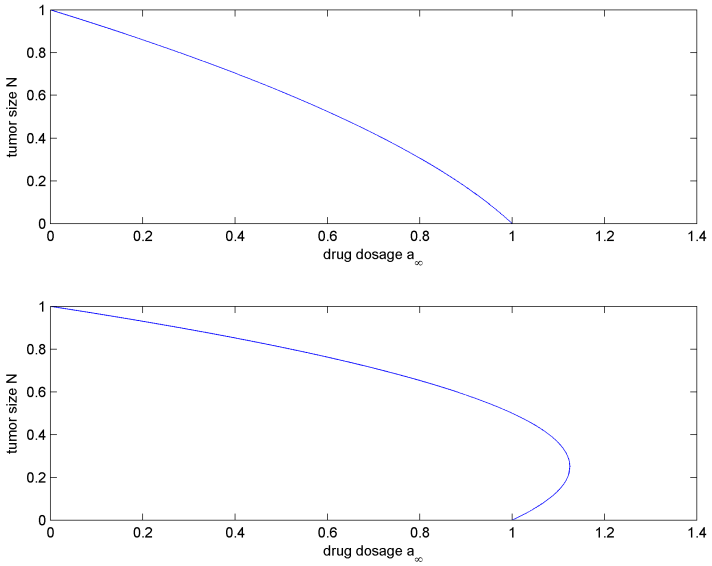


Figure 5.5: Bifurcation diagrams showing how the tumor size N depends on c_∞. Above case: $\gamma K/\lambda < 1$ with parameters $K = \lambda = \nu = r = 1, \gamma = 0.5$. Below case: $\gamma K/\lambda > 1$ with parameters $K = \lambda = \nu = r = 1, \gamma = 2$. Figure based on [Pre03].

Let I be the unit matrix, then:

$$\begin{aligned}\det(J - x \cdot I) &= \det \begin{pmatrix} j_1 - x & j_2 \\ j_3 & j_4 - x \end{pmatrix} \\ &= (j_1 - x)(j_4 - x) - j_2 j_4 = x^2 - (j_1 + j_4)x + (j_1 j_4 - j_2 j_3) \\ &= x^2 - \operatorname{trace}(J)x + \det(J).\end{aligned}$$

Thus the eigenvalues $x_{1/2}$ of J can be calculated as follows:

$$x_{1/2} = \frac{\operatorname{trace}(J) \pm \sqrt{(\operatorname{trace}(J))^2 - 4\det(J)}}{2}. \tag{5.33}$$

If a nontrivial equilibria is asymptotically stable it has to hold that $x_{1/2} < 0$. By looking at (5.33) it can be seen that if $\det(J) < 0$ there is always one positive eigenvalue. If $\det(J) > 0$ and $\operatorname{trace}(J) > 0$ there is also at least one positive eigenvalue. Only if $\det(J) > 0$ and $\operatorname{trace}(J) < 0$ both eigenvalues can be negative.
We differentiate again between the two cases $\frac{\gamma K}{\lambda} < 1$ and $\frac{\gamma K}{\lambda} > 1$. In the first case the parameters are chosen as in figure 5.5:

$$K = \lambda = \nu = r = 1,\ \gamma = \frac{1}{2}.$$

Thus the equations (5.23) and (5.25) reduce to

$$c = 1 - N \quad \text{and}$$
$$N_{\pm} = \frac{-1 \pm \sqrt{9 - 8c_{\infty}}}{2},$$

and hence the Jacobian $J(N, c)$ reads as

$$J(N,c) = \begin{pmatrix} (1-2N) - c & -N \\ -\frac{1}{2}c & -1 - \frac{1}{2}N \end{pmatrix} = \begin{pmatrix} -N & -N \\ -\frac{1}{2} + \frac{1}{2}N & -1 - \frac{1}{2}N \end{pmatrix}.$$

Now the trace and the determinant can be calculated easily:

$$\begin{aligned} \operatorname{trace}(J) &= -1 - \frac{3}{2}N < 0 \\ \det(J) &= \left(1 + \frac{1}{2}N\right) N + N\left(\frac{1}{2}N - \frac{1}{2}\right) = N^2 + \frac{1}{2}N > 0. \end{aligned}$$

Hence the nontrivial (realistic) equilibrium is stable.
In the second case $\frac{\gamma K}{\lambda} > 1$, we choose the parameters as follows:

$$K = \lambda = \nu = r = 1,\ \gamma = 2.$$

This time the equations (5.23) and (5.25) reduce to

$$c = 1 - N \quad \text{and}$$
$$N_{\pm} = \frac{\frac{1}{2} \pm \sqrt{\frac{9}{4} - 2c_{\infty}}}{2},$$

and hence the Jacobian reads as

$$J(N,c) = \begin{pmatrix} (1-2N) - c & -N \\ -2c & -1 - 2N \end{pmatrix} = \begin{pmatrix} -N & -N \\ -2 + 2N & -1 - 2N \end{pmatrix}.$$

Like before the trace and the determinant can be calculated. They read as follows:

$$\begin{aligned} \operatorname{trace}(J) &= -1 - 3N < 0 \\ \det(J) &= N(1 + 2N) + N(2N - 2) = 4N^2 - N. \end{aligned}$$

Thus we need to determine when the determinant is greater than zero, i.e.

$$4N^2 - N > 0.$$

Since we only consider the cases where $N > 0$ this is equivalent to

$$\begin{aligned} & 4N - 1 > 0 \\ \Leftrightarrow\ & 4N > 1 \\ \Leftrightarrow\ & 1 \pm 2\sqrt{\frac{9}{4} - 2c_{\infty}} > 1 \\ \Leftrightarrow\ & \pm\sqrt{\frac{9}{4} - 2c_{\infty}} > 0. \end{aligned}$$

Hence only the greater one of the nontrivial equilibria is stable. The other one is unstable and acts like a boundary between the two stable steady states (the greater nontrivial and the trivial one) [Pre03]. This is illustrated in figure 5.6. The stable solutions are represented by solid lines and the unstable solutions by a dotted line. Figure 5.7 shows the different direction fields including the equilibria for different values of γ and c_∞.

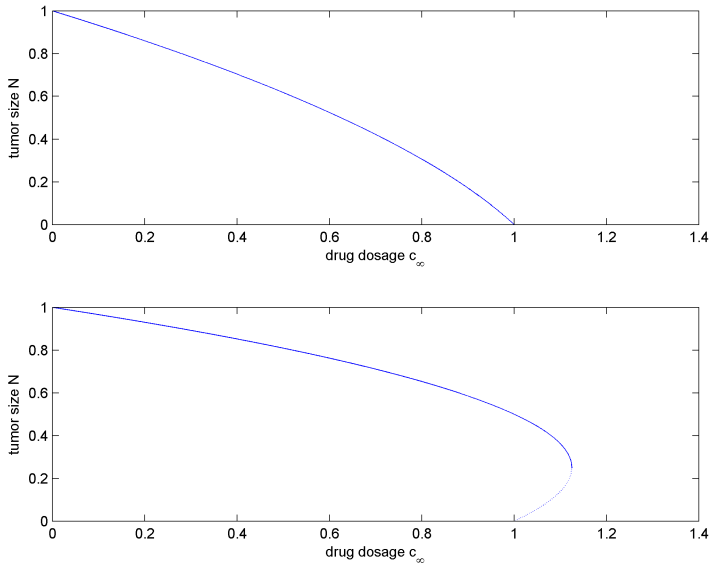


Figure 5.6: Bifurcation diagrams with stability analysis. The parameters in the cases $\gamma K/\lambda < 1$ and $\gamma K/\lambda > 1$ are the same as in figure 5.5. Solid lines represent stable solutions and the dotted line represents an unstable solution. Based on a figure in [Pre03].

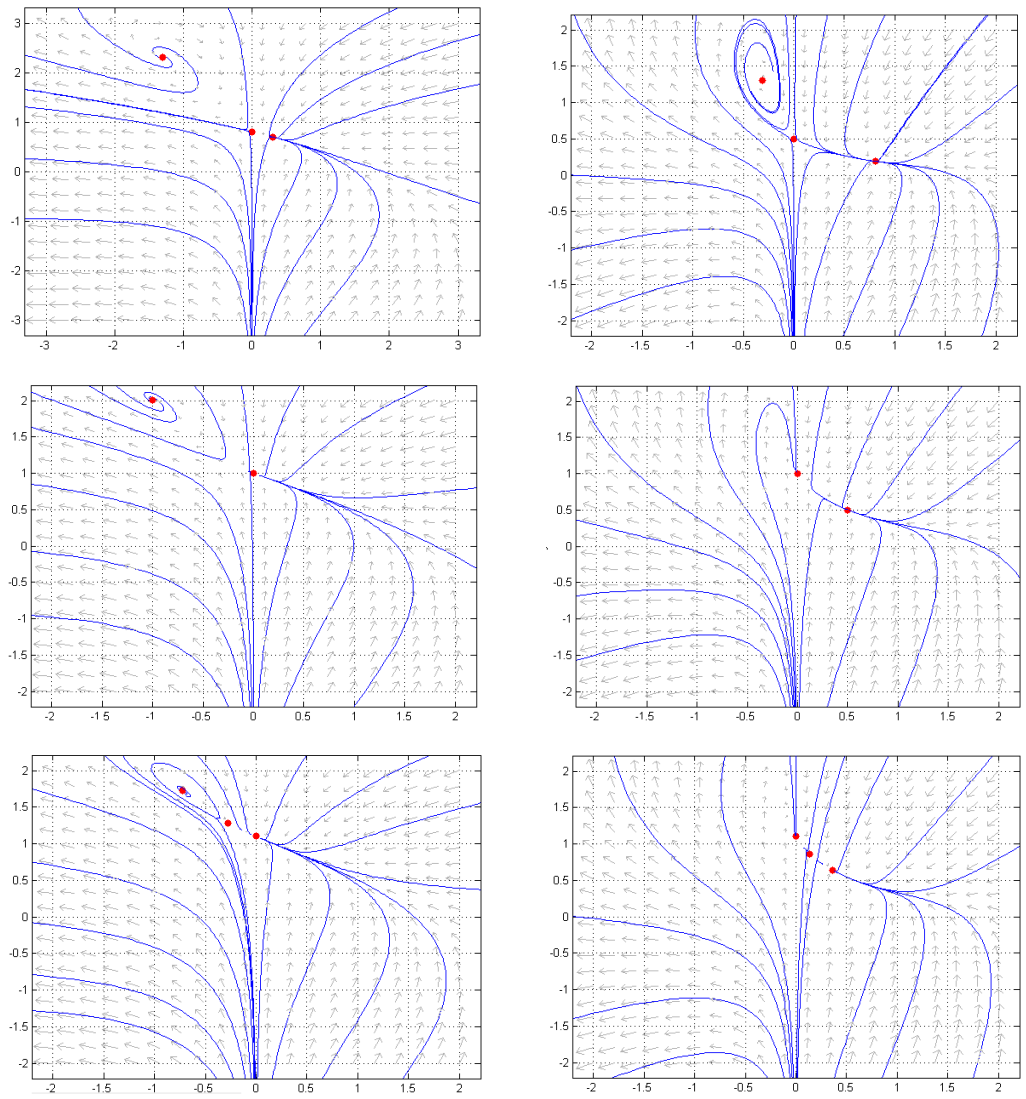


Figure 5.7: Direction fields. Used parameters are $\nu = K = r = \lambda = 1$. Left column: $\gamma = 0.5$ and thus $\gamma K/\lambda < 1$. Right column: $\gamma K/\lambda > 1$ with $\gamma = 2$. In the first row one has $c_\infty < \frac{\lambda r}{\nu}$, in the second row $c_\infty = \frac{\lambda r}{\nu}$ and in the last row $\frac{\lambda r}{\nu} < c_\infty < c_\infty^{max}$. The x-axis corresponds to the cell number N and the y-axis to the drug concentration c. Figures are made with pplane in Matlab.

5.4. Cell Cycle Specific Model

In this section a pulsed model will be discussed first, which can be found in [RDIK11]. After that the more realistic piecewise continuous model will be touched upon.

5.4.1. Pulsed Model

Here a certain fraction μ of tumor cells (or cells generally) is killed immediately, like after a bolus injection. Let $N(n\tau)$ be the number of cells before, and $N(n\tau+\tau) = N((n+1)\tau)$ the number of cells after a single injection. Introducing the survival fraction $\eta = 1 - \mu$ yields

$$N((n+1)\tau) = (1-\mu)N(n\tau) = \eta N(n\tau). \tag{5.34}$$

To keep the model simple the tumor cells are assumed to grow exponentially. This is a justifiable assumption since, because of the treatment, the number of tumor cells should be kept away from their capacity. So the number of cells at time $n\tau$ is

$$N(n\tau) = N(0)e^{rn\tau}. \tag{5.35}$$

Since there are many different treatments and therefore also many different chemotherapeutic drugs disposable for almost every type of cancer, the treatment with two different drugs A and B will be considered in more detail. Of course the model is simply expandable to more than two drugs. For this purpose we have now different killing and survival rates, namely

μ_i = killing fraction of drug i,
$\eta_i = 1 - \mu_i$ = survival fraction of drug i.

An advantage of using more than one drug can be the synergistic effects of some drugs. But it is also possible that specific drugs have an antagonistic effect if they are used together [RDIK11]. Now a sequence of injections can be modeled. Let τ be the time between two treatments. In the first case m injections of drug A are followed by m injections of drug B. Thus the number of cells after the whole treatment is

$$N(2m\tau) = (\eta_A e^{r\tau})^m(\eta_B e^{r\tau})^m N(0) = (\eta_A\eta_B e^{2r\tau})^m N(0). \tag{5.36}$$

In the second case after each injection of drug A there is an injection of drug B. Thus after one injection of each there are

$$N(2\tau) = (\eta_A e^{r\tau})(\eta_B e^{r\tau})N(0) \tag{5.37}$$

cells and consequently after m such cycles

$$N(2m\tau) = (\eta_A\eta_B e^{2r\tau})^m N(0). \tag{5.38}$$

You can see that the equations (5.36) and (5.38) are equivalent. Thus it does not matter in which order the drugs are applied. But it is well-known that the order of drug treatment has a crucial influence on the efficacy of the treatment. To undo this inaccuracy we will extend this model to a cell cycle specific model.
There are many ways to model a cycle specific treatment. In [RDIK11] they only consider proliferating cells and differentiate between cells in the phases G_1 and S and cells in

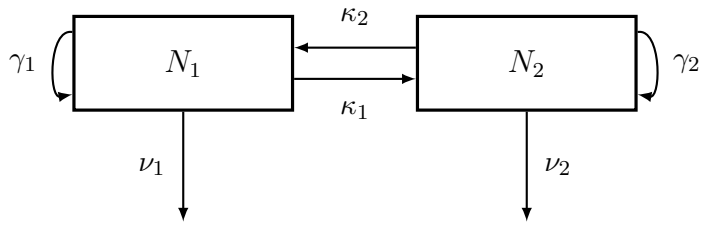


Figure 5.8: Two Compartment Cell Cycle Model: In this model the cells are divided into the two compartments N_1 and N_2, which are proliferating with rates γ_1 and γ_2 respectively and dying with rates ν_1 and ν_2 respectively. The cells transition from one compartment into the other with rates κ_1 and κ_2.

the phases G_2 and M, whereas in [PA95] they differentiate between proliferating cells and cells in the phase G_0, i.e. quiescent cells. Here a more generalized model will be discussed.
In Figure 5.8 the cells are divided into two compartments with N_1 and N_2 tumor cells respectively, which are proliferating with rates γ_1 and γ_2 and dying with rates ν_1 and ν_2 respectively. The cells transition from one compartment into the other with rates κ_1 and κ_2. Now the differential equations, which describe the change in N_1 and N_2 can be established. In the following all parameters $\kappa_i, \gamma_i, \nu_i > 0, i = 1, 2$.

$$\frac{dN_1}{dt} = \gamma_1 N_1 - \kappa_1 N_1 + \kappa_2 N_2 - \nu_1 N_1 = (\gamma_1 - \kappa_1 - \nu_1)N_1 + \kappa_2 N_2 \tag{5.39a}$$

$$\frac{dN_2}{dt} = \gamma_2 N_2 - \kappa_2 N_2 + \kappa_1 N_1 - \nu_2 N_2 = (\gamma_2 - \kappa_2 - \nu_2)N_2 + \kappa_1 N_1. \tag{5.39b}$$

Here we assume the cells to have a positive net growth rate, i.e. $\gamma_i > \nu_i$, for $i = 1, 2$. Unfortunately this equations cover not all cell cycle models. It is mentioned above that the first compartment can be chosen to be the cells in the G_1 and S phase and the second compartment to be the cells in the G_2 and M phase [RDIK11]. So the cells in the first compartment have two copies of DNA and the ones in the second compartment have four copies. So when the cells in compartment one pass into compartment two the number of cells stays the same. But when the cells from compartment two pass into compartment one, mitosis occurs and the number of cells is doubled. Hence the differential equation would look a bit different:

$$\frac{dN_1}{dt} = -\kappa_1 N_1 + \mathbf{2}\kappa_2 N_2 - \nu_1 N_1 \tag{5.40a}$$

$$\frac{dN_2}{dt} = -\kappa_2 N_2 + \kappa_1 N_1 - \nu_2 N_2. \tag{5.40b}$$

Please note that in this special case the γ-term does not have to be considered. But since this is just a slight change and the further procedure would be the same, the model will be based on the equations (5.39). Written in vector form the system of equations

(5.39) yields

$$\begin{aligned}\frac{dN}{dt} = \begin{pmatrix}\frac{dN_1}{dt}\\ \frac{dN_2}{dt}\end{pmatrix} &= \begin{pmatrix}\gamma_1-\kappa_1-\nu_1 & \kappa_2\\ \kappa_1 & \gamma_2-\kappa_2-\nu_2\end{pmatrix}\begin{pmatrix}N_1\\N_2\end{pmatrix}\\ &= \begin{pmatrix}\gamma_1-\kappa_1-\nu_1 & \kappa_2\\ \kappa_1 & \gamma_2-\kappa_2-\nu_2\end{pmatrix} N =: CN.\end{aligned} \tag{5.41}$$

There are further assumptions which can be made on our equations. For example one could neglect the ν-terms, since the normal cell death is minimal compared to the cell death caused by chemotherapy. Considering the model in [PA95], where compartment one represents cycling cells and compartment two the resting cells, it holds that $\gamma_2 = 0$ since the resting cells do not proliferate. Further it can be assumed that $(\gamma_1-\kappa_1-\nu_1) < 0$ since the majority of the cycling cells become resting cells and only a small proportion keeps cycling. The solution for the differential equation (5.41) is given by

$$N(t) = e^{Ct}N(0) =: MN(0), \tag{5.42}$$

with the growth matrix $M = e^{Ct}$.
Like before the treatment with the drugs A and B can be modeled. With the assumption that each drug kills different amounts of cells in the different compartments the following parameters are needed:

μ_i^j = killing fraction of drug i in compartment j,
$\eta_i^j = 1 - \mu_i$ = survival fraction of drug i in compartment j.

Now the treatment matrices T_i, $i = A, B$, can be constructed:

$$T_A = \begin{pmatrix}\eta_A^1 & 0\\ 0 & \eta_A^2\end{pmatrix}, \qquad T_B = \begin{pmatrix}\eta_B^1 & 0\\ 0 & \eta_B^2\end{pmatrix}, \tag{5.43}$$

which depict the treatment with drug A and drug B respectively. If one compartment represents the resting cells (for example compartment two, like in the example before) we can assume $\eta_A^2 = \eta_B^2 = 1$ since the drugs have nearly no effect on resting cells. Please note, that in general η_i^j is not a constant but rather decreasing function of the drug dose d, i.e. $\eta_i^j(d)$ with $0 < \eta_i^j(d) < 1$.
Next the different orders of treatments with different drugs can be modeled. The pulsing periodic condition is

$$N((n+1)\tau) = T_A N(n\tau) \tag{5.44}$$

for the drug A and

$$N((n+1)\tau) = T_B N(n\tau) \tag{5.45}$$

for the drug B. The time between two treatments is again τ. As before first the treatment, where m doses of drug A are followed by m doses of drug B is considered. Hence the number of cells after the whole treatment is

$$N(2m\tau) = (T_B M)^m (T_A M)^m N(0). \tag{5.46}$$

In the second case, where m times each dose of drug A is followed by a dose of drug B the number of cells left is

$$N(2m\tau) = (T_B M T_A M)^m N(0). \tag{5.47}$$

Since the matrix product is only commutative in special cases, it holds in general that

$$(T_B M)^m (T_A M)^m \neq (T_B M T_A M)^m, \tag{5.48}$$

which means that the equations (5.46) and (5.47) are usually not the same. Thus the order of the treatment of the different drugs has an impact on the effectiveness of the whole treatment.

5.4.2. Piecewise Continuous Case

This paragraph will cover the piecewise continuous case. Here the treatment is added to equation (5.41) in the following way:

$$\frac{dN}{dt} = \begin{pmatrix} \gamma_1 - \kappa_1 - \nu_1 & \kappa_2 \\ \kappa_1 & \gamma_2 - \kappa_2 - \nu_2 \end{pmatrix} N - \begin{pmatrix} g_1(t) & 0 \\ 0 & g_2(t) \end{pmatrix} N, \tag{5.49}$$

which describes the chemotherapeutic treatment with only one drug. Since the piecewise continuous case is treated, the function $g_i(t)$ $(i = 1, 2)$ is a piecewise continuous function which describes how the treatment impacts the different compartments. As it is often the case, there are many ways to model $g_i(t)$. In the case, where N_1 represents the number of proliferating cells and N_2 the number of resting cells, we can set

$$g_2(t) = 0, \tag{5.50}$$

since there is almost no effect of the drugs on quiescent cells. For the proliferating cells an exponential decay function is chosen, namely

$$g_1(t) = he^{-\delta(t-n\tau)}, \qquad n\tau \leq t < (n+1)\tau, \tag{5.51}$$

where h is the cell kill parameter, and δ is the decay of the drug. It can be seen easily in figure (5.9) that a large value of δ signifies a high decay of the drug. This corresponds to a high survival fraction η_i^j in the pulsed case. In contrast to the pulsed case, in the piecewise case the cells are destroyed over the whole period, and not instantly.
There is one aspect, we have not considered here, but which we have to keep in mind. Of course, not only the tumor cells are killed by the drug, also the normal tissue is affected. Hence it is the aim to find the right way between killing the tumor and hopefully not to damage the normal tissue too much.

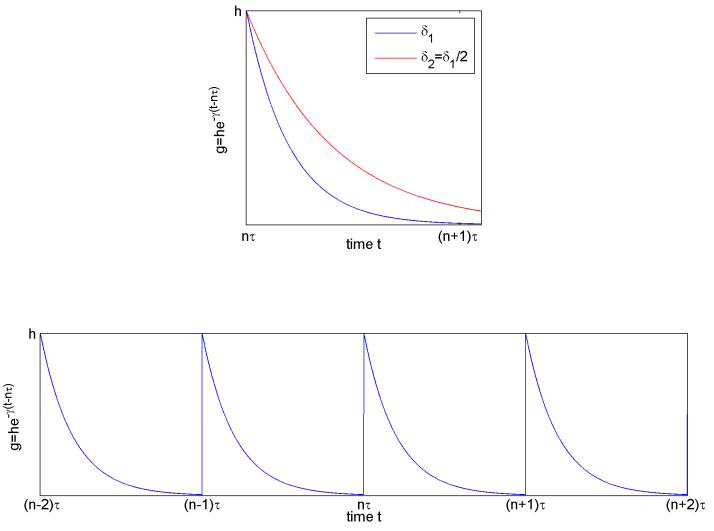


Figure 5.9: Exponential Decay Function.

5.5. Fitting the model to data

Also in this section we try to fit the mathematical model to given data points. The normalized data from [AH14] can be seen in table 3.

Number of cells	**Days**				
Concentration of drug (μM)	0	3	6	9	12
0.3	596.3	1479.5	2303.3	2134.1	3480.3
1	596.3	1337.8	2694.8	2730.1	2984.1
3	596.3	1260.3	2427.1	2538.9	1959.4
10	596.3	959.1	1639.7	1624.0	1212.8
30	596.3	924.3	1827.5	1657.2	1405.2

Table 3: Number of cells treated with chemotherapy over a period of 12 days. Data taken from [AH14].

This time the T47D cells were treated with a chemotherapeutic drug called vinblastine. On day zero $1\mu M$ of the $1000\mu M$ stock was taken and mixed with the drug, such that different solutions, like a $10\mu M$, solution were formed. After six days of chemotherapy the drug was washed away. Since there is only one infusion at the beginning, it can be represented by the initial value. Thus $c_\infty = 0\frac{\mu M}{h}$. We begin with the two initial concentrations $c_0 = 0.3\mu M$ and $c_0 = 10\mu M$, respectively, to model the treatment. Since we do not have any data about the drug concentration after day zero, it is very difficult to find appropriate values for the parameters λ and γ. Additionally these two parameters

would imply another two degrees of freedom. Thus we simplify this equation and set $\lambda = 0\frac{1}{h}$ and $\gamma = 0.00002\frac{1}{cells \cdot h}$ in advance. The parameter $r = 0.0116\frac{1}{h}$ is set according to the previous modeling. K and ν are set by algorithm 3 in order to find the best approximation. Algorithm 3 goes through possible values of K and ν and plugs them in the numerical solution of the system (5.17) including (5.18a), which is obtained by the forward euler method. Then the values which yield the smallest error are returned. For $c_0 = 0.3\mu M$ the algorithm returns the parameter values $\nu = 0\frac{1}{\mu M h}$ and $K = 4320$ cells with an error of 0.167 and for $c_0 = 10\mu M$ the parameter values $\nu = 0\frac{1}{\mu M h}$ and $K = 1860$ cells with an error of 0.1453. Figure 5.10 shows the resulting curves.

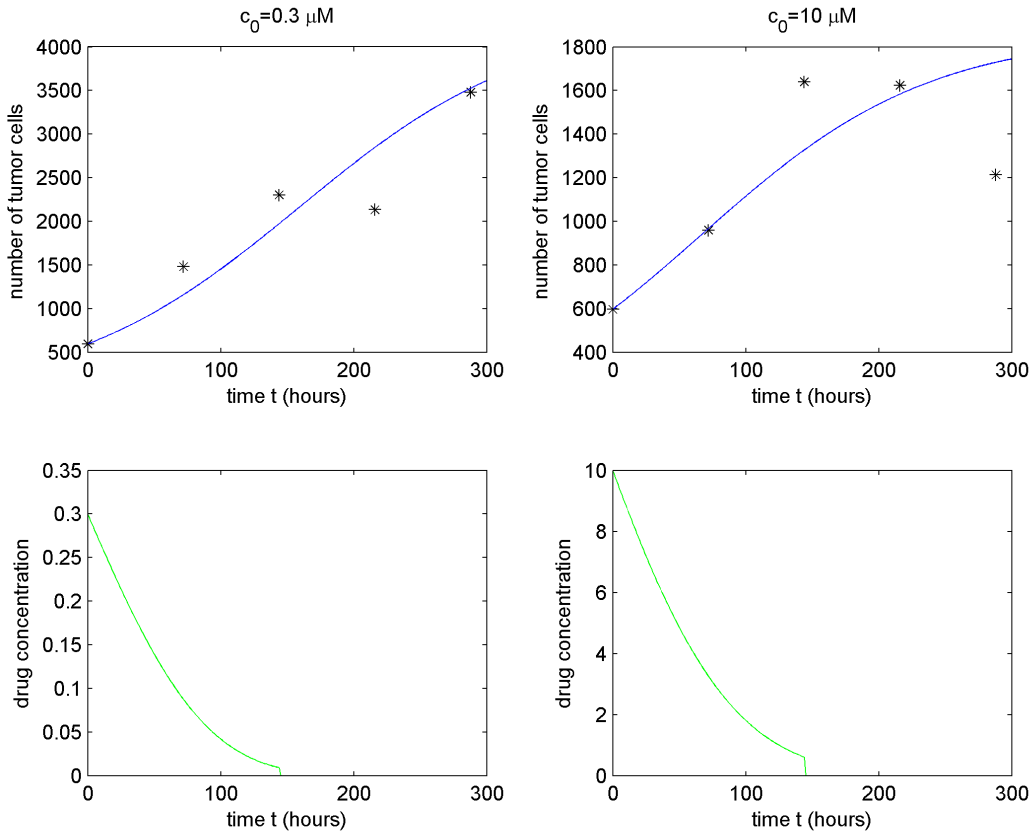


Figure 5.10: Modeling tumor growth including chemotherapy. Used parameters: $\lambda = 0\frac{1}{h}$, $\gamma = 0.00002\frac{1}{cells \cdot h}$, $r = 0.0116\frac{1}{h}$, $c_\infty = 0\frac{\mu M}{h}$ and $N_0 = 596.3$. Additionally for $c_0 = 0.3\mu M$: $\nu = 0\frac{1}{\mu M h}$ and $K = 4320$ cells. And for $c_0 = 10\mu M$: $\nu = 0\frac{1}{\mu M h}$ and $K = 1860$ cells. Parameters were plugged in the numerical solution of (5.17) including (5.18a).

Since the errors are quite high and also the curves do not look satisfying, the next step is to include the parameter $\alpha = 0.203$ from the generalized logistic growth equation in

equation (5.17a):

$$\frac{dN}{dt} = \frac{r}{\alpha} N \left(1 - \left(\frac{N}{K}\right)^{\alpha}\right) - \nu c N. \tag{5.52}$$

This time the algorithm returns the parameter values $\nu = 0.001 \frac{1}{\mu M h}$ and $K = 3320$ cells with an error of 0.0745 for $c_0 = 0.3 \mu M$ and $\nu = 0 \frac{1}{\mu M h}$ and $K = 1710$ cells with an error of 0.1142 for $c_0 = 10 \mu M$. Figure 5.11 shows the corresponding curves.

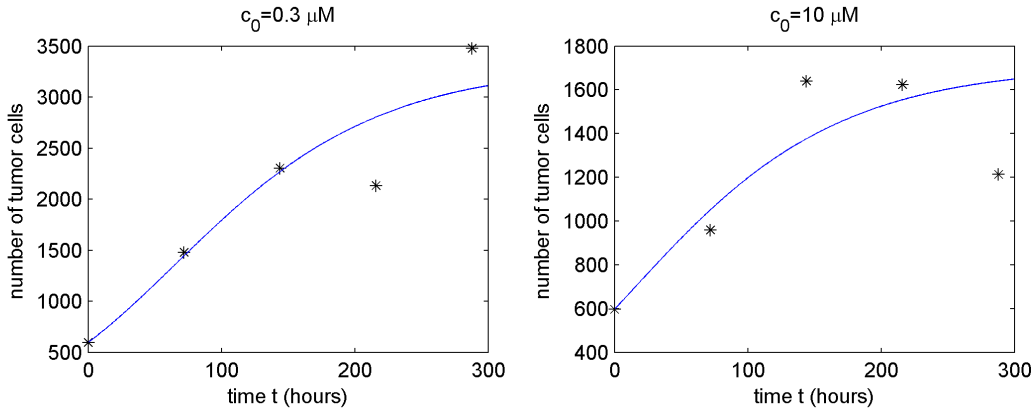


Figure 5.11: Modeling tumor growth including chemotherapy. Used parameters: $\lambda = 0 \frac{1}{h}$, $\gamma = 0.00002 \frac{1}{cells \cdot h}$, $r = 0.0116 \frac{1}{h}$, $\alpha = 0.203$, $c_\infty = 0 \frac{\mu M}{h}$, $N_0 = 596.3$. Additionally for $c_0 = 0.3 \mu M$: $\nu = 0,001 \frac{1}{\mu M h}$ and $K = 3320$ cells. And for $c_0 = 10 \mu M$: $\nu = 0 \frac{1}{\mu M h}$ and $K = 1710$ cells. The parameters were plugged in the numerical solutions of the model (5.52) and (5.17b) including (5.18a).

For $c_0 = 0.3 \mu M$ this seems to be the best fit we get since the last two data points spread quite far. Apparently after day 6 relatively many cells die, but after day 9 the population recovers quite fast. Since this happens also with the cells which are treated only with radiotherapy in the same way, it does not seem to be related to the treatment, but rather has another cause. Therefore we will not discuss this circumstance further. Besides that for $c_0 = 10 \mu M$ it seems that the model does not cover everything. In the model the number of cells can either rise or fall, but it cannot increase first and then decrease after some time. This can also be seen in figure 5.7. Thus we have to include another aspect in the model. For this purpose we include a Hill-function in our model. We do this by replacing the drug concentration c in equation 5.52 by the Hill-function

$$\frac{c^p}{Q^p + c^p}, \tag{5.53}$$

where p and Q are positive constants, which are determined from experimental data [Mur89a]. This formula can be obtained from the pharmacodynamical equation (5.9),

too. Thus the whole model reads as

$$\frac{dN}{dt} = \frac{r}{\alpha} N \left(1 - \left(\frac{N}{K}\right)^{\alpha}\right) - \nu \frac{c^p}{Q^p + c^p} N \tag{5.54a}$$

$$\frac{dc}{dt} = c_\infty - \lambda c - \gamma c N \tag{5.54b}$$

$$N(0) = N_0 \tag{5.54c}$$

$$c(0) = c_0. \tag{5.54d}$$

With algorithm 4 we try to find the best fitting by varying K, ν, p and Q. Also this time the algorithm uses the numerical solutions of the model, which are obtained by the forward euler method. From now on we also include the initial drug concentrations $c_0 = 1\mu M$, $c_0 = 3\mu M$ and $c_0 = 30\mu M$. The following parameters are fixed: $N_0 = 596.3$ cells, $c_\infty = 0\mu M$, $\alpha = 0.203$, $r = 0.0116\frac{1}{h}$, $\lambda = 0\frac{1}{h}$ and $\gamma = 0.00002\frac{1}{cells \cdot h}$. The best fitting, which can be seen in figure 5.12, is obtained with the following further parameters: $K = 3300$ cells, $\nu = 0.0001\frac{1}{h}$, $p = 1$ and $Q = 0.01\mu M$ for $c_0 = 0.3\mu M$ with an error of 0.0744, $K = 3400$ cells, $\nu = 0.0001\frac{1}{h}$, $p = 3$ and $Q = 0.506\mu M$ for $c_0 = 1\mu M$ with an error of 0.0395, $K = 2800$ cells, $\nu = 0\frac{1}{h}$, $p = 1$ and $Q = 0.01\mu M$ for $c_0 = 3\mu M$ with an error of 0.1143, $K = 1700$ cells, $\nu = 0\frac{1}{h}$, $p = 1$ and $Q = 0.01\mu M$ for $c_0 = 10\mu M$ with an error of 0.1142 and $K = 1900$ cells, $\nu = 0\frac{1}{h}$, $p = 1$ and $Q = 0.01\mu M$ for $c_0 = 30\mu M$ with an error of 0.1297. It can be seen very easily that including the Hill-function does not give us satisfying results either. Thus we try another attempt. As it is mentioned in section 2.2 vinblastine inhibits the microtubule assembly and thus the affected cell cannot proliferate anymore. So with time the proliferating rate will decrease, since more and more cells are still alive, but do not proliferate. Thus instead of using the constant proliferating rate $r(t) = 0.0116\frac{1}{h}$ for all t, we now use a linear function $r(t)$ which starts at $r(0) = 0.0116\frac{1}{h} := r_0$ and decreases continuously to a rate $r^* = r(t = 300h)$. The rate r^* could also be negative and in this case it would not be a proliferating rate anymore, but rather a dying rate. Thus the function which describes the proliferation rate over the whole time reads as

$$r(t) = r_0 + \frac{r^* - r_0}{300h} t = 0.0116\frac{1}{h} + \frac{r^* - 0.0116\frac{1}{h}}{300h} t. \tag{5.55}$$

Thus the model reads as

$$\frac{dN}{dt} = \frac{r(t)}{\alpha} N \left(1 - \left(\frac{N}{K}\right)^{\alpha}\right) - \nu c N \tag{5.56a}$$

$$\frac{dc}{dt} = c_\infty - \lambda c - \gamma c N \tag{5.56b}$$

$$N(0) = N_0 \tag{5.56c}$$

$$c(0) = c_0. \tag{5.56d}$$

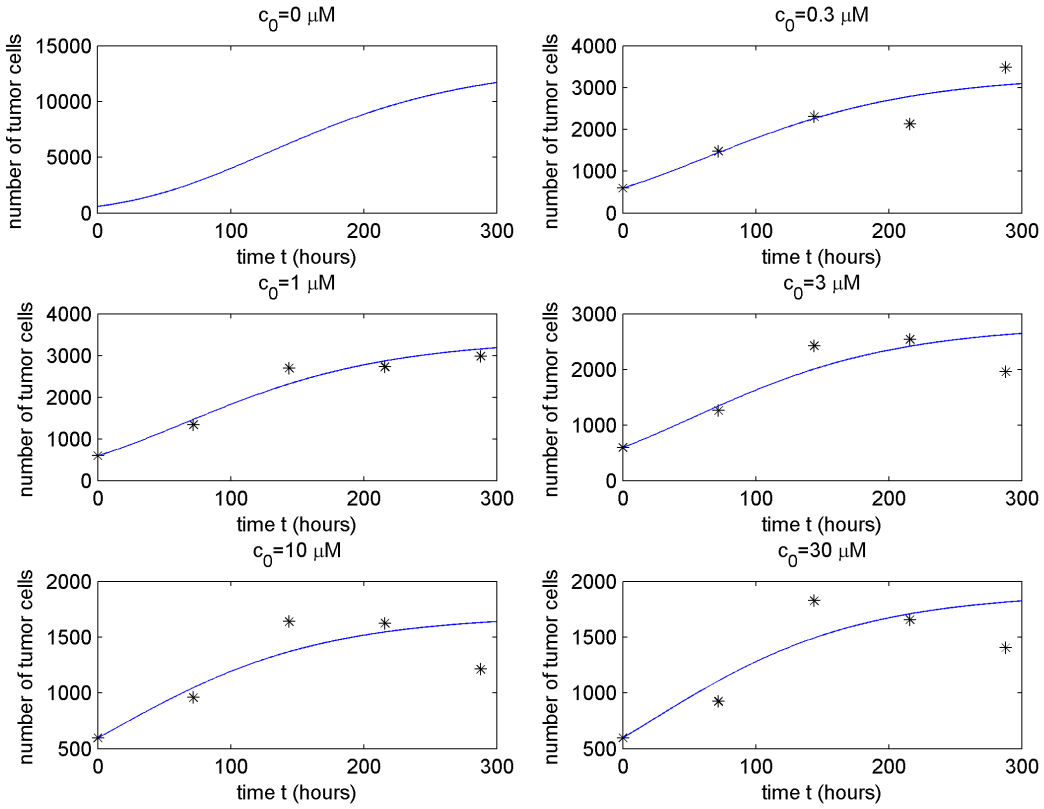


Figure 5.12: Modeling tumor growth including chemotherapy. Used parameters: $\lambda = 0\frac{1}{h}$, $\gamma = 0.00002\frac{1}{cells \cdot h}$, $r = 0.0116\frac{1}{h}$, $\alpha = 0.203$, $c_\infty = 0\frac{\mu M}{h}$ and $N_0 = 596.3$ cells. Additional parameters: $K = 3300$ cells, $\nu = 0.0001\frac{1}{h}$, $p = 1$ and $Q = 0.01\mu M$ for $c_0 = 0.3\mu M$, $K = 3400$ cells, $\nu = 0.0001\frac{1}{h}$, $p = 3$ and $Q = 0.506\mu M$ for $c_0 = 1\mu M$, $K = 2800$ cells, $\nu = 0\frac{1}{h}$, $p = 1$ and $Q = 0.01\mu M$ for $c_0 = 3\mu M$, $K = 1700$ cells, $\nu = 0\frac{1}{h}$, $p = 1$ and $Q = 0.01\mu M$ for $c_0 = 10\mu M$ and $K = 1900$ cells, $\nu = 0\frac{1}{h}$, $p = 1$ and $Q = 0.01\mu M$ for $c_0 = 30\mu M$. The parameters were plugged in the numerical solutions of the model (5.54). The figure top left is without treatment for comparison. Parameters and equation are the same as in figure 3.3.

So algorithm 5 varies this time also r^* to find the best approximation. The way of doing this is the same as before. The following parameter values are returned: $r^* = 0.006\frac{1}{h}$, $\nu = 0.0025\frac{1}{\mu M h}$ and $K = 3700$ cells with an error of 0.0708 for $c_0 = 0.3\mu M$, $r^* = -0.003\frac{1}{h}$, $\nu = 0.0100\frac{1}{\mu M h}$ and $K = 9100$ cells with an error of 0.0245 for $c_0 = 1\mu M$, $r^* = -0.006\frac{1}{h}$, $\nu = 0.0045\frac{1}{\mu M h}$ and $K = 13500$ cells with an error of 0.0117 for $c_0 = 3\mu M$, $r^* = -0.006\frac{1}{h}$, $\nu = 0.0020\frac{1}{\mu M h}$ and $K = 11200$ cells with an error of 0.0098 for $c_0 = 10\mu M$ and $r^* = -0.006\frac{1}{h}$, $\nu = 0.0005\frac{1}{\mu M h}$ and $K = 8200$ cells with an error of 0.0442 for

$c_0 = 30\mu M$. As we assumed before, the error for $c_0 = 0.3\mu M$ improved not really, but the error for $c_0 = 10\mu M$ is much better. The results can be seen in figure 5.13. The first figure top left shows the tumor growth without any treatment for comparison.

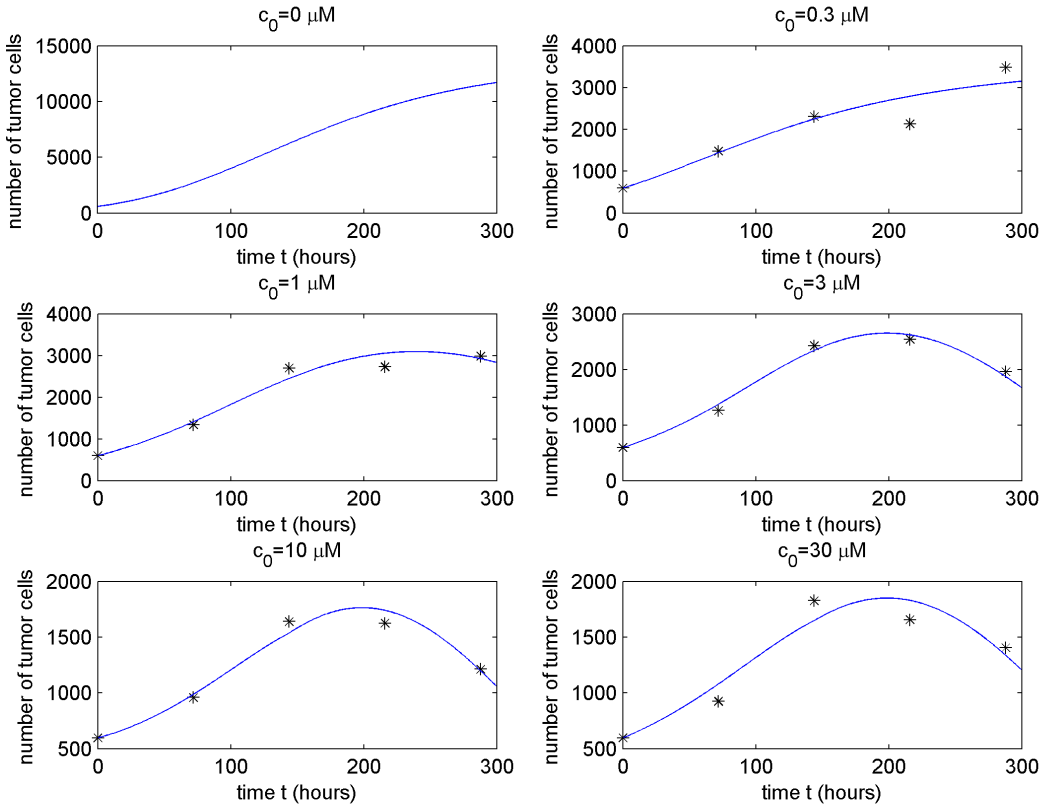


Figure 5.13: Modeling tumor growth including chemotherapy. Used parameters: $\lambda = 0\frac{1}{h}$, $\gamma = 0,00002\frac{1}{cells \cdot h}$, $r = 0.0116\frac{1}{h}$, $N_0 = 596.3$ cells, $c_\infty = 0\frac{\mu M}{h}$ and $\alpha = 0.203$. Additionally for $c_0 = 0.3\mu M$: $r^* = 0.006\frac{1}{h}$, $\nu = 0,0025\frac{1}{\mu M h}$ and $K = 3700$ cells. For $c_0 = 1\mu M$: $r^* = -0.003\frac{1}{h}$, $\nu = 0.0100\frac{1}{\mu M h}$ and $K = 9100$ cells. For $c_0 = 3\mu M$: $r^* = -0.006\frac{1}{h}$, $\nu = 0.0045\frac{1}{\mu M h}$ and $K = 13500$ cells. For $c_0 = 10\mu M$: $r^* = -0.006\frac{1}{h}$, $\nu = 0.0020\frac{1}{\mu M h}$ and $K = 11200$ cells. And for $c_0 = 30\mu M$: $r^* = -0.006\frac{1}{h}$, $\nu = 0.0005\frac{1}{\mu M h}$ and $K = 8200$ cells. The parameters were plugged in the numerical solutions of the model (5.56)including (5.18a). For comparison the top left figure shows the tumor growth without treatment, i.e. $c_0 = 0\mu M$. The parameters are the same as in figure 3.3.

So this model yields quite good results, although there are two problems left. The first problem is that the model is not homogeneous anymore because of the non-constant proliferation rate $r(t)$. The second problem is that the carrying capacity K as well as the proliferation rate r are not the same as in the basic case without any treatment. We will first wade into the second problem. We can see in the above simulations, that with

fixed parameters, the number of tumor cells can either rise or fall, but it cannot rise first and than fall after some time. Thus we only get satisfying results, if the dying rate of chemotherapy is small enough at the beginning such that the number of tumor cells can increase and then high enough such that the number of tumor cells decreases. Thus the dying rate has to increase over time. But since the drug concentration decreases, the dying rate and the drug concentration cannot correlate linearly. We try another approach and use the efficacy of the drug. We assume that over time, the drug concentration inside the tumor cells increase linearly, depending on the particular initial drug concentration. Thus the efficacy ϵ can be represented by the formula

$$\epsilon = \nu \frac{c_0 t}{Q + c_0 t}, \tag{5.57}$$

which can be obtained by the equations (5.9) or (5.53). Q is again a positive constant which is given by the data. The model reduces to a one dimensional differential equation, which reads

$$\frac{dN}{dt} = \frac{r}{\alpha} N \left(1 - \left(\frac{N}{K}\right)^{\alpha}\right) - \nu \frac{c_0 t}{Q + c_0 t} N \tag{5.58a}$$

$$N(0) = N_0. \tag{5.58b}$$

The results which are returned by algorithm 6 can be seen in figure 5.14. The following parameters and errors are returned: $Q = 2\mu Mh$ and $\nu = 0.014\frac{1}{h}$ with and error of 0.0699 for $c_0 = 0.3\mu M$, $Q = 11\mu Mh$ and $\nu = 0.014\frac{1}{h}$ with and error of 0.0474 for $c_0 = 1\mu M$, $Q = 143\mu Mh$ and $\nu = 0.021\frac{1}{h}$ with and error of 0.0953 for $c_0 = 3\mu M$, $Q = 162\mu Mh$ and $\nu = 0.022\frac{1}{h}$ with and error of 0.1081 for $c_0 = 10\mu M$, $Q = 300\mu Mh$ and $\nu = 0.020\frac{1}{h}$ with and error of 0.1336 for $c_0 = 30\mu M$.
The values for ν do not differ very much. For $c_0 = 0.3\mu M$ and $c_0 = 1\mu M$ they are actually the same and also for $c_0 = 3\mu M$, $c_0 = 10\mu M$ and $c_0 = 30\mu M$ they are nearly the same. Only the value of the parameter Q is definitely not the same for different concentrations. In figure 5.15 one can see how Q is related to c_0. But since Q can be seen as an accumulation parameter for the drug concentration inside the cell, it makes no sense for this parameter to change for different drug concentrations.
So there are again to problems. Also the model (5.58) is inhomogeneous and thus the analysis we can do on the model is very limited. The second problem is that all parameters should be nearly the same for all different drug concentrations. We try a new attempt by representing ϵ by a differential equation instead of a hyperbolic function:

$$\frac{d\epsilon}{dt} = (d \cdot c_0)\epsilon \left(1 - \frac{\epsilon}{E}\right), \tag{5.59}$$

where ϵ is the efficacy of the drug, $d \cdot c_0$ is the growth rate of the efficacy, E is the maximal efficacy, c_0 is the drug concentration at time $t = 0$ and ϵ_0 is the initial efficacy at time $t = 0$. So like before the efficacy is increasing in time, depends on the drug

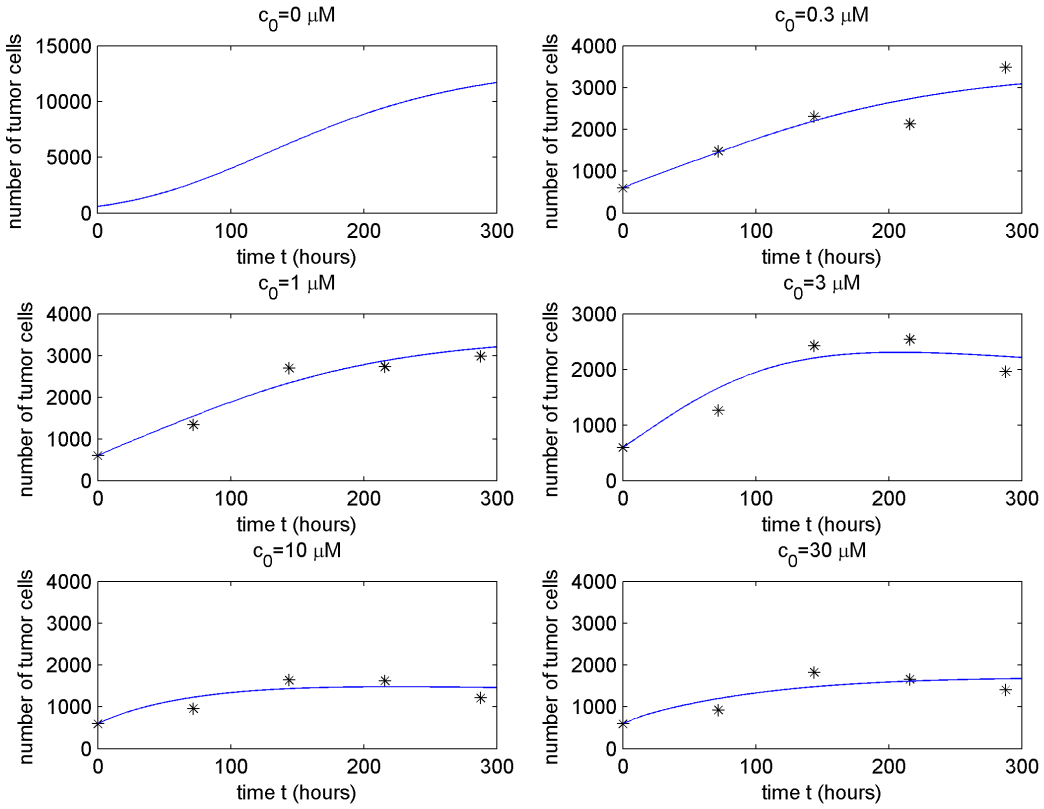


Figure 5.14: Modeling tumor growth including efficacy of chemotherapy with hill-equation. Parameters: $r = 0.0116\frac{1}{h}$, $K = 13380$ cells, $\alpha = 0.203$, $N_0 = 596.3$ cells. Additionally $Q = 2\mu Mh$ and $\nu = 0.014\frac{1}{h}$ for $c_0 = 0.3\mu M$, $Q = 11\mu Mh$ and $\nu = 0.014\frac{1}{h}$ for $c_0 = 1\mu M$, $Q = 143\mu Mh$ and $\nu = 0.021\frac{1}{h}$ for $c_0 = 3\mu M$, $Q = 162\mu Mh$ and $\nu = 0.022\frac{1}{h}$ for $c_0 = 10\mu M$, $Q = 300\mu Mh$ and $\nu = 0.020\frac{1}{h}$ for $c_0 = 30\mu M$. Figure is obtained by using the numerical solution of model (5.58).

concentration, and reaches a capacity after some time. This leads us to a complete new model, which will be discussed in detail in section 6.2:

$$\frac{dN}{dt} = \frac{r}{\alpha} N \left(1 - \left(\frac{N}{K}\right)^{\alpha}\right) - \epsilon N \tag{5.60a}$$

$$\frac{d\epsilon}{dt} = (d \cdot c_0)\epsilon \left(1 - \frac{\epsilon}{E}\right) \tag{5.60b}$$

$$N(0) = N_0 \tag{5.60c}$$

$$\epsilon(0) = \epsilon_0. \tag{5.60d}$$

Of course, one could also include the decrease of the drug concentration by adding the differential equation (5.17b) to the system and substituting c_0 by c in equation (5.60b).

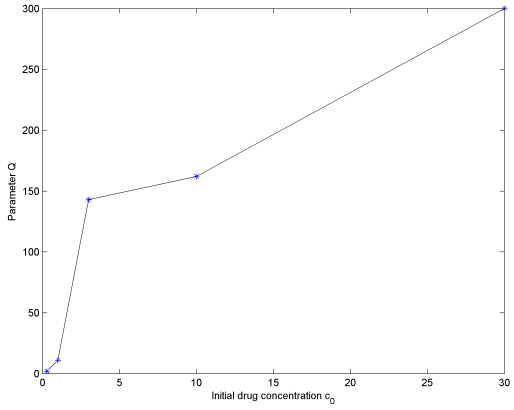


Figure 5.15: c_0-Q-correlation.

But this makes the model much more complicated, since it is a three dimensional system then and the resulting errors are not reduced further.
So this time we fix all the parameters we got from the basic model without treatment: $r = 0.0116\frac{1}{h}$, $K = 13380$ cells, $\alpha = 0.203$ and $N_0 = 596.3$ cells. Additionally we set $E = 1$, since the maximal efficacy can be set to $100\% = 1$. Testing yields that the best initial efficacy is around $\epsilon_0 = 0.012\frac{1}{h}$ and the growth rate parameter d is around $d = 0.0003\frac{1}{\mu Mh}$ for all different drug concentrations. As a result we get an error of 0.0859 for $c_0 = 0.3\mu M$, an error of 0.0559 for $c_0 = 1\mu M$, an error of 0.1095 for $c_0 = 3\mu M$, an error of 0.0629 for $c_0 = 10\mu M$ and an error of $3.4415 \cdot 10^6$ for $c_0 = 30\mu M$. As one can see in figure 5.16, model (5.60) seems to be able to cope with the data in nearly all cases. Solely for the drug concentration $c_0 = 30\mu M$, the model seems to fail. A possible reason could be that this drug concentration is so high that the cells are not able to absorb the same percentage of the drug quantity as in the other cases, since there is a limit of how much drug the cells can absorb in a particular amount of time. In figure 5.17 two exemplary curves for the efficacy can be seen. There you can see that in both cases the capacity of the efficacy is not reached.

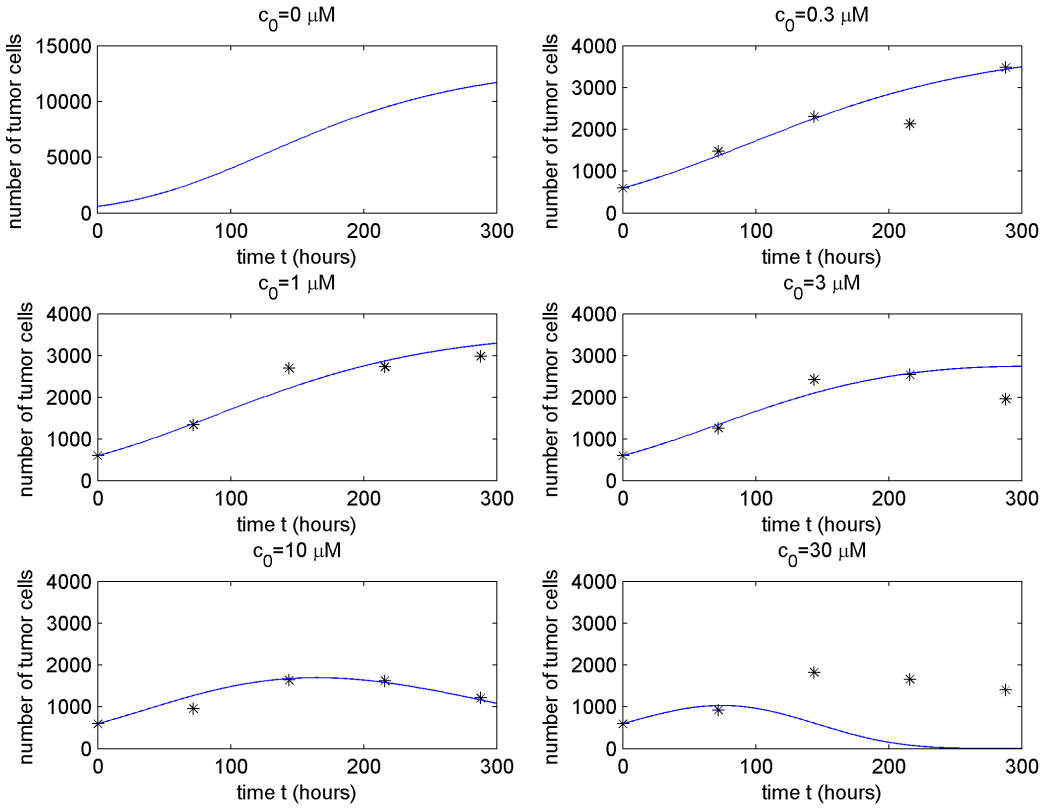


Figure 5.16: Modeling tumor growth including chemotherapy with the efficacy approach. Parameters: $r = 0.0116\frac{1}{h}$, $K = 13380$ cells, $\alpha = 0.203$, $N_0 = 596.3$ cells, $E = 1\frac{1}{h}$, $\epsilon_0 = 0.012\frac{1}{h}$ and $d = 0.0003\frac{1}{\mu M h}$. Figure is obtained by using the analytical solution of equation (5.60b) and the numerical solution of equation (5.60a).

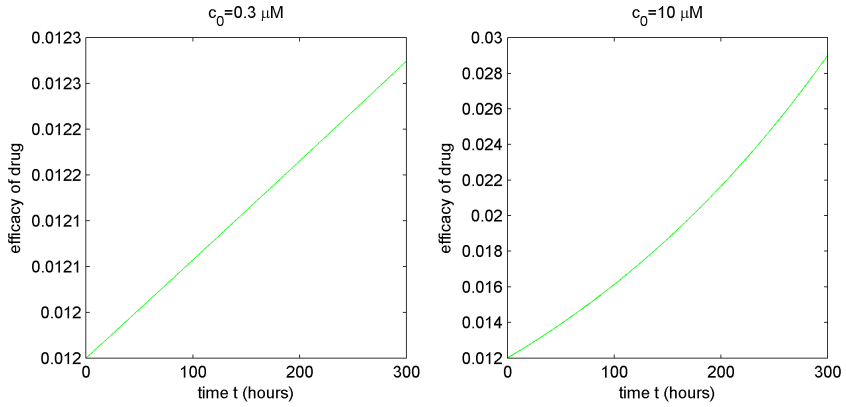


Figure 5.17: Efficacy curves. Parameters are the same as in figure 5.16. Figure is obtained by using the analytical solution of equation (5.60b).

6. Combined Therapy

This section covers models of tumor growth, treated with a combined therapy, i.e. with radio- and chemotherapy. A possible advantage of combined therapies is a synergistic effect, i.e. an effect that is greater than the sum of the single effects. But also an antagonistic effect is possible. Like before we consider a solid, homogeneous and avascular tumor with no structure first. After that we will finish this chapter with a spatial model which considers the three layer scheme.

6.1. Improved LQ-Model

Since the linear quadratic model is one of the most used models in radiotherapy and has many variations, it will be discussed in this section. The aim is to get a model which also includes chemotherapy besides the radiotherapy. Since the standard LQ-model and its more complex variations have already been discussed in [Web13], it will be discussed rather short in this section. For more detailed background [OMH09] and [CHN09] are recommended.
The equation to start with is

$$Y = \alpha D + \beta D^2 \text{ with } \alpha, \beta > 0, \tag{6.1}$$

which describes the yield of lethal lesions. Here D is the radiation dose of the radiotherapy in Gy, αD are the lethal lesions caused by a single radiation dose and βD^2 the lesions caused by different ones. Thus α represents the single-hit double-strand breaks and β depicts the combination of two sub-lethal single-strand breaks which form a double-strand break. DNA double strand breaks can be repaired in two ways: homologous recombination or non-homologous end-joining mechanisms. It was mentioned before that tumor cells lack of such repair mechanisms. Thus the genetic damage is carried on and in about 1-2% of all radiation induced double-strand breaks the cell cannot survive any longer because of this mutations [EAC$^+$05]. If the radiation dose is given in n portions of dose d instead one dose D, equation (6.1) can be written as

$$Y = n(\alpha d + \beta d^2) \text{ with } \alpha, \beta > 0. \tag{6.2}$$

Thus the LQ-model reads as follows:

$$S = \frac{S^*}{S_0} = \exp(-Y) = e^{-n(\alpha d + \beta d^2)}, \tag{6.3}$$

where S represents the survival fraction, which is obtained from the fraction of the number of cells left after radiation S^* and the initial number of cells S_0. Figure 6.1 shows how the surviving fraction depends on different radiation dosages and different α/β ratios. Now the chemotherapy has to be included in this model. There are two ways to do this. The first one is based on the assumption that the effect of chemotherapy is the sensitization of the tumor to radiotherapy. The second is based on the assumption that the chemotherapy has its own killing effect [JD05, BBJ$^+$10].

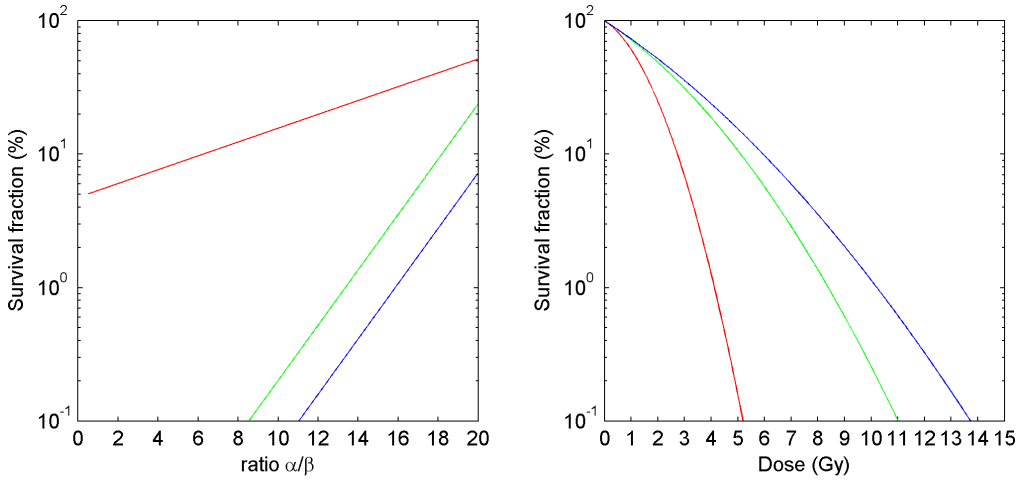


Figure 6.1: LQ-model. On the left side: The red line represents $2Gy$, the green one represents $4Gy$ and the blue line $8Gy$. On the right side: The ratio $\alpha/\beta = 1.5Gy$ is depicted by the red line, the ration $\alpha/\beta = 10Gy$ by the green line and the ratio $\alpha/\beta = 20Gy$ by the blue line. Equation (6.3) was used to obtain the curves.

Sensitization Effect Based on the assumption above in this paragraph a dose d of radiation operates like a radiation dose ds when it is given together with a chemotherapeutic drug. Of course it would be very helpful to know something about the value of s for a specific drug. But right now nothing about this can be stated. Replacing d by ds in equation (6.2) yields

$$Y_{total} = n(\alpha ds + \beta d^2 s^2), \tag{6.4}$$

and the survival fraction becomes analogously

$$S_{total} = e^{-n(\alpha ds + \beta d^2 s^2)}. \tag{6.5}$$

Some dose-surviving fraction-curves depending on different values of s are depicted in figure 6.2. In figure 6.1 we see that less radiation is needed to almost extinct the tumor, i.e. survival fraction=0.1% , if the ratio α/β is greater. But for a particular tumor in a particular tissue this ratio is fixed. Thus the only way to (almost) extinct the tumor is to use enough radiation. For $\alpha/\beta = 10Gy$ the needed radiation dose is about $11Gy$. But in figure 6.2 it is shown that the needed amount of radiation can be changed with s. So if s is high enough, i.e. $s = 2$, the needed radiation dose can be reduced from $11Gy$ to about $6.5Gy$, which is a quite big reduction. Of course, one has to find a chemotherapeutic drug which causes the value $s = 2$. And even if this drug is found, one has to check the side effects of the drug combined with radiotherapy. Because even if the amount

of radiation is reduced, the burden for the patient, treated with a combined therapy instead of radiotherapy alone, can be increased.

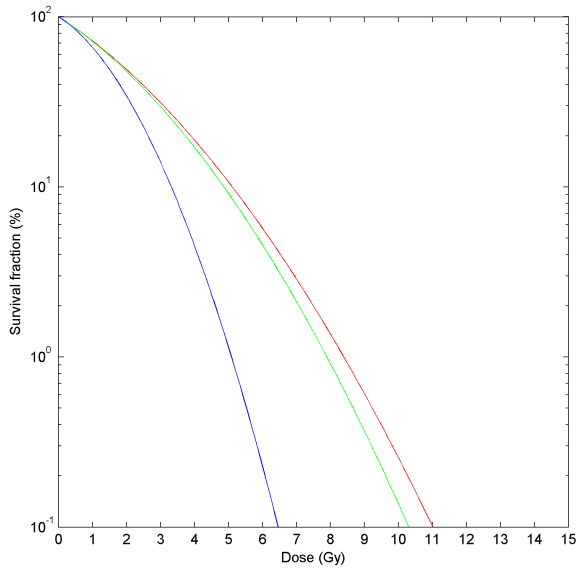


Figure 6.2: LQ-model with sensitization effect: $s = 1$ is represented by the red line, $s = 1.1$ by the green line and $s = 2$ by the blue line. Further parameters are $\alpha = 0.2985Gy^{-1}$ and $\beta = 0.02985Gy^{-2}$. Used equation: (6.5).

Own Killing Effect With the assumption that the chemotherapy has its own killing effect, we have have to add this "cell kill effect" to Y:

$$Y_{total} = n(\alpha d + \beta d^2) + Y_C. \tag{6.6}$$

Thus Y_C is the cell kill effect of the chemotherapeutic drug from all cycles of chemotherapy. The survival fraction reads accordingly

$$S_{total} = e^{-n(\alpha d+\beta d^2)+Y_C} = e^{-n(\alpha d+\beta d^2)}e^{Y_C} = Se^{Y_C} \tag{6.7}$$

6.1.1. Biological Effective Dose

With the biological effective dose (BED) you can see if two different treatment schedules have the same total effect on the same tissue [OMH09, CHN09]. It is defined as

$$\begin{aligned} \mathrm{BED} :&= \frac{-\ln S}{\alpha} \\ &= \frac{\alpha n d + \beta n d^2}{\alpha} \\ &= D \underbrace{\left(1 + \frac{\beta}{\alpha} d\right)}_{\text{relative effectiveness}} . \end{aligned} \tag{6.8}$$

From the definition you can see that an increased BED, i.e. an increased biological effect, results in a reduced survival fraction S and vice versa. In equation (6.8) we can include the chemotherapeutic effects again [JD05].

Sensitization Effect Like before the radiation dose d is replaced by ds in the definition of the BED. In order to do this, D has to be split into the fractions nd:

$$\mathrm{BED}_{total} = nds \left(1 + \frac{\beta}{\alpha} ds\right). \tag{6.9}$$

If only few of the radiation fractions are sensitized by chemotherapy the total BED is calculated as follows:

$$\mathrm{BED}_{total} = \mathrm{BED}_{of\ sensitized\ fractions} + \mathrm{BED}_{of\ unsensitized\ fractions} . \tag{6.10}$$

Own Killing Effect According to the section before also the total BED is the sum of the BED of the radiotherapy and the BED of the chemotherapy, i.e.

$$\mathrm{BED}_{total} = \mathrm{BED}_{of\ radiotherapy} +_{equivalent} \mathrm{BED}_{of\ chemotherapy} . \tag{6.11}$$

6.1.2. Tumor Control Probability

The tumor control probability (TCP) is the probability that no tumor cell survives the treatment [OMH09, CHN09]. Like before the initial number of cells is denoted by S_0 and the number of cells which are left after treatment is denoted by S^*. By assumption S^* is random with Poisson distribution $P(S^*)$. Of course, there are many other distributions possible, for example a binomial distribution [Web13]. Per definition the TCP is the probability that no tumor cell is left and thus

$$\mathrm{TCP} := P(0). \tag{6.12}$$

Since $P(S^*)$ is assumed to be Poisson distributed we get

$$P(S^* = k) = \lambda^k \cdot \frac{e^{-\lambda}}{k!}, \tag{6.13}$$

with the expected value $\lambda = S_0 \cdot S$ and hence

$$\mathrm{TCP} = P(0) = e^{-S_0 \cdot S}. \tag{6.14}$$

For later purposes equation (6.14) is written slightly different:

$$\mathrm{TCP} = e^{-S_0 \cdot S} = e^{-S_0 \cdot e^{-\alpha\,\mathrm{BED}}} = e^{-S_0 \cdot e^{-\alpha D\left(1+\frac{\beta}{\alpha}d\right)}}. \tag{6.15}$$

Based on [JD05] chemotherapy is included once again.

Sensitization Effect The easiest way to include chemotherapy here is to take equation (6.15) and replace d by ds:

$$\mathrm{TCP}_{total} = e^{-S_0 \cdot e^{-\alpha Ds\left(1+\frac{\beta}{\alpha}ds\right)}}. \tag{6.16}$$

With this equation we can devise a formula to calculate s. For that purpose a randomized trial with two arms is needed. On both radiation is given, but only one arm gets chemotherapy additionally. This yields the following state:

Radiotherapy alone $\rightarrow$ survival outcome 1
Radiotherapy + Chemotherapy $\rightarrow$ survival outcome 2

These two conditions correspond to two TCP's. So dividing the first TCP by the other one yields an equation to calculate s:

$$\begin{aligned}
& \frac{\ln \mathrm{TCP}}{\ln \mathrm{TCP}_{total}} = \frac{-S_0 \cdot e^{-\alpha D\left(1+\frac{\beta}{\alpha}d\right)}}{-S_0 \cdot e^{-\alpha Ds\left(1+\frac{\beta}{\alpha}ds\right)}} \\
\Leftrightarrow \quad & \ln\left(\frac{\ln \mathrm{TCP}}{\ln \mathrm{TCP}_{total}}\right) = \alpha Ds\left(1+\frac{\beta}{\alpha}ds\right) - \alpha D\left(1+\frac{\beta}{\alpha}d\right) \\
\Leftrightarrow \quad & s\left(1+\frac{\beta}{\alpha}ds\right) - \left(1+\frac{\beta}{\alpha}d\right) - \frac{1}{\alpha D}\ln\left(\frac{\ln \mathrm{TCP}}{\ln \mathrm{TCP}_{total}}\right) = 0 \\
\Leftrightarrow \quad & \frac{\beta}{\alpha}ds^2 + s - \left(1+\frac{\beta}{\alpha}d\right) - \frac{1}{\alpha D}\ln\left(\frac{\ln \mathrm{TCP}}{\ln \mathrm{TCP}_{total}}\right) = 0.
\end{aligned} \tag{6.17}$$

Hence the positive root for s can be calculated:

$$s = \frac{-1 + \sqrt{1 + 4d\frac{\beta}{\alpha}\left(-\left(1+\frac{\beta}{\alpha}d\right) - \frac{1}{\alpha D}\ln\left(\frac{\ln \mathrm{TCP}}{\ln \mathrm{TCP}_{total}}\right)\right)}}{2d\frac{\beta}{\alpha}}. \tag{6.18}$$

In [JD05] an example is given: Assume that TCP $= 0.45$, $\text{TCP}_{total} = 0.67$, $\alpha = 0.3Gy^{-1}$ and $d = 2Gy$ is given for 30 fractions of radiation. Thus $D = 60Gy$. Let $\frac{\alpha}{\beta} = 10Gy$. Then the solution for s is 1.03. This is a quite small value since all fractions of radiotherapy are sensitized by the chemotherapeutic drug.
In the next part the value of s is considered in the case that not all fractions are sensitized. Equation (6.10) is used to calculate the total TCP of the therapy where m_1 fractions of radiation are sensitized, and m_2 are not.

$$\text{TCP}_{combined} = e^{-S_0 \cdot e^{-\alpha m_1 ds\left(1+\frac{\beta}{\alpha}ds\right) - \alpha m_2 d\left(1+\frac{\beta}{\alpha}d\right)}}. \tag{6.19}$$

This time equation (6.15) is divided by (6.19):

$$m_1 d^2 s^2 \frac{\beta}{\alpha} + m_1 ds + m_2 d\left(1+\frac{\beta}{\alpha}d\right) - nd\left(1+\frac{\beta}{\alpha}d\right) - \frac{1}{\alpha}\ln\left(\frac{\ln \text{TCP}}{\ln \text{TCP}_{combined}}\right) = 0. \tag{6.20}$$

This equation can be simplified slightly by using the fact that $m_1 + m_2 = n$:

$$m_1 d^2 s^2 \frac{\beta}{\alpha} + m_1 ds - m_1 d\left(1+\frac{\beta}{\alpha}d\right) - \frac{1}{\alpha}\ln\left(\frac{\ln \text{TCP}}{\ln \text{TCP}_{combined}}\right) = 0. \tag{6.21}$$

Again the positive root of s can be calculated:

$$\begin{aligned} s &= \frac{-m_1 d + \sqrt{m_1^2 d^2 + 4 m_1 d^2 \frac{\beta}{\alpha}\left(m_1 d\left(1+\frac{\beta}{\alpha}d\right) + \frac{1}{\alpha}\ln\left(\frac{\ln \text{TCP}}{\ln \text{TCP}_{combined}}\right)\right)}}{2 m_1 d^2 \frac{\beta}{\alpha}} \\ &= \frac{-1 + \sqrt{1 + 4\frac{1}{m_1}\frac{\beta}{\alpha}\left(m_1 d\left(1+\frac{\beta}{\alpha}d\right) + \frac{1}{\alpha}\ln\left(\frac{\ln \text{TCP}}{\ln \text{TCP}_{combined}}\right)\right)}}{2 m_1 d^2 \frac{\beta}{\alpha}}. \end{aligned} \tag{6.22}$$

Like one would expect, the value of s depends only on m_1, the number of sensitized fractions, and not on n.

Own Killing Effect According to equation (6.11) the TCP for the combined therapy reads as follows

$$\text{TCP}_{total} = e^{-S_0 \cdot S} = e^{-S_0 \cdot e^{-Y_{total}}} = e^{-S_0 \cdot e^{-Y_R - Y_C}}, \tag{6.23}$$

where Y_R is the radiation cell kill and Y_C the equivalent and independent chemotherapy cell kill from before. To obtain Y_C we divide equation (6.15) by equation (6.23):

$$\begin{aligned} \frac{\ln \text{TCP}}{\ln \text{TCP}_{total}} &= \frac{S_0 e^{-Y_R}}{S_0 e^{-Y_R - Y_C}} = e^{Y_C} \\ \Leftrightarrow \quad Y_C &= \ln\left(\frac{\ln \text{TCP}}{\ln \text{TCP}_{total}}\right). \end{aligned} \tag{6.24}$$

6.2. Cell Population Model

In this section I will combine the radiotherapeutic treatment from section 4.1 with the chemotherapeutic treatment from the end of section 5.5. Analogously to this sections we assume the tumor to be homogeneous, solid and in an avascular stage. To model the tumor growth we use the generalized logistic growth model and for the different treatments we use the terms which have been introduced in the models (4.1) and (5.60) respectively.

6.2.1. Mathematical Model

Let N be the number of tumor cells and ϵ the efficacy of the drug. With the assumptions made above the model reads

$$\frac{dN}{dt} = \frac{r}{\alpha}N\left(1-\left(\frac{N}{K}\right)^{\alpha}\right) - \mu AN - \epsilon N =: f(N) \tag{6.25a}$$

$$\frac{d\epsilon}{dt} = (d\cdot c_0)\epsilon\left(1-\frac{\epsilon}{E}\right) =: f(\epsilon) \tag{6.25b}$$

$$N(0) = N_0$$

$$\epsilon(0) = \epsilon_0,$$

where $r > 0$ is the proliferation rate of the tumor cells, $\alpha > 0$ is the parameter of the generalized logistic growth equation, $K > 0$ is the carrying capacity, A is the amount of radiation which is administered in Gray, $\mu > 0$ is the rate the tumor cells are killed by the radiation, $d \cdot c_0$ is the growth rate of the efficacy, where c_0 is the drug concentration at time $t = 0$ and E is the maximal efficacy.
If no treatment is administered, then $c_0 = 0$ and also $A = 0$ and equation (6.25a) reduces to the generalized logistic growth equation. Since we want to consider a combined treatment, we assume that both $A > 0$ and $c_0 > 0$.
First we want to find the equilibria and figure out, for what values of A and c_0 they are stable. For this purpose we calculate first the Jacobian matrix $J(N, \epsilon)$:

$$\begin{aligned} J(N,c) &= \begin{pmatrix} \frac{df(N)}{dN} & \frac{df(N)}{d\epsilon} \\ \frac{df(\epsilon)}{dN} & \frac{df(\epsilon)}{d\epsilon} \end{pmatrix} \\ &= \begin{pmatrix} \frac{r}{\alpha} - \frac{r(\alpha+1)}{\alpha}\left(\frac{N}{K}\right)^{\alpha} - \mu A - \epsilon & N \\ 0 & dc_0\left(1-2\frac{\epsilon}{E}\right) \end{pmatrix}. \end{aligned} \tag{6.26}$$

We continue and set $f(\epsilon) = 0$. This is equivalent to

$$dc_0\epsilon\left(1-\frac{\epsilon}{E}\right) = 0.$$

Obviously this equation holds true if $\epsilon = 0$ or $\epsilon = E$. If $\epsilon = 0$, $f(N) = 0$ reduces to

$$\frac{r}{\alpha}N\left(1-\left(\frac{N}{K}\right)^{\alpha}\right) - \mu AN = 0. \tag{6.27}$$

One solution of this equation is $N = 0$ and our first equilibrium is consequently

$$(\hat{N}_1, \hat{\epsilon}_1) = (0, 0).$$

In order to investigate the stability of this equilibrium, we plug it in the Jacobian:

$$J(\hat{N}_1, \hat{\epsilon}_1) = \begin{pmatrix} \frac{r}{\alpha} - \mu A & 0 \\ 0 & dc_0 \end{pmatrix}. \tag{6.28}$$

Since this matrix is diagonal, the eigenvalues of it are the diagonal entries. Since $dc_0 > 0$, it never happens that both eigenvalues are smaller than zero and thus this eigenvalue is never stable.
The other solution of equation (6.27) is $N = K\left(1 - \frac{\alpha\mu A}{r}\right)^{1/\alpha}$ and thus

$$(\hat{N}_2, \hat{\epsilon}_2) = (K\left(1 - \frac{\alpha\mu A}{r}\right)^{1/\alpha}, 0).$$

Also this equilibrium can never be stable since the Jacobian

$$J(\hat{N}_2, \hat{\epsilon}_2) = \begin{pmatrix} \frac{r}{\alpha} - \frac{r(\alpha+1)}{\alpha}\left(1 - \frac{\alpha\mu A}{r}\right) - \mu A & K\left(1 - \frac{\alpha\mu A}{r}\right)^{1/\alpha} \\ 0 & dc_0 \end{pmatrix} \tag{6.29}$$

is a triangular matrix and thus one eigenvalue is the diagonal entry $dc_0 > 0$.
In the second case $\epsilon = E$, $f(N) = 0$ is equivalent to

$$\frac{r}{\alpha} N\left(1 - \left(\frac{N}{K}\right)^{\alpha}\right) - \mu A N - EN = 0. \tag{6.30}$$

The first solution is $N = 0$ which yields the equilibrium

$$(\hat{N}_3, \hat{\epsilon}_3) = (0, E).$$

Hence

$$J(\hat{N}_3, \hat{\epsilon}_3) = \begin{pmatrix} \frac{r}{\alpha} - \mu A - E & 0 \\ 0 & -dc_0 \end{pmatrix}. \tag{6.31}$$

So one eigenvalue is $-dc_0 < 0$. The other eigenvalue $\frac{r}{\alpha} - \mu A - E$ is less than zero if

$$A > \frac{r}{\alpha\mu} - \frac{E}{\mu}$$

Thus the equilibrium $(\hat{N}_3, \hat{\epsilon}_3) = (0, E)$ is stable if $A > \frac{r}{\alpha\mu} - \frac{E}{\mu}$, and unstable otherwise.
Equation (6.30) is equivalent to

$$N = K\left(1 - \frac{\alpha(\mu A + E)}{r}\right)^{\frac{1}{\alpha}}.$$

Hence the last equilibrium is

$$(\hat{N}_4, \hat{\epsilon}_4) = (K\left(1 - \frac{\alpha(\mu A + E)}{r}\right)^{\frac{1}{\alpha}}, E),$$

which yields

$$J(\hat{N}_4, \hat{\epsilon}_4) = \begin{pmatrix} \frac{r}{\alpha} - \frac{r(\alpha+1)}{\alpha}\left(1 - \frac{\alpha(\mu A+E)}{r}\right) - \mu A - E & K\left(1 - \frac{\alpha(\mu A+E)}{r}\right)^{1/\alpha} \\ 0 & -dc_0 \end{pmatrix}. \tag{6.32}$$

As before $-dc_0$ is always less than zero. The second eigenvalue $\frac{r}{\alpha} - \frac{r(\alpha+1)}{\alpha}\left(1 - \frac{\alpha(\mu A+E)}{r}\right) - \mu A$ is less than zero if $A < \frac{r}{\alpha\mu} - \frac{E}{\mu}$ and unstable otherwise. To see how the final number of tumor cells changes with increasing radiation dosage A, see figure 6.3.

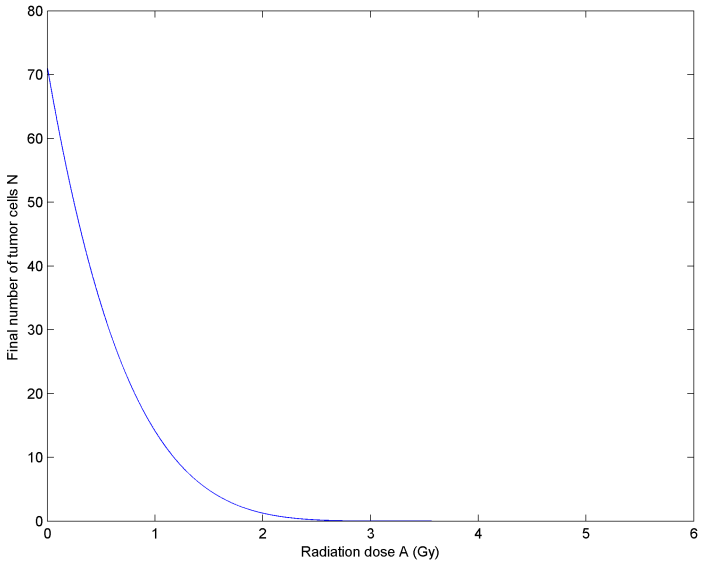


Figure 6.3: Final number of tumor cells, depending on the radiation dosage. Parameters: $r = 0.0116\frac{1}{h}$, $K = 2000000$ cells, $\alpha = 0.203$, $E = 0.05\frac{1}{h}$, $\mu = 0.002\frac{1}{Gy \cdot h}$.

In figure 6.4 you can see how the tumor cell population increases and decreases, depending on different radiation dosages and drug concentrations.

6.2.2. Fitting the model to data

Also in this section we want to prove if our model can reflect the reality. For this purpose we compare the model to data points, which are from [AH14]. This time the cells got a radiation treatment at the beginning, as it is described in section 4.2 and additionally a chemotherapeutic treatment, as it is described in section 5.5. We consider

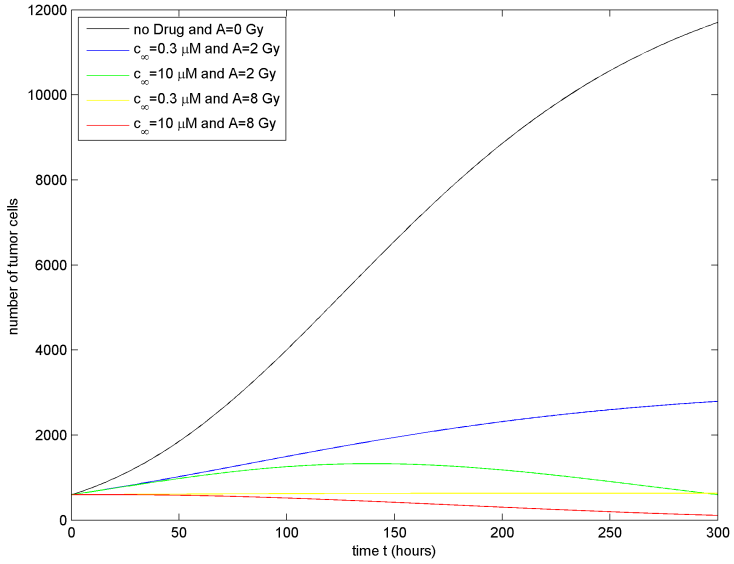


Figure 6.4: Number of tumor cells, depending on different radiation dosages and drug concentrations. Parameters: $r = 0.0116\frac{1}{h}$, $K = 13380$ cells, $\alpha = 0.203$, $E = 1\frac{1}{h}$, $\mu = 0.002\frac{1}{Gy \cdot h}$, $N_0 = 596.3$ cells, $\epsilon_0 = 0.01\frac{1}{h}$, $d = 0.0004\frac{1}{\mu M \cdot h}$. To obtain the curves, the analytical solution (3.6), the analytical solution of equation (6.25b) and the numerical solution of equation (6.25a) were used.

the same radiation dosages and drug concentrations as in the single treatments, in order to compare the results. $c_0 = 30\mu M$ is the only drug concentration we do not consider, since we saw in section 5.5 that this concentration is not as efficient as the other drug concentrations. Thus we cannot compare it well with the other concentrations.
We start with the drug concentration $c_0 = 0.3\mu M$ and all different radiation dosages $A = 2Gy$, $A = 4Gy$, $A = 6Gy$ and $A = 8Gy$. The corresponding normalized data can be seen in table 4. The following parameters are fixed according to the previous calculations and experimental settings: $r = 0.0116\frac{1}{h}$, $\alpha = 0.203$, $N_0 = 596.3$, $\mu = (0.0024, 0.0023, 0.0015, 0.0015)\frac{1}{Gy \cdot h}$ for $A = (2, 4, 6, 8)Gy$ and $E = 1\frac{1}{h}$. To see if the model can cope with the data, we try to find a good approximation by finding appropriate values for ϵ_0 and d with algorithm 7. The principle of this algorithm is the same as in the others. It returns the following results: For $A = 2Gy$ we get $\epsilon_0 = 0.008\frac{1}{h}$ and $d = 0.012\frac{1}{\mu M \cdot h}$ with an error of 0.0032, for $A = 4Gy$ we get $\epsilon_0 = 0.004\frac{1}{h}$ and $d = 0.009\frac{1}{\mu M \cdot h}$ with an error of 0.007, for $A = 6Gy$ we get $\epsilon_0 = 0.004\frac{1}{h}$ and $d = 0.016\frac{1}{\mu M \cdot h}$ with an error of 0.0352 and for $A = 8Gy$ we get $\epsilon_0 = 0.003\frac{1}{h}$ and $d = 0.017\frac{1}{\mu M \cdot h}$ with an error of 0.0212. For the corresponding curves, see the blue lines in figure 6.5. For comparison there are the red lines which represent the curves which are calculated with the parameter values $\epsilon_0 = 0.012\frac{1}{h}$ and $d = 0.0003\frac{1}{\mu M \cdot h}$ from the previous simulations in section 5.5.

Number of cells	**Days**				
Radiation (Gy)	0	3	6	9	12
2	596.3	1258.1	1695.7	1588.9	1283.0
4	596.3	1202.1	1992.4	2242.5	2191.6
6	596.3	1037.9	1842.7	1905.6	1442.5
8	596.3	1195.5	1606.8	1424.7	1416.8

Table 4: Number of tumor cells treated with radio- and chemotherapy, $c_0 = 0.3\mu M$. Data taken from [AH14].

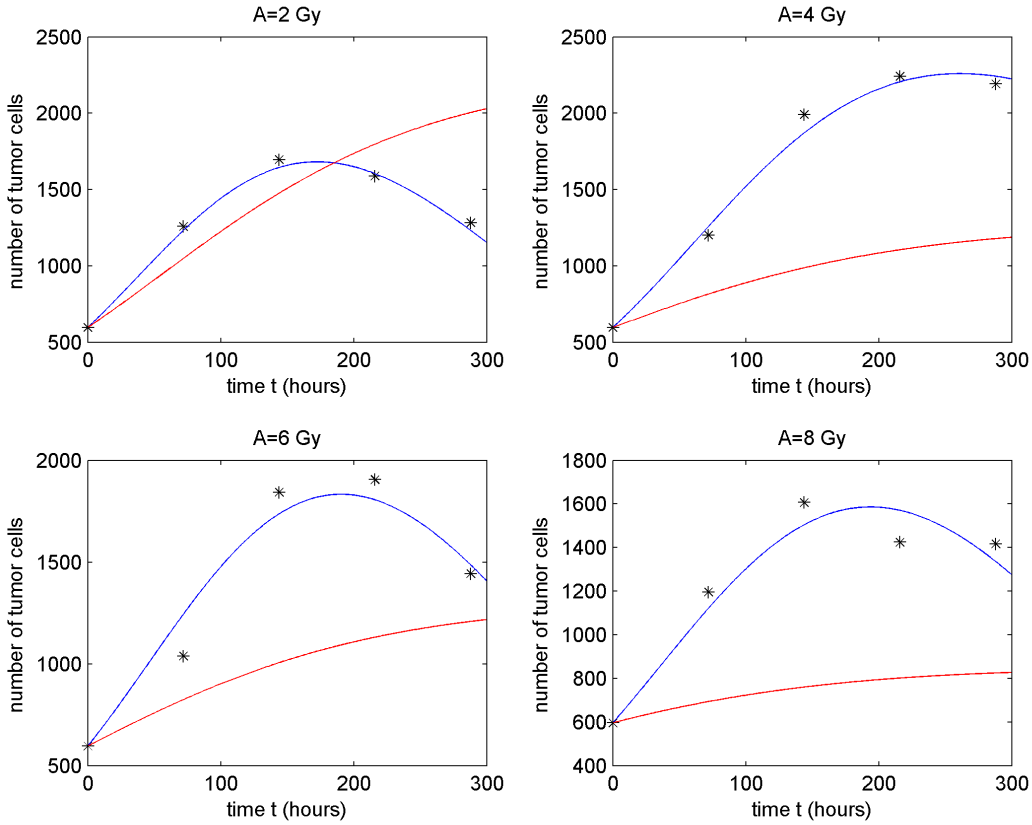


Figure 6.5: Modeling tumor growth including radio- and chemotherapy. Used parameters: $r = 0.0116\frac{1}{h}$, $\alpha = 0.203$, $N_0 = 596.3$ cells, $c_0 = 0.3\mu M$, $E = 1\frac{1}{h}$ and $\mu = (0.0024, 0.0023, 0.0015, 0.0015)\frac{1}{Gy \cdot h}$ for $A = (2, 4, 6, 8)Gy$. Additionally for the blue lines: $\epsilon_0 = 0.008\frac{1}{h}$ and $d = 0.012\frac{1}{\mu M \cdot h}$ for $A = 2Gy$, $\epsilon_0 = 0.004\frac{1}{h}$ and $d = 0.009\frac{1}{\mu M \cdot h}$ for $A = 4Gy$, $\epsilon_0 = 0.004\frac{1}{h}$ and $d = 0.016\frac{1}{\mu M \cdot h}$ for $A = 6Gy$ and $\epsilon_0 = 0.003\frac{1}{h}$ and $d = 0.017\frac{1}{\mu M \cdot h}$ for $A = 8Gy$. For the red lines: $\epsilon_0 = 0.012\frac{1}{h}$ and $d = 0.0003\frac{1}{\mu M \cdot h}$. The parameters were plugged in the numerical solutions of the model (6.25).

Number of cells	**Days**				
Radiation (Gy)	0	3	6	9	12
2	596.3	1208.9	1507.9	1436.8	850.9
4	596.3	1005.3	1663.7	1537.5	1403.4
6	596.3	1156.8	1669.3	1742.6	1097.7
8	596.3	967.5	1485.0	1542.5	1136.1

Table 5: Number of tumor cells treated with radio- and chemotherapy, $c_0 = 1\mu M$. Data taken from [AH14].

Number of cells	**Days**				
Radiation (Gy)	0	3	6	9	12
2	596.3	1268.2	1708.5	1197.2	892.7
4	596.3	965,0	1667.3	1492.7	1531.6
6	596.3	925.6	1594.8	1359.8	764.6
8	596.3	982.9	1377.4	1371.2	1079.1

Table 6: Number of tumor cells treated with radio- and chemotherapy, $c_0 = 3\mu M$. Data taken from [AH14].

We continue with the drug concentration $c_0 = 1\mu M$. The normalized data can be seen in table 5. The fixed parameters are the same as for $c_0 = 0.3\mu M$. This time algorithm 7 returns the following results: For $A = 2Gy$ we get $\epsilon_0 = 0.007\frac{1}{h}$ and $d = 0.005\frac{1}{\mu M \cdot h}$ with an error of 0.0123, for $A = 4Gy$ we get $\epsilon_0 = 0.005\frac{1}{h}$ and $d = 0.004\frac{1}{\mu M \cdot h}$ with an error of 0.0257, for $A = 6Gy$ we get $\epsilon_0 = 0.003\frac{1}{h}$ and $d = 0.007\frac{1}{\mu M \cdot h}$ with an error of 0.0212 and for $A = 8Gy$ we get $\epsilon_0 = 0.003\frac{1}{h}$ and $d = 0.006\frac{1}{\mu M \cdot h}$ with an error of 0.0277. For the corresponding curves, see the blue lines in figure 6.6. Also here there are the red lines which represent the curves which are calculated with the parameter values $\epsilon_0 = 0.012\frac{1}{h}$ and $d = 0.0003\frac{1}{\mu M \cdot h}$ from the previous simulations in section 5.5.
Next is the drug concentration $c_0 = 3\mu M$. The normalized data can be seen in table 6. The fixed parameters are the same as before. This time algorithm 7 returns the following results: For $A = 2Gy$ we get $\epsilon_0 = 0.006\frac{1}{h}$ and $d = 0.002\frac{1}{\mu M \cdot h}$ with an error of 0.0654, for $A = 4Gy$ we get $\epsilon_0 = 0.006\frac{1}{h}$ and $d = 0.0009\frac{1}{\mu M \cdot h}$ with an error of 0.0365, for $A = 6Gy$ we get $\epsilon_0 = 0.005\frac{1}{h}$ and $d = 0.002\frac{1}{\mu M \cdot h}$ with an error of 0.0917 and for $A = 8Gy$ we get $\epsilon_0 = 0.003\frac{1}{h}$ and $d = 0.002\frac{1}{\mu M \cdot h}$ with an error of 0.0177. For the corresponding curves, see the blue lines in figure 6.7. Also here there are the red lines which represent the curves which are calculated with the parameter values $\epsilon_0 = 0.012\frac{1}{h}$ and $d = 0.0003\frac{1}{\mu M \cdot h}$ from the previous simulations in section 5.5.
We continue with the drug concentration $c_0 = 10\mu M$. This time algorithm 7 returns the following results: For $A = 2Gy$ we get $\epsilon_0 = 0.011\frac{1}{h}$ and $d = 0.00003\frac{1}{\mu M \cdot h}$ with an error of 0.0253, for $A = 4Gy$ we get $\epsilon_0 = 0.008\frac{1}{h}$ and $d = 0.0001\frac{1}{\mu M \cdot h}$ with an error of

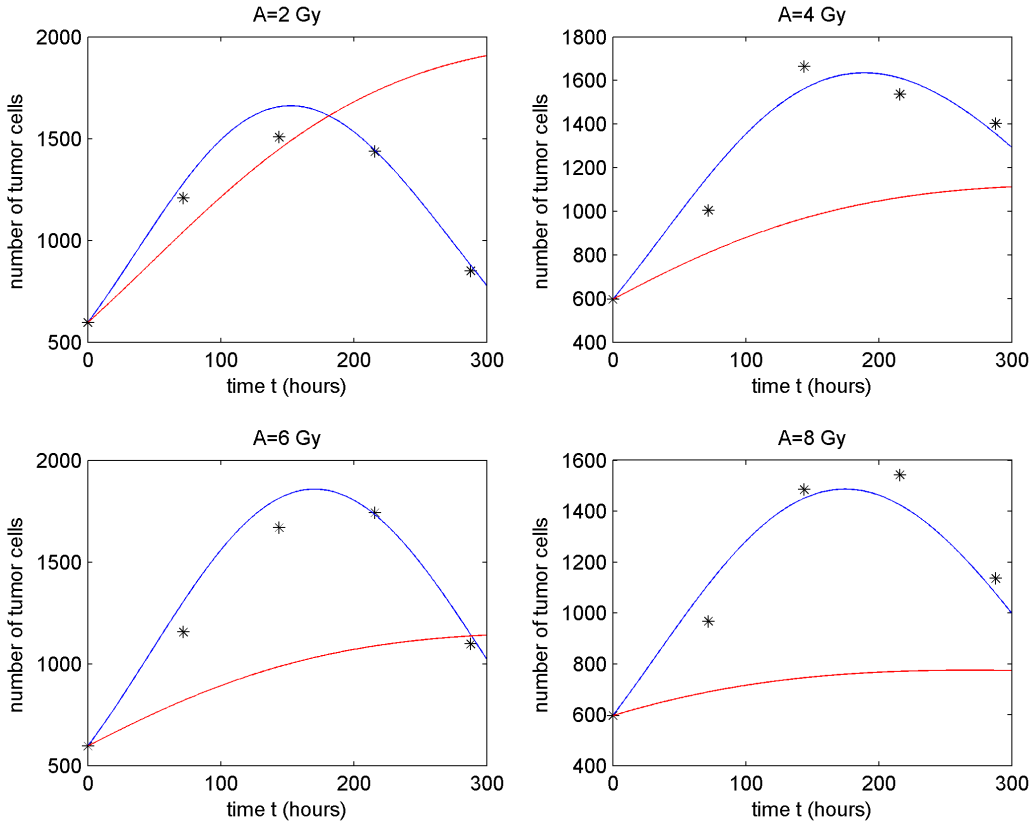


Figure 6.6: Modeling tumor growth including radio- and chemotherapy. Used parameters: $r = 0.0116\frac{1}{h}$, $\alpha = 0.203$, $N_0 = 596.3$ cells, $c_0 = 1\mu M$, $E = 1\frac{1}{h}$ and $\mu = (0.0024, 0.0023, 0.0015, 0.0015)\frac{1}{Gy \cdot h}$ for $A = (2, 4, 6, 8)Gy$. Additionally for the blue lines: $\epsilon_0 = 0.007\frac{1}{h}$ and $d = 0.005\frac{1}{\mu M \cdot h}$ for $A = 2Gy$, $\epsilon_0 = 0.005\frac{1}{h}$ and $d = 0.004\frac{1}{\mu M \cdot h}$ for $A = 4Gy$, $\epsilon_0 = 0.003\frac{1}{h}$ and $d = 0.007\frac{1}{\mu M \cdot h}$ for $A = 6Gy$ and $\epsilon_0 = 0.003\frac{1}{h}$ and $d = 0.006\frac{1}{\mu M \cdot h}$ for $A = 8Gy$. For the red lines: $\epsilon_0 = 0.012\frac{1}{h}$ and $d = 0.0003\frac{1}{\mu M \cdot h}$. The parameters were plugged in the numerical solutions of the model (6.25).

Number of cells	**Days**				
Radiation (Gy)	0	3	6	9	12
2	596.3	1134.1	1274.6	1097.1	711.1
4	596.3	1079.4	1305.0	1383.0	1619.8
6	596.3	905.6	1566.5	1568.2	1023.8
8	596.3	1138.6	1443.0	1280.1	905.1

Table 7: Number of tumor cells treated with radio- and chemotherapy, $c_0 = 10\mu M$. Data taken from [AH14].

0.0166, for $A = 6Gy$ we get $\epsilon_0 = 0.005\frac{1}{h}$ and $d = 0.0005\frac{1}{\mu M \cdot h}$ with an error of 0.0616 and for $A = 8Gy$ we get $\epsilon_0 = 0.003\frac{1}{h}$ and $d = 0.0007\frac{1}{\mu M \cdot h}$ with an error of 0.0226. For the corresponding curves, see the blue lines in figure 6.8. Also here there are the red lines which represent the curves which are calculated with the parameter values $\epsilon_0 = 0.012\frac{1}{h}$ and $d = 0.0003\frac{1}{\mu M \cdot h}$ from the previous simulations in section 5.5.
In most of the cases the red lines lie distinctly below the curves. Thus the model which combines radio- and chemotherapy predicts much more cell death as it actually happens according to the data points. Hence the combined therapy is not as good as the sum of the single therapies. Of course one have to keep in mind that already the number of cells which was used here, was only an approximation. Thus one has always to be cautious about stating facts. For a better comparison there are the best fitting curves for the single therapies together with the particular best fitting curves of the combined therapy outlined in one graph each, see figure 6.9.

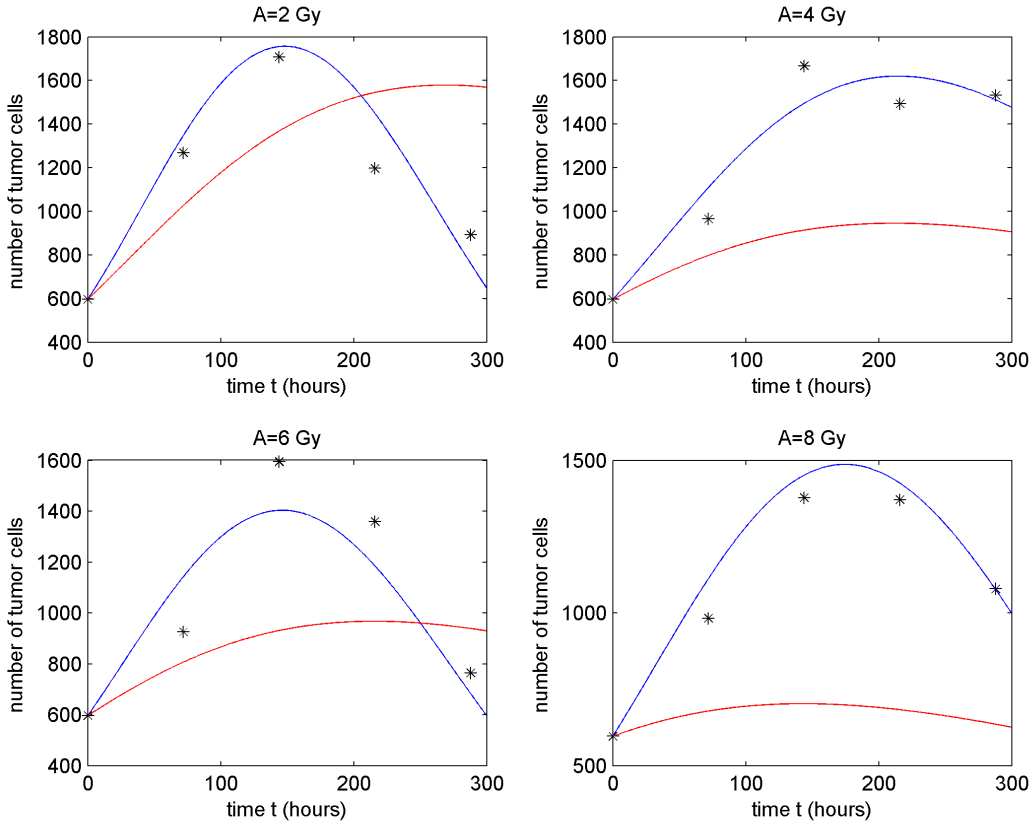


Figure 6.7: Modeling tumor growth including radio- and chemotherapy. Used parameters: $r = 0.0116\frac{1}{h}$, $\alpha = 0.203$, $N_0 = 596.3$ cells, $c_0 = 3\mu M$, $E = 1\frac{1}{h}$ and $\mu = (0.0024, 0.0023, 0.0015, 0.0015)\frac{1}{Gy \cdot h}$ for $A = (2, 4, 6, 8)Gy$. Additionally for the blue lines: $\epsilon_0 = 0.006\frac{1}{h}$ and $d = 0.002\frac{1}{\mu M \cdot h}$ for $A = 2Gy$, $\epsilon_0 = 0.006\frac{1}{h}$ and $d = 0.0009\frac{1}{\mu M \cdot h}$ for $A = 4Gy$, $\epsilon_0 = 0.005\frac{1}{h}$ and $d = 0.002\frac{1}{\mu M \cdot h}$ for $A = 6Gy$ and $\epsilon_0 = 0.003\frac{1}{h}$ and $d = 0.002\frac{1}{\mu M \cdot h}$ for $A = 8Gy$. For the red lines: $\epsilon_0 = 0.012\frac{1}{h}$ and $d = 0.0003\frac{1}{\mu M \cdot h}$. The parameters were plugged in the numerical solutions of the model (6.25).

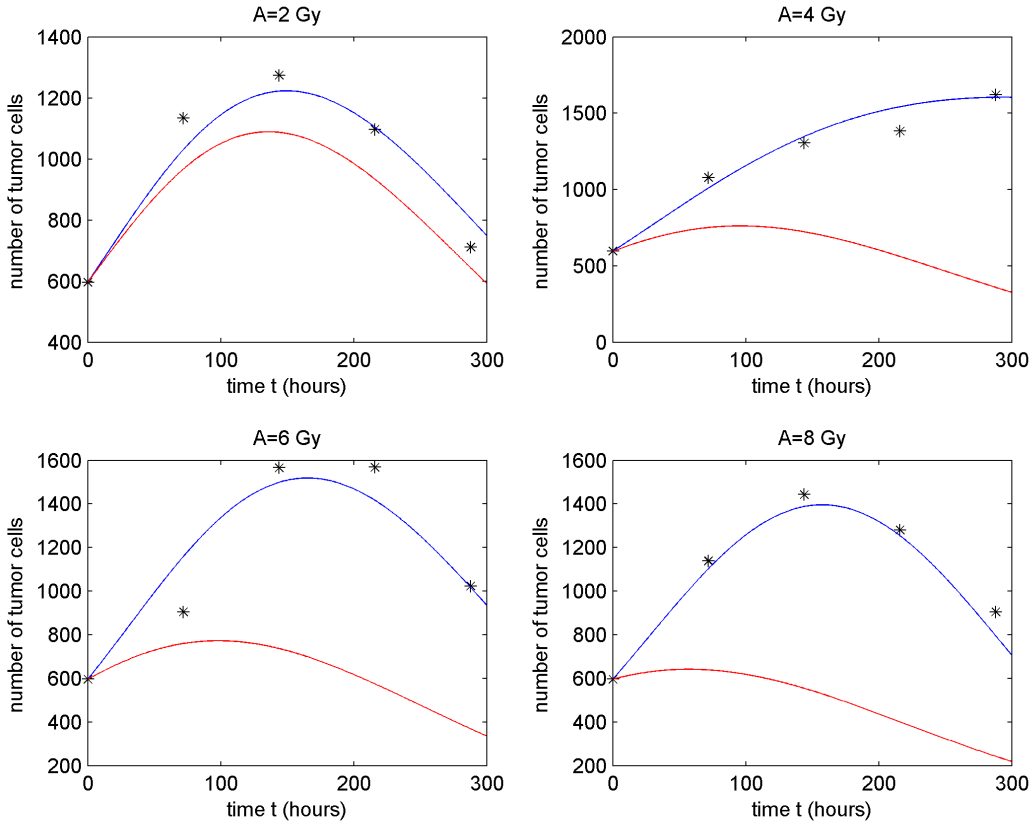
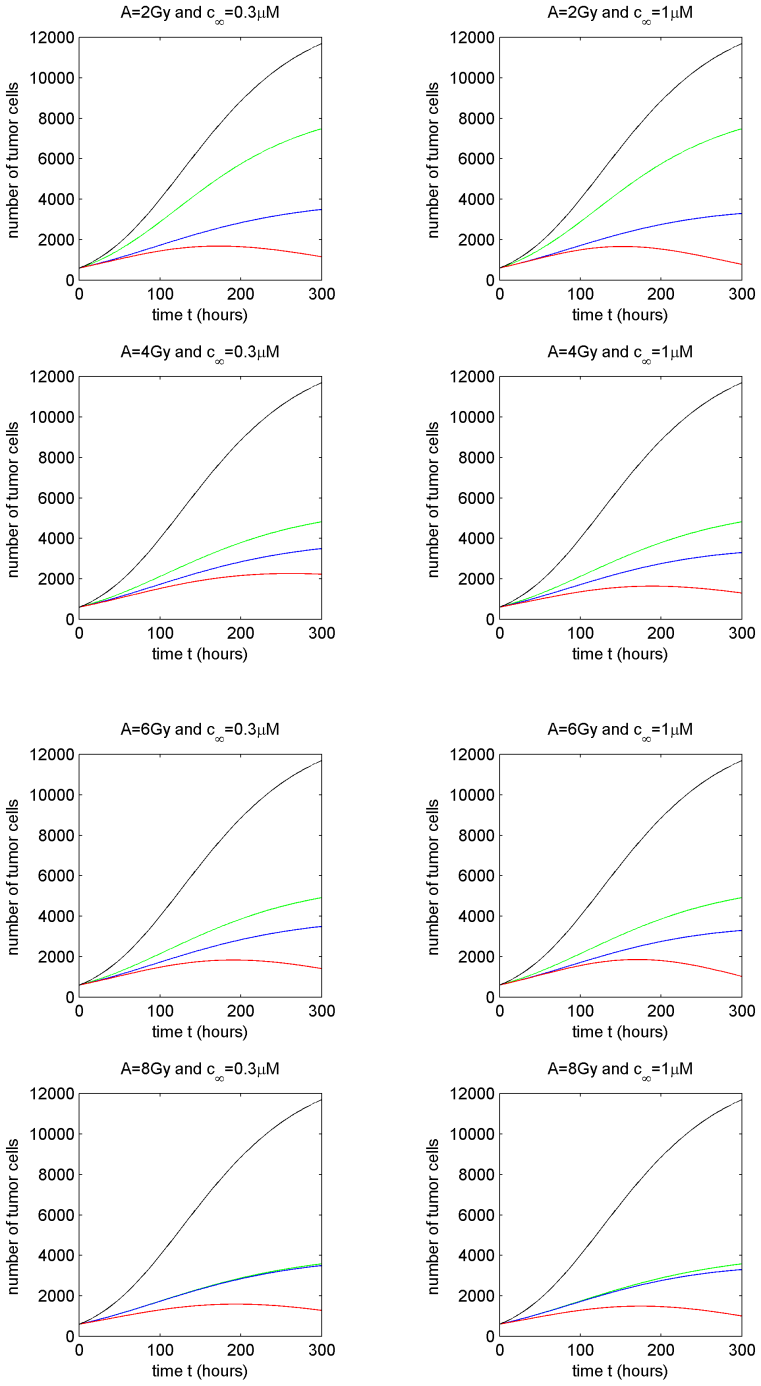


Figure 6.8: Modeling tumor growth including radio- and chemotherapy. Used parameters: $r = 0.0116\frac{1}{h}$, $\alpha = 0.203$, $N_0 = 596.3$ cells, $c_0 = 10\mu M$, $E = 1\frac{1}{h}$ and $\mu = (0.0024, 0.0023, 0.0015, 0.0015)\frac{1}{Gy \cdot h}$ for $A = (2, 4, 6, 8)Gy$. Additionally for the blue lines: $\epsilon_0 = 0.011\frac{1}{h}$ and $d = 0.0003\frac{1}{\mu M \cdot h}$ for $A = 2Gy$, $\epsilon_0 = 0.008\frac{1}{h}$ and $d = 0.00011\frac{1}{\mu M \cdot h}$ for $A = 4Gy$, $\epsilon_0 = 0.005\frac{1}{h}$ and $d = 0.0005\frac{1}{\mu M \cdot h}$ for $A = 6Gy$ and $\epsilon_0 = 0.003\frac{1}{h}$ and $d = 0.0007\frac{1}{\mu M \cdot h}$ for $A = 8Gy$. For the red lines: $\epsilon_0 = 0.012\frac{1}{h}$ and $d = 0.0003\frac{1}{\mu M \cdot h}$. The parameters were plugged in the numerical solutions of the model (6.25).


A=2Gy and c∞=0.3μM
A=2Gy and c∞=1μM
A=4Gy and c∞=0.3μM
A=4Gy and c∞=1μM
A=6Gy and c∞=0.3μM
A=6Gy and c∞=1μM
A=8Gy and c∞=0.3μM
A=8Gy and c∞=1μM
number of tumor cells
time t (hours)
0
2000
4000
6000
8000
10000
12000
100
200
300

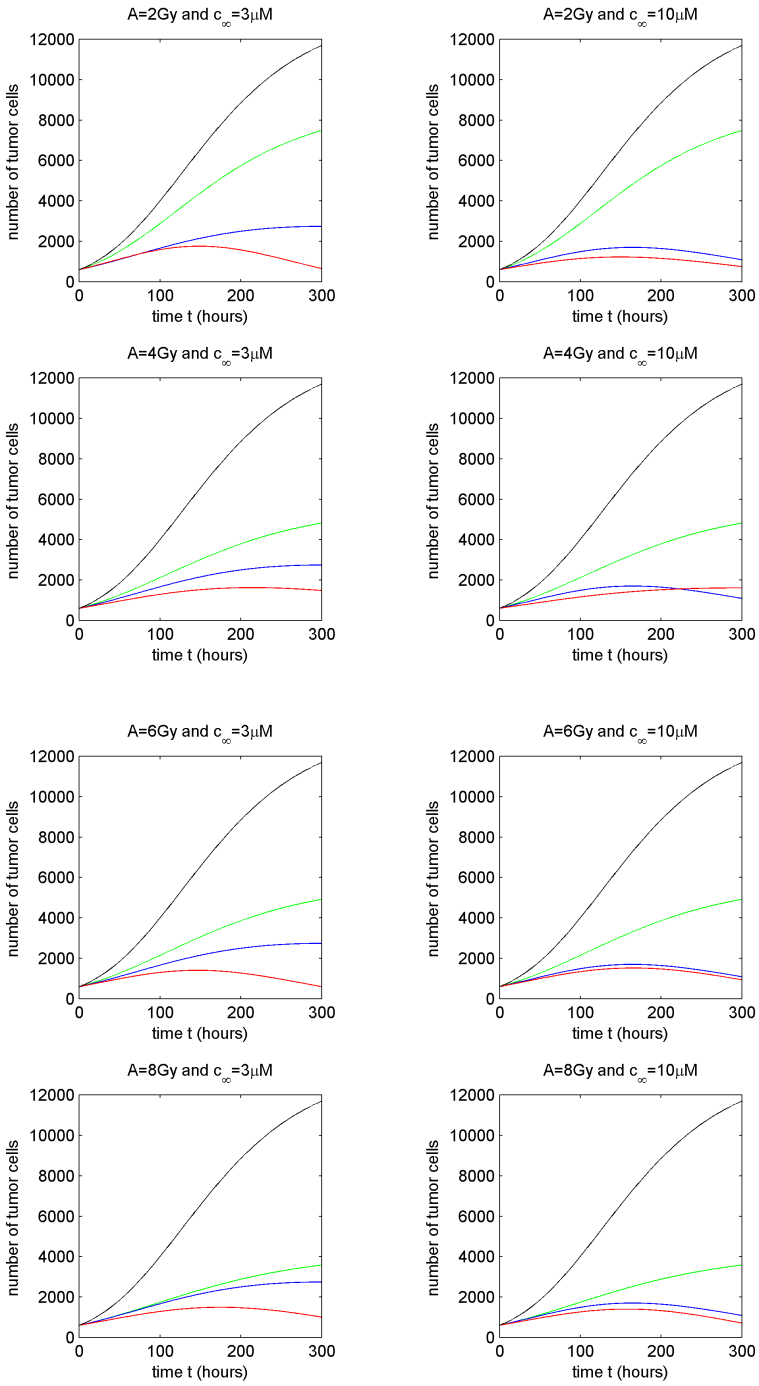


Figure 6.9: Single and Combined therapy outlined in one graph. Only radiotherapy is represented by the green line, only chemotherapy by the blue line and the combined therapy is represented by the red line. The black line depicts the tumor growth without therapy. The curves are obtained in the same way as in the figures 3.3, 4.2, 5.16, 6.5, 6.6, 6.7 and 6.8.

6.3. Spatial Model

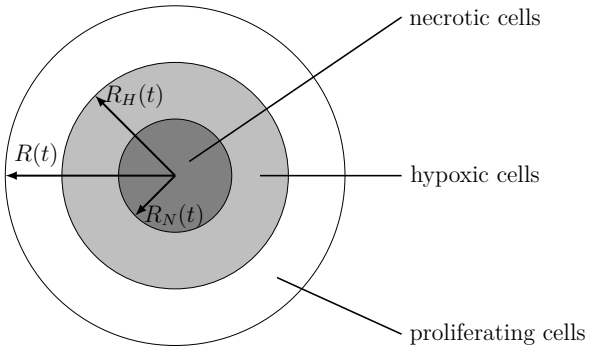


Figure 6.10: Three layer scheme, representing a slide of the tumor.

In comparison to the previous sections this section will cover a spatial model. Thus instead of the number of tumor cells, this time the length of the radius will give us information about the size of the tumor. In our spatial model also the internal structure of the tumor will be considered. As we saw in section 2.1 an avascular tumor may consist of three layers. The outer tumor radius is denoted by $R(t)$, the quiescent radius, which separates the proliferating and quiescent layer is denoted by $R_H(t)$ and the necrotic radius, which separates the quiescent and the necrotic layer is denoted by $R_N(t)$, see figure 6.10. All of them depend on the time t, since with time the tumor changes its size. Thus this section deals with a moving boundary problem. The next important parameter in this model is the concentration of a chemical $g(r,t)$ at time t and radius r (the radius is enough to represent the location, since the tumor is assumed to be radially symmetric). This chemical could be nutrients or oxygen, for example. $R(t)$ and $g(r,t)$ are defined by equations, which are derived by the principle of mass balance, whereas $R_H(t)$ and $R_N(t)$ are defined implicitly by particular chemical concentration thresholds g_H and g_N. g_N represents the maximal nutrient concentration at which necrosis occurs and g_H depicts the concentration where the cells start to proliferate [Pre03]. A common diffusion equation looks like

$$\frac{\partial h}{\partial t} = D\nabla^2 h + \rho h, \tag{6.33}$$

where D ($distance^2/time$) is the diffusion coefficient of the substance and ρ ($time^{-1}$) is the rate of increase or decrease of the substance h [Mur89b]. Thus the constant diffusion equation for nutrients reads as

$$\frac{\partial g}{\partial t} = D_g\nabla^2 g - \Gamma_\star H(r - R_N), \tag{6.34}$$

where D_g is the diffusion coefficient of the chemical drug g and denotes the degree of random motion [Pre03, Bri03]. $-\Gamma_\star H(r - R_N)$ is the reaction term and describes

the consumption of nutrients at a rate $\Gamma_\star$. Since only quiescent and proliferating cells consume nutrients (at the same rate) the Heaviside function H is included here. Thus it is one for radii which are longer than the necrotic radius and zero otherwise. By assumption the tumor is radially symmetric and thus with polar coordinates the diffusion term reads

$$D_g \nabla^2 g = D_g \frac{1}{r^2} \frac{\partial}{\partial r} \left(r^2 \frac{\partial g}{\partial r} \right). \tag{6.35}$$

The differential equation for the radius R reads

$$\begin{aligned} \frac{1}{3}\frac{dR^3}{dt} &= R^2 \frac{dR}{dt} \\ &= \underbrace{\int_{R_H}^{R} s\gamma g r^2 \,\mathrm{d}\, r}_{\text{total rate of cell proliferation}} - \underbrace{\int_0^R s(\lambda_A + \lambda_N H(R_N - r) + \nu c + \mu A) r^2 \,\mathrm{d}\, r}_{\text{total rate of cell death}}. \end{aligned} \tag{6.36}$$

The total rate of cell proliferation is proportional to the nutrient concentration g and the proliferation rate $\gamma > 0$. Moreover the integral starts at R_H and consequently it is only greater than zero for a radius $r > R_H$, since necrotic and quiescent cells do not proliferate. The total rate of cell death consists of different terms. The constant $\lambda_A > 0$ depicts the rate of apoptosis, i.e. normal cell death, whereas $\lambda_N > 0$ is the rate of necrosis. Since necrosis only happens in the region which is inside R_N, the Heaviside function is needed again. s is another positive constant. The term νc depicts the cell death caused by the chemotherapy and μA depicts the cell death caused by the radiotherapy. Since the radiation reaches all tumor cells equally, we set $A(r,t) = A\ const$ [Web13]. The chemotherapy however affects the cells in the outer parts of the tumor more than the ones in the inner parts. Thus $c(r,t)$ is not constant, but rather represented by another diffusion equation:

$$\frac{\partial c}{\partial t} = D_c \frac{1}{r^2} \frac{\partial}{\partial r} \left(r^2 \frac{\partial c}{\partial r} \right) - \Gamma_1 H(r - R_H) - \Gamma_2 H(r - R_N) H(R_H - r). \tag{6.37}$$

The equation is very similar to equation (6.34). There is again a diffusion term, this time with a different diffusion parameter D_c. In contrast to equation (6.34), there are two different reaction terms. $-\Gamma_1 H(r - R_H)$ describes the rate the chemotherapeutic drug is consumed by cells in the proliferating area and $-\Gamma_2 H(r - R_N) H(R_H - r)$ depicts the rate the drug is consumed by the quiescent cells.
Previously it was mentioned that R_H and R_N are defined implicitly by the nutrient concentration. Now it is time to define these radii more concrete [Pre03]:

- $g(r,t) > g_H \forall\ r \in (0,R)$
  $\Rightarrow R_N = R_H = 0$
- $\exists\ r \in (0, R(t))$ s.t. $g_N < g(r,t) \leq c_H$
  $\Rightarrow R_N = 0 < R_H < R$ with $g(R_H, t) = g_H$

- $\exists\ r \in (0, R(t))$ s.t. $g(r,t) \leq c_N < c_H$
  $\Rightarrow 0 < R_N < R_H < R$ with $g(R_N, t) = g_N$ and $g(R_H, t) = g_H$

The last thing which is needed are the boundary and initial conditions for both g an c. We start with the conditions which affect the nutrient concentration [Pre03]:

- $\frac{\partial g}{\partial r} = 0$ at $r = 0$
- $g = g_\infty$ on $r = R(t)$
- g, $\frac{\partial g}{\partial r}$ continuous across $r = R_H(t)$ and $r = R_N(t)$
- $g(r, 0) = g_0(r)$, $R(t = 0) = R_0$

The initial and boundary conditions for the drug concentration c are nearly the same:

- $\frac{\partial c}{\partial r} = 0$ at $r = 0$
- $c = c_\infty(t)$ on $r = R(t)$
- c, $\frac{\partial c}{\partial r}$ continuous across $r = R_H(t)$ and $r = R_N(t)$
- $c(r, 0) = c_0(r)$, $R(t = 0) = R_0$

The only difference is that the concentration of the drug outside the tumor is time dependent, since it is possible to give chemotherapy in certain time slots.

Nondimensionalization To analyze the model correctly, the model needs to be brought into a dimensionless form. To do this, the typical nutrient concentration G, the drug concentration C, the typical lengthscale X and timescale T are introduced. The choice of G, C, X and T is based on typical measurements. So far, they remain unspecified [Pre03]. So the dimensionless variables read as

$$g^* = \frac{g}{G}, \qquad c^* = \frac{c}{C}, \qquad t^* = \frac{t}{T}, \qquad r^* = \frac{r}{X},$$
$$R^* = \frac{R}{X}, \qquad {R_H}^* = \frac{R_H}{X}, \qquad {R_N}^* = \frac{R_N}{X}.$$

So writing the model equations (6.34), (6.36) and (6.37) in terms of the dimensionless variables yields

$$\frac{\partial g}{\partial t} = \left(\frac{D_g T}{X^2}\right) \frac{1}{r^{*2}} \frac{\partial}{\partial r^*} \left(r^{*2} \frac{\partial g^*}{\partial r^*}\right) - \Gamma_\star T H(r^* - {R_N}^*) \tag{6.38a}$$

$$\begin{aligned} \frac{\partial c}{\partial t} = &\left(\frac{D_c T}{X^2}\right) \frac{1}{r^{*2}} \frac{\partial}{\partial r^*} \left(r^{*2} \frac{\partial c^*}{\partial r^*}\right) - \Gamma_1 T H(r^* - R_H^*) \\ &- \Gamma_2 T H(r^* - R_N^*) H(R_H^* - r^*) \end{aligned} \tag{6.38b}$$

$$\begin{aligned} {R^*}^2 \frac{dR^*}{dt^*} = &\int_0^{R^*} s\{g^* G T H(r^* - R_N^*) - T\lambda_A - T\lambda_N H(R_N^* - r^*) \\ &- T\nu c^* C - T\mu A\} {r^*}^2 \,\mathrm{d}\, r^*. \end{aligned} \tag{6.38c}$$

There are several different timescales implicit in the model equations, which are for example the

- Nutrient diffusion timescale $\frac{X^2}{D}$
- Tumor doubling timescale $\frac{1}{sG}$
- Nutrient consumption timescale $\frac{1}{\Gamma_\star}$
- Drug consumption timescales $\frac{1}{\Gamma_1}$ and $\frac{1}{\Gamma_2}$

Now the longest timescale should be used, since changes in the spatial structure of the tumor are simulated and analyzed. Experimental parameter measurements show that the tumor doubling timescale $\frac{1}{sG}$ corresponds to weeks and is therefore the longest timescale [Pre03]. Thus we choose

$$T = \frac{1}{sG}.$$

Furthermore the following quasi-steady assumptions are made

$$\begin{aligned} O(\Gamma_\star) &= O(D_g/X^2) \gg O(1/T) \\ O(\Gamma_1) &= O(D_c/X^2) \gg O(1/T) \\ O(\Gamma_2) &= O(D_c/X^2) \gg O(1/T). \end{aligned}$$

Including all assumptions from above and exclude $\cdot s$ for clearness, the model (6.38) can be reduced to

$$0 = \frac{1}{r^{*2}}\frac{\partial}{\partial r^*}\left(r^{*2}\frac{\partial g^*}{\partial r^*}\right) - \Gamma_\star^* H(r^* - {R_N}^*) \tag{6.39a}$$

$$0 = \frac{1}{r^{*2}}\frac{\partial}{\partial r^*}\left(r^{*2}\frac{\partial c^*}{\partial r^*}\right) - \Gamma_1^* H(r^* - R_H^*) - \Gamma_2^* H(r^* - R_N^*)H(R_H^* - r^*) \tag{6.39b}$$

$$R^{*2}\frac{dR^*}{dt^*} = \int_0^{R^*} \{\gamma g^* H(r^* - R_N^*) - \lambda_A^* - \lambda_N^* H(R_N^* - r^*) - \nu^* c^* - \mu^* A\} r^{*2}\,\mathrm{d}\,r^*, \tag{6.39c}$$

$$\text{where} \qquad \Gamma_\star^* = \frac{\Gamma_\star X^2}{D_g}, \qquad \Gamma_1^* = \frac{\Gamma_1 X^2}{D_c}, \qquad \Gamma_2^* = \frac{\Gamma_2 X^2}{D_c}, \qquad \gamma = \frac{1}{C},$$

$$\lambda_A^* = \frac{\lambda_A}{GC}, \qquad \lambda_N^* = \frac{\lambda_N}{GC}, \qquad \nu^* = \frac{\nu}{G}, \qquad \mu^* = \frac{\mu}{GC},$$

with the following boundary and initial conditions of the nutrient and the drug concentrations:

- $R_H^* = 0$ if $g^* > g_H^*\ \forall\ r$ and otherwise $g^*(R_H^*, t^*) = g_H^*$
- $R_N^* = 0$ if $g^* > g_N^*\ \forall\ r$ and otherwise $g^*(R_N^*, t^*) = g_N^*$
- $\frac{\partial g^*}{\partial r^*} = 0$ at $r^* = 0$

- $g^* = g^*_\infty$ on $r^* = R^*$
- $\frac{\partial c^*}{\partial r^*} = 0$ at $r^* = 0$
- $c^* = c^*_\infty(t)$ on $r^* = R^*$
- $R^*(0) = R^*_0$,

$$\text{where} \qquad g^*_H = \frac{g_H}{G}, \qquad g^*_N = \frac{g_N}{G}, \qquad g^*_\infty = \frac{g_\infty}{G}, \qquad c^*_\infty(t) = \frac{c_\infty(t)}{C}$$

To keep the model clear, the superscript stars are omitted in the following.

6.3.1. Model Analysis and Simplification

Since an avascular tumor does not have three layers from the beginning, this section also considers the prestages. There are three stages in total. In the first stage there are only proliferating cells. Later, when the tumor becomes bigger, the substrate level (for example the oxygen level) in the interior of the tumor drops down to a level where proliferation is not possible anymore. Thus these cells become quiescent and the tumor consists of two layers now. In the third stage finally, the tumor is even bigger and the substrate concentration drops down to a level where the cells start to become necrotic. Hence in this stage the tumor consists of three layers as discussed above.

First stage Since the tumor consists of proliferating cells only, it holds that $R_N = R_H = 0$ and $g > g_H \ \forall\ r \in (0, R)$. Thus equation (6.39a) reads as

$$0 = \frac{1}{r^2}\frac{\partial}{\partial r}\left(r^2 \frac{\partial g}{\partial r}\right) - \Gamma_\star,$$

which can be solved easily:

$$g(r,t) = \frac{\Gamma_\star}{6} r^2 - \frac{p_1}{r} + p_2,$$

with p_1, $p_2 \in \mathbb{R}$. Including the boundary conditions yields

$$g(r,t) = g_\infty - \frac{\Gamma_\star}{6}(R^2 - r^2). \tag{6.40}$$

This can be done in the same way for the drug concentration. Applying the condition $R_N = R_H = 0$ to equation (6.39b) yields

$$0 = \frac{1}{r^2}\frac{\partial}{\partial r}\left(r^2 \frac{\partial c}{\partial r}\right) - \Gamma_1.$$

The solution can be computed in the same way as above. Including the boundary conditions yields the exact solution

$$c(r,t) = c_\infty(t) - \frac{\Gamma_1}{6}(R^2 - r^2). \tag{6.41}$$

Further the condition $g > g_H \ \forall\ r \in (0,R)$ is equal to

$$\begin{aligned} & g_\infty - \frac{\Gamma_\star}{6}(R^2 - r^2) > g_H \\ \Leftrightarrow\ & \frac{6}{\Gamma_\star}(g_\infty - g_H) > R^2 - r^2. \end{aligned}$$

Thus at this stage it has to hold for the tumor radius $R(t)$ that

$$0 < R^2(t) < \frac{6}{\Gamma_\star}(g_\infty - g_H).$$

Hence if $R^2(t) \to \frac{6}{\Gamma_\star}(g_\infty - g_H)$, i.e. the tumor radius tends to the maximum for which only proliferating cells exist, the nutrient concentration $g \to g_H$ for $r \to 0$. Now we can plug in the solutions (6.40) and (6.41) and the condition $R_N = R_H = 0$ in equation (6.39c) to get an equation for the radius R:

$$\begin{aligned} R^2\frac{dR}{dt} =& \int_0^R \{\gamma(g_\infty - \frac{\Gamma_\star}{6}(R^2 - r^2)) - \lambda_A - \nu(c_\infty(t) \\ & - \frac{\Gamma_1}{6}(R^2 - r^2)) - \mu A\} r^2 \,\mathrm{d}\, r \\ \Rightarrow\ R^2\frac{dR}{dt} =& \frac{1}{3}R^3\gamma g_\infty - \frac{1}{3}R^5\frac{\Gamma_\star}{6}\gamma + \frac{1}{5}R^5\frac{\Gamma_\star}{6}\gamma - \frac{1}{3}R^3\lambda_A - \frac{1}{3}R^3\nu c_\infty(t) \\ & + \frac{1}{3}R^5\frac{\Gamma_1}{6}\nu - \frac{1}{5}R^5\frac{\Gamma_1}{6}\nu - \frac{1}{3}\mu A R^3 \\ \Leftrightarrow\ \frac{dR}{dt} =& \frac{1}{3}R\left(\gamma g_\infty - \frac{1}{15}R^2\Gamma_\star\gamma - \lambda_A - \nu c_\infty(t) + \frac{1}{15}R^2\Gamma_1\nu - \mu A\right). \end{aligned} \tag{6.42}$$

Second stage In this stage only proliferating and quiescent cells exist. Thus we have the following conditions:

(a) $R_N = 0$

(b) $g(r,t) > g_N \ \forall\ r \in (0,R)$

(c) $g(R_H,t) = g_H$

Hence the solution for the nutrient concentration is the same as in the first stage, namely

$$g(r,t) = g_\infty - \frac{\Gamma_\star}{6}(R^2 - r^2). \tag{6.43}$$

To find the solution for the drug concentration, two cases are needed:

- $r > R_H$
  (6.39b) $\Leftrightarrow\ 0 = \frac{1}{r^2}\frac{\partial}{\partial r}\left(r^2\frac{\partial c}{\partial r}\right) - \Gamma_1$
- $r < R_H$
  (6.39b) $\Leftrightarrow\ 0 = \frac{1}{r^2}\frac{\partial}{\partial r}\left(r^2\frac{\partial c}{\partial r}\right) - \Gamma_2$

Thus the solution for the drug concentration, which can be computed in the same way as the solution of the nutrient concentration in the first stage, reads

$$c(r,t) = \begin{cases} c_\infty(t) - \frac{\Gamma_1}{6}(R^2 - r^2) & \text{if } R_H < r < R \\ c_\infty(t) - \frac{\Gamma_2}{6}(R^2 - r^2) & \text{if } 0 < r < R_H \end{cases}. \tag{6.44}$$

Condition (c) is equivalent to

$$g_H = g_\infty - \frac{\Gamma_\star}{6}(R^2 - R_H^2) \tag{6.45}$$

$$\Leftrightarrow R_H^2 = R^2 - \frac{6}{\Gamma_\star}(g_\infty - g_H), \tag{6.46}$$

and condition (b) is the same as

$$\frac{6}{\Gamma_\star}(g_\infty - g_N) > R^2 - r^2. \tag{6.47}$$

Since R_H has to be greater than zero we have two boundaries for the radius $R(t)$ in this stage. Condition (c) yields a lower bound and condition (b) an upper bound (which is obtained in the same way as in the first stage):

$$\frac{6}{\Gamma_\star}(g_\infty - g_H) < R^2(t) < \frac{6}{\Gamma_\star}(g_\infty - g_N). \tag{6.48}$$

Now we can establish an equation for the radius, by plugging in the solutions for the concentrations as well as condition (a) in equation (6.39c). Simple calculation yields

$$\begin{aligned} R^2\frac{dR}{dt} =& \int_0^{R_H}\{-\lambda_A - \nu(c_\infty(t) - \frac{\Gamma_2}{6}(R^2 - r^2)) - \mu A\}r^2\,\mathrm{d}\,r \\ &+ \int_{R_H}^{R}\{\gamma(g_\infty - \frac{\Gamma_\star}{6}(R^2 - r^2)) - \lambda_A - \nu(c_\infty(t) - \frac{\Gamma_1}{6}(R^2 - r^2))\}r^2\,\mathrm{d}\,r \\ \Rightarrow\ \frac{dR}{dt} =& \frac{1}{3}R\left((\gamma g_\infty - \mu A)\left(1 - \frac{R_H^3}{R^3}\right) - \lambda_A - \nu c_\infty(t)\right) \\ &+ \frac{1}{3}R^3\left(\frac{1}{15}\left(-\gamma\Gamma_\star + \nu\Gamma_1\right) + \frac{1}{6}\left(\gamma\Gamma_\star + \nu\Gamma_2 - \nu\Gamma_1\right)\frac{R_H^3}{R^3}\right) \\ &+ \frac{1}{3}R^3\left(\frac{1}{10}\left(-\gamma\Gamma_\star - \nu\Gamma_2 + \nu\Gamma_1\right)\frac{R_H^5}{R^5}\right). \end{aligned} \tag{6.49}$$

In this calculation it is also considered that quiescent cells do not proliferate and are not damaged by radiotherapy.

Third stage In this final stage there are proliferating, quiescent and also necrotic cells. Thus the following assumptions are necessary:

(a) $g(R_H, t) = g_H$

(b) $g(R_N, t) = g_N$

Since proliferating and quiescent cells need the same amount of nutrients, but necrotic cells need no nutrients at all, the nutrient concentration in the region for all $r < R_N$ is different as in the region where $r > R_N$. With the above assumptions the concentration reads as

$$g(r,t) = \begin{cases} g_N & 0 < r \leq R_N \\ g_N + \frac{\Gamma_\star}{6r}(r - R_N)^2(r + 2R_N) & R_N < r < R, \end{cases} \tag{6.50}$$

[Pre03]. Depending on the layer, the concentration of the drug varies, too. Since necrotic cells are not doing any cell metabolism, they are not consuming any drug. Thus for all $r \leq R_N$ the drug concentration stays the same. Since we do not have boundary conditions for c, we take the same concentration for the necrotic core as for the rim $r = R_N$. Thus the drug concentration reads as

$$c(r,t) = \begin{cases} c_\infty(t) - \frac{\Gamma_2}{6}(R^2 - R_N^2) & \text{if } 0 < r < R_N \\ c_\infty(t) - \frac{\Gamma_2}{6}(R^2 - r^2) & \text{if } R_N < r < R_H \\ c_\infty(t) - \frac{\Gamma_1}{6}(R^2 - r^2) & \text{if } R_H < r < R\ . \end{cases} \tag{6.51}$$

Analogous to the second stage, the tumor needs a minimal size to be in the third stage. Here the following has to hold for the radius:

$$R^2(t) > \frac{6}{\Gamma_\star}(g_\infty - g_N). \tag{6.52}$$

The conditions for R_H stay the same as in the second stage. Analogously we can now relate R_N and g_N:

$$R_N^2 = R^2 - \frac{6}{\Gamma_\star}(g_\infty - g_N). \tag{6.53}$$

So there is only one thing left to do. Including the conditions and solutions for the concentrations in equation (6.39c) yields

$$\begin{aligned}
R^2\frac{dR}{dt} =& \int_0^{R_N}\{-\lambda_A-\lambda_N\}r^2\,\mathrm{d}\,r + \int_{R_N}^{R_H}\{-\lambda_A-\nu(c_\infty(t)-\frac{\Gamma_2}{6}(R^2-r^2))r^2\,\mathrm{d}\,r \\
&+\int_{R_H}^{R}\{\gamma(g_N+\frac{\Gamma_\star}{6r}(r-R_N)^2(r+2R_N))\}r^2\,\mathrm{d}\,r \\
&-\int_{R_H}^{R}\{\lambda_A-\nu(c_\infty(t)-\frac{\Gamma_1}{6}(R^2-r^2))-\mu A\}r^2\,\mathrm{d}\,r \\
\frac{dR}{dt} =& \frac{R}{3}\left[(\gamma g_N-\mu A)\left(1-\frac{R_H^3}{R^3}\right)-\nu c_\infty\left(1-\frac{R_N^3}{R^3}\right)-\left(\lambda_A+\lambda_N\frac{R_N^3}{R^3}\right)\right] \\
&+\frac{\gamma\Gamma_\star R^3}{6}\left[\frac{1}{5}\left(1-\frac{R_H^5}{R^5}\right)-\frac{R_N^2}{R^2}\left(1-\frac{R_H^3}{R^3}\right)+\frac{R_N^3}{R^3}\left(1-\frac{R_H^2}{R^2}\right)\right] \\
&+\frac{\nu\Gamma_1 R^3}{6}\left[\frac{1}{3}\left(1-\frac{R_H^3}{R^3}\right)-\frac{1}{5}\left(1-\frac{R_H^5}{R^5}\right)\right] \\
&+\frac{\nu\Gamma_2 R^3}{6}\left[\frac{1}{3}\left(\frac{R_H^3}{R^3}-\frac{R_N^3}{R^3}\right)-\frac{1}{5}\left(\frac{R_H^5}{R^5}-\frac{R_N^5}{R^5}\right)\right].
\end{aligned} \tag{6.54}$$

Since this model is finally finished, the data analysis can start.

6.3.2. Fitting the model to data

Once again we want to know how well the model fits the data. For this question we need to know which model we have to take, since in every stage the tumor growth and death is modeled different. Thus we need to make the following assumptions. If the tumor radius is larger than $200\mu m$ the tumor has a necrotic core and if the radius is larger than $100\mu m$ there are quiescent cells. These assumptions arose from histological examination [TG55, DS81]. Thus the model is chosen by the following simple rule:

- $R < 100\mu m \;\Rightarrow$ First Stage $\Rightarrow$ Using equation (6.42)
- $100\mu m < R < 200\mu m \;\Rightarrow$ Second Stage $\Rightarrow$ Using equations (6.49) and (6.46)
- $200\mu m \;\Rightarrow$ Third Stage $\Rightarrow$ Using equations (6.54), (6.53) and (6.46)

Since the data stemmed from an in-vitro experiment, the external nutrient concentration can be set to one. The other nutrient concentration boundaries can be obtained from the model boundaries above. To get g_H for example, just plug in $R = 100$ and $R_H = 0$ in equation (6.45). Thus the nutrient concentrations are:

- $g_\infty = 1$
- $g_H = 1 - \frac{\Gamma_\star}{6}100^2$

- $g_N = 1 - \frac{\Gamma_\star}{6} 200^2$

Since we want to compare the model to the given data from [AH14] and the data only includes the tumor area, we have to convert the area into the radius. This is quite easy with the formula

$$Radius = \sqrt{\frac{Area}{\pi}}$$

and the results can be seen in table 8.

Days	0	3	6	9	12
Area (μm^2)	79312.42	131492.7	194451.8	222105.0	233064.7
Radius (μm)	158.890	204.586	248.789	265.891	272.372

Table 8: Mean area measured over a period of 12 days. Data taken from [AH14].

We want to start with the case where no radiation and no chemotherapeutic drug is administered to obtain the parameters λ_A, λ_N, γ and $\Gamma_\star$ first. Since no radiation and no chemotherapeutic drug is administered, we set $A = 0$ and $c_\infty(t) = 0$. Algorithm 8 returns the best approximation with an error of 0.0030 for the following parameters: $\lambda_A = \lambda_N = 0$, $\gamma = 0.03$ and $\Gamma_\star = 0.00012$. According to the definition of the model λ_A and λ_N are greater than zero. But we can assume that both values are so small that we can approximate them with zero. The fitting can be seen in figure 6.11. This simulation and all further ones are made with MATLAB and with the numerical solutions of the above mentioned equations, obtained by the euler method. In all simulations the blue line represents the outer radius R, the red line represents the radius R_H and the green line represents R_N.
The next step is to include radiation. The available data can be seen in table 9. The radii are normalized in order to compare them.

Radius of Tumor	**Days**				
Radiation (Gy)	0	3	6	9	12
2	158.890	198.014	230.050	239.573	251.654
4	158.890	193.470	212.807	223.183	225.769
6	158.890	199.823	213.748	209.756	224.324
8	158.890	196.593	202.409	196.075	211.284

Table 9: Mean radius of tumor treated with radiotherapy. Data taken from [AH14].

We vary μ and keep all other parameters as before. The other parameters are fixed, so $\lambda_A = \lambda_N = 0$, $g_\infty = 1$, $\gamma = 0.03$ and $\Gamma_\star = 0.00012$. We get the following results, which can be seen in figure 6.12: For $A = 2$ we get $\mu = 0.0034$ with an error of 0.0013. For

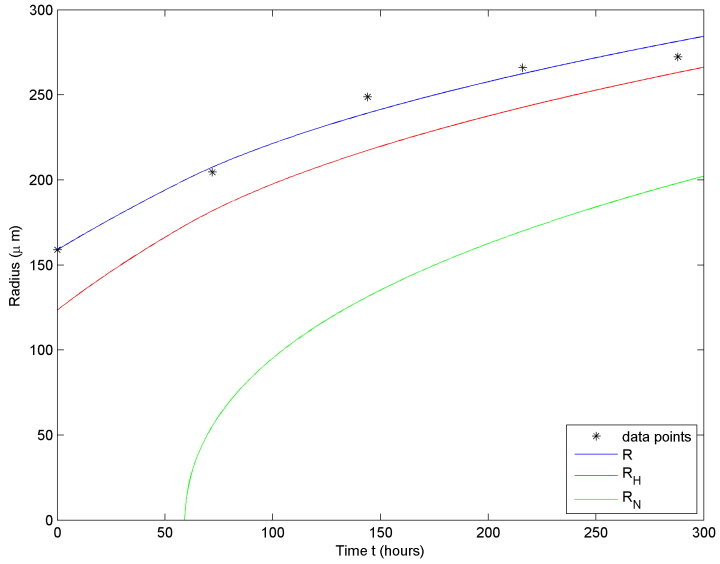


Figure 6.11: Approximation of the radius without treatment. Used parameters: $g_\infty = 1$, $\lambda_A = \lambda_N = 0$, $\gamma = 0.03$ and $\Gamma_\star = 0.00012$. Data points taken from [AH14].

$A = 4$ we get $\mu = 0.0032$ with an error of 0.0032. For $A = 4$ we get $\mu = 0.0022$ with an error of 0.0114 and for $A = 8$ we get $\mu = 0.0021$ with an error of 0.0172. Like in the cell population model the values of μ are almost the same for drug dosages greater than 5 Gray, but differ from the similar values for drug dosages less than 5 Gray.
Now we will include only chemotherapy. The normalized radii are shown in table 10.

Radius of Tumor	**Days**				
Concentration of drug (μM)	0	3	6	9	12
0.3	158.890	187.719	202.966	200.259	218.354
1	158.890	185.684	210.558	211.043	214.376
3	158.890	183.276	206.101	207.743	198.439
10	158.890	173.483	190.881	190.559	180.951
30	158.890	172.535	194.972	191.632	186.101

Table 10: Mean radius of tumor treated with chemotherapy. Data taken from [AH14].

Like in the fitting without treatment we choose $g_\infty = 1$, $\lambda_A = \lambda_N = 0$, $\gamma = 0.03$ and $\Gamma_\star = 0.00012$. Additionally we choose $\Gamma_2 = 0$, since vinblastine inhibits cell division and thus only proliferating cells are affected. ν and Γ_1 and are varied to get the best approximation. Algorithm 10 returns the following results: $\nu = 0.0365$ and $\Gamma_1 = 0.0004$ are returned with an error of 0.0026 for $c_\infty(0) = 0.3$, $\nu = 0.0132$ and $\Gamma_1 = 0.002$ are

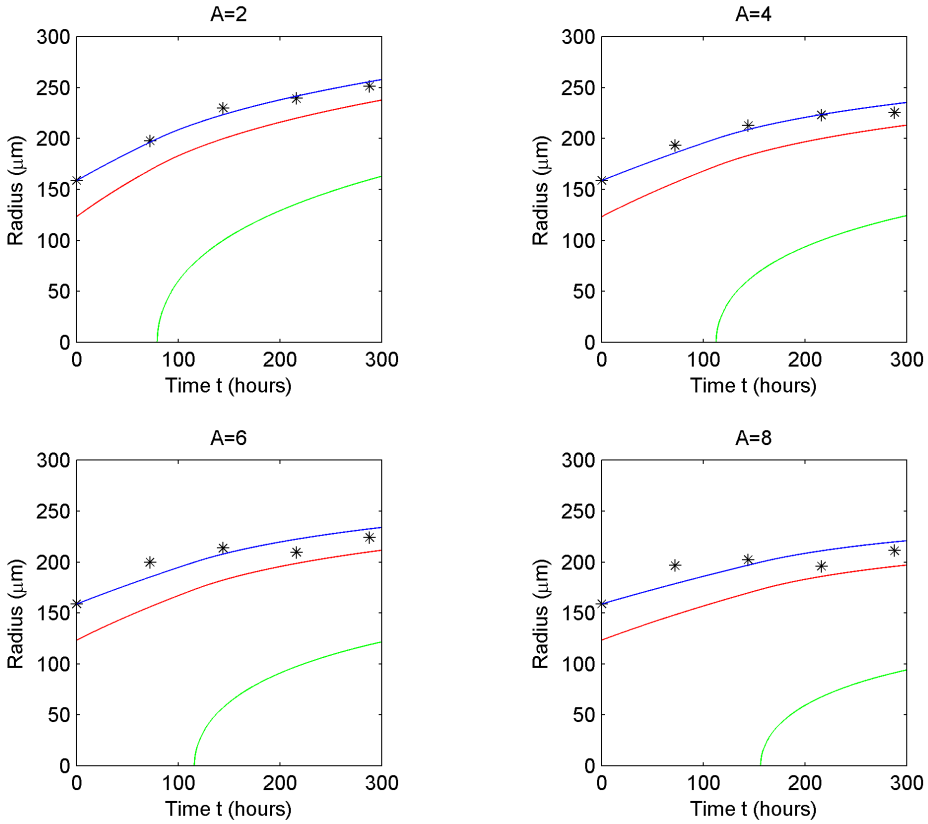


Figure 6.12: Approximation of the radius including radiotherapy. Used parameters: $g_\infty = 1$, $\lambda_A = \lambda_N = 0$, $\gamma = 0.03$ and $\Gamma_\star = 0.00012$. Additional parameters: $\mu = 0.0034$ for $A = 2$, $\mu = 0.0032$ for $A = 4$, $\mu = 0.0022$ for $A = 6$ and $\mu = 0.0021$ for $A = 8$. Data points taken from [AH14].

returned with an error of 0.0014 for $c_\infty(0) = 1$, $\nu = 0.0074$ and $\Gamma_1 = 0.007$ are returned with an error of 0.0030 for $c_\infty(0) = 3$, $\nu = 0.0036$ and $\Gamma_1 = 0.023$ are returned with an error of 0.0035 for $c_\infty(0) = 10$ and $\nu = 0.0003$ and $\Gamma_1 = 0.017$ are returned with an error of 0.0115 for $c_\infty(0) = 30$. The curves can be seen in figure 6.13.
Now it is time to combine both treatments, i.e. radio- and chemotherapy. The normalized radii can be seen in table 11 and 12 for $c_\infty(0) = 0.3$ and $c_\infty(0) = 10$, respectively.

Radius of Tumor	**Days**				
Radiation (Gy)	0	3	6	9	12
2	158.890	182.110	191.982	189.793	182.746
4	158.890	180.725	197.622	201.778	200.964
6	158.890	176.152	195.129	196.287	186.861
8	158.890	180.306	189.976	185.993	185.810

Table 11: Mean radius of tumor treated with radio- and chemotherapy, $c_\infty(0) = 0.3$. Data taken from [AH14].

Radius of Tumor	**Days**				
Radiation (Gy)	0	3	6	9	12
2	158.890	178.539	182.275	177.517	164.145
4	158.890	177.064	195.070	185.027	190.254
6	158.890	171.778	189.521	189.557	175.654
8	158.890	178.820	186.495	182.585	171.600

Table 12: Mean radius of tumor treated with radio- and chemotherapy, $c_\infty(0) = 10$. Data taken from [AH14].

We start with $c_\infty(0) = 0.3$ and set all parameters according to the previous calculations: $g_\infty = 1$, $\lambda_A = \lambda_N = 0$, $\Gamma_\star = 0.00012$, $\gamma = 0.03$, $\mu = (0.0034, 0.0032, 0.0022, 0.0021)$ for $A = (2, 4, 6, 8)$, $\nu = 0.0365$, $\Gamma_1 = 0.0004$ and $\Gamma_2 = 0$. The results can be seen in figure 6.14. The following values for the minimal error, which is again calculated by (3.7), are returned: For $A = 2$ we get an error of 0.0161, for $A = 4$ we get an error of 0.00075, for $A = 6$ we get an error of 0.0136 and for $A = 8$ we get an error of 0.0220.
We continue with $c_\infty(0) = 10$ and the following parameters: $g_\infty = 1$, $\lambda_A = \lambda_N = 0$, $\gamma = 0.03$, $\Gamma_\star = 0.00012$, $\mu = (0.0034, 0.0032, 0.0022, 0.0021)$ for $A = (2, 4, 6, 8)$, $\nu = 0.0036$, $\Gamma_1 = 0.023$ and $\Gamma_2 = 0$. This time we get the following results: For $A = 2$ we get an error of 0.0178, for $A = 4$ we get an error of 0.0033, for $A = 6$ we get an error of 0.0081 and for $A = 8$ we get an error of 0.0093. The results can be seen in figure 6.15.

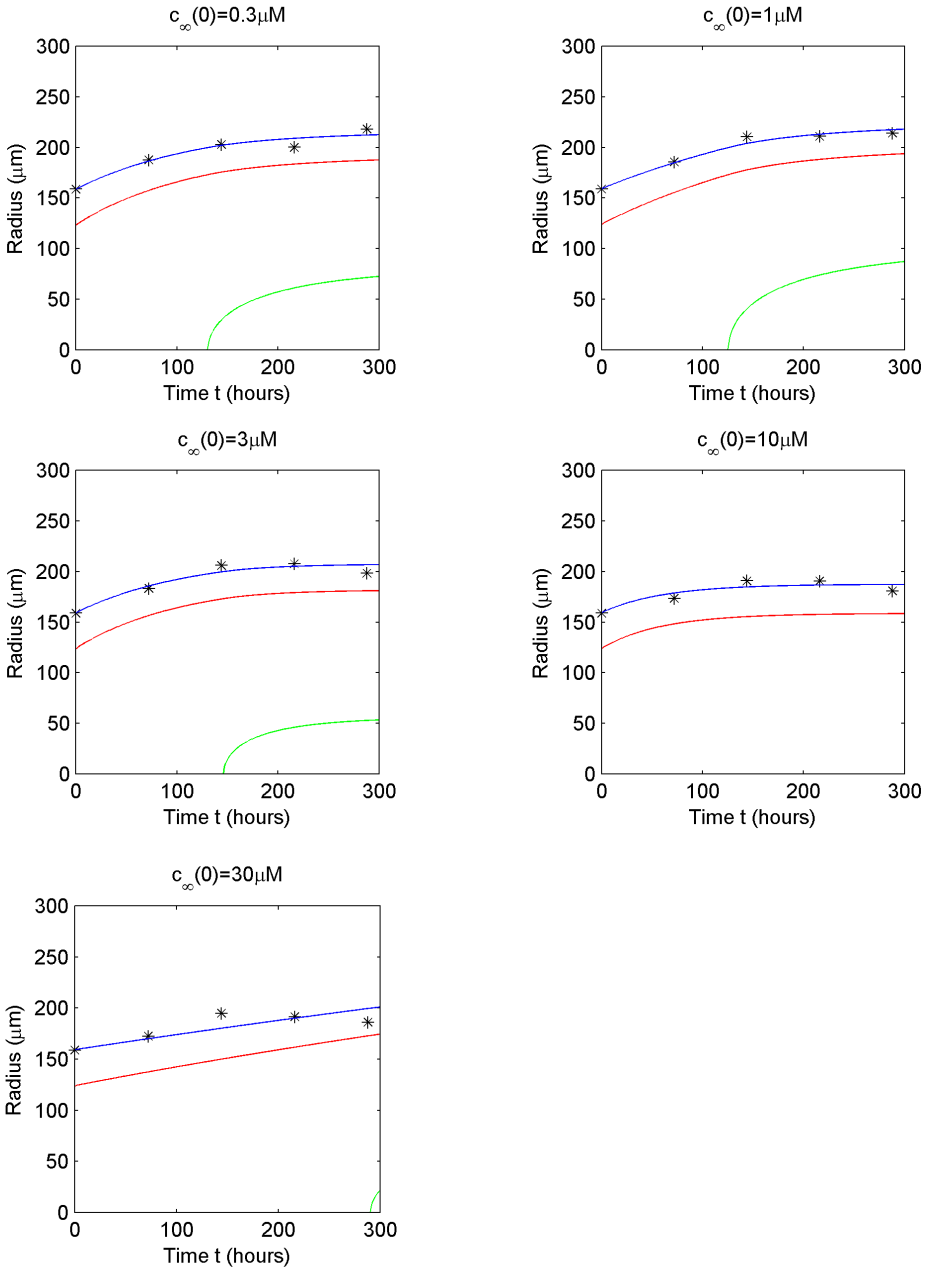


Figure 6.13: Approximation of the radius including chemotherapy. Used parameters: $g_\infty = 1$, $\lambda_A = \lambda_N = 0$, $\gamma = 0.03$, $\Gamma_\star = 0.00012$ and $\Gamma_2 = 0$. Additional parameters: $\nu = 0.0365$ and $\Gamma_1 = 0.0004$ for $c_\infty(0) = 0.3\mu M$, $\nu = 0.0132$ and $\Gamma_1 = 0.002$ for $c_\infty(0) = 1$, $\nu = 0.0074$ and $\Gamma_1 = 0.007$ for $c_\infty(0) = 3$, $\nu = 0.0036$ and $\Gamma_1 = 0.023$ for $c_\infty(0) = 10$ and $\nu = 0.0003$ and $\Gamma_1 = 0.017$ for $c_\infty(0) = 30$. Data points taken from [AH14].

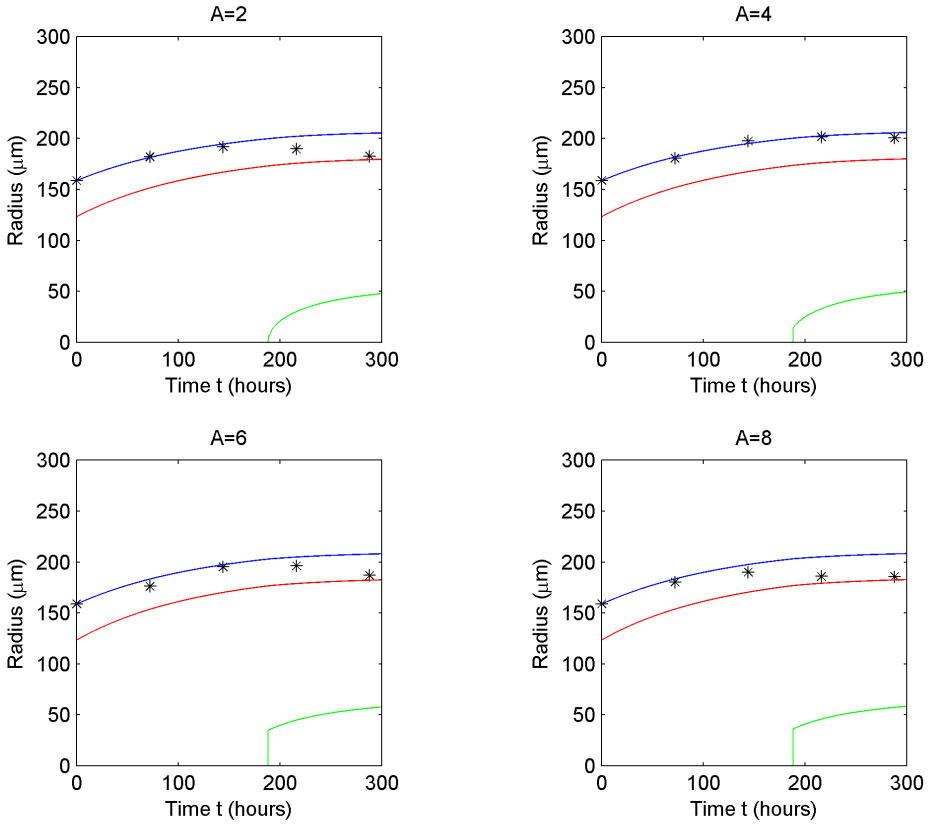


Figure 6.14: Approximation of the radius including radio- and chemotherapy, $c_\infty(0) = 0.3$. Used parameters: $g_\infty = 1$, $\lambda_A = \lambda_N = 0$, $\Gamma_\star = 0.00012$, $\gamma = 0.03$, $\mu = (0.0034, 0.0032, 0.0022, 0.0021)$ for $A = (2, 4, 6, 8)$, $\nu = 0.0365$, $\Gamma_1 = 0.0004$ and $\Gamma_2 = 0$. Data points taken from [AH14].

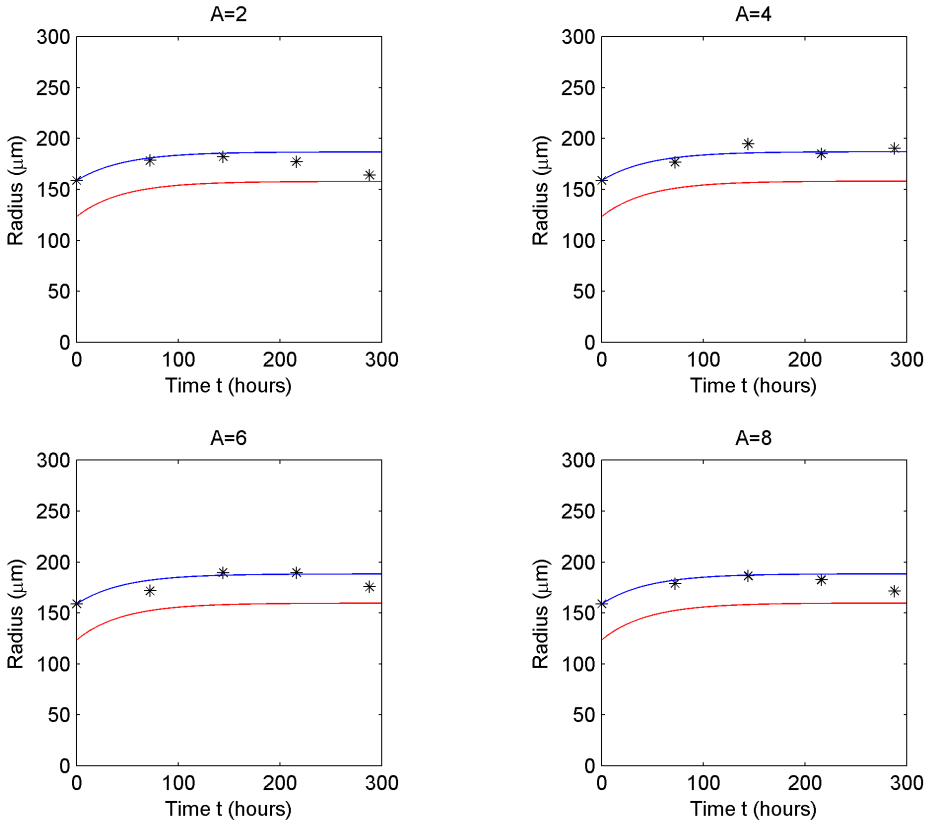


Figure 6.15: Approximation of the radius including radio- and chemotherapy, $c_\infty(0) = 10$. Used parameters: $g_\infty = 1$, $\lambda_A = \lambda_N = 0$, $\gamma = 0.03$, $\Gamma_\star = 0.00012$, $\mu = (0.0034, 0.0032, 0.0022, 0.0021)$ for $A = (2, 4, 6, 8)$, $\nu = 0.0036$, $\Gamma_1 = 0.023$ and $\Gamma_2 = 0$. Data points taken from [AH14].

For $A = 4$ and both drug concentrations, a really good fitting is returned, but for the other three radiations dosages the last data points are located below the curve. This suggests the assumption that the efficacy of the combined therapy is even better than the sum of the single therapies. But since the errors are still very small and the distances between data points and the calculated curves are also not really wide, this can also be a coincidence. Moreover the results from section 6.2.2 suggest clearly the opposite, in particular that the combined therapy is not as good as the sum of the single therapies.

7. Conclusion

7.1. Discussion

In this thesis I elucidated different combined therapy models. For this purpose I started to state models for tumor growth without any therapy, included first radiotherapy alone and then chemotherapy alone. To model chemotherapy I used two different approaches. The first was a cell population model and the second a cell cycle model which I got by combining two different preexisting cell cycle models. After each of these chapters I compared the models with collected data for a breast cancer cell line. Comparing the data with the generalized logistic growth model for tumor growth without treatment and with the radiation model yielded quite good fits. In the case of chemotherapy I forbore to compare the given data to the cell cycle model, since the drug vinblastine does not kill cells in a specific phase of the cell cycle. But comparing the data with the cell population model did not give satisfying results either. Thus I advanced the model by including a linear decreasing proliferation rate, since vinblastine inhibits cell proliferation. This addition improved the fitting very much, but also this model implied problems, like inhomogeneity and changing of parameters, which should not change. So I stated a new model, which includes the efficacy of the drug. This model yielded quite good fits.
The last chapter finally covered the combined therapy. Getting started I presented an already existing extension of the LQ-model. I also forbore to compare this model with the data, since no time course could be included. Next I developed a cell population model for the combined therapy by combining two cell population models from previous chapters. This model yielded quite good fits. Finally I covered a spatial model, whereby I included the chemotherapeutic treatment. Also this model was compared with the given data. It turned out that fitting this model to the data yielded a quite good fit, without the need for improvements of the model.
Altogether all final models were able to cope with the data. However the spatial model yielded results that were converse to the results of the cell population model. But there are many possible reasons for that. For example the number of cells for the cell population model was only estimated according to a previous cell counting experiment, and not measured directly. Moreover the area which was measured was maybe not an exact sphere and thus the approximation with the radius is not an exact translation.

7.2. Outlook

Since in the area measuring process only the fluorescing cells were considered, it would be possible that only a subpopulation was measured instead of all tumor cells. This could be also the reason, why the initially stated cell population model for chemotherapy was not able to cope with the data. Since vinblastine inhibits the proliferation of cells, a

simple two compartment model with proliferating and quiescent cells could be a solution:

$$\begin{aligned}
\frac{dP}{dt} &= \frac{r}{\alpha}P\left(1-\left(\frac{P+Q}{K}\right)^{\alpha}\right) - \nu cP - k_{PQ}P + k_{QP}Q \\
\frac{dQ}{dt} &= k_{PQ}P - k_{QP}Q \\
\frac{dc}{dt} &= C(t) - \lambda c - \gamma cN =: f(c) \\
P(0) &= P_0 \\
Q(0) &= Q_0 \\
c(0) &= c_0,
\end{aligned}$$

where P is the number of proliferating cells, Q is the number of quiescent cells, r is the proliferation rate, K the carrying capacity, α the parameter of the generalized logistic growth equation, ν is the dying rate of the proliferating cells due to the chemotherapeutic drug, k_{PQ} the rate proliferating cells become quiescent and k_{QP} the rate quiescent cells become proliferating. Such a two compartment model was already stated in [Web13] for radiotherapy and is similar to the cell-cycle specific model in this thesis. Here only the number of proliferating cells would be considered and compared with the data. But unfortunately considering this model and fitting it to the data would go beyond the constraints of this thesis. Figure 7.1 shows how the tumor growth including chemotherapy could look like.

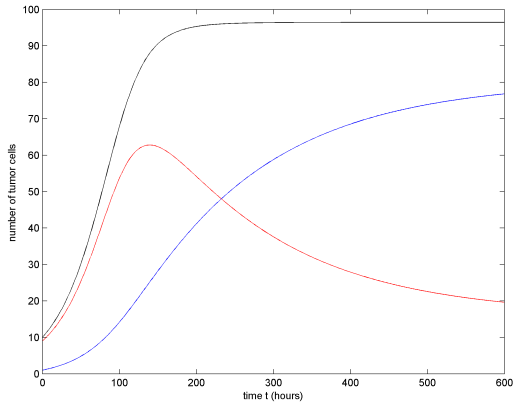


Figure 7.1: Proliferating and quiescent cell model. The red line represents the proliferating cells, the blue line the quiescent cells and the black line represents all cells together. Used parameters are $K = 100$ cells, $\alpha = 2$, $r = 0.0578\frac{1}{h}$, $\lambda = 0.002\frac{1}{h}$, $c_\infty = 0\frac{\mu M}{h}$, $c_0 = 0.1\mu M$, $\gamma = 0\frac{1}{cells \cdot h}$, $\nu = 0.02\frac{1}{\mu M h}$, $P_0 = 9$ cells, $Q_0 = 1$ cells, $k_{PQ} = 0.005\frac{cells}{h}$ and $k_{QP} = 0.001\frac{cells}{h}$. Parameters were plugged in the numerical solution of the above stated model.

Another attempt could be to postulate a new model for tumor growth including radiotherapy, similar to the model (5.60) which was established for tumor growth including

chemotherapy:

$$\begin{aligned}
\frac{dN}{dt} &= \frac{r}{\alpha} N \left(1 - \left(\frac{N}{K}\right)^{\alpha}\right) - \epsilon N \\
\frac{d\epsilon}{dt} &= dA\epsilon \left(1 - \frac{\epsilon}{E}\right) \\
N(0) &= N_0 \\
\epsilon(0) &= \epsilon_0.
\end{aligned}$$

This time ϵ represents the efficacy of the radiotherapy and the growth of this efficacy depends on the amount of radiation A.

A. List of Variables

Variables used in Section 3	
t	time
$N(t)$	number of tumor cells at time t
N_0	number of tumor cells at time $t = 0$
$r > 0$	net proliferation rate
$K > 0$	carrying capacity
$\alpha > 0$	control variable of the generalized logistic growth equation

Variables used in Section 4	
t	time
$N(t)$	number of tumor cells at time t
N_0	number of tumor cells at time $t = 0$
$r > 0$	net proliferation rate
$K > 0$	carrying capacity
$\alpha > 0$	control variable of the generalized logistic growth equation
$\mu > 0$	rate of damage of radiation
A	amount of radiation in Gy

Variables used in Section 5.1	
$c(t)$	drug concentration at time t
c_0	drug concentration at time $t = 0$
k_{12}	microconstant, defining distribution from compartment 1 to compartment 2
k_{21}	microconstant, defining distribution from compartment 2 to compartment 1
k_{10}	microconstant, defining distribution from compartment 1 outbound
α	slope
β	slope
A	to α corresponding intercept
B	to β corresponding intercept
$T_{1/2}$	half life
V_c	Volume of the central compartment
V_p	Volume of the peripheral compartment
V_t	total Volume
D	administered dosage
V_d	Volume of distribution
AUC	area under the curve
CL	plasma clearance

Variables used in Section 5.2	
C	molar concentration of the drug
R	molar concentration unoccupied receptors
RC	molar concentration of the drug's receptor complex
k_{on}	rate constant for the forward process
k_{off}	rate constant for the backward process
R_T	total molar concentration of receptors
K_d	drug's dissociation constant
E	response
E_{max}	maximum possible response
α	intrinsic activity
S	value of stimulus
e	efficacy
χ	intrinsic efficacy

Variables used in Section 5.3	
t	time
$N(t)$	number of tumor cells at time t
N_0	number of tumor cells at time $t = 0$
$c(t)$	concentration of chemotherapeutic drug at time t
c_0	concentration of chemotherapeutic drug at time $t = 0$
$r > 0$	net proliferation rate
$K > 0$	carrying capacity
$\nu > 0$	drug induced death rate
κ	constant rate of drug supply, release or activation
D	constant diffusion coefficient
u	velocity of the interstitial fluid
α	decay or deactivation rate constant
β	rate constant of drug uptake by the cell
$\lambda > 0$	drugs half-life (or decay rate)
$\gamma > 0$	rate at which the drug becomes ineffective as a result of cell kill
$C(t)$	rate at which the drug is delivered to the tumor
c_∞	constant drug-delivering-rate

Variables used in Section 5.4	
t	time
$N(t)$	number of tumor cells at time t
τ	duration of one chemotherapy session
n	treatment session
$r > 0$	net proliferation rate

$\mu_i^j > 0$	killing fraction of drug i in compartment j
$\eta_i^j > 0$	survival fraction of drug i in compartment j
m	number of injections
$\gamma > 0$	proliferating rate
$\nu > 0$	dying rate
$\kappa > 0$	transition rate
M	growth matrix
T	treatment matrix
d	drug dose
$g(t)$	piecewise continuous function which describes how the treatment impacts the tumor cells at time t
h	cell kill parameter
δ	decay of the drug

Variables used in Section 5.5	
t	time
$N(t)$	number of tumor cells at time t
N_0	number of tumor cells at time $t = 0$
$c(t)$	concentration of chemotherapeutic drug at time t
c_0	concentration of chemotherapeutic drug at time $t = 0$
$r > 0$	net proliferation rate
$K > 0$	carrying capacity
$\nu > 0$	drug induced death rate
$\lambda > 0$	drugs half-life (or decay rate)
$\gamma > 0$	rate at which the drug becomes ineffective as a result of cell kill
$C(t)$	rate at which the drug is delivered to the tumor
c_∞	constant drug-delivering-rate
r_0	proliferation rate at time $t = 0h$
r^*	proliferation rate at time $t = 300h$
p	positive constant of Hill-function
Q	positive constant of Hill-function
$\epsilon(t)$	efficacy of the drug at time t
ϵ_0	efficacy of the drug at time $t = 0$
d	parameter of the growth rate of the efficacy
E	maximal efficacy

Variables used in Section 6.1	
Y	yield of lethal lesions.
$\alpha > 0$	single-hit double-strand breaks
$\beta > 0$	combination of two sub-lethal single-strand breaks which form a double-strand break

D	total radiation dose in Gy
n	number of radiation fractions
d	radiation fraction in Gy
S	survival fraction
S_0	initial number of cells
S^*	number of cells left after radiation
s	value of change of a radiation dose d by giving it with a chemotherapeutic drug
λ	expected value of the Poisson distribution
BED	Biological Effective Dose
TCP	Tumor Control Probability
m_1	number of sensitized fractions
m_2	number of non-sensitized fractions

Variables used in Section 6.2	
t	time
$N(t)$	number of tumor cells at time t
N_0	number of tumor cells at time $t = 0$
$r > 0$	net proliferation rate
$K > 0$	carrying capacity
$\alpha > 0$	control variable of the generalized logistic growth equation
$\nu > 0$	drug induced death rate
$\mu > 0$	rate of damage of radiation
A	amount of radiation in Gy
$\epsilon(t)$	efficacy of the drug at time t
ϵ_0	efficacy of the drug at time $t = 0$
d	parameter of the growth rate of the efficacy
c_0	concentration of chemotherapeutic drug at time $t = 0$
E	maximal efficacy

Variables used in Section 6.3	
t	time
r	radius
$R(t)$	outer tumor radius at time t
$R_H(t)$	quiescent radius at time t
$R_N(t)$	necrotic tumor radius at time t
$g(r,t)$	nutrient concentration at time t and radius r
g_H	concentration where the cells start to proliferate
g_N	maximal nutrient concentration at which necrosis occurs
h	substrate concentration
D	diffusion coefficient

ρ	rate of increase or decrease
D_g	diffusion coefficient of the nutrients
$\Gamma_\star$	consumption rate of nutrients
$\lambda_A > 0$	rate of apoptosis
$\lambda_N > 0$	rate of necrosis
$s > 0$	constant
$\gamma > 0$	proliferation rate
$\nu > 0$	drug induced death rate
$c(r,t)$	concentration of chemotherapeutic drug at time t and radius r
$\mu > 0$	rate of damage of radiation
A	amount of radiation in Gy
Γ_1	consumption rate of nutrients by proliferating cells
Γ_2	consumption rate of nutrients by quiescent cells
g_∞	external nutrient concentration
$g_0(r)$	initial nutrient concentration at radius r
$c_\infty(t)$	external drug concentration at time t
$c_0(r)$	initial drug concentration at radius r
R_0	outer radius at time $t = 0$

B. MatLab Codes

Used for figure 3.1 on page 13.

```
t=0:0.001:300;                          %time
l=length(t);
r=0.0289;                               %proliferating rate
N0=10;                                  %initial number of cells
K=100;                                  %carrying capacity
alpha1=0.5;
alpha2=2;                               %general logistic equation parameters

%number of cells (exponetial grwoth equation)
N1=N0*exp(r*t);
%number of cells (logistic grwoth equation)
N2=N0*K*ones(1,l)./(N0*ones(1,l)+exp(-r*t)*(K-N0));
%number of cells (generalized logistic grwoth equation)
N3=N0*K*ones(1,l)./(N0^alpha1*ones(1,l)+ ...
    exp(-r*t)*(K^alpha1-N0^alpha1)).^(1/alpha1);
%number of cells (generalized logistic grwoth equation)
N4=N0*K*ones(1,l)./(N0^alpha2*ones(1,l)+ ...
    exp(-r*t)*(K^alpha2-N0^alpha2)).^(1/alpha2);

%figure compiling
f=figure;
plot(t,N1,'k',t,N2,'b',t,N3,'g',t,N4,'r');
xlabel('time t')
ylabel('number of tumor cells N')
set(gca,'YLim',[0 120])
```

Used for figure 3.2 on page 14.

```
%parameter setting
K=0.069;
N0=0.001;
r=0.000013;
alpha=0.325;
x=0:1:300000;  %area

%number of cells per square micrometer
nocells=K*N0./(N0^alpha+(K^alpha-N0^alpha)*exp(-r*x)).^(1/alpha);

%figure compiling
f=figure;
plot(x,nocells,'k')
xlabel('Area (\mum^2)')
ylabel('Cell Number per \mum^2')
grid on
```

Algorithm 1: Used to find the parameters α and K in section 3.2 on page 14.

```
%parameter setting
N0=596.2603 ;
r=log(2)/60;
alphas=0:0.001:1;
Ks=1000:10:100000;
t=0:72:288;

error=inf;
alpha=-1;
K=-1;

%given data points
data=[596.2603,2424.5,6986.6,9581.6,10659];

%finding of best alpha and K with the aid of the analytical solution of the
%generalized logistic grwoth equation
for i=1:length(alphas)
    for j=1:length(Ks)
        model=Ks(j)*N0./(N0^alphas(i)+(Ks(j)^alphas(i)...
            -N0^alphas(i))*exp(-r*t)).^(1/alphas(i));
        e=sum(((data-model)./model).^2);
        if e< error
            error=e;
            alpha=alphas(i);
            K=Ks(j);
        end
    end
end
```

Used for figure 3.3 on page 16.

```
%parameter setting
N0=596.2603 ;
r=log(2)/60;
alpha=0.2030;
K=13380;

%data points
t1=0:72:288;
data=[596.2603,2424.5,6986.6,9581.6,10659];

%curve given by the analytical solution of the logistic growth equation;
%alpha and K are given according to algorithm 1
t2=0:0.1:300;
curve=K*N0./(N0^alpha+(K^alpha-N0^alpha)*exp(-r*t2)).^(1/alpha);

%figure compiling
```

```
f=figure;
plot(t1,data,'*k')
hold on
plot(t2,curve,'b')
xlabel('time t (hours)')
ylabel('number of tumor cells N')
```

Used for figure 4.1 on page 18.

```
%parameter setting
N0=10;
K=100;
alpha=2;
r=log(2)/12;
t=0:1:300;
mu=0.3;         %damaging rate per Gy
A1=0.05;        %radiation dosages
A2=0.25;

%number of cells without treatment
N=K*N0./(((N0^alpha)+(K^alpha-N0^alpha)*exp(-r*t)).^(1/alpha));
%number of cells, treated with different dosages of radiation
N1=K*N0./(((N0^alpha*r)/(r-alpha*mu*A1)+(K^alpha-(N0^alpha*r)/...
    (r-alpha*mu*A1))*exp(-r*t+alpha*mu*A1*t)).^(1/alpha));
N2=K*N0./(((N0^alpha*r)/(r-alpha*mu*A2)+(K^alpha-(N0^alpha*r)/...
    (r-alpha*mu*A2))*exp(-r*2+alpha*mu*A2*t)).^(1/alpha));

%figure compiling
f=figure;
plot(t,N,'k')
hold on
plot(t,N1,'b')
plot(t,N2,'r')
xlabel('time t (hours)')
ylabel('number of tumor cells')
```

Algorithm 2: Used to find the parameter μ in section 4.2 on page 18 and for figure 4.2 on page 20.

```
%parameter setting
N0=596.3;
alpha=0.2030;
r=log(2)/60;
t1=0:1/60:300;
mus=0:0.0001:0.02;
K=13380;
A=2:2:8;

```

```
%data points
t=0:72:288;
data=[596.3,2048.9,4636.0,5681.7,7167.2;
    596.3,1801.4,3063.3,3950.6,4194.8;
    596.3,2145.8,3130.3,2819.0,4072.0;
    596.3,1968.3,2319.7,1939.2,2944.5];

model=zeros(length(A),length(t1));
curve=zeros(length(A),length(t1));  %final curve
test=zeros(size(data));
error=inf*ones(4,1);
e=zeros(4,1);
mu=zeros(4,1);                      %final values for mu

%finding the best value for mu with the aid of the analytical
%solutions for tumor growth including radiation
for i=1:length(mus)
    for j=1:length(A)
        %interval, where radiation is administered
        model(j,:)=K*N0./(((N0^alpha*r)/(r-alpha...
            *mus(i)*A(j))+(K^alpha-(N0^alpha*r)/(r-alpha*mus(i)*A(j)))...
            *exp(-r*t1+alpha*mus(i)*A(j)*t1)).^(1/alpha));
        test=model(j,[1,72*60+1,144*60+1,216*60+1,288*60+1]);
        e=sum(((data(j,:)-test)./test).^2);
        if e < error(j)
            error(j)= e;
            mu(j)= mus(i);
            curve(j,:)=model(j,:);
        end
    end
end

%compiling figure
f=figure;
subplot(2,2,1)
plot(t,data(1,:),'*k')
hold on
plot(t1,curve(1,:),'b')
xlabel('time t (hours)')
ylabel('number of tumor cells')
title('A=2')
subplot(2,2,2)
plot(t,data(2,:),'*k')
hold on
plot(t1,curve(2,:),'b')
xlabel('time t (hours)')
ylabel('number of tumor cells')
title('A=4')
subplot(2,2,3)
plot(t,data(3,:),'*k')
```

```
hold on
plot(t1,curve(3,:),'b')
xlabel('time t (hours)')
ylabel('number of tumor cells')
title('A=6')
subplot(2,2,4)
plot(t,data(4,:),'*k')
hold on
plot(t1,curve(4,:),'b')
xlabel('time t (hours)')
ylabel('number of tumor cells')
title('A=8')
```

Used for figure 5.2 on page 22.

```
%parameter setting
alpha=1;
beta=2;
A=3;
B=4;
t=0:0.001:3;
c=A*exp(- alpha*t)+B*exp(-beta*t);      %biexponential fuction
d=(A+B-0.4)+(-alpha*A-beta*B)*t;        %slope
e=A*exp(- alpha*3)+B*exp(-beta*3)+(-alpha*A*exp(- alpha*3)-beta*...
    B*exp(-beta*3))*(t-3);               %slope
g=e(1);

%figure compiling
f=figure;
    plot(t,c,'k',t,d,'k--',t,e,'k--');
    xlabel('time t')
    ylabel('concentration c(t)')
    set(gca,'YLim',[0 7.5])
    set(gca,'YTick',7)
    set(gca,'YTickLabel','c_0')
    set(gca,'XLim',[0 3])
    set(gca,'XTick',3)
    set(gca,'XTickLabel','')
    text(-0.1, 6.6, 'A', 'HorizontalAlignment', 'center')
    text(-0.1, g, 'B', 'HorizontalAlignment', 'center')
    text(0.3, 2, '\alpha', 'HorizontalAlignment', 'center')
    text(1, 0.9, '\beta', 'HorizontalAlignment', 'center')
```

Used for figure 5.4 on page 25.

```
x=0:0.001:20;                           %drug concentration scale
y=x./(ones(1,length(x))+x);             %RC/R_T
x2=0:0.1:1;                             %horizontal line
```

```
y2=0.5*ones(1,length(x2));
x3=0:0.1:10;                                    %horizontal line
y3=(10/11+0.01)*ones(1,length(x3));
y4=0:0.1:0.5;                                   %vertical line
x4=ones(1,length(y4));

%compiling figure
f=figure;
plot(x,y,'k');
hold on
plot(x2,y2,':k');
plot(x3,y3,':k');
plot(x4,y4,':k');
xlabel('Drug Concentration')
ylabel('RC/R_T')
set(gca,'YLim',[0 1])
set(gca,'YTick',[0 0.5 10/11+0.01])
set(gca,'YTickLabel',[0 0.5 1])
set(gca,'XLim',[0 10])
set(gca,'XTick',1)
set(gca,'XTickLabel','K_d')
```

Used for figure 5.5 on page 30 and for figure 5.6 on page 32.

```
%parameter setting
K=1;              %carrying capacity
lambda=1;         %drugs half life
nu=1;             %rate at which the tumor cells are killed by the drug
r=1;              %net proliferating rate
gamma1=0.5;       %rates at which the drug becomes ineffective as a result
gamma2=2;         %of cell kill
%bifurcation points
cmax1=lambda*r/nu*(lambda/(4*K*gamma1)*(1-gamma1*K/lambda)^2+1);
cmax2=lambda*r/nu*(lambda/(4*K*gamma2)*(1-gamma2*K/lambda)^2+1);
cinfinity1=0:0.001:cmax1;  %administered amount of drug
cinfinity2=0:0.001:cmax2;
l1=length(cinfinity1);
l2=length(cinfinity2);
K1=1*ones(1,l1);       %carrying capacity
K2=1*ones(1,l2);
lambda1=1*ones(1,l1); %drugs half life
lambda2=1*ones(1,l2);
nu1=1*ones(1,l1);      %rate at which the tumor cells are killed by the drug
nu2=1*ones(1,l2);
r1=1*ones(1,l1);       %net proliferating rate
r2=1*ones(1,l2);
gamma1=0.5*ones(1,l1);%rates at which the drug becomes ineffective as a
gamma2=2*ones(1,l2);  %result of cell kill
o1=ones(1,l1);
o2=ones(1,l2);
```

```
27
28 %number of cells
29 N11=0.5*(- lambda1./gamma1.*(o1-gamma1.*K1./lambda1) + ...
30     (lambda1.^2./gamma1.^2.*(o1-gamma1.*K1./lambda1).^2 - ...
31     4*lambda1.*K1./gamma1.*(cinfinity1.*nu1./(lambda1.*r1)-1)).^(1/2));
32 N12=0.5*(- lambda1./gamma1.*(o1-gamma1.*K1./lambda1) - ...
33     (lambda1.^2./gamma1.^2.*(o1-gamma1.*K1./lambda1).^2 - ...
34     4*lambda1.*K1./gamma1.*(cinfinity1.*nu1./(lambda1.*r1)-1)).^(1/2));
35 N21=0.5*(- lambda2./gamma2.*(o2-gamma2.*K2./lambda2) + ...
36     (lambda2.^2./gamma2.^2.*(o2-gamma2.*K2./lambda2).^2 - ...
37     4*lambda1.*K2./gamma2.*(cinfinity2.*nu2./(lambda2.*r2)-1)).^(1/2));
38 N22=0.5*(- lambda2./gamma2.*(o2-gamma2.*K2./lambda2) - ...
39     (lambda2.^2./gamma2.^2.*(o2-gamma2.*K2./lambda2).^2 - ...
40     4*lambda1.*K2./gamma2.*(cinfinity2.*nu2./(lambda2.*r2)-1)).^(1/2));
41
42 %compiling first figure
43 f1=figure;
44 subplot(2,1,1)
45 plot(cinfinity1, N11,'b', cinfinity1, N12,'b');
46     xlabel('drug dosage c_{\infty}')
47     ylabel('tumor size N')
48     set(gca,'YLim',[0 1])
49     set(gca,'XLim',[0 1.4])
50
51 subplot(2,1,2)
52 plot(cinfinity2, N21,'b', cinfinity2, N22,'b');
53     xlabel('drug dosage c_{\infty}')
54     ylabel('tumor size N')
55     set(gca,'YLim',[0 1])
56     set(gca,'XLim',[0 1.4])
57
58 %compiling second figure (with stability analysis)
59 f2=figure;
60 subplot(2,1,1)
61 plot(cinfinity1, N11,'b', cinfinity1, N12,'b');
62     xlabel('drug dosage c_{\infty}')
63     ylabel('tumor size N')
64     set(gca,'YLim',[0 1])
65     set(gca,'XLim',[0 1.4])
66
67 subplot(2,1,2)
68 plot(cinfinity2, N21,'b', cinfinity2, N22,':b');
69     xlabel('drug dosage c_{\infty}')
70     ylabel('tumor size N')
71     set(gca,'YLim',[0 1])
72     set(gca,'XLim',[0 1.4])
```

Used for figure 5.9 on page 38.

```
%parameter setting
h=1;                              % cell kill parameter
delta_1=5;                        % decay of the drug
delta_2=2.5;
tau=1;                            % time step
t_1=0:0.001:1.1;                  % time t
t_2=0:0.001:4;
n = floor(t_2);

g_1=h*exp(-delta_1*(t_1));        % exponential decay function
g_2=h*exp(-delta_2*(t_1));
g_3=h*exp(-delta_1*(t_2-n*tau));

%compiling figure
f=figure;
subplot(2,1,1)
a_1=plot(t_1,g_1,t_1,g_2,'r');
legend('\delta_1','\delta_2=\delta_1/2');
axis equal;
xlabel('time t')
ylabel('g=he^{-\gamma(t-n\tau)} ')
set(gca,'YLim',[0 1])
set(gca,'YTick',1)
set(gca,'YTickLabel','h')
set(gca,'XLim',[0 1.1])
set(gca,'XTick',1)
set(gca,'XTickLabel','')
text(0.01, -0.05, 'n\tau', 'HorizontalAlignment', 'center')
text(0.99, -0.05, '(n+1)\tau', 'HorizontalAlignment', 'center')

subplot(2,1,2)
plot(t_2,g_3);
axis equal
xlabel('time t')
ylabel('g=he^{-\gamma(t-n\tau)} ')
set(gca,'YLim',[0 1])
set(gca,'YTick',1)
set(gca,'YTickLabel','h')
set(gca,'XLim',[0 4])
set(gca,'XTick',1)
set(gca,'XTickLabel','')
text(0.01, -0.05, '(n-2)\tau', 'HorizontalAlignment', 'center')
text(1, -0.05, '(n-1)\tau', 'HorizontalAlignment', 'center')
text(2, -0.05, 'n\tau', 'HorizontalAlignment', 'center')
text(3, -0.05, '(n+1)\tau', 'HorizontalAlignment', 'center')
text(3.99, -0.05, '(n+2)\tau', 'HorizontalAlignment', 'center')
```

Algorithm 3: Used to find the parameters ν and K in section 5.5 on page 38, for figure 5.10 on page 39 and for figure 5.11 on page 40.

```
%data points
data=[596.3,1479.5,2303.3,2134.1,3480.3;
    596.3,959.1,1639.7,1624.0,1212.8];
tdata=0:72:288;
%parameter setting
N0=596.3;
cinf=0;                                 %drug infusion
alpha=1;                                %or alpha=0.203;
r=log(2)/60;
c0=[0.3,10];                            %initial drug concentration
lambda=0;
gamma=0.00002;
Ks=0:10:5000;
nus=0:0.0001:0.0015;
s=1;                                    %stepsize for forward euler method
t=0:s:301;
t1=0:s:144;
t2=145:s:301;
NC=zeros(length(c0),length(t),2);
NC(:,1,1)=N0*ones(1,length(c0));
NC(:,1,2)=c0;
error=inf*ones(length(c0),1);
e=zeros(length(c0),1);
nu=zeros(length(c0),1);                  %best fitting nu
K=zeros(length(c0),1);                   %best fitting K
curvecell=zeros(length(c0),length(t));
curvedrug=zeros(length(c0),length(t));

%varying K and nu to find the best fit with the aid of the euler method
%NC(.,.,1)=number of tumor cells
%NC(.,.,2)=drug concentration
for m=1:length(Ks)
    for i=1:length(nus)
        for h=1:length(c0)
            for l=1:length(t1)-1
                %intervall, where drug is administered
                NC(h,l+1,1)=NC(h,l,1)+s*(r/alpha*NC(h,l,1)*(1-(NC(h,l,1)...
                    /Ks(m))^alpha)-nus(i)*NC(h,l,2)*NC(h,l,1));
                NC(h,l+1,2)=NC(h,l,2)+s*(cinf-lambda*NC(h,l,2)...
                    -gamma*NC(h,l,2)*NC(h,l,1));
                if NC(h,l+1,2)<0
                    NC(h,l+1,2)=0;
                end
                if NC(h,l+1,1)<0
                    NC(h,l+1,1)=0;
                end
            end
            for l=length(t1):length(t)-1
                %intervall, where the drug is washed away
                NC(h,l+1,1)=NC(h,l,1)+s*(r/alpha*NC(h,l,1)*(1-(NC(h,l,1)...
```

```
51                      /Ks(m))^alpha)-nus(i)*NC(h,l,2)*NC(h,l,1));
52                  NC(h,l+1,2)=0;
53                  if NC(h,l+1,1)<0
54                      NC(h,l+1,1)=0;
55                  end
56              end
57              model=NC(h,[1,73,145,217,289],1);
58              e=sum(((data(h,:)-model)./model).^2);
59              if e < error(h)
60                  nu(h)=nus(i);
61                  K(h)=Ks(m);
62                  curvecell(h,:)=NC(h,:,1);
63                  curvedrug(h,:)=NC(h,:,2);
64                  error(h)=e;
65              end
66          end
67      end
68  end
69
70  %figure compiling
71  f=figure;
72  subplot(2,2,1)
73  plot(tdata,data(1,:),'*k')
74  hold on
75  plot(t,curvecell(1,:),'b')
76  xlabel('time t (hours)')
77  ylabel('number of tumor cells')
78  title('c_0=0.3 \muM')
79  xlim([0 300])
80  subplot(2,2,2)
81  plot(tdata,data(2,:),'*k')
82  hold on
83  plot(t,curvecell(2,:),'b')
84  xlabel('time t (hours)')
85  ylabel('number of tumor cells')
86  title('c_0=10 \muM')
87  xlim([0 300])
88
89  %only for alpha=1; stays the same for alpha=0.203
90  subplot(2,2,3)
91  plot(t,curvedrug(1,:),'g')
92  xlabel('time t (hours)')
93  ylabel('drug concentration')
94  xlim([0 300])
95  subplot(2,2,4)
96  plot(t,curvedrug(2,:),'g')
97  xlabel('time t (hours)')
98  ylabel('drug concentration')
99  xlim([0 300])
```

Algorithm 4: Used to find the parameters ν, K, p and Q in section 5.5 on page 38 and

for figure 5.12 on page 42.

```
%data points
data=[596.3,1479.5,2303.3,2134.1,3480.3;
    596.3 , 1337.8 , 2694.8, 2730.1, 2984.1;
    596.3 , 1260.3 ,2427.1, 2538.9, 1959.4;
    596.3,959.1,1639.7,1624.0,1212.8;
    596.3,924.3,1827.5,1657.2,1405.2];
tdata=0:72:288;

%parameter setting
N0=596.3;
cinf=0;
alpha=0.203;
r=log(2)/60;
lambda=0;
gamma=0.00002;
c0=[0.3,1,3,10,30];
nus=0.00001:0.00001:0.0001;
Ks=1000:100:4000;
p=1:3;                                  %positive parameter from Hill-equation
Q=0:0.01:0.15;                          %positive parameter from Hill-equation

s=1;                                    %time step for euler method
t=0:s:301;                              %time scales
t1=0:s:144;
t2=145:s:301;

NC=zeros(length(c0),length(t),2);
NC(:,1,1)=N0*ones(1,length(c0));
NC(:,1,2)=c0;
error=inf*ones(length(c0),1);
e=zeros(length(c0),1);
nu=zeros(length(c0),1);                 %best fitting nu
K=zeros(length(c0),1);                  %best fitting K
pfinal=zeros(length(c0),1);             %best fitting p
Qfinal=zeros(length(c0),1);             %best fitting Q
curvecell=zeros(length(c0),length(t));
curvedrug=zeros(length(c0),length(t));

%varying K, nu, Q and p to find the best fit with the aid of the euler
%method
for n=1:length(Q)
    for j=1:length(p)
        for m=1:length(Ks)
            for i=1:length(nus)
                for h=1:length(c0)
                    for l=1:length(t1)-1
                        NC(h,l+1,1)=NC(h,l,1)+s*(r/alpha*NC(h,l,1)*...
                            (1-(NC(h,l,1)/Ks(m))^alpha)-nus(i)*NC(h,l,2)...
```

```
                                    ^p(j)/(Q(n)+NC(h,l,2)^p(j))*NC(h,l,1));
                                NC(h,l+1,2)=NC(h,l,2)+s*(cinf-lambda*NC(h,l,2) -...
                                    gamma*NC(h,l,2)*NC(h,l,1));
                                if NC(h,l+1,2)<0
                                    NC(h,l+1,2)=0;
                                end
                                if NC(h,l+1,1)<0
                                    NC(h,l+1,1)=0;
                                end
                            end
                            for l=length(t1):length(t)-1
                                NC(h,l+1,1)=NC(h,l,1)+s*(r/alpha*NC(h,l,1)*...
                                    (1-(NC(h,l,1)/Ks(m))^alpha)-nus(i)*NC(h,l,2)...
                                    ^p(j)/(Q(n)+NC(h,l,2)^p(j))*NC(h,l,1));
                                NC(h,l+1,2)=0;
                                if NC(h,l+1,1)<0
                                    NC(h,l+1,1)=0;
                                end
                            end
                            model=NC(h,[1,73,145,217,289],1);
                            e=sum(((data(h,:)-model)./model).^2);
                            if e < error(h)
                                nu(h)=nus(i);
                                K(h)=Ks(m);
                                pfinal(h)=p(j);
                                Qfinal(h)=Q(n);
                                curvecell(h,:)=NC(h,:,1);
                                curvedrug(h,:)=NC(h,:,2);
                                error(h)=e;
                            end
                        end
                    end
                end
            end
        end
    end
end

%number of cells without treatment for comparison
K=13380;
curve=K*N0./(N0^alpha+(K^alpha-N0^alpha)*exp(-r*t)).^(1/alpha);

%figure compiling
f=figure;
subplot(3,2,1)
plot(t,curve,'b')
xlabel('time t (hours)')
ylabel('number of tumor cells')
title('c_0=0 \muM')
xlim([0 300])
subplot(3,2,2)
plot(tdata,data(1,:),'*k')
```

```
hold on
plot(t,curvecell(1,:),'b')
xlabel('time t (hours)')
ylabel('number of tumor cells')
title('c_0=0.3 \muM')
xlim([0 300])
subplot(3,2,3)
plot(tdata,data(2,:),'*k')
hold on
plot(t,curvecell(2,:),'b')
xlabel('time t (hours)')
ylabel('number of tumor cells')
title('c_0=1 \muM')
xlim([0 300])
subplot(3,2,4)
plot(tdata,data(3,:),'*k')
hold on
plot(t,curvecell(3,:),'b')
xlabel('time t (hours)')
ylabel('number of tumor cells')
title('c_0=3 \muM')
xlim([0 300])
subplot(3,2,5)
plot(tdata,data(4,:),'*k')
hold on
plot(t,curvecell(4,:),'b')
xlabel('time t (hours)')
ylabel('number of tumor cells')
title('c_0=10 \muM')
xlim([0 300])
subplot(3,2,6)
plot(tdata,data(5,:),'*k')
hold on
plot(t,curvecell(5,:),'b')
xlabel('time t (hours)')
ylabel('number of tumor cells')
title('c_0=30 \muM')
xlim([0 300])
```

Algorithm 5: Used to find the parameters ν, K and r^* in section 5.5 on page 38 and for figure 5.13 on page 43.

```
%data points
data=[596.3,1479.5,2303.3,2134.1,3480.3;
    596.3 , 1337.8 , 2694.8, 2730.1, 2984.1;
    596.3 , 1260.3 ,2427.1, 2538.9, 1959.4;
    596.3,959.1,1639.7,1624.0,1212.8;
    596.3,924.3,1827.5,1657.2,1405.2];
tdata=0:72:288;
```

```
%parameter setting
N0=596.3;
cinf=0;
alpha=0.203;
r=log(2)/60;
c0=[0.3,1,3,10,30];
lambda=0;
gamma=0.00002;
Ks=0:100:14000;
nus=0:0.0005:0.012;
rs=-0.01:0.001:0.01;                    %net proliferation rate at time t=301

s=1;
t=0:s:301;
t1=0:s:144;
t2=145:s:301;
NC=zeros(length(c0),length(t),2);
NC(:,1,1)=N0*ones(1,length(c0));
NC(:,1,2)=c0;

error=inf*ones(length(c0),1);
e=zeros(length(c0),1);
nu=zeros(length(c0),1);
K=zeros(length(c0),1);
rfinal=zeros(length(c0),1);
curvecell=zeros(length(c0),length(t));
curvedrug=zeros(length(c0),length(t));

%varying K and nu and r* to find the best fit with the aid of the euler
%method
for j=1:length(rs)
    rate=r+(rs(j)-r)/301*t;
    for m=1:length(Ks)
        for i=1:length(nus)
            for h=1:length(c0)
                for l=1:length(t1)-1
                    NC(h,l+1,1)=NC(h,l,1)+s*(rate(l)/alpha*NC(h,l,1)*...
                        (1-(NC(h,l,1)/Ks(m))^alpha)-nus(i)*NC(h,l,2)*...
                        NC(h,l,1));
                    NC(h,l+1,2)=NC(h,l,2)+s*(cinf-lambda*NC(h,l,2)-...
                        gamma*NC(h,l,2)*NC(h,l,1));
                    if NC(h,l+1,2)<0
                        NC(h,l+1,2)=0;
                    end
                    if NC(h,l+1,1)<0
                        NC(h,l+1,1)=0;
                    end
                end
                for l=length(t1):length(t)-1
                    NC(h,l+1,1)=NC(h,l,1)+s*(rate(l)/alpha*NC(h,l,1)*...
```

```
                        (1-(NC(h,l,1)/Ks(m))^alpha)-nus(i)*NC(h,l,2)*...
                        NC(h,l,1));
                    NC(h,l+1,2)=0;
                    if NC(h,l+1,1)<0
                        NC(h,l+1,1)=0;
                    end
                end
                model=NC(h,[1,73,145,217,289],1);
                e=sum(((data(h,:)-model)./model).^2);
                if e < error(h)
                    nu(h)=nus(i);
                    K(h)=Ks(m);
                    rfinal(h)=rs(j);
                    curvecell(h,:)=NC(h,:,1);
                    curvedrug(h,:)=NC(h,:,2);
                    error(h)=e;
                end
            end
        end
    end
end

%number of cells without treatment
K=13380;
curve=K*N0./(N0^alpha+(K^alpha-N0^alpha)*exp(-r*t)).^(1/alpha);

%compiling figure
f=figure;
subplot(3,2,1)
plot(t,curve,'b')
xlabel('time t (hours)')
ylabel('number of tumor cells')
title('c_0=0 \muM')
xlim([0 300])
subplot(3,2,2)
plot(tdata,data(1,:),'*k')
hold on
plot(t,curvecell(1,:),'b')
xlabel('time t (hours)')
ylabel('number of tumor cells')
title('c_0=0.3 \muM')
xlim([0 300])
subplot(3,2,3)
plot(tdata,data(2,:),'*k')
hold on
plot(t,curvecell(2,:),'b')
xlabel('time t (hours)')
ylabel('number of tumor cells')
title('c_0=1 \muM')
xlim([0 300])
```

```
subplot(3,2,4)
plot(tdata,data(3,:),'*k')
hold on
plot(t,curvecell(3,:),'b')
xlabel('time t (hours)')
ylabel('number of tumor cells')
title('c_0=3 \muM')
xlim([0 300])
subplot(3,2,5)
plot(tdata,data(4,:),'*k')
hold on
plot(t,curvecell(4,:),'b')
xlabel('time t (hours)')
ylabel('number of tumor cells')
title('c_0=10 \muM')
xlim([0 300])
subplot(3,2,6)
plot(tdata,data(5,:),'*k')
hold on
plot(t,curvecell(5,:),'b')
xlabel('time t (hours)')
ylabel('number of tumor cells')
title('c_0=30 \muM')
xlim([0 300])
```

Algorithm 6: Used to find the parameters ν and Q in section 5.5 on page 38 and for figure 5.14 on page 45.

```
%data points
data=[596.3,1479.5,2303.3,2134.1,3480.3;
    596.3 , 1337.8 , 2694.8, 2730.1, 2984.1;
    596.3 , 1260.3 ,2427.1, 2538.9, 1959.4;
    596.3,959.1,1639.7,1624.0,1212.8;
    596.3,924.3,1827.5,1657.2,1405.2];
tdata=0:72:288;

%parameter setting
N0=596.3;
alpha=0.203;
r=log(2)/60;
c0=[0.3,1,3,10,30];
K=13380;
Q=1:300;                              %positive parameter from Hill-equation
nu=0:0.001:0.1;
s=1;
t=0:s:301;
t1=0:s:144;
t2=145:s:301;
NC=zeros(length(c0),length(t),2);
```

```
NC(:,1,1)=N0*ones(1,length(c0));

error=inf*ones(length(c0),1);
e=zeros(length(c0),1);
Qfinal=zeros(length(c0),1);
nufinal=zeros(length(c0),1);
curvecell=zeros(length(c0),length(t));
curvedrug=zeros(length(c0),length(t));

%varying Q and nu and to find the best fit with the aid of the euler
%method
for k=1:length(nu)
    for i=1:length(Q)
        for h=1:length(c0)
            NC(h,:,2)=nu(k)*c0(h)*t./(Q(i)+c0(h)*t);
            for l=1:length(t)-1
                NC(h,l+1,1)=NC(h,l,1)+s*(r/alpha*NC(h,l,1)*...
                    (1-(NC(h,l,1)/K)^alpha)-NC(h,l,2)*NC(h,l,1));
                if NC(h,l+1,2)<0
                    NC(h,l+1,2)=0;
                end
                if NC(h,l+1,1)<0
                    NC(h,l+1,1)=0;
                end
            end
            model=NC(h,[1,73,145,217,289],1);
            e=sum(((data(h,:)-model)./model).^2);
            if e < error(h)
                nufinal(h)=nu(k);
                Qfinal(h)=Q(i);
                curvecell(h,:)=NC(h,:,1);
                curvedrug(h,:)=NC(h,:,2);
                error(h)=e;
            end
        end
    end
end

%number of cells without treatment
K=13380;
curve=K*N0./(N0^alpha+(K^alpha-N0^alpha)*exp(-r*t)).^(1/alpha);

%compiling figure
f=figure;
subplot(3,2,1)
plot(t,curve,'b')
xlabel('time t (hours)')
ylabel('number of tumor cells')
title('c_0=0 \muM')
xlim([0 300])
```

```
subplot(3,2,2)
plot(tdata,data(1,:),'*k')
hold on
plot(t,curvecell(1,:),'b')
xlabel('time t (hours)')
ylabel('number of tumor cells')
title('c_0=0.3 \muM')
xlim([0 300])
subplot(3,2,3)
plot(tdata,data(2,:),'*k')
hold on
plot(t,curvecell(2,:),'b')
xlabel('time t (hours)')
ylabel('number of tumor cells')
title('c_0=1 \muM')
xlim([0 300])
subplot(3,2,4)
plot(tdata,data(3,:),'*k')
hold on
plot(t,curvecell(3,:),'b')
xlabel('time t (hours)')
ylabel('number of tumor cells')
title('c_0=3 \muM')
xlim([0 300])
subplot(3,2,5)
plot(tdata,data(4,:),'*k')
hold on
plot(t,curvecell(4,:),'b')
xlabel('time t (hours)')
ylabel('number of tumor cells')
title('c_0=10 \muM')
xlim([0 300])
ylim([0 4000])
subplot(3,2,6)
plot(tdata,data(5,:),'*k')
hold on
plot(t,curvecell(5,:),'b')
xlabel('time t (hours)')
ylabel('number of tumor cells')
title('c_0=30 \muM')
xlim([0 300])
ylim([0 4000])
```

Used for figure 5.15 on page 46.

```
%parameter setting
c0=[0.3,1,3,10,30];
Q=[2,11,143,162,300];

%figure compiling
```

```
f=figure;
plot(c0,Q,'k')
hold on
plot(c0,Q,'*b')
xlabel('Initial drug concentration c_0')
ylabel('Parameter Q')
```

Used for figure 5.16 on page 47 and for figure 5.17 on page 48.

```
%data points
data=[596.3,1479.5,2303.3,2134.1,3480.3;
    596.3 , 1337.8 , 2694.8, 2730.1, 2984.1;
    596.3 , 1260.3 ,2427.1, 2538.9, 1959.4;
    596.3,959.1,1639.7,1624.0,1212.8;
    596.3,924.3,1827.5,1657.2,1405.2];
tdata=0:72:288;

%parameter setting
N0=596.3;
cinf=0;
alpha=0.203;
r=log(2)/60;
c0=[0.3,1,3,10,30];
K=13380;
E=1;                                        %maximal efficacy
e0=0.012;                                   %initial efficacy
d=0.0003*ones(1,5);                         %growth rate of efficacy
s=1;
t=0:s:301;
t1=0:s:144;
t2=145:s:301;
NC=zeros(length(c0),length(t),2);
NC(:,1,1)=N0*ones(1,length(c0));

error=inf*ones(length(c0),1);
e=zeros(length(c0),1);
curvecell=zeros(length(c0),length(t));
curvedrug=zeros(length(c0),length(t));

for h=1:length(c0)
    NC(h,:,2)=E*e0./(e0+(E-e0)*exp(-d(h)*c0(h)*t));
    for l=1:length(t)-1
        NC(h,l+1,1)=NC(h,l,1)+s*(r/alpha*NC(h,l,1)*(1-(NC(h,l,1)/K)...
            ^alpha)-NC(h,l,2)*NC(h,l,1));
        if NC(h,l+1,2)<0
            NC(h,l+1,2)=0;
        end
        if NC(h,l+1,1)<0
            NC(h,l+1,1)=0;
        end
```

```
42      end
43      model=NC(h,[1,73,145,217,289],1);
44      e=sum(((data(h,:)-model)./model).^2);
45      if e < error(h)
46          curvecell(h,:)=NC(h,:,1);
47          curvedrug(h,:)=NC(h,:,2);
48          error(h)=e;
49      end
50  end
51
52  %number of cells without treatment
53  K=13380;
54  curve=K*N0./(N0^alpha+(K^alpha-N0^alpha)*exp(-r*t)).^(1/alpha);
55
56  %compiling figure
57  f1=figure;
58  subplot(3,2,1)
59  plot(t,curve,'b')
60  xlabel('time t (hours)')
61  ylabel('number of tumor cells')
62  title('c_0=0 \muM')
63  xlim([0 300])
64  subplot(3,2,2)
65  plot(tdata,data(1,:),'*k')
66  hold on
67  plot(t,curvecell(1,:),'b')
68  xlabel('time t (hours)')
69  ylabel('number of tumor cells')
70  title('c_0=0.3 \muM')
71  xlim([0 300])
72  ylim([0 4000])
73  subplot(3,2,3)
74  plot(tdata,data(2,:),'*k')
75  hold on
76  plot(t,curvecell(2,:),'b')
77  xlabel('time t (hours)')
78  ylabel('number of tumor cells')
79  title('c_0=1 \muM')
80  xlim([0 300])
81  ylim([0 4000])
82  subplot(3,2,4)
83  plot(tdata,data(3,:),'*k')
84  hold on
85  plot(t,curvecell(3,:),'b')
86  xlabel('time t (hours)')
87  ylabel('number of tumor cells')
88  title('c_0=3 \muM')
89  xlim([0 300])
90  ylim([0 4000])
91  subplot(3,2,5)
```

```
92 plot(tdata,data(4,:),'*k')
93 hold on
94 plot(t,curvecell(4,:),'b')
95 xlabel('time t (hours)')
96 ylabel('number of tumor cells')
97 title('c_0=10 \muM')
98 xlim([0 300])
99 ylim([0 4000])
100 subplot(3,2,6)
101 plot(tdata,data(5,:),'*k')
102 hold on
103 plot(t,curvecell(5,:),'b')
104 xlabel('time t (hours)')
105 ylabel('number of tumor cells')
106 title('c_0=30 \muM')
107 xlim([0 300])
108 ylim([0 4000])
109
110 f2=figure;
111 subplot(1,2,1)
112 plot(t,curvedrug(1,:),'g')
113 xlabel('time t (hours)')
114 ylabel('efficacy of drug')
115 title('c_0=0.3 \muM')
116 axis square
117 xlim([0 300])
118 subplot(1,2,2)
119 plot(t,curvedrug(4,:),'g')
120 xlabel('time t (hours)')
121 ylabel('efficacy of drug')
122 title('c_0=10 \muM')
123 axis square
124 xlim([0 300])
```

Used for figure 6.1 on page 50.

```
1 %parameter setting
2 ratio=0.5:0.01:20;                                %ratio (alpha/beta) scale
3 alpha=1/3.35;
4 beta=linspace((alpha/0.5),(alpha/20),length(ratio));
5 D1=2;                                             %different radiation dosages
6 D2=4;
7 D3=8;
8
9 %different survivial fractions, depending on the different dosages
10 S1=100*exp(-alpha.*D1-beta.*D1.^2);
11 S2=100*exp(-alpha.*D2-beta.*D2.^2);
12 S3=100*exp(-alpha.*D3-beta.*D2.^2);
13
14 %compiling left figure
```

```
15 f=figure;
16 subplot(1,2,1)
17 semilogy(ratio,S1,'Color','r')
18 hold on
19 semilogy(ratio,S2,'Color','g')
20 hold on
21 semilogy(ratio,S3,'Color','b')
22 axis square
23 xlabel('ratio \alpha/\beta')
24 ylabel('Survival fraction (%)')
25 xlim([0 20])
26 ylim([0.1 100])
27 set(gca,'YTick',[0.1,1,10,100])
28 set(gca,'XTick',[0:2:20])
29
30 alpha=1/3.35;
31 beta1=alpha/1.5;
32 beta2=alpha/10;
33 beta3=alpha/20;
34 D=0:0.05:15;                                    %dosage scale
35
36 %different survivial fractions, depending on different beta values
37 S1=100*exp(-alpha.*D-beta1.*D.^2);
38 S2=100*exp(-alpha.*D-beta2.*D.^2);
39 S3=100*exp(-alpha.*D-beta3.*D.^2);
40
41 %compiling right figure
42 subplot(1,2,2)
43 semilogy(D,S1,'Color','r')
44 hold on
45 semilogy(D,S2,'Color','g')
46 hold on
47 semilogy(D,S3,'Color','b')
48 axis square
49 xlabel('Dose (Gy)')
50 ylabel('Survival fraction (%)')
51 xlim([0 15])
52 ylim([0.1 100])
53 set(gca,'YTick',[0.1,1,10,100])
54 set(gca,'XTick',[0:1:15])
```

Used for figure 6.2 on page 51.

```
1 %parameter setting
2 alpha=1/3.35;
3 beta=alpha/10;
4 D=0:0.05:15;                %dosage scale
5
6 s1=1;                       %different sensitization factors
7 s2=1.1;
```

```
s3=2;

%different survivial fractions, depending on different sensitization
%factors
S1=100*exp(-alpha*D-beta*D.^2*s1^2);
S2=100*exp(-alpha*D-beta*D.^2*s2^2);
S3=100*exp(-alpha*D-beta*D.^2*s3^2);

%compiling figure
f=figure;
semilogy(D,S1,'Color','r')
hold on
semilogy(D,S2,'Color','g')
hold on
semilogy(D,S3,'Color','b')
axis square
xlabel('Dose (Gy)')
ylabel('Survival fraction (%)')
xlim([0 15])
ylim([0.1 100])
set(gca,'YTick',[0.1,1,10,100])
set(gca,'XTick',[0:1:15])
```

Used for figure 6.3 on page 57.

```
%parameter setting
r=0.0116;
K=2000000;
alpha=0.203;
E=0.05;
mu=0.002;
A=0:0.001:6;

%calculation of the final number of tumor cells
N=K*(ones(size(A))-alpha*(mu*A+ones(size(A))*E)./r).^(1/alpha);
N(A>(r/(alpha*mu)-E/mu))=0;

%figure compiling
f=figure;
plot(A,N)
xlabel('Radiation dose A (Gy)')
ylabel('Final number of tumor cells N')
```

Used for figure 6.4 on page 58.

```
%parameter setting
N0=596.3;
alpha=0.203;
```

```
r=log(2)/60;
c0=[0.3,10];
K=13380;
E=1;                                                    %maximal efficacy
e0=0.01;                                                %initial efficacy
d=0.0004;                                               %efficacy grwoth rate
s=1;
mu=0.002;
A=[2,8];
t=0:s:301;
t1=0:s:144;
t2=145:s:301;
NC=zeros(length(A),length(c0),length(t),2);
NC(:,:,1,1)=N0*ones(length(A),length(c0));

%curves are obtained with the analytical solution for the efficacy equation
%and the numerical solution (euler method) of the tumor cell number
%equation
for k=1:length(A)
    for h=1:length(c0)
        NC(k,h,:,2)=E*e0./(e0+(E-e0)*exp(-d*c0(h)*t));
        for l=1:length(t)-1
            NC(k,h,l+1,1)=NC(k,h,l,1)+s*(r/alpha*NC(k,h,l,1)*...
                (1-(NC(k,h,l,1)/K)^alpha)-A(k)*mu*NC(k,h,l,1)-NC(k,h,l,2)*NC(k,h,l,1));
            if NC(k,h,l+1,2)<0
                NC(k,h,l+1,2)=0;
            end
            if NC(k,h,l+1,1)<0
                NC(k,h,l+1,1)=0;
            end
        end
    end
end

%number of cells without treatment
K=13380;
curve=K*N0./(N0^alpha+(K^alpha-N0^alpha)*exp(-r*t)).^(1/alpha);

%compiling figure
f=figure;
plot(t,curve,'k')
hold on
plot(t,squeeze(NC(1,1,:,1)),'b')
plot(t,squeeze(NC(1,2,:,1)),'g')
plot(t,squeeze(NC(2,1,:,1)),'y')
plot(t,squeeze(NC(2,2,:,1)),'r')
xlabel('time t (hours)')
ylabel('number of tumor cells')
xlim([0 300])
legend('no Drug and A=0 Gy', 'c_{\infty}=0.3 \muM and A=2 Gy',...
```

```
54      'c_{\infty}=10 \muM and A=2 Gy', 'c_{\infty}=0.3 \muM and A=8 Gy',...
55      'c_{\infty}=10 \muM and A=8 Gy','Location','NorthWest')
```

Algorithm 7: Used to find the parameters ϵ_0 and d in section 6.2.2 on page 57, for figure 6.5 on page 59, for figure 6.6 on page 61, for figure 6.7 on page 63 and for figure 6.8 on page 64.

```
1  %data points
2  c0=0.3;
3  data=[596.3 , 1258.1 , 1695.7 , 1588.9 , 1283.0;
4   596.3 , 1202.1 ,  1992.4 , 2242.5 , 2191.6;
5   596.3 , 1037.9 , 1842.7 , 1905.6 , 1442.5;
6   596.3 , 1195.5 , 1606.8 ,  1424.7 , 1416.8];
7
8  % c0=1;
9  % data=[ 596.3 ,  1208.9 , 1507.9 , 1436.8 , 850.9;
10 %  596.3 , 1005.3 , 1663.7 , 1537.5 , 1403.4;
11 %  596.3 , 1156.8 , 1669.3 , 1742.6 , 1097.7;
12 %  596.3 , 967.5 , 1485.0 , 1542.5 , 1136.1];
13
14 % c0=3;
15 % data=[ 596.3 , 1268.2 , 1708.5 , 1197.2 , 892.7;
16 %  596.3 , 965.0 , 1667.3 , 1492.7 , 1531.6;
17 %  596.3 , 925.6 , 1594.8 , 1359.8 , 764.6;
18 %  596.3 , 982.9 , 1377.4 , 1371.2 , 1079.1];
19
20 % c0=10;
21 % data=[596.3 , 1134.1, 1274.6 ,1097.1 ,  711.1;
22 %  596.3 , 1079.4 , 1305.0 , 1383.0 , 1619.8;
23 %  596.3 , 905.6 , 1566.5 , 1568.2 , 1023.8;
24 %  596.3 , 1138.6 , 1443.0 , 1280.1 , 905.1];
25
26 tdata=0:72:288;
27
28 %parameter setting
29 N0=596.3;
30 alpha=0.203;
31 r=log(2)/60;
32 K=13380;
33 E=1;
34 e0=0:0.001:0.02;
35 d=[0:0.0001:0.001,0.002:0.001:0.02];
36 A=2:2:8;
37 mu=[0.0024,0.0023,0.0015,0.0015];
38
39 s=1;
40 t=0:s:301;
41 t1=0:s:144;
42 t2=145:s:301;
```

```
NC=zeros(length(A),length(t),2);
NC(:,1,1)=N0*ones(1,length(A));

error=inf*ones(length(A),1);
error2=inf*ones(length(A),1);
e0final=zeros(length(A),1);                    %final initial efficacy
dfinal=zeros(length(A),1);                     %final efficacy growth rate
curvecell=zeros(length(A),length(t));          %best fitting curve
curvecell2=zeros(length(A),length(t));         %curve with previous
                                               %parameters for comparison

%varying epsilon_0 and d to find the best fit with the aid of the euler
%method; blue lines
for h=1:length(A)
    for k=1:length(e0)
        for i=1:length(d)
            NC(h,:,2)=E*e0(k)./(e0(k)+(E-e0(k))*exp(-d(i)*c0*t));
            for l=1:length(t)-1
                NC(h,l+1,1)=NC(h,l,1)+s*(r/alpha*NC(h,l,1)*(1-(NC(h,l,1)...
                    /K)^alpha)-mu(h)*A(h)*NC(h,l,1)-NC(h,l,2)*NC(h,l,1));
                if NC(h,l+1,2)<0
                    NC(h,l+1,2)=0;
                end
                if NC(h,l+1,1)<0
                    NC(h,l+1,1)=0;
                end
            end
            model=NC(h,[1,73,145,217,289],1);
            e=sum(((data(h,:)-model)./model).^2);
            if e < error(h)
                curvecell(h,:)=NC(h,:,1);
                error(h)=e;
                e0final(h)=e0(k);
                dfinal(h)=d(i);
            end
        end
    end
end

e0=0.012;
d=0.0003;
%red lines
for h=1:length(A)
    NC(h,:,2)=E*e0./(e0+(E-e0)*exp(-d*c0*t));
    for l=1:length(t)-1
        NC(h,l+1,1)=NC(h,l,1)+s*(r/alpha*NC(h,l,1)*(1-(NC(h,l,1)...
            /K)^alpha)-mu(h)*A(h)*NC(h,l,1)-NC(h,l,2)*NC(h,l,1));
        if NC(h,l+1,2)<0
            NC(h,l+1,2)=0;
        end
```

```
93            if NC(h,l+1,1)<0
94                NC(h,l+1,1)=0;
95            end
96        end
97        model=NC(h,[1,73,145,217,289],1);
98        error2(h)=sum(((data(h,:)-model)./model).^2);
99        curvecell2(h,:)=NC(h,:,1);
100   end
101
102   %compiling figure
103   f=figure;
104   subplot(2,2,1)
105   plot(tdata,data(1,:),'*k')
106   hold on
107   plot(t,curvecell(1,:),'b')
108   plot(t,curvecell2(1,:),'r')
109   xlabel('time t (hours)')
110   ylabel('number of tumor cells')
111   title('A=2 Gy')
112   xlim([0 300])
113   subplot(2,2,2)
114   plot(tdata,data(2,:),'*k')
115   hold on
116   plot(t,curvecell(2,:),'b')
117   plot(t,curvecell2(2,:),'r')
118   xlabel('time t (hours)')
119   ylabel('number of tumor cells')
120   title('A=4 Gy')
121   xlim([0 300])
122   subplot(2,2,3)
123   plot(tdata,data(3,:),'*k')
124   hold on
125   plot(t,curvecell(3,:),'b')
126   plot(t,curvecell2(3,:),'r')
127   xlabel('time t (hours)')
128   ylabel('number of tumor cells')
129   title('A=6 Gy')
130   xlim([0 300])
131   subplot(2,2,4)
132   plot(tdata,data(4,:),'*k')
133   hold on
134   plot(t,curvecell(4,:),'b')
135   plot(t,curvecell2(4,:),'r')
136   xlabel('time t (hours)')
137   ylabel('number of tumor cells')
138   title('A=8 Gy')
139   xlim([0 300])
```

Used for figure 6.9 on page 66.

```
%parameter setting
N0=596.3;
alpha=0.203;
r=log(2)/60;
K=13380;
E=1;
c0=[0.3,1,3,10];
e0=0.012;
e0comb=[0.008,0.007,0.006,0.011;
    0.004,0.005,0.006,0.008;
    0.004,0.003,0.005,0.005;
    0.003,0.003,0.003,0.003];
dcomb=[0.012,0.005,0.002,0.0003;
    0.009,0.004,0.0009,0.0001;
    0.016,0.007,0.002,0.0005;
    0.017,0.006,0.002,0.0007];
d=0.0003;
A=6:2:8;
mu=[0.0024,0.0023,0.0015,0.0015];

s=1;
t=0:s:301;
t1=0:s:144;
t2=145:s:301;
efficacy=zeros(length(t),2);

cells=zeros(length(t),3);
cells(1,2)=N0;
cells(1,3)=N0;

%tumor growth without treatment
curve=K*N0./(N0^alpha+(K^alpha-N0^alpha)*exp(-r*t)).^(1/alpha);

f=figure;

for h=1:length(A)
    for i=1:length(c0)
        %efficacy for the combined model
        efficacy(:,1)=E*e0comb(h,i)./(e0comb(h,i)+(E-e0comb(h,i))*...
            exp(-dcomb(h,i)*c0(i)*t));
        %efficacy for chemotherapy alone
        efficacy(:,2)=E*e0./(e0+(E-e0)*exp(-d*c0(i)*t));
        for l=1:length(t)-1
            %tumor growth including combined therapy
            cells(l+1,3)=cells(l,3)+s*(r/alpha*cells(l,3)*(1-(cells(l,3)...
                /K)^alpha)-mu(h)*A(h)*cells(l,3)-efficacy(l,1)*cells(l,3));
            %tumor growth including chemotherapy
            cells(l+1,2)=cells(l,2)+s*(r/alpha*cells(l,2)*(1-(cells(l,2)...
                /K)^alpha)-efficacy(l,2)*cells(l,2));
        end
```

```
51          %tumor growth including radiotherapy
52          cells(:,1)=K*N0./(((N0^alpha*r)/(r-alpha*mu(h)*A(h))+(K^alpha -...
53              (N0^alpha*r)/(r-alpha*mu(h)*A(h)))*exp(-r*t+alpha*mu(h)*A(h)...
54              *t)).^(1/alpha));
55          subplot(2,2,4*h-4+i)
56          plot(t,cells(:,1),'g')
57          hold on
58          plot(t,cells(:,2),'b')
59          plot(t,cells(:,3),'r')
60          plot(t,curve,'k')
61          xlabel('time t (hours)')
62          ylabel('number of tumor cells')
63          titel =['A=' num2str(A(h)) 'Gy and c_{\infty}=' num2str(c0(i))...
64              '\muM'];
65          title(titel)
66          xlim([0 300])
67          axis square
68      end
69  end
```

Algorithm 8: Used to find the parameters $\Gamma_\star$, γ, λ_A and λ_N in section 6.3.2 on page 75 and for figure 6.11 on page 77.

```
1  %data points
2  t1=0:72:288;
3  data=[158.890,204.586,248.789,265.891,272.372];
4
5  h=1;                                    %time steps for euler
6  t2=0:h:301;
7  R0=[158.890,0,0];                       %start point for euler from data
8  Rs=zeros(length(t2),length(R0));        %Rs(.,1)=R(.)
9                                          %Rs(.,2)=R_H(.)
10                                         %Rs(.,3)=R_N(.)
11 Rs(1,:)=R0;
12
13 %parameter setting
14 ginf=1;                                 %nutrient concentration
15 lambdaAs=0:0.01:1;                      %rate of apoptosis
16 lambdaNs=0:0.01:1;                      %rate of necrosis
17 gammas=0:0.01:1;                       %proliferation rate
18 Gamma_stars=0.0001:0.00001:0.0002;      %nutrient diffusion rate
19 error=inf;
20
21 %solution is calculated with the forward euler method;
22 %parameters are varied to get the best fit
23 for i=1:length(Gamma_stars)
24      gH=ginf-100^2*Gamma_stars(i)/6;    %nutrient concentration thresholds
25      gN=ginf-200^2*Gamma_stars(i)/6;
26      for j=1:length(gammas)
```

```
27          for k=1:length(lambdaAs)
28              for l=1:length(lambdaNs)
29                  for t=1:(length(t2)-1)
30                      s=t+1;
31                      if Rs(t,1)<=100
32                          Rs(s,1)=Rs(t,1)+h*1/3*Rs(t,1)*(gammas(j)*ginf -...
33                              1/(15)*Rs(t,1)^2*Gamma_stars(i)*gammas(j) -...
34                              lambdaAs(k));
35                          Rs(s,2)=0;
36                          Rs(s,3)=0;
37                      elseif Rs(t,1)<200
38                          Rs(t,2)=sqrt((Rs(t,1))^2-6/Gamma_stars(i)*...
39                              (ginf-gH));
40                          Rs(t,3)=0;
41                          Rs(s,1)=Rs(t,1)+h*1/3*Rs(t,1)*(gammas(j)*ginf*...
42                              (1-(Rs(t,2)/Rs(t,1))^3)-lambdaAs(k))+h*1/3*...
43                              (Rs(t,1))^3*(-1/(15)*gammas(j)*...
44                              Gamma_stars(i)+1/6*gammas(j)*Gamma_stars(i)*...
45                              (Rs(t,2)/Rs(t,1))^3)-h*1/3*(Rs(t,1))^3*1/10  ...
46                              *gammas(j)*Gamma_stars(i)*(Rs(t,2)/Rs(t,1))^5;
47                      else
48                          Rs(t,2)=sqrt((Rs(t,1))^2-6/Gamma_stars(i)*...
49                              (ginf-gH));
50                          Rs(t,3)=sqrt((Rs(t,1))^2-6/Gamma_stars(i)*...
51                              (ginf-gN));
52                          Rs(s,1)=Rs(t,1)+h*1/3*Rs(t,1)*(gammas(j)*gN*(1-...
53                              (Rs(t,2)/Rs(t,1))^3)-lambdaAs(k)-lambdaNs(l)...
54                              *(Rs(t,3)/Rs(t,1))^3)+h*gammas(j)*...
55                              Gamma_stars(i)*1/6*  (Rs(t,1))^3*(1/5*(1-...
56                              (Rs(t,2)/Rs(t,1))^5)-(Rs(t,3)/Rs(t,1))^2*...
57                              (1-(Rs(t,2)/Rs(t,1))^3)+(Rs(t,3)/Rs(t,1))^3  ...
58                              *(1-(Rs(t,2)/Rs(t,1))^2));
59                      end
60                  end
61                  model=[Rs(1,1),Rs(73,1),Rs(145,1),Rs(217,1),Rs(289,1)];
62                  e=sum(((data-model)./model).^2);
63                  if e< error
64                    error=e;
65                    lambdaA=lambdaAs(k);
66                    lambdaN=lambdaNs(l);
67                    gamma=gammas(j);
68                    Gamma_star=Gamma_stars(i);
69                    Rfinal=Rs;
70                  end
71              end
72          end
73      end
74  end
75
76  %compiling figure
```

```
77 f=figure;
78 plot(t1,data,'*k')
79 hold on
80 plot(t2,Rfinal(:,1))
81 plot(t2,Rfinal(:,2),'r')
82 plot(t2,Rfinal(:,3),'g')
83 axis([0,300,0,300])
84 xlabel('Time t (hours)')
85 ylabel('Radius (\mu m)')
86 legend('data points','R','R_H','R_N','Location', 'SouthEast')
```

Algorithm 9: Used to find the parameters μ in section 6.3.2 on page 75 and for figure 6.12 on page 78.

```
1 %data points
2 t1=0:72:288;
3 data=[158.890,198.014,230.050,239.573,251.654;
4       158.890,193.470,212.807,223.183,225.769;
5       158.890,199.823,213.748,209.756,224.324;
6       158.890,196.593,202.409,196.075,211.284];
7
8 %parameter setting
9 ginf=1;
10 lambdaA=0;
11 lambdaN=0;
12 gamma=0.03;
13 Gamma_star=0.00012;
14 A=[2,4,6,8];                                  %radiation dosages
15 mus=0:0.0001:0.02;                            %dying rate per Gy
16
17 h=2/60;                                       %time steps for euler
18 t2=0:h:301;
19 R0=repmat([158.890;0;0],1,4);                 %start point for euler from data
20 Rs=zeros(length(t2),3,length(A));
21 Rs(1,:,:)=R0;
22
23 error=ones(4,1)*inf;
24 mu=zeros(4,1);
25 Rfinal=zeros(size(Rs));
26 modelfinal=zeros(size(data));
27
28 gH=ginf-100^2*Gamma_star/6;
29 gN=ginf-200^2*Gamma_star/6;
30
31 %solution is calculated with the forward euler method;
32 %parameters are varied to get the best fit
33 for i=1:length(A)
34     for j=1:length(mus)
35         for t=1:length(t2)-1
```

```
36              s=t+1;
37              if Rs(t,1,i)<=100
38                  Rs(s,1,i)=Rs(t,1,i)+h*1/3*Rs(t,1,i)*(gamma*ginf-1/...
39                      (15)*Rs(t,1,i)^2*Gamma_star*gamma-lambdaA-mus(j)...
40                      *A(i));
41                  Rs(s,2,i)=0;
42                  Rs(s,3,i)=0;
43              elseif Rs(t,1,i)<200
44                  Rs(t,2,i)=sqrt((Rs(t,1,i))^2-6/Gamma_star*(ginf-gH));
45                  Rs(t,3,i)=0;
46                  Rs(s,1,i)=Rs(t,1,i)+h*1/3*Rs(t,1,i)*((gamma*ginf-mus...
47                      (j)*A(i))*(1-(Rs(t,2,i)/Rs(t,1,i))^3)-lambdaA)+h*...
48                      1/3*(Rs(t,1,i))^3*(-1/(15)*gamma*Gamma_star+1/6*...
49                      gamma* Gamma_star*(Rs(t,2,i)/Rs(t,1,i))^3)-h*...
50                      1/3*(Rs(t,1,i))^3*1/10*gamma*Gamma_star*...
51                      (Rs(t,2,i)/Rs(t,1,i))^5;
52              else
53                  Rs(t,2,i)=sqrt((Rs(t,1,i))^2-6/Gamma_star*(ginf-gH));
54                  Rs(t,3,i)=sqrt((Rs(t,1,i))^2-6/Gamma_star*(ginf-gN));
55                  Rs(s,1,i)=Rs(t,1,i)+h*1/3*Rs(t,1,i)*((gamma*gN-...
56                      mus(j)*A(i))*(1-(Rs(t,2,i)/Rs(t,1,i))^3)-lambdaA-...
57                      lambdaN*(Rs(t,3,i)/Rs(t,1,i))^3)+h*gamma*...
58                      Gamma_star*1/6*(Rs(t,1,i))^3*(1/5*(1-(Rs(t,2,i)/...
59                      Rs(t,1,i))^5)-(Rs(t,3,i)/Rs(t,1,i))^2*(1-...
60                      (Rs(t,2,i)/Rs(t,1,i))^3)+(Rs(t,3,i)/Rs(t,1,i))...
61                      ^3*(1-(Rs(t,2,i)/Rs(t,1,i))^2));
62              end
63          end
64          model=[Rs(1,1,i),Rs(72*30+1,1,i),Rs(144*30+1,1,i),...
65              Rs(216*30+1,1,i),Rs(288*30+1,1,i)];
66          e=sum(((data(i,:)-model)./model).^2);
67          if e < error(i)
68              error(i)=e;
69              mu(i)=mus(j);
70              Rfinal(:,:,i)=Rs(:,:,i);
71              modelfinal(i,:)=model;
72          end
73      end
74  end
75
76  %compiling figure
77  f=figure;
78  subplot(2,2,1)
79  plot(t1,data(1,:),'*k')
80  hold on
81  plot(t2,Rfinal(:,1,1))
82  plot(t2,Rfinal(:,2,1),'r')
83  plot(t2,Rfinal(:,3,1),'g')
84  axis([0,300,0,300])
85  axis square
```

```
xlabel('Time t (hours)')
ylabel('Radius (\mum)')
title('A=2')

subplot(2,2,2)
plot(t1,data(2,:),'*k')
hold on
hold on
plot(t2,Rfinal(:,1,2))
plot(t2,Rfinal(:,2,2),'r')
plot(t2,Rfinal(:,3,2),'g')
axis([0,300,0,300])
axis square
xlabel('Time t (hours)')
ylabel('Radius (\mum)')
title('A=4')

subplot(2,2,3)
plot(t1,data(3,:),'*k')
hold on
plot(t2,Rfinal(:,1,3))
plot(t2,Rfinal(:,2,3),'r')
plot(t2,Rfinal(:,3,3),'g')
axis([0,300,0,300])
axis square
xlabel('Time t (hours)')
ylabel('Radius (\mum)')
title('A=6')

subplot(2,2,4)
plot(t1,data(4,:),'*k')
hold on
plot(t2,Rfinal(:,1,4))
plot(t2,Rfinal(:,2,4),'r')
plot(t2,Rfinal(:,3,4),'g')
axis([0,300,0,300])
axis square
xlabel('Time t (hours)')
ylabel('Radius (\mum)')
title('A=8')
```

Algorithm 10: Used to find the parameters Γ_1 and ν in section 6.3.2 on page 75 and for figure 6.13 on page 80.

```
%data points
t1=0:72:288;
data=[158.890,187.719,202.966,200.259,218.354;
    158.89,185.684,210.558,211.043,214.376;
    158.89,183.276,206.101,207.743,198.439;
```

```
6       158.890,173.483,190.881,190.559,180.951;
7       158.89,172.535,194.972,191.632,186.101];
8
9  h=1;                                          %time steps for euler
10 t2=0:h:301;
11 R0=repmat([158.890;0;0],1,5);                 %start point for euler from data
12 Rs=zeros(length(t2),3,5);
13 Rs(1,:,:)=R0;
14
15 %parameter setting
16 ginf=1;
17 cinf=[0.3,1,3,10,30];
18 lambdaA=0;
19 lambdaN=0;
20 gamma=0.03;
21 Gamma_star=0.00012;
22 Gamma1=[0:0.0001:0.001,0.001:0.001:0.03];   %first drug diffusion parameter
23 Gamma2=0;                                    %second drug diffusion parameter
24 nu=0:0.0001:0.05;                           %drug killing rate
25
26 error=inf*ones(1,5);
27 Gamma1final=zeros(1,5);
28 nufinal=zeros(1,5);
29 Rfinal=zeros(size(Rs));
30 c=zeros(1,length(t2));
31
32 gH=ginf-100^2*Gamma_star/6;
33 gN=ginf-200^2*Gamma_star/6;
34
35 %solution is calculated with the forward euler method;
36 %parameters are varied to get the best fit
37 for i=1:length(cinf)
38     for j=1:length(Gamma1)
39         for l=1:length(nu)
40             for t=1:(length(t2)-1)
41                 s=t+1;
42                 if Rs(t,1)<=100
43                     Rs(s,1,i)=Rs(t,1,i)+h*1/3*Rs(t,1,i)*(gamma*ginf-...
44                         1/(15)*Rs(t,1,i)^2*Gamma_star*gamma-lambdaA-...
45                         nu(l)*cinf(i)+1/15*Rs(t,1,i)^2*Gamma1(j)*nu(l));
46                     Rs(s,2,i)=0;
47                     Rs(s,3,i)=0;
48                 elseif Rs(t,1)<200
49                     if ((Rs(t,1,i))^2-6/Gamma_star*(ginf-gH))<=0
50                         Rs(t,2,i)=0;
51                     else Rs(t,2,i)=sqrt((Rs(t,1,i))^2-6/Gamma_star*...
52                             (ginf-gH));
53                     end
54                     Rs(t,3,i)=0;
55                     Rs(s,1,i)=Rs(t,1,i)+h*1/3*Rs(t,1,i)*(gamma*ginf*(1-...
```

```
56                          (Rs(t,2,i)/Rs(t,1,i))^3)-lambdaA-nu(l)*cinf(i))+...
57                          h*1/3*(Rs(t,1,i))^3*(1/(15)*(-gamma*Gamma_star+...
58                          nu(l)*Gamma1(j))+1/6*(gamma*Gamma_star+nu(l)*...
59                          (Gamma2-Gamma1(j)))*(Rs(t,2,i)/Rs(t,1,i))^3)+h*...
60                          1/3*(Rs(t,1,i))^3*(1/10*(-gamma*Gamma_star+nu(l)...
61                          *(-Gamma2+Gamma1(j)))*(Rs(t,2,i)/Rs(t,1,i))^5);
62                  else
63                      if ((Rs(t,1,i))^2-6/Gamma_star*(ginf-gH))<=0
64                          Rs(t,2,i)=0;
65                      else Rs(t,2,i)=sqrt((Rs(t,1,i))^2-6/Gamma_star*...
66                              (ginf-gH));
67                      end
68                      if ((Rs(t,1,i))^2-6/Gamma_star*(ginf-gN))<=0
69                          Rs(t,3,i)=0;
70                      else Rs(t,3,i)=sqrt((Rs(t,1,i))^2-6/Gamma_star*...
71                              (ginf-gN));
72                      end
73                      Rs(s,1,i)=Rs(t,1,i)+h*1/3*Rs(t,1,i)*(gamma*gN*(1-...
74                          (Rs(t,2,i)/Rs(t,1,i))^3)-nu(l)*cinf(i)*(1-...
75                          (Rs(t,3,i)/Rs(t,1,i))^3)-lambdaA-lambdaN*...
76                          (Rs(t,3,i)/Rs(t,1,i))^3)+h*gamma*Gamma_star*...
77                          1/6*(Rs(t,1,i))^3*(1/5*(1-(Rs(t,2,i)/Rs(t,1,i)))...
78                          ^5)-(Rs(t,3,i)/Rs(t,1,i))^2*(1-(Rs(t,2,i)/...
79                          Rs(t,1,i))^3)+(Rs(t,3,i)/Rs(t,1,i))^3*(1-...
80                          (Rs(t,2,i)/Rs(t,1,i))^2))+h*nu(l)*Gamma1(j)*1/6*...
81                          (Rs(t,1,i))^3*(1/3*(1-(Rs(t,2,i)/Rs(t,1,i))^3)-...
82                          1/5*(1-(Rs(t,2,i)/Rs(t,1,i))^5))+h*nu(l)*Gamma2...
83                          *1/6*(Rs(t,1,i))^3*(1/3*((Rs(t,2,i)/Rs(t,1,i)))...
84                          ^3-(Rs(t,3,i)/Rs(t,1,i))^3)-1/5*((Rs(t,2,i)/...
85                          Rs(t,1,i))^5-(Rs(t,3,i)/Rs(t,1,i))^5));
86                  end
87              end
88              model=[Rs(1,1,i),Rs(73,1,i),Rs(145,1,i),Rs(217,1,i),...
89                  Rs(289,1,i)];
90              e=sum(((data(i,:)-model)./model).^2);
91              if e < error(i)
92                  error(i)=e;
93                  Gamma1final(i)=Gamma1(j);
94                  nufinal(i)=nu(l);
95                  Rfinal(:,:,i)=Rs(:,:,i);
96              end
97          end
98      end
99  end
100
101 %figure compiling
102 f1=figure;
103 subplot(2,2,1)
104 plot(t1,data(1,:),'*k')
105 hold on
```

```
106 plot(t2,Rfinal(:,1,1))
107 plot(t2,Rfinal(:,2,1),'r')
108 plot(t2,Rfinal(:,3,1),'g')
109 axis([0,300,0,300])
110 axis square
111 xlabel('Time t (hours)')
112 ylabel('Radius (\mum)')
113 title('c_{\infty}(0)=0.3\muM')
114
115 subplot(2,2,2)
116 plot(t1,data(2,:),'*k')
117 hold on
118 plot(t2,Rfinal(:,1,2))
119 plot(t2,Rfinal(:,2,2),'r')
120 plot(t2,Rfinal(:,3,2),'g')
121 axis([0,300,0,300])
122 axis square
123 xlabel('Time t (hours)')
124 ylabel('Radius (\mum)')
125 title('c_{\infty}(0)=1\muM')
126
127 subplot(2,2,3)
128 plot(t1,data(3,:),'*k')
129 hold on
130 plot(t2,Rfinal(:,1,3))
131 plot(t2,Rfinal(:,2,3),'r')
132 plot(t2,Rfinal(:,3,3),'g')
133 axis([0,300,0,300])
134 axis square
135 xlabel('Time t (hours)')
136 ylabel('Radius (\mum)')
137 title('c_{\infty}(0)=3\muM')
138
139 subplot(2,2,4)
140 plot(t1,data(4,:),'*k')
141 hold on
142 plot(t2,Rfinal(:,1,4))
143 plot(t2,Rfinal(:,2,4),'r')
144 plot(t2,Rfinal(:,3,4),'g')
145 axis([0,300,0,300])
146 axis square
147 xlabel('Time t (hours)')
148 ylabel('Radius (\mum)')
149 title('c_{\infty}(0)=10\muM')
150
151 f2=figure;
152
153 subplot(2,2,1)
154 plot(t1,data(5,:),'*k')
155 hold on
```

```
156 plot(t2,Rfinal(:,1,5))
157 plot(t2,Rfinal(:,2,5),'r')
158 plot(t2,Rfinal(:,3,5),'g')
159 axis([0,300,0,300])
160 axis square
161 xlabel('Time t (hours)')
162 ylabel('Radius (\mum)')
163 title('c_{\infty}(0)=30\muM')
```

Used for figure 6.14 on page 81 and for figure 6.15 on page 82 and to calculate the corresponding errors.

```
1 %data points
2 t1=0:72:288;
3 cinf=0.3;
4 data=[158.890 , 182.110 , 191.982 , 189.793 , 182.746;
5  158.890 , 180.725 ,  197.622 , 201.778 , 200.964;
6  158.890 , 176.152 , 195.129 , 196.287 , 186.861;
7  158.890 , 180.306 , 189.976 ,  185.993 , 185.810];
8 %c_inf=10
9 % data=[ 158.890 , 178.539 , 182.275 , 177.517 , 164.145;
10 %  158.890 , 177.064 ,  195.070 , 185.027 , 190.254;
11 %  158.890 , 171.778 , 189.521 , 189.557 , 175.654;
12 %  158.890 , 178.820 , 186.495 , 182.585 , 171.600];
13
14 h=2/60;                                          %time steps for euler
15 t2=0:h:301;
16 R0=repmat([158.890;0;0],1,4);
17 A=[2,4,6,8];
18 Rs=zeros(length(t2),3,length(A));
19 Rs(1,:,:)=R0;
20
21 %parameter setting
22 ginf=1;
23 lambdaA=0;
24 lambdaN=0;
25 gamma=0.03;
26 Gamma_star=0.00012;
27 Gamma1=0.0004;                                   %for cinf=10: Gamma1=0.023;
28 Gamma2=0;
29 nu=0.0365;                                       %for cinf=10: nu=0.0036;
30 mu=[0.0034,0.0032,0.0022,0.0021];
31
32 error=ones(4,1)*inf;
33
34 gH=ginf-100^2*Gamma_star/6;
35 gN=ginf-200^2*Gamma_star/6;
36
37 %solution is calculated with the forward euler method;
```

```
for i=1:length(A)
    for t=1:(length(t2)-1)
        s=t+1;
        if Rs(t,1)<=100
            Rs(s,1,i)=Rs(t,1,i)+h*1/3*Rs(t,1,i)*(gamma*ginf-1/(15)*...
                Rs(t,1,i)^2*Gamma_star*gamma-lambdaA-mu(i)*1-nu*cinf+...
                1/15*Rs(t,1,i)^2*Gamma1*nu);
            Rs(s,2,i)=0;
            Rs(s,3,i)=0;
        elseif Rs(t,1)<200
            if ((Rs(t,1,i))^2-6/Gamma_star*(ginf-gH))<=0
                Rs(t,2,i)=0;
            else Rs(t,2,i)=sqrt((Rs(t,1,i))^2-6/Gamma_star*(ginf-gH));
            end
            Rs(t,3,i)=0;
            Rs(s,1,i)=Rs(t,1,i)+h*1/3*Rs(t,1,i)*((gamma*ginf-mu(i)*1)*...
                (1-(Rs(t,2,i)/Rs(t,1,i))^3)-lambdaA-nu*cinf)+h*1/3*...
                (Rs(t,1,i))^3*(1/(15)*(-gamma*Gamma_star+nu*Gamma1)+1/6*...
                (gamma*Gamma_star+nu*(Gamma2-Gamma1))*(Rs(t,2,i)/...
                Rs(t,1,i))^3)+h*1/3*(Rs(t,1,i))^3*(1/10*(-gamma*...
                Gamma_star+nu*(-Gamma2+Gamma1))*(Rs(t,2,i)/Rs(t,1,i))^5);
        else
            if ((Rs(t,1,i))^2-6/Gamma_star*(ginf-gH))<=0
                Rs(t,2,i)=0;
            else Rs(t,2,i)=sqrt((Rs(t,1,i))^2-6/Gamma_star*(ginf-gH));
            end
            if ((Rs(t,1,i))^2-6/Gamma_star*(ginf-gN))<=0
                Rs(t,3,i)=0;
            else Rs(t,3,i)=sqrt((Rs(t,1,i))^2-6/Gamma_star*(ginf-gN));
            end
            Rs(s,1,i)=Rs(t,1,i)+h*1/3*Rs(t,1,i)*((gamma*gN-mu(i)*1)*(1-...
                (Rs(t,2,i)/Rs(t,1,i))^3)-nu*cinf*(1-(Rs(t,3,i)/Rs(t,1,i)...
                )^3)-lambdaA-lambdaN*(Rs(t,3,i)/Rs(t,1,i))^3)+h*gamma*...
                Gamma_star*1/6*(Rs(t,1,i))^3*(1/5*(1-(Rs(t,2,i)/...
                Rs(t,1,i))^5)-(Rs(t,3,i)/Rs(t,1,i))^2*(1-(Rs(t,2,i)/...
                Rs(t,1,i))^3)+(Rs(t,3,i)/Rs(t,1,i))^3*(1-(Rs(t,2,i)/...
                Rs(t,1,i))^2))+h*nu*Gamma1*1/6*(Rs(t,1,i))^3*(1/3*(1-...
                (Rs(t,2,i)/Rs(t,1,i))^3)-1/5*(1-(Rs(t,2,i)/Rs(t,1,i))...
                ^5))+h*nu*Gamma2*1/6*(Rs(t,1,i))^3*(1/3*((Rs(t,2,i)/...
                Rs(t,1,i))^3-(Rs(t,3,i)/Rs(t,1,i))^3)-1/5*((Rs(t,2,i)/...
                Rs(t,1,i))^5-(Rs(t,3,i)/Rs(t,1,i))^5));
        end
    end
    model=[Rs(1,1,i),Rs(72*30+1,1,i),Rs(144*30+1,1,i),Rs(216*30+1,1,i),...
        Rs(288*30+1,1,i)];
    error(i)=sum(((data(i,:)-model)./model).^2);
end

%figure compiling
f=figure;
```

```
88 subplot(2,2,1)
89 plot(t1,data(1,:),'*k')
90 hold on
91 plot(t2,Rs(:,1,1))
92 plot(t2,Rs(:,2,1),'r')
93 plot(t2,Rs(:,3,1),'g')
94 axis([0,300,0,300])
95 axis square
96 xlabel('Time t (hours)')
97 ylabel('Radius (\mum)')
98 title('A=2')
99
100 subplot(2,2,2)
101 plot(t1,data(2,:),'*k')
102 hold on
103 hold on
104 plot(t2,Rs(:,1,2))
105 plot(t2,Rs(:,2,2),'r')
106 plot(t2,Rs(:,3,2),'g')
107 axis([0,300,0,300])
108 axis square
109 xlabel('Time t (hours)')
110 ylabel('Radius (\mum)')
111 title('A=4')
112
113 subplot(2,2,3)
114 plot(t1,data(3,:),'*k')
115 hold on
116 plot(t2,Rs(:,1,3))
117 plot(t2,Rs(:,2,3),'r')
118 plot(t2,Rs(:,3,3),'g')
119 axis([0,300,0,300])
120 axis square
121 xlabel('Time t (hours)')
122 ylabel('Radius (\mum)')
123 title('A=6')
124
125 subplot(2,2,4)
126 plot(t1,data(4,:),'*k')
127 hold on
128 plot(t2,Rs(:,1,4))
129 plot(t2,Rs(:,2,4),'r')
130 plot(t2,Rs(:,3,4),'g')
131 axis([0,300,0,300])
132 axis square
133 xlabel('Time t (hours)')
134 ylabel('Radius (\mum)')
135 title('A=8')
```

Used for figure 7.1 on page 84.

```
%parameter setting
N0=10;
K=100;
alpha=2;
r=log(2)/12;
lambda=0.002;
cinf=0;
c0=0.1;
gamma=0;
nu=0.02;
h=1;                %stepsize for the euler method
P0=9;               %initial number of proliferating cells
Q0=1;               %initial number of quiescent cells
kPQ=0.005;          %rate at which proliferating cells become quiescent
kQP=0.001;          %rate at which quiescent cells become proliferating
t2=0:h:600;
curve=zeros(3,length(t2));
curve(1,1)=P0;
curve(2,1)=Q0;
curve(3,1)=c0;
curve(4,1)=P0+Q0;

%number of proliferating, quiescent and all cells together; forward euler
%method is used
for i=1:length(t2)-1
    curve(1,i+1)=curve(1,i)+h*(r/alpha*curve(1,i)*(1-((curve(1,i)+...
        curve(2,i))/K)^alpha)-nu*curve(3,i)*curve(1,i)-kPQ*curve(1,i)+...
        kQP*curve(2,i));
    curve(2,i+1)=curve(2,i)+h*(kPQ*curve(1,i)-kQP*curve(2,i));
    curve(3,i+1)=curve(3,i)+h*(cinf-lambda*NC(h,l,2)-gamma*NC(h,l,2)*NC(h,l,1));
    curve(4,i+1)=curve(1,i+1)+curve(2,i+1);
end

f=figure;
plot(t2,curve(4,:),'k')
hold on
plot(t2,curve(1,:),'r')
plot(t2,curve(2,:),'b')
xlabel('time t (hours)')
ylabel('number of tumor cells')
```

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List of Figures

List of Tables